Development and validation of a bioluminescence assay for high throughput screening of potent and rapidly cytocidal compounds against intraerythrocytic *Plasmodium falciparum*

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Abstract

The emergence of *P. falciparum* resistant to current front-line artemisinin combination therapies underscores the urgent demand for new candidate molecules for a single exposure radical cure and prophylaxis drug. Developing a suitable candidate component that is both potent and effects a rapid rate of kill to replace artemisinins requires a new and innovative *in vitro* screening assays to support discovery. A standard Bioluminescence Relative Rate of Kill (BRRoK) assay to quickly triage rapid cytocidal antimalarial compounds *in vitro* has been developed. Recognizing limitations in the BRRoK assay necessitated a subsequent development of a modified-BRRoK assay. This mBRRoK assay explores a compound's RoK and potency together in a fixed-concentration assay format more amenable to a high throughput screening of a large compound libraries.

Proof-of-principle for the mBRRoK assay was developed using the Medicine for Malaria Venture (MMV) Malaria Box compounds for which BRRoK data was available. A subsequent validation of mBRRoK was carried out using the MMV Pathogen Box open source discovery library. Potential new leads were identified, of a particular interest are novel PfeEF2 inhibitors (MMV634140 and MMV667494) that show a rapid initial relative rate of kill. These compounds are suggested for further optimization and characterization.

The mBRRoK assay was adapted, miniaturized and optimized for high throughput screening of 12,514 TCAMS library. The results demonstrated that this assay is simple, sensitive (81% true discovery rate), reliable and robust with Z´ value of 0.74-0.98 and S/B ratio of 160 to 475. Predicted fast-acting hits were selected and confirmed using the standard BRRoK assay in both the original $Dd2^{luc}$ reporter strain, but also in a new $NF54^{luc}$ (chloroquine-sensitive) strain. The results demonstrated the utility of mBRRoK assay not only for rapid screening of potent and fast-acting compound, but also to study drug-resistance profiles across different parasite strains.

The mBRRoK assay offers significant opportunities during early stage of antimalarial drug discovery and development to triage compound sets through understanding potency and initial rate of kill, but is also an assay system amenable to adaptations such as assays in artemisinin resistant reporter strains and the study of stage-specific action.

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Abbreviations

AQ	Amodiaquine
ACTs	Artemisinin Combination Therapies
ATQ	Atovaqoune
BOC	British Oxygen Company
BRRoK	Bioluminescence Relative Rate of Kill
BSD	Blasticidin S Hydrochloride
CA	Califonia
CDC	Centre for Disease Control and Prevention
ChEMBL17	Chemical molecules from the European Bioinformatics Institute
CQ	Chloroquine
CQR	Chloroquine Resistant
CQS	Chloroquine Sensitive
DAPI	4', 6-diamidino-2-phenylindole
DDT	Dichorodiphenyltrichloroethane
DHA	Dihydroartemisinin
DHFR	Dihydrofolate Reductase
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOX	Doxycycline
EC_{50}	50% effective concentration
EDTA	Ethylene Diamine Tetra acetic Acid
GFP	Green fluorescence protein
GSK	GlaxoSmithKline
GM	Genetically Modified Parasites
HCT	Heamatocrit
HEPES	N-(2-Hydroxyethyl) piperazine-N^1-(2-ethanesulfonic acid
HepG2	Human hepatoma
Hrs	Hours
HRP	Histidine Rich Protein
HTA	Human Tissue Authority
HTS	High Throughput Screening
ICAM-1	Intercellular Adhesion Molecule-1
IFN-γ	Interferon-Gamma
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IL	Interleukin
IRS	Indoor Residual Spraying
ISTM	Institute for Science and Technology in Medicine
KAHRP	Knob-Associated Histidine Rich Protein
L	Litres
LSTM	Liverpool School of Tropical Medicine
LDH	Lactate Dehydrogenate
Log	Logarithm
$LOPAC^{1280}$	Library of Pharmacologically Active Compounds
^{luc}	Luciferase
M	Molar

MQ	Mefloquine
mL	millilitre
mM	Millimolar
MMV	Medicine for Malaria Venture
MSF	Malaria Sybr-Green-1 Fluorescence
n	Number
NA	Not available
NBTS	National Blood and Transfusion Service
NCEs	New chemical entities
N_{FN}	Number of False positive
N_{FP}	Number of False Negative
N_{TN}	Number of True Negative
N_{TP}	Number of True positive
PC	Principle Component
PCA	Principle Component analysis
PCT	Parasite clearance time
P*f*EMP1	*P. falciparum* Erythrocyte Membrane Protein 1
P*f*ATP4	*P. falciparum* P-type ATPase
PfeEF2	*P. falciparum* translocation elongation factor 2
PfPI4K	*P. falciparum* Phosphatidylinositol-4-kinase
PfENT1	*P.falciparum* Equilibrative nucleoside Transporter type 1
PPQ	Piperaquine
PRR	Parasite reduction ratio
QN	Quinine
qRT-PCR	Quantitative real time polymerase reaction
RDTs	Rapid Diagnostic Tests
RLU	Relative light unit
RNA	Ribonucleic acid
RoK	Rate of kill
RPMI	Roswell Park Memorial Institute
S/N	Signal-to-noise
S/B	Signal-to-background
SCID	Severe combined immune deficiency
SEC	Single Exposure Chemo-protectant
SERCaP	Single Exposure Radical Cure and Prophylaxis
TCAMS	Tres Cantos antimalarial compound set
TCP	Target Candidates Profiles
TNF-α	Tumor necrosis factor alpha
TPP	Target Product Profile
UK	United Kingdom
USA	United State of America
VCAM-1	Vascular Cell Adhesion Molecule
v	Version
v/v	Volume per volume
w/v	Weight per volume
WHO	World Health Organisation
X	Concentration
%	Percentage

[^{3}H]	Tritiated
µL	Microliter
µM	microMolar
^{0}C	Degree Celsius
g	Gram

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1 CHAPTER 1: Introduction

1.1 Epidemiology of malaria

Malaria is a protozoan disease that is endemic in the tropics and sub-tropics. The disease is caused by an apicomplexan obligate parasite belonging to the genus *Plasmodium.* Six species of *Plasmodium* cause human malaria: *P. falciparum, P. vivax, P. ovale curtisi, P. ovale wallikeri, P. malariae* and *P. knowlesi.* Of these, the most prevalent species are the *P. vivax* and *P. falciparum* that are responsible for the majority of the cases of malaria globally (WHO, 2018). About 228 million malaria cases (range between 206-258 million) and 405,000 death, of which 67% (272,000) of the mortality occurred in children under 5 years of age (WHO, 2019). *P. falciparum* is the most virulent and widely studied species. The majority of global malaria death are attributed to *P. falciparum* infection mostly in the WHO African region (WHO, 2019). After this, *P. vivax* is responsible for the majority of cases found in the Southeast Asia and South America. *P. vivax* is not prevalent in Africa because of the lack of Duffy antigen erythrocyte receptor that is essential for the parasite to invade erythrocytes (Guerra *et al*., 2006). However, there is growing evidence of *P. vivax* infection in all regions of Africa (Twohig *et al.*, 2019). *P. falciparum* and *P. vivax* malaria often occur together in some regions, except in some areas in Southeast Asia, for instance South Korea where only *P. vivax* is found (Howes *et al*., 2016). *P. vivax* has a characteristic clinical feature of causing relapsing malaria and this is attributed to the persistence of a dormant liver form (hypnozoite) which can become reactivated later after the initial infection. These hypnozoites can persist in the liver for up to two years after the initial inoculation of sporozoites into the blood stream by the mosquito vector (Imwong *et al*., 2007). Presently, primaquine and tafenoquine (8-aminoquinoline) are the drug of choice to prevent relapse by killing the dormant liver forms that result from *P. vivax* infection. However, these drugs can cause haemolytic anaemia in glucose-6-phosphate dehydrogenase (G6PD) deficient patients. *P. ovale curtisi* and *P. ovale wallikeri* and *P.*

malariae are morphologically indistinguishable sympatric species. *P. ovale curtisi* and *P. ovale wallikeri* cases are underestimated with seriousness of the disease resembling that of uncomplicated *P. vivax* malaria. *P. knowlesi* is a zoonotic infection in Southeast Asia, and can also cause severe malaria (Singh *et al*., 2004).

1.2 The current status of global malaria

There has been a significant reduction in the global malaria incidence rate (figure 1.1) between 2010 (71%) and 2018 (57%) (WHO, 2019). This substantial reduction has been attributed to the intensive deployment of insecticide-treated bed nets (ITN), indoor residual spraying and effective use of Artemisinin-based combination therapies (ACT). However, in 2018, the WHO reported that data from 2015-2017 shows that the significant progress achieved in the last decade in reducing global malaria is stagnant (Figure 1.2) (WHO, 2018). The likely contributing factors to the stall in progress were highlighted as threats to malaria control in the WHO's Global Technical Strategy for Malaria 2016-2030 (WHO, 2018). Among these, is resistance to the current first line drug for the treatment of uncomplicated malaria (ACTs). Since 2008 when artemisinin treatment failure was reported in the Greater Mekong Sub-region (Noedl *et al.*, 2008 and Dondorp *et al.*, 2009), collective efforts towards malaria eradication have seen major setbacks in the *P. falciparum* malaria-endemic area (WHO, 2017). In addition, mosquito resistance to pyrethroids, frequently used in the insecticide-treated nets (ITNs) and indoor residual spraying of home, is becoming rampant in malaria-endemic areas (WHO, 2017; Alonso and Noor, 2017). To further buttress this point, the WHO reported that 552 million ITNs were delivered worldwide and 83% of this total were distributed in sub-Saharan Africa between 2015 and 2017 (WHO, 2018). Although the level of intervention is high, there is a coverage gap that is another major challenge in malaria control (Alonso and Noor, 2017).

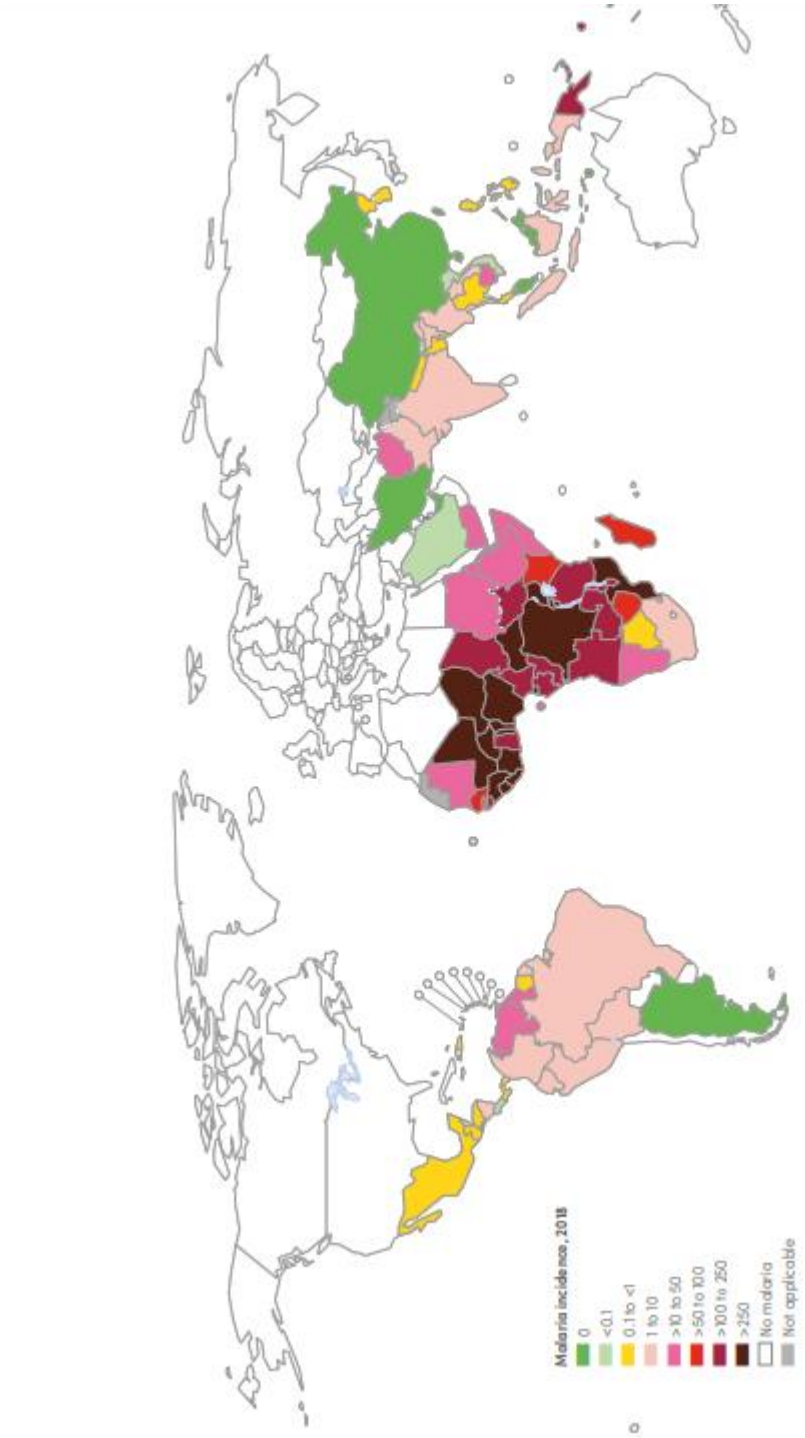


Figure 1.1: 2018 Global malaria case incidence rate by country
The key show the malaria incidence rate on country basis. The countries indicated in white have eradicated malaria while those in brown still have significant number of malaria cases
Source: WHO, (2019)

Another likely contributing factor is the level of malaria funding which has remained unchanged since 2010 (Alonso and Noor, 2017). The available fund for malaria control was only 41% of what was recommended to be the annual need in order to meet the targets stated in the WHO's Global Technical Strategy for Malaria 2016-2030 (WHO, 2017). Most of the malaria high-burden countries that rely almost entirely on international donor support also report more malaria cases in 2016 than in 2014 (Alonso and Noor, 2017). In view of the above points, the present malaria control status will be a challenge to achieving the targets set in the WHO's Global Technical Strategy for Malaria 2016-2030.

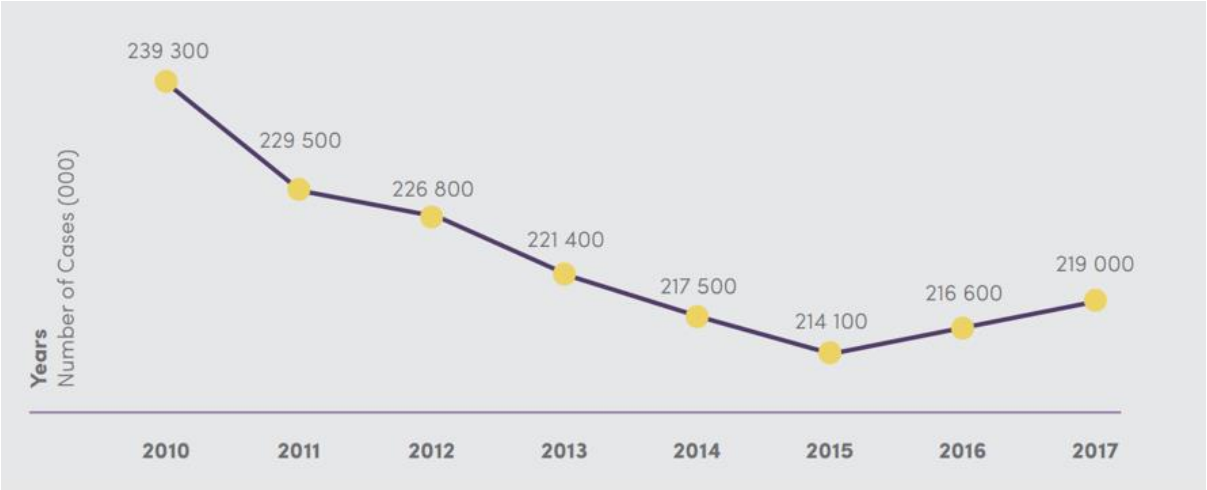


Figure 1.2 Global malaria cases between 2010 and 2017
The incidence of malaria has steadily decreased from 2010 until 2015. However, there has been a stall in this progress between 2015 and 2017 leading to reduced trend in global malaria control. Source: (WHO, 2018)

Considering the current status of global malaria control, there is an urgent need to change the course of how the disease can be effectively managed in the countries with the highest burden. In response to this, the WHO and Roll Back Malaria Partnership have brought about a country-led approach that is termed "high burden to high impact" (WHO, 2018). This call has made the work of Ministries of Health in the affected countries to be synergized more closely to share best practice in order to reverse the current downward trend in malaria control (WHO, 2018). According to the WHO (2018) Global Malaria Report, the "high burden to high impact" call is

anchored on four major pillars. First, the call to galvanize both national and international commitment into actions that will reduce malaria death. Second, the strategic use of information to maximize the effective deployment of control measures for optimum benefit. Third, the establishment of best global guidance, policies and strategies that is acceptable to all malaria-endemic nations. And fourth, the execution of a well harmonized national malaria response that involves other areas such as environment, education and agriculture. The malaria-endemic communities are optimistic that if a "high burden to high impact" response is globally implemented there should be a move to malaria control progress being back on the previous downward track (WHO, 2018).

1.3 Transmission of the human malaria parasite

Human malaria parasites are naturally transmitted by the female *Anopheles* mosquitoes of which there are about 430 species out of which 30-40 species transmit the disease in human (Figure 1.3) (CDC, 2016). Female *Anopheles* mosquitoes are anthropophilic blood feeders and the blood meal is used for their egg production. Three main factors determine the capability of *Anopheles* mosquitoes to transmit malaria parasites: innate susceptibility, host preference, and duration of its life span (CDC, 2016). Female *Anopheles* mosquitoes that are good vectors of malaria parasites are typically nocturnal endophagic feeders and these can be successfully targeted through the use of insecticide-treated bed nets (ITNs), mosquito window screen nets or indoor residual spraying of insecticides (CDC, 2016) . However, some are exophagic feeders which can be controlled by destroying their breeding habitats. Malaria can also be transmitted congenitally. This is the transfer of parasitized erythrocytes from the infected mother either transplacentally to the fetus or during labour to the new-born. Another mode of transmission is through blood transfusion and the risk of acquiring transfusion malaria is very low CDC (2016).

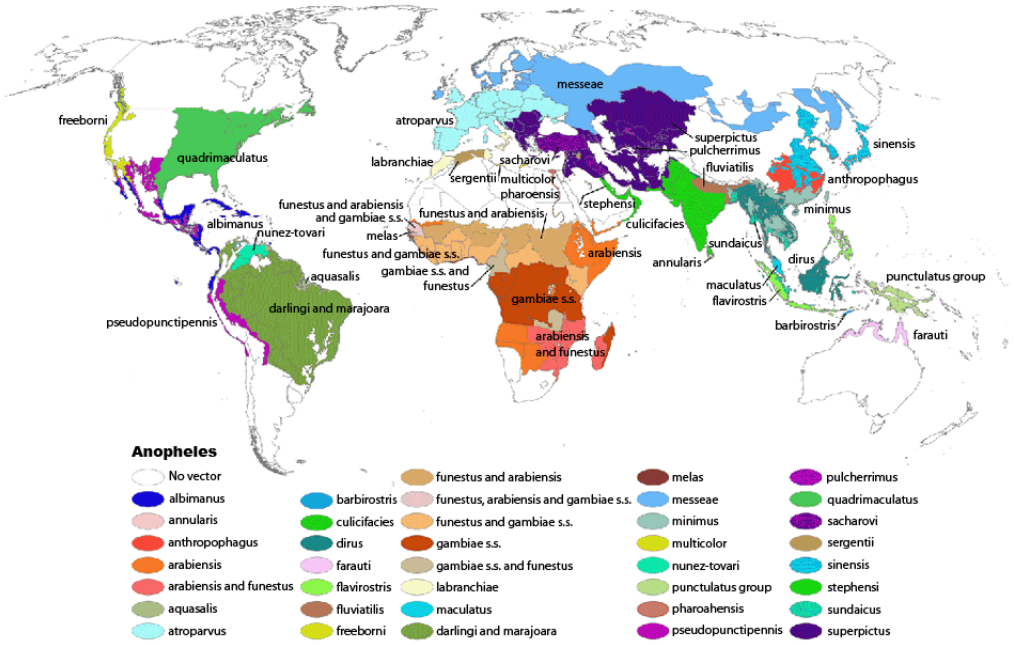


Figure 1.3: Map showing global distribution of the mosquito malaria vectors
The colour areas in the map show the distribution of Anopheles species that transmit malaria parasite across the world (see key). Source: (CDC, 2016)

1.4 Life cycle of *Plasmodium* species

Plasmodium species have a complex multistage life-cycle that is similar in all the species that infect human with the exception of intra-hepatic development cycles (Figure 1.4). The parasite utilizes two independent hosts to complete its life cycle, where asexual development (schizogony) predominantly occurs in the human (intermediate host) and the sexual development (sporogony) predominantly occurs in the mosquito (definitive host).

1.4.1 Exo-erythrocytic schizogony

Human infection with a malaria parasite is initiated when a female *Anopheles* mosquitoes inoculates sporozoites into the dermis while obtaining a blood meal. The sporozoites are rapidly transported in the blood circulation to invade the hepatocytes through the transversal process (Cowman *et al.*, 2016). This involves penetrating the sinusoidal barrier that is made up of fenestrated endothelial cells and macrophage-like Küpffer cells (Tavares *et al.*, 2013). Inside the hepatocyte, the sporozoite undergoes repeated mitotic division leading to the production of

daughter merozoites over approximately 6-8 days. The hepatocytes heavily laden with daughter merozoites become distended, burst and egress about 40,000 merozoites into the blood circulation by budding from merosomes (Sturm *et al.*, 2006). However, in *P. vivax* and *P. ovale*, some of the parasites persist in the hepatocytes as dormant liver forms (hypnozoites) for a period of about two weeks to one year. These hypnozoites can become re-activated resulting in a relapsing malaria clinical presentation that is particular to *P. vivax* and *P. ovale* infection (White, 2011).

1.4.2 Intraerythrocytic schizogony

Merozoites in the hepatic circulation invade the red blood cells within two minutes through three main steps: pre-invasion, invasion and echinocytosis (Weiss *et al.*, 2015). Parasites invade the erythrocytes, degrade the haemoglobin and manipulate the host cell membrane architecture to aid its nutrient trafficking in and out of the red blood cells. The parasites undergo different developmental changes from rings to trophozoites and then to schizonts within the erythrocytes. Inside the erythrocytes the parasites catabolise haemoglobin and modify the host membrane including the development of characteristic knob-like projections. These modifications include a novel channel through which the parasite transports its nutrient as well as the sequestering of toxic haem by-product through a lipid-mediated crystallization into haemozoin. Merozoites inside the erythrocytes undergo repeated mitosis otherwise called schizogony in 48 hours in *P. falciparum*, *P.vivax* and *P. ovale*, over 72 hours in *P. malariae* and over 24 hours in *P. knowlesi*. Schizonts eventually burst to release between 8-32 daughter merozoites into the blood circulation depending on the *Plasmodium spp*. After about three rounds of erythrocytic cycles, some of the parasites differentiate into non-dividing male and female gametocyte stages that are taken up by female *Anopheles* mosquitoes while obtaining a blood meal.

1.4.3 Sporogony

The male and female gametocytes develop into microgametes and macrogametes respectively inside the mosquitoes' midgut. The microgametes undergo exflagellation to form eight motile flagellated microgametes which fertilize the macrogametes, resulting in the formation of zygotes. The zygotes develop to form motile ookinetes that penetrate the mosquito's gut wall and encyst to form an oocyst. The oocyst divides through meiosis to produce thousands of haploid sporozoites which are released into the mosquitoes' salivary gland. When the infected mosquitoes obtain a blood meal, these sporozoites are injected into the bloodstream of the susceptible host and the life cycle is perpetuated.

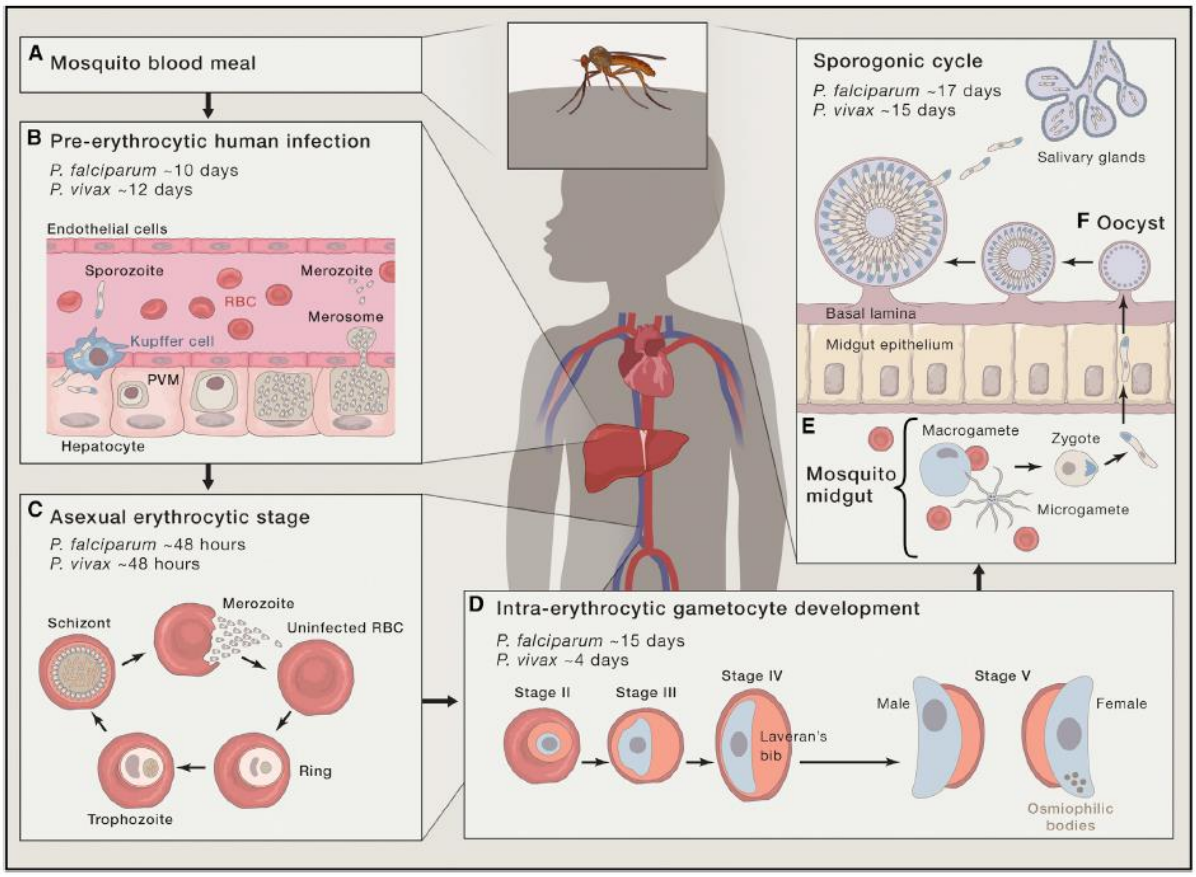


Figure 1.4: Life-cycle of human Plasmodium species
The parasite life cycle is broadly divided into an exo-erythrocytic stage which occurs inside the hepatocytes (B); an erythrocytic phase which occurs inside the erythrocytes with (C); gametogenesis (D), and the, sporogony predominantly occurring inside mosquito vector (E and F). Source: Cowman et al., (2016)

1.5 Clinical manifestation of malaria

The clinical features associated with malaria are related principally to the effects of intraerythrocytic cycle of the parasite on the human host. Haemozoin that is released when the parasite-infected red blood cells rupture likely act as the predominant trigger for the host immune response that results in the characteristic periodic fever. The clinical manifestation of malaria can be broadly divided into mild and severe disease. Initial symptoms of malaria are non-specific and resemble that of an influenza-like illness and include; headache, fatigue, muscle aches, nausea and vomiting (White *et al.*, 2014). These could be followed by a recovery which may occur without drug treatment. The clinical manifestation of severe malaria in highly endemic regions is usually age-dependent with the signs and symptoms more pronounced in children aged under five years. However, in a low endemic region, a wider age group are more susceptible to the disease. Other groups of people that are more susceptible to the disease are pregnant women and non-immune travellers to the endemic regions. Figure 1.5 illustrates the clinical manifestation of severe malaria and its association with the malaria parasite life-cycle.

1.5.1 Severe anaemia

This is common among children in the malaria-endemic region and is due to the repeated infections that resulted from the increase in splenic clearance of uninfected and infected red blood cells which is complicated by inefficient erythropoiesis (Price *et al*., 2001; Buffet *et al*; 2011).

1.5.2 Cerebral malaria

This results from serious sequestration of infected red blood cells to the cerebral microvasculature which can lead to obstruction of brain vessels. Clinical features of cerebral malaria include impaired consciousness, convulsions and long-term neurological abnormalities.

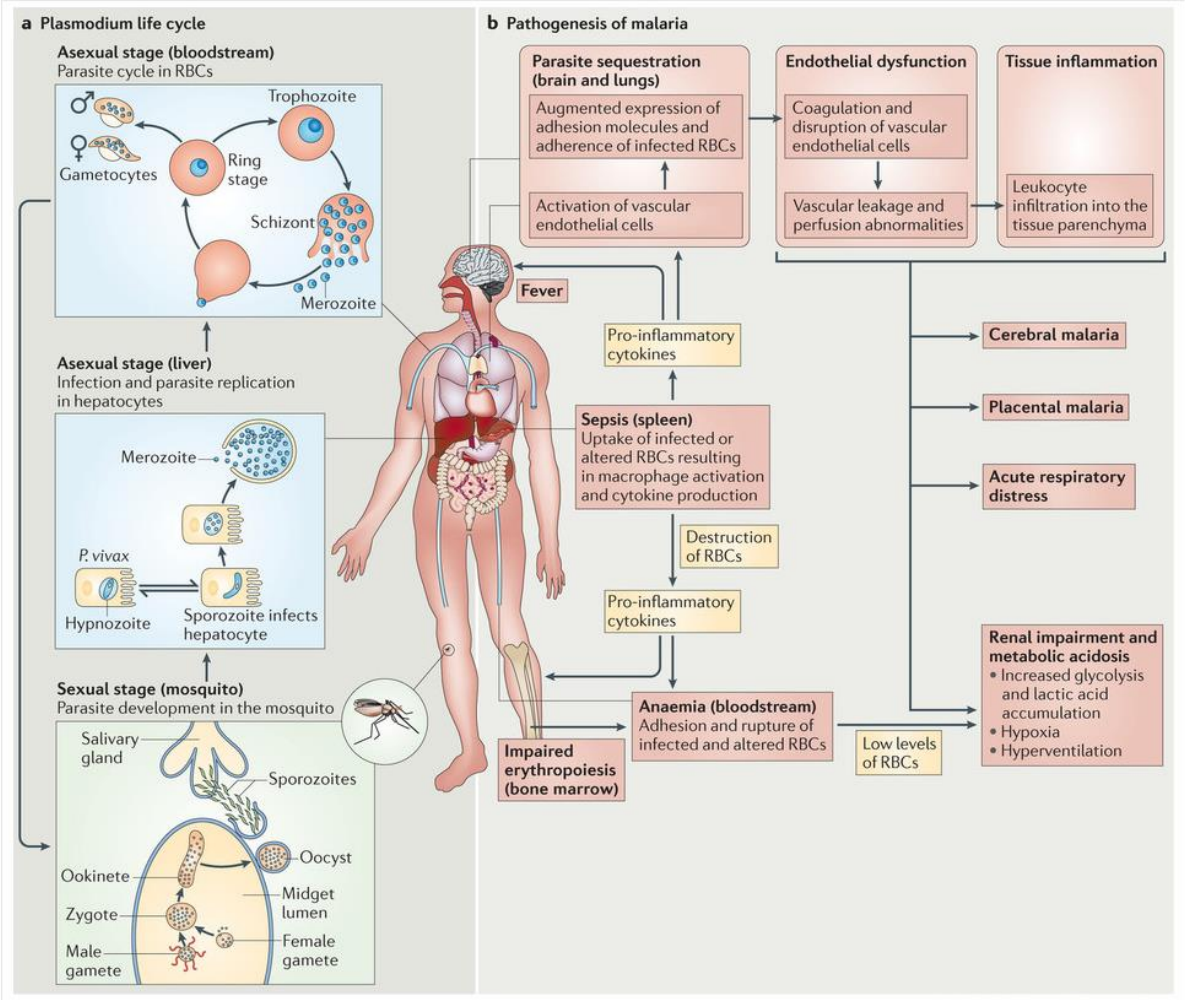


Figure 1.5: Relationship between the malaria parasite life-cycle and pathogenesis
Illustration relating the life cycle of the parasite (left) with the clinical features observed for mild and severe malaria (right). Source: Gazzinelli et al., (2014)

1.5.3 Acidosis and hypoglycaemia

Acidosis occurs as a result of building up of organic acids such as lactic acid which can lead to lactic acidosis (Day *et al.*, 2000). Lactic acid is a waste product of anaerobic glycolysis by sequestered parasites in the deep tissues and this is aggravated by the lactate produced by the *Plasmodium spp* and inability of hepatic and renal lactate clearance mechanisms to function effectively (White *et al*., 2014).

Hypoglycaemia and lactic acidosis are related to causing problems most importantly in children and expectant mothers (White *et al*., 2014). Hypoglycaemia occurs as a result of hepatic

gluconeogenesis failure and accelerated tissues glucose consumption (Krishna *et al.*, 1994; Day *et al.*, 2000)

1.5.4 Respiratory distress

Acute respiratory distress syndrome is a serious complication associated with *P. falciparum* infection in expectant mothers; it could also result from *P. vivax* and *P. knowlesi* infections (Anstey *et al.*, 2007; Daneshvar *et al.*, 2009).

1.5.5 Renal Impairment and jaundice

Acute renal failure is a more serious complication of *P. falciparum* malaria especially in children and is seriously linked to jaundice. However, adults who are chronically infected with the hepatitis B virus may be predisposed to severe malaria (Barcus *et al*., 2002).

1.6 Pathogenesis of severe *P. falciparum* malaria

The pathology of severe *P. falciparum* malaria is strongly linked with the sequestration of infected erythrocytes in the deep tissues. This normally has an adverse effect on the related vital organs in which the infected erythrocytes sequester (Figure 1.6). Sequestration of *P. falciparum* infected erythrocytes in the brain and placenta causes cerebral and placental malaria respectively. Adherence of the infected erythrocytes to the endothelial cells is mediated by the parasite variant surface proteins termed *Plasmodium falciparum*-erythrocyte membrane protein -1(*PfEMP*-1). The parasite expresses and transports the protein out through the parasitophorous vacuole and on to the knobs to be display on the external face of the erythrocyte membrane. *PfEMP*-1 is encoded by approximately 60 *var* genes in two exons; exon 1 codes for the polymorphic sequence that forms the extracellular domain while exon 2 codes for the semi-conserved intracellular domain. The two are joined by a single intron which is highly conserved (Kyes *et al.*, 2001).

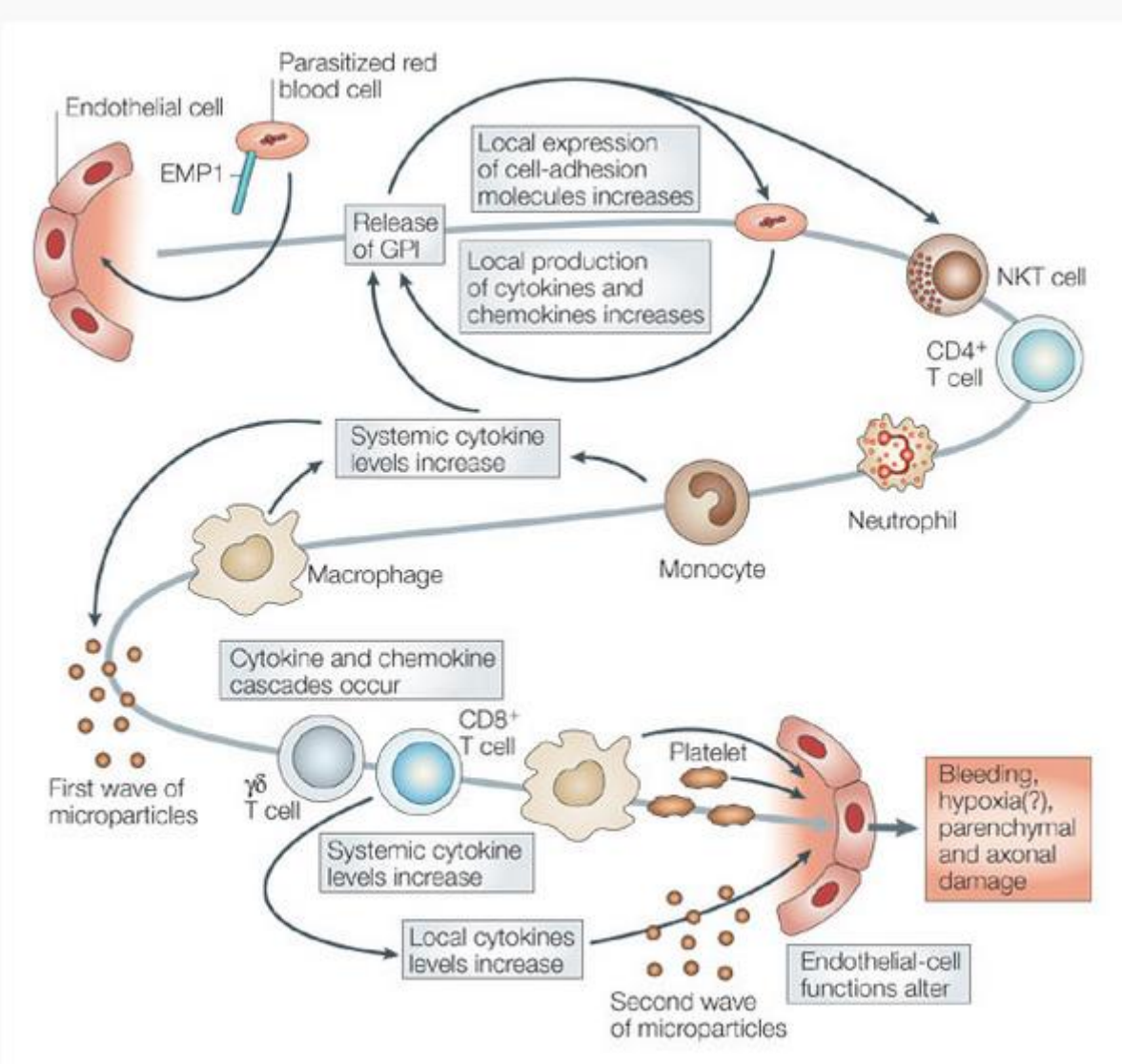


Figure 1.6: Schematic description of pathogenesis of severe P. falciparum malaria
The figure illustrates the processes involve in the adhesion of malaria parasite ligands, Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP-1) to the host receptor in the endothelial cell, intercellular adhesion molecule 1 (ICAM1) particularly in the brain. Source: Schofield and Grau, (2005).

1.6.1 Adhesion phenotypes in *Plasmodium falciparum (PfEMP-1)* sequestration

Adherence of *Plasmodium falciparum* erythrocytes membrane protein -1(*PfEMP*-1) to the deep tissues is mediated through receptor-ligand interaction. There are three basic types of adhesion of infected erythrocytes to the receptor on human cells: cytoadherence to the endothelial cells, adherence of infected erythrocytes to uninfected erythrocytes (rosetting) and platelet-mediated agglutination (Figure 1.7). In addition, infected erythrocytes also sequestered in the placenta

through the receptor termed syncytiotrophoblasts. Human receptors for *P. falciparum* erythrocytes membrane protein-1 (*PfEMP*-1) are diverse (Table 1.1), because the parasite expresses only one ligand but with different domains that mediate various adhesive events.

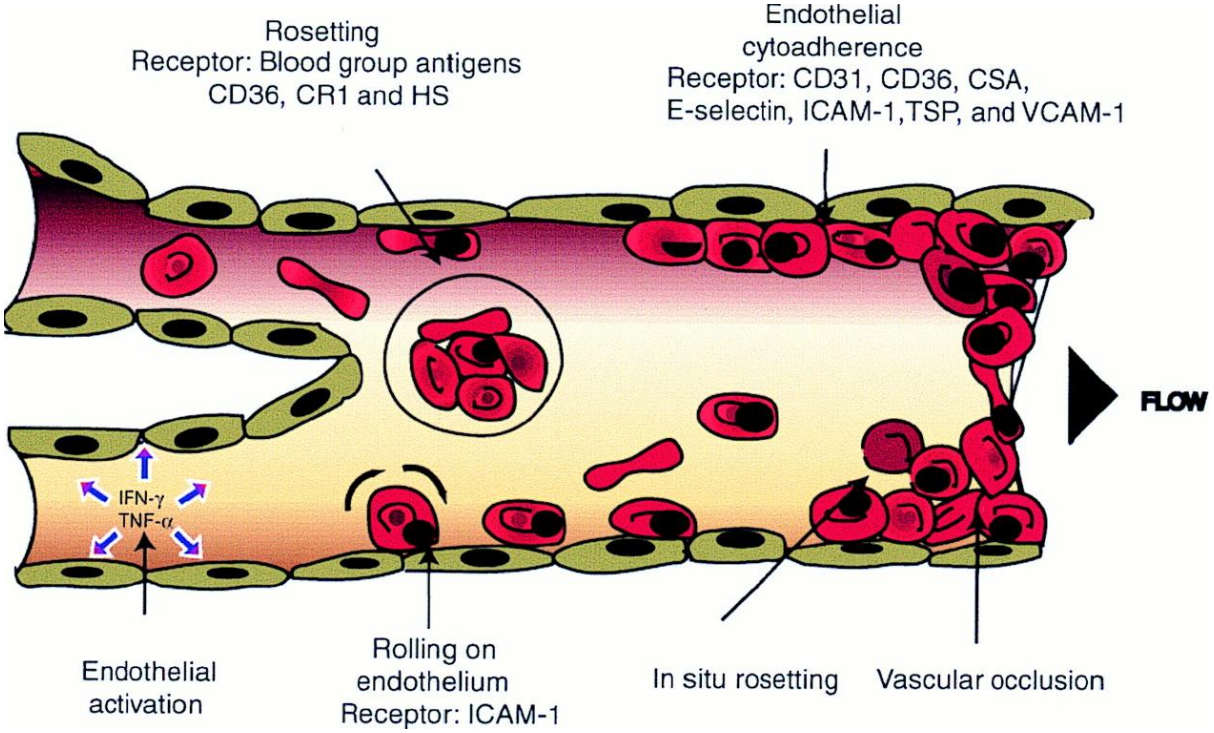


Figure 1.7: Diagramatic representation of cytoadherence and rosetting in the postcapillary vasculature
Plasmodium falciparum-infected erythrocytes (red cells with black dot) adhere to the postcapillary endothelial line (green) and to uninfected erythrocytes. Both events lead to obstruction of blood flow that can result in severe disease. Source: Chen et al., (2000)

Host receptor(s)	Receptor location	Parasite ligand
HS-like GAGs	**RBC**	**PfEMP1 (DBL-1α)**
CD35 (CR1)	**RBC**	**PfEMP1 (DBL-1α)**
Blood group antigen A and B	**RBC**	**PfEMP1?**
TSP	**Serum, endothelium**	**PfEMP1?**
CD36	**Endothelium, RBC**	**PfEMP1 (CIDR1-α)**
ICAM-1	**Endothelium**	**PfEMP1 (DBL-2β)**
CD31	**Endothelium**	**PfEMP1?**
VCAM-1	**Endothelium**	**?**
E-selectin	**Endothelium**	**?**
CSA	**Endothelium**	**PfEMP1 (DBL-3)**
IgM and IgG	**Serum**	**PfEMP1?**
EPCR	**Endothelium, RBC**	**PfEMP1 (CIDR1-α)**

Table 1.1: Human receptors and parasite ligands for the adhesion of PfEMP-1
Source: Modified from Chen et al., (2000)

1.7 Immune response to malaria parasites infection

1.7.1 Innate Immune response

Immune response to malaria parasites can be categorised into innate and adaptive immunity. When there is a primary infection, the innate immune response is first activated and the spleen is the major centre for this immune protective effect (Buffet *et al*., 2009; Del Portillo *et al*., 2012). The innate immune response is mediated by the phagocytic activities of the monocytes and the macrophages which lowers the risk of developing severe malaria but unable to clear the malaria infection. The macrophages in the liver and spleen play a key role in the phagocytic removal of malaria parasites (Lee *et al*., 1986; Deroost *et al*., 2012; Menezes *et al*., 2012). However, in acute malaria infection, monocytes from the bone marrow coupled with local proliferation contribute to the hepatosplenomegaly normally seen in malaria patients (Lee *et al*., 1986; Belyaev *et al*., 2013).

1.7.2 Adaptive Immune response

Acquired immunity to malaria parasite infection entails the activation of humoral and cellular immune response (Langhorne *et al*., 2008, Stevenson and Riley, 2004). Naturally acquired

immunity to malaria has been found to take as long as 10-15 years of repeated parasitic exposure to develop (Baird, 1998). The immunity lowers the risk of severe and uncomplicated malaria but does not clear the parasitaemia. Antibody-mediated immune response plays a crucial role in the reduction of parasitaemia, thereby reducing the clinical symptoms of the disease. However, a synergy between monocytes and antibody-response is important in the acquisition of protective immunity (Groux and Gysin, 1990).

T cells play a central role in the clearance of the erythrocytic stage of malaria parasites by releasing cytokines that activate other effector cells. $CD4^+$ T cells are basically classified into T helper 1 (Th1) and T helper 2 (Th2) cells according to the cytokines they produce. Th1 cells produce interleukin (IL)-2, interferon (IFN) γ and tumour necrosis factor (TNF), whereas Th2 cells produce IL-4, IL-5, IL-6 and IL-10 (Abbas *et al*., 1996). Th1 cells are responsible for cell-mediated immunity; they activate macrophages and other cells to produce mediators through the release of inflammatory cytokines whereas Th2 cells regulate the humoral immune response by activating B cells to produce antibodies. Both Th1 and Th2 cells are involved in protective immunity against blood stage malaria and the balance of cytokines produced by these two subsets is crucial in determining the outcome of the disease (Wipasa *et al.*, 2002).

1.8 Diagnosis of Malaria

Prompt diagnosis of malaria is crucial in the effective control and management of the disease in the endemic areas where diagnosis of malaria could be based on the evaluation of clinical signs and symptoms or a laboratory-based test. The former means of diagnosis is not always reliable as malaria symptoms usually overlap with that of other tropical diseases. In the laboratory, malaria is diagnosed using different techniques ranging from gold standard microscopic methods to a more sensitive polymerase chain reaction assay.

1.8.1 Microscopy

The conventional means of diagnosing malaria is by microscopic examination of thin and thick (species identification) blood films using Giemsa, Wright's or Field stains (Warhurst and Williams, 1996). Light microscopic examination of stained blood film describes the parasitaemia, species, and different morphological stages of the malaria parasites (Figure 1.8). Although, the technique is simple and inexpensive, it has a limitation of low sensitivity (especially at low parasitaemia), being labour intensive, time-consuming and requires a trained microscopist particularly for the identification of species accurately at low parasite levels or in a mixed infection.

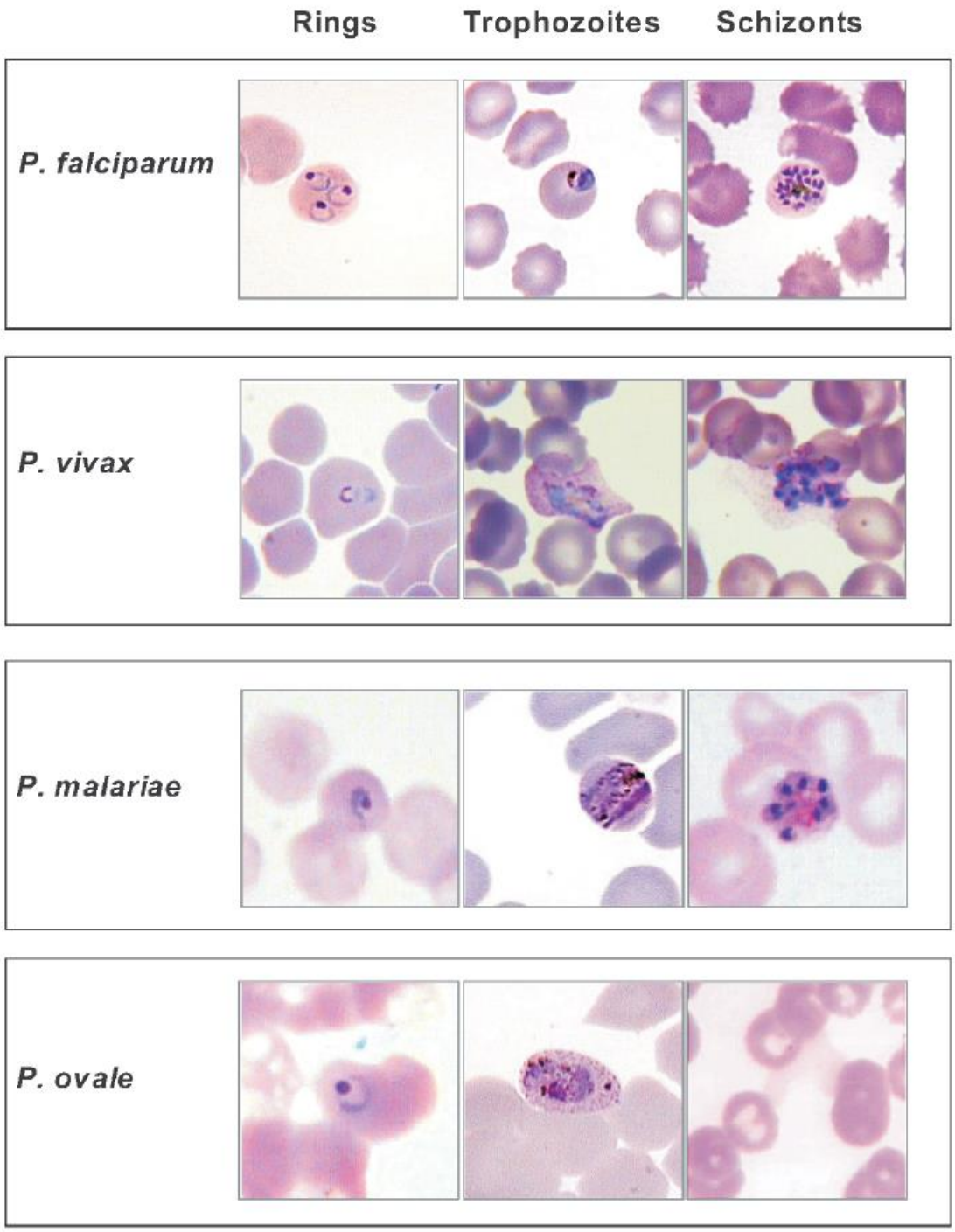


Figure 1.8: Photomicrographs of different developmental stages of Plasmodium species *P. falciparum, P. vivax , P. malariae and P. ovale . From thin blood smear*
Source: Chotivanich et al., (2007)

1.8.2 Quantitative Buffy Coat Technique

The shortcomings of microscopic diagnosis of malaria parasites led to the development of the Quantitative Buffy Coat technique (QBC). The method involves the staining of parasite deoxyribonucleic acid in micro-haematocrit tubes with fluorescent dyes such as acridine orange and its subsequent detection by fluorescence microscopy or by flow cytometry (Moody, 2002). Although the QBC technique is simple, reliable and user-friendly, it has the limitation of requiring specialised instrumentation which makes it more expensive than the light microscopy coupled with the fact that it is poor at determining parasites species and numbers (Tangpukdee *et al*., 2009).

1.8.3 Malaria Rapid Diagnostic tests

Malaria Rapid Diagnostic tests (RDTs) were developed in the mid-1990s (Dietze *et al*., 1995; Makler *et al*., 1998). They work on the principle of immuno-chromatography whereby a chromophore-labelled antibody binds to lysed parasite antigen. This is carried by capillary action on a nitrocellulose strip and arrested by a capture antibody giving a colour band on a test strip. Immunological RDT techniques are useful in malaria-endemic areas where a large proportion of infected people can be readily screened within a short period of time. The most available RDTs target *P. falciparum* histidine-rich protein 2 (*PfHRP2*) and two enzymes of the glycolytic pathway in *Plasmodium*, namely; lactate dehydrogenase (*pLDH*) and aldolase (see Table 1.2). RDTs extends the benefits of parasite-based diagnosis of malaria beyond the technical limitations of light microscopy and offer significant advances in the management of malaria in remote endemic areas (Tangpukdee *et al*., 2009).

Type	Description
1	HRP-2 (*Plasmodium falciparum* specific)
2	HRP-2 (*P. falciparum* specific) and aldolase (panspecific)
3	HRP-2 (*P. falciparum* specific) and *p*LDH (panspecific)
4	*p*LDH (*P. falciparum* specific) and *p*LDH (panspecific)
5	*p*LDH (*P. falciparum* specific) and *p*LDH (*Plasmodium vivax* specific)
6	HRP-2 (*P. falciparum* specific), *p*LDH (panspecific), and *p*LDH (*P. vivax* specific)
7	Aldolase (panspecific)

Table 1.2: Malaria rapid diagnostic tests
HRP (histidine-rich protein), pLDH (Plasmodium lactate dehydrogenase)
Source: Wilson, (2012)

1.8.4 Serological methods

Serological method for malaria diagnosis is usually based on the principle of detecting antibodies against the asexual erythrocytic stage of malaria parasites. Immunofluorescence antibody testing (IFA) is a reliable serological technique; although, it is time-consuming but with high sensitivity and specificity. The technique is highly reliable and has been documented in the literature as the gold standard for malarial serology testing (Doderer *et al*., 2007).

1.8.5 Polymerase Chain Reaction

Recent development in malaria diagnosis have used Polymerase Chain Reaction (PCR)-based techniques. These have proven to be one of the most specific and sensitive diagnostic methods, particularly in malaria cases with low parasitaemia or mixed infections (Morassin *et al*., 2002). The technique was found out to be more sensitive than QBC and some RDTs (Makler *et al*., 1998; Rakotonirina *et al*., 2008) and has been used to confirm malaria infection, follow-up therapeutic response and identification of drug resistance (Chotivanich *et al*., 2007).

1.9 Malaria control strategies

Two major tools are employed in the control of malaria; entomological and medical. The entomological tool relies on the use of insecticide interventions such as the insecticide-treated nets (INTs) and indoor residual insecticide sprays (IRSs). Both significantly decrease the daily survival rates of the mosquito vector (Enayati and Hemingway, 2010).There is presently no effective vaccine against the malaria parasite. The stall in progress reported in malaria control over the last few years necessitates the development of new control and elimination tools that should include a vaccine. Breaking the cycle of parasite transmission with vaccines will likely target three major developmental stages; the pre-erythrocytic, erythrocytic and the gametocytic stages. Figure 1.9 illustrates the different approaches that target these three strategic stages of the malaria parasites life cycle.

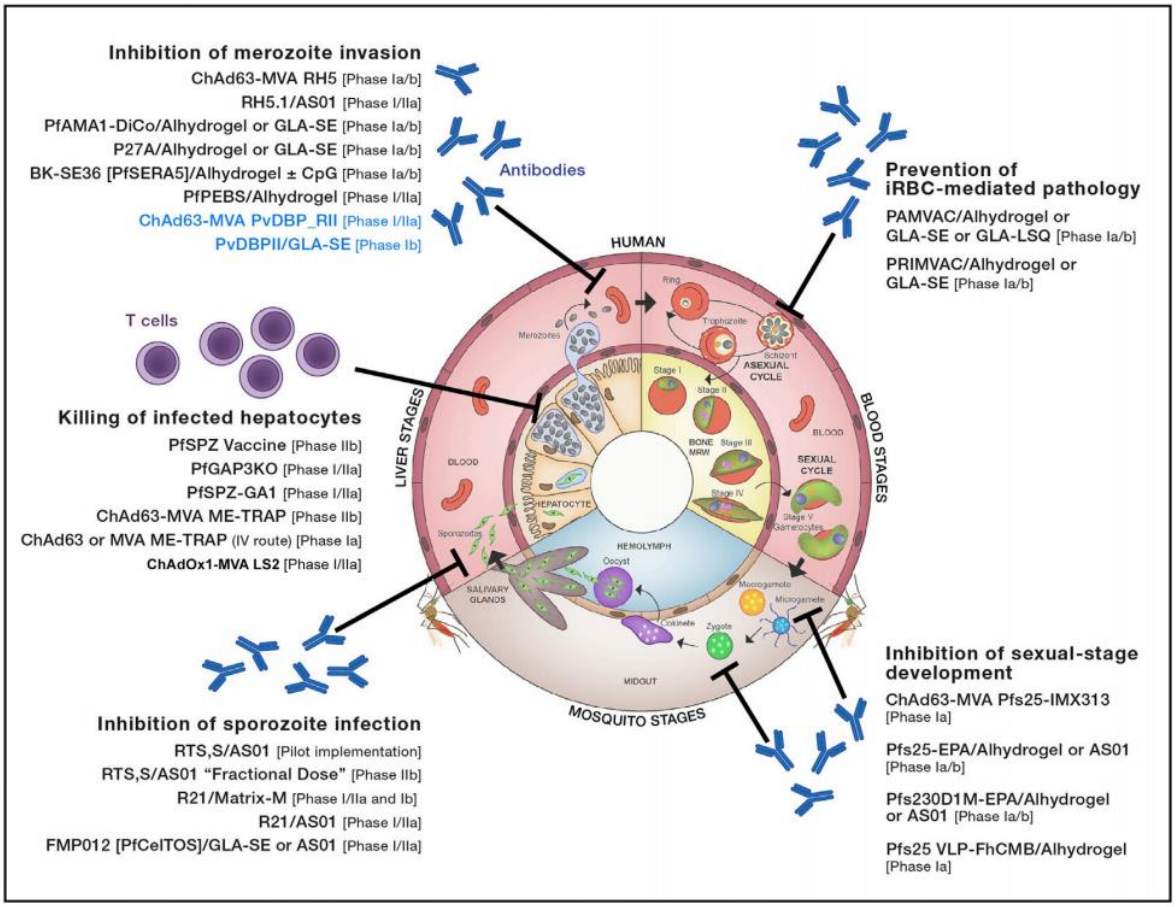


Figure 1.9: Vaccine targeting different stages of malaria parasite's life cycle in clinical development.
Vaccines target majorly target the P. falciparum, few that target the P. vivax are in colour blue
Source: Draper et al., (2018)

Over 30 *P. falciparum* malaria vaccines projects are in the pipeline as of 2015 (Figure 1.10). The most advanced malaria vaccine project is the RTS,S/AS01 which passed the phase II and III clinical trials in 2007 and 2009 respectively (Leach *et al.*, 2011). The results of phase III clinical trial of the vaccine in sub-Saharan African children were published in 2015. The findings show that vaccine efficacy decreases rapidly in infants aged 6 to 12 weeks and young children 5 to 15 months old. Although the administration of three booster doses after 12 months as a follow up decreases malaria cases in young children and infants by 28% and 18% respectively (Greenwood and Doumbo, 2016). A setback for RTS,S/AS01 was the failure to elicit sterile immunity which would be a hallmark of life-long protection against the parasite.

The European Medicines Agency for immunization (EPI) endorsed the use of the vaccine for children aged 6 weeks to 17 months in July 2015. Subsequently, an extensive pilot implementation to further assess the practicality of administering four doses was recommended by WHO. Also, the possibility of the vaccine to decrease childhood mortality and to produce supplementary data on safety with regards to its routine use.

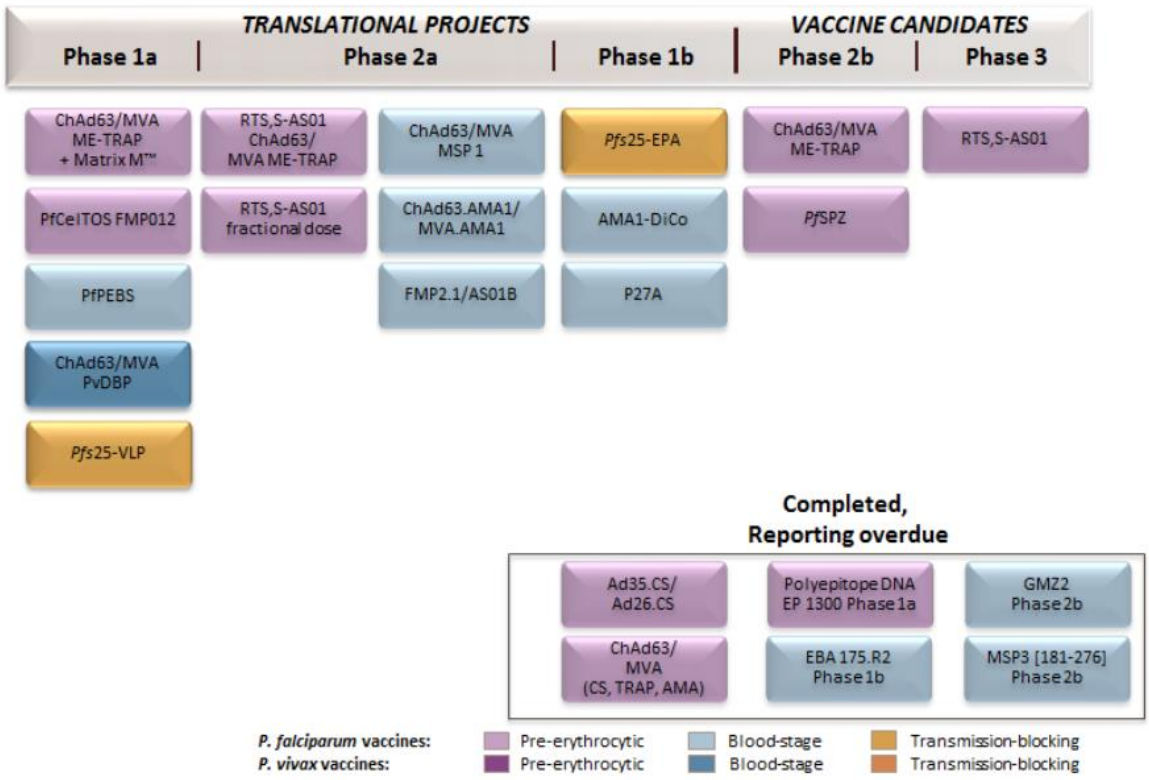


Figure 1.10: Worldwide malaria vaccine portfolio as of September 2015
Source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

Chemotherapy is highly indispensable towards the goal of malaria eradication in the absence of a highly effective vaccine. The role of drugs in malaria control can be divided into those that offer an effective treatment of a parasite infection or those that are used as a prophylactic against infection in malaria-endemic regions (Greenwood, 2010). Antimalarial agents can be similarly categorised based on the stage of the malarial parasite the drug is targeting. Blood schizonticides are active against the asexual intraerythrocytic stages of the parasites and tissue schizonticides targets the hepatic schizonts thereby preventing erythrocytic invasion. The

hypnozoiticides targets the dormant intra-hepatic stages of *P. vivax* and *P. ovale* thereby serving as anti-relapse therapy. And gametocytocides kill the sexual intraerythrocytic stages of the parasites and serve to block the transmission of the parasite. The most commonly used antimalarial can be divided into seven principle classes; 4-aminoquinolines (chloroquine, amodiaquine), aminoalcohols or aryl alcohols (quinine, mefloquine, halofantrine and lumenfantrine), 8-aminoquinolines (primaquine and tafenoquine), artemisinins derivatives (artemisinin, artesunate, artemether, and dihydroartemisinin), antifolates (pyrimethamine, proguanil and sulfadoxine), naphthoquinone (atovaquone) and antibiotics (doxycycline, clindamycin).

The first antimalarial agent was quinine in the form of an extract from the bark of the cinchona tree. This tree is indigenous to the inhabitants of Peru in South America and had been used for treating malaria for centuries. The active antimalarial ingredient, quinine, was isolated in 1820 by two French chemists (Joseph Pelletier and Jean Bienaime Caventou). The drug has a short elimination half-life of 8-10 hours and the first case of resistance was reported in 1910 . During World War II, the Japanese merchant of Cinchona discontinued its supply to many parts of the world (Parkard, 2014). This led to the urgent search for alternative therapy to quinine. Chloroquine, the first synthetic antimalarial drug, was developed by a German scientist in 1934 . The drug was introduced in 1945 , and has an estimated serum half-life of about 60 days. However, the parasites are also exposed to a longer period of time when the drug's plasma concentration would be reduced below a therapeutic level, thereby potentially selecting for resistant parasites (Stepniewska and White, 2008). Chloroquine resistance was first reported in Thailand in 1957, followed by Northern South America in 1960, with resistance spreading to Southeast Asia and Papua New Guinea in the 1970s and finally to Africa in the 1980s (Figure 1.11).

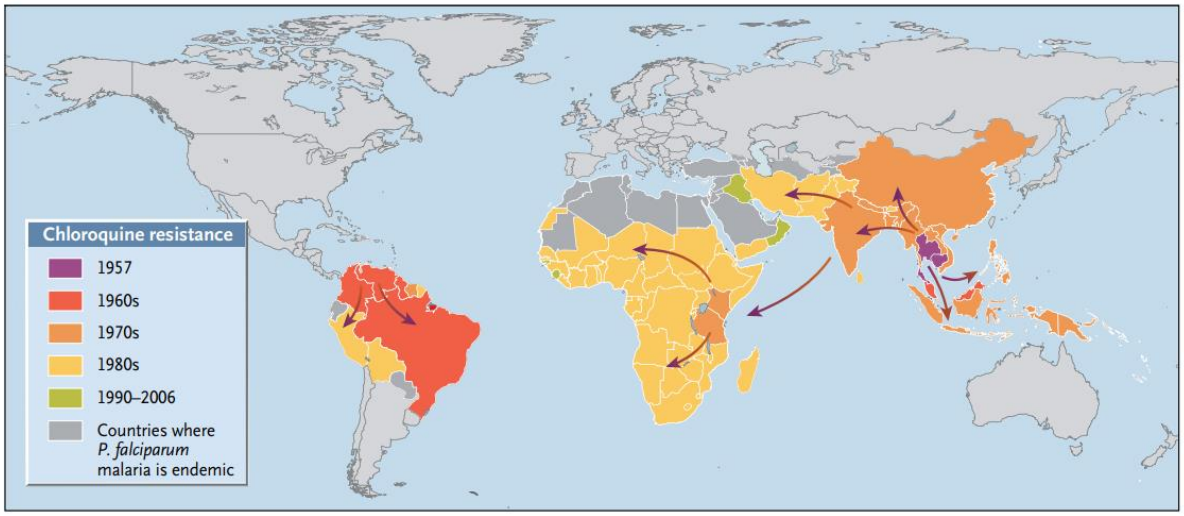


Figure 1.11: Map showing the origin and distribution of chloroquine resistance across the world.
Source: Parkard, (2014).

Antifolates drugs, Proguanil and Pyrimethamine, were developed in the 1940s (. Proguanil was introduced as an antimalarial agent in 1948 and following the success of proguanil in treating malaria, pyrimethamine was later developed and the two drug were used as monotherapy, unfortunately giving an opportunity for resistance to develop (Malisa *et al.*, 2011). The first case of resistance to proguanil was reported in 1949, barely a year after its introduction . In order to improve the efficacy and curtail the resistance development, sulfones and sulphonamides were combined with proguanil or pyrimethamine . Sulfadoxine–Pyrimethamine was introduced in 1967 in Thailand and the first case of resistance was reported the same year which later spread fast to SouthEast Asia .

Primaquine (8-aminoquinoline) has been the drug of choice for the treatment of dormant liver form of *P. vivax* infection (Krudsood *et al.*, 2008). The drug was also recommended by WHO and approved by FDA as prophylactic agent against *P. vivax* malaria relapse (Fernando *et al.*, 2011). However, there have been reports about treatment failure which have been attributed to factors such as insufficient dose, improper dosing intervals, risk of reinfection, combination with blood schizontocidals and non-adherence to the prescribed dose (Thomas *et al.*, 2016).

Recently, FDA has approved the use of tafenoquine (another 8-aminoquinoline) as a replacement drug for the radical cure of *P. vivax* hypnozoites malaria infection (Lacerda *et al.*, 2019). Tafenoquine was recommended as a single-dose treatment drug, potentially because of its longer serum half-life of about 15 days (Llanos-Cuentas *et al.*, 2014; Green *et al*., 2016). Of a note is that both primaquine and tafenoquine cause hemolysis in individual with G6PD deficiency, therefore, screening for this phenotype is recommended before commencing the drug for treatment (Dern *et al.*, 1981; Rochford *et al.*, 2013; Rueangweerayut *et al.*, 2017).

The current frontline antimalarial, artemisinin was discovered by the Chinese scientist from the sweet wormwood (*Artemisia annua*) in the 1970s and the chemical structure was published in 1979. The antimalarial property of artemisinin in the treatment of malaria was fully explored in the 1990s. This was a period when an urgent malaria intervention was most needed in Southeast Asia, as a result of all the frontline antimalarial fallen to resistance. In the same vein, chloroquine and pyrimethamine-resistant strains of *P. falciparum* are prevalent in Africa leading to a rise in childhood death (Fidock *et al.*, 2000, Snow *et al.*, 2001, and Roper *et al*., 2004). Artemisinin has the shortest half-life of 0.5-1.4 hours (Bloland, 2001), being a potent and fast-acting antimalarial that is capable of reducing parasite biomass by 99.9% within 48hours. White *et al*., (1999) recommended the combination of a fast-acting and highly efficacious artemisinin with a slowly eliminated drug. This is to reduce resistance development and enhance treatment rate. Against this background, the WHO also recommended the partnering of artemisinin with a slowly eliminated drug that can clear the residual parasites. Artemisinin combination therapies, (ACTs) became a prescribed drug for the treatment of uncomplicated malaria globally in 2006 (WHO, 2015). Artemether-lumenfantrine (Coartem, Novartis) was the first ACT manufactured that satisfied the global standard of good manufacturing practice and was endorsed by the US Food and Drug Administration in April

2009 (Premji, 2009). There are now six ACTs approved by WHO for the treatment of malaria (Table 1.3), of which resistance against four partner drugs have been reported.

Resistance to ACTs first appeared in 2008 in Thai-Cambodia, this manifested clinically as a delay in parasite clearance time (Dondrop *et al*., 2009). Some of the factors attributed to the treatment failure could be the use of artesunate monotherapy in the region for many years and fake or counterfeit drugs (Ashley and Phyo, 2018). In 2014, the molecular marker for artemisinin resistance was identified to be a mutation in the Kelch gene on chromosome 13 of the parasite genome (Ariey *et al*., 2014). In other malaria-endemic regions such as India and South America, a few artemisinin-resistant parasites have been recorded (Chenet *et al*., 2016; Mishra *et al*., 2016). The case of artemisinin resistance is yet to be established in Africa (WHO, 2018). Meanwhile, triple artemisinin-based combination therapies that will consist of a standard dual ACT with another slowly eliminated drug are being assessed clinically as the alternative until new drug is available (Maxmen, 2016).

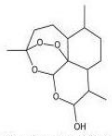
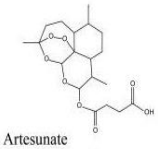
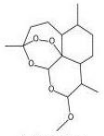
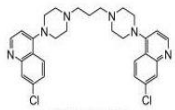
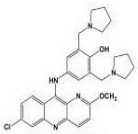
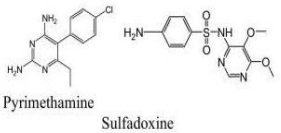
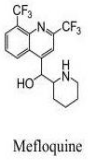
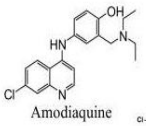
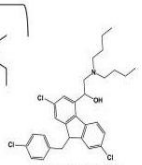
ACTs	Dihydroartemisinin - piperaquine	Artesunate-pyronaridine	Artesunate-sulfadoxine-pyrimethamine	Artesunate-mefloquine	Artesunate-amodiaquine	Artemether-lumefantrine
Brand name (suppliers)	Eurartesim® (Sigma-Tau) Artekin® (Holleykin) Diphos® (Genix Pharma)	Pyramax® Shin Poong Pharmaceutical Co. Ltd.	Artesunate + Sulfadoxine + Pyrimethamine Tablets (Advacare PHARMA) Malosunate® (Anhui)	ASM FDC (DNDI/Cipla Ltd	ASAQ Winthrop® (Sanofi)	Coartem® Riamet® (Novartis)
Artemisinin derivative	 Dihydroartemisinin		 Artesunate			 Artemether
Partner drug	 Piperaquine	 Pyronaridine	 Pyrimethamine Sulfadoxine	 Mefloquine	 Amodiaquine	 Lumefantrine
Target of the partner drug	Hemozoin synthesis	Hemozoin synthesis	DHPS - DHFR	Hemozoin synthesis	Hemozoin synthesis	Hemozoin synthesis
Resistance mechanism of the partner drug	*Plasmepsin 2-3* amplification [4, 83]	Not identified	Modification of the drug target [28]	Amplification of *Pfmdr1* copy number [64]	*Pfcrt* and *Pfmdr1* mutations [25]	Amplification of *Pfmdr1* copy number [65]

Table 1.3: Current ACTs approved for malaria treatment, their targets and resistance mechanisms
Source:Ouji et al.,(2018)

1.10 New candidates in the antimalarial drug pipeline

Considering the present stalled progress in malaria control over the past two years, new drugs are urgently needed. Currently, the pipeline for the discovery of new antimalarial agents is robust. There are some 13 candidates presently in the pre-clinical and phase 2 of development. Most of these are blood schizonticides proposed for the treatment of uncomplicated *P. falciparum* malaria (Figure 1.12)

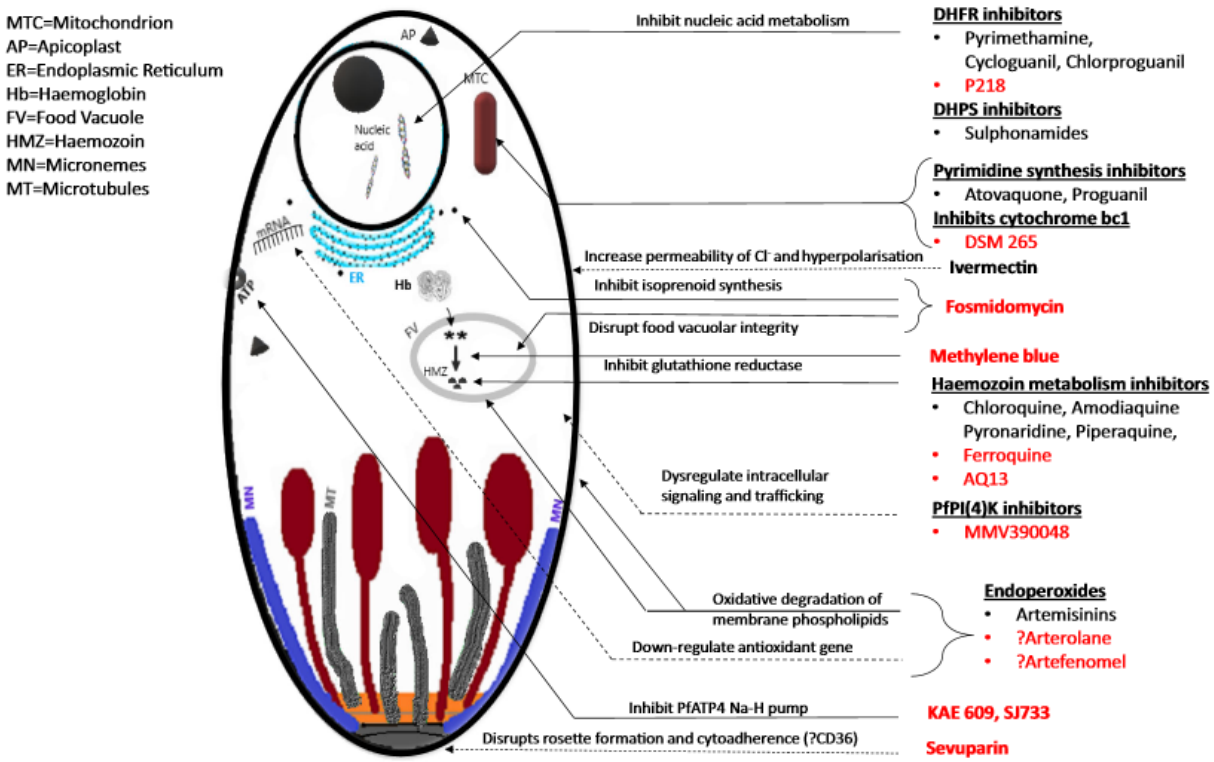


Figure 1.12: Representation of the targets of the current antimalarial pipeline candidates based on their activity against asexual intraerythrocytic parasites.
Candidates in reds are currently being developed. Source: Ashley and Phyo (2018).

At the forefront of this antimalarial discovery process is a Product Development Partnership (PDP) called the Medicine for Malaria Venture (MMV). Presently, the MMV antimalarial pipeline contains many promising candidates at different stages of development (translational, product development and access) (Figure 1.13) with selected emerging antimalarial in this portfolio presented in Table 1.4. Although the antimalarial pipeline is filled with many promising candidates, there is currently no novel compound that can be employed in areas where ACTs are failing. Hence, the search for new drugs that can replace the existing ones continues.

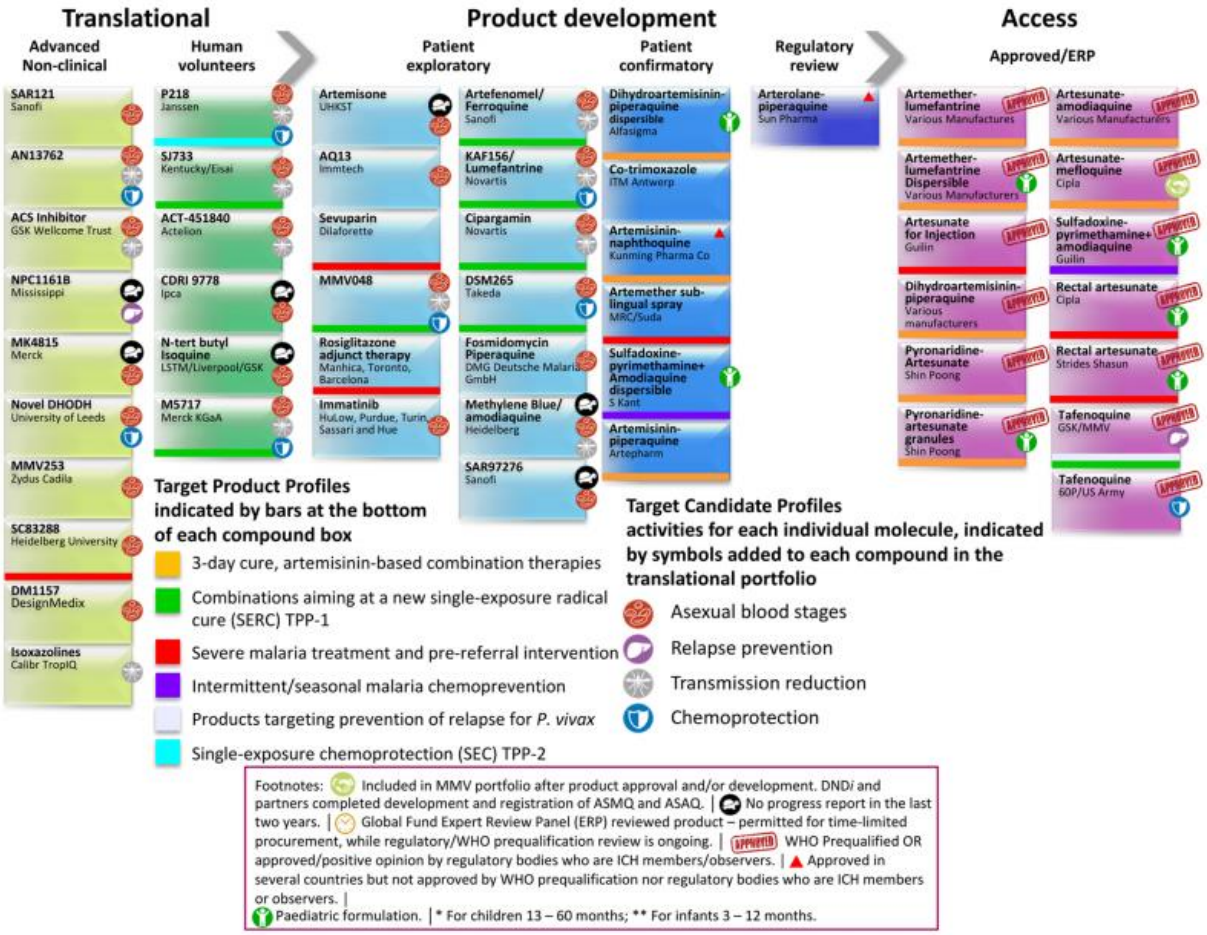


Figure* 1.13*: Global Portfolio of Antimalarial Medicines
Source: Adapted from MMV website

Antimalarial compound	Alternative names	Protein target/predicted target	Target candidate profiles[a]	Current status in MMV pipeline[b]
Artefenomel	OZ439	Unknown	Asexual parasite clearance; transmission blocking	Combined artefenomel–ferroquine is in the patient-exploratory stage
Cipargamin	KAE609, NITD609	*Pf*ATP4, based on resistance screen mutations[23]	Asexual parasite clearance; transmission blocking	Patient-exploratory stage
DSM265	Not applicable	*Plasmodium* DHODH[24]	Asexual parasite clearance; targeting liver schizonts	Patient-exploratory stage
Ferroquine	SSR97193	Unknown	Asexual parasite clearance; transmission blocking	Combined artefenomel–ferroquine is in the patient-exploratory stage
KAF156	GNF156	*Pf*CARL[25], *Pf*ACT, and *Pf*UGT[26], based on resistance screen mutations	Asexual parasite clearance; transmission blocking; targeting liver schizonts	Combined KAF156–lumefantrine is in the patient-exploratory stage
MMV048	MMV390048	*Plasmodium* PI4K[27]	Asexual parasite clearance; transmission blocking; targeting liver schizonts	Patient-exploratory stage
SJ733	(+)-SJ000557733	*Pf*ATP4, based on resistance screen mutations[28,29]	Asexual parasite clearance; transmission blocking	Human volunteer stage
Tafenoquine	WR 238605, Etaquine	Unknown	Targeting *Plasmodium* hypnozoites	Regulatory review stage

DHODH, dihydroorotate dehydrogenase
PI4K, phosphatidylinositol 4-kinase
[a]According to Medicines for Malaria Venture (MMV) Target Candidate Profile classification.
[b]Status as of 31 July 2018.

Table 1.4: Promising antimalarial agents in the MMV portfolio
Source: Mathews and John, (2018)

1.10 The search for new antimalarial drugs: defining target candidate profiles

The last decade has seen a resurgence in the discovery and development of antimalarial medicines. High throughput phenotypic screening of millions of compounds for antimalarial activity coupled with improvement on the existing antimalarial drugs has resulted in the generation of new chemo-types. Many of these agents are currently being evaluated in pre-clinical and early clinical development. Understanding and comparing the relative performance of these molecules has led to the defining of ideal target candidate and target product profiles for a new antimalarial clinical entity. The target product profile (TPP) is the final product, or antimalarial medicine that is anticipated to contain at least two or more active ingredients and is defined by how the medicine is intended to be used (Figure 1.14). There are currently two TPP; (i) a combination of candidates molecules that have the potential to clear the erythrocytic stage infection, block transmission and possess anti-hypnozoitic activities is capable of providing post-treatment prophylactic action and is termed a Single Exposure Radical cure and Prophylactic (SERCaP) and (ii) a single-exposure chemoprotection medicine (SEC) potentially

for use in mass drug administration (Burrows *et al*., 2017). These TPP anticipate a formulation of active compounds that are combined based on their individual properties against the TPP targets that are described within target candidate profiles (TCP). The TCPs are tactical targets employed to provide guidelines during drug development (Burrows *et al*., 2017) and the MMV have published proposal characteristics of an ideal and minimally acceptable TCP (Burrows *et al.,* 2013; Leroy *et al.,* 2014).

TCP1 – a fast acting molecules to clear the initial erythrocytic stage biomass.

TCP2- a long duration molecules to complete the clearance of the erythrocytic stage biomass.

TCP3- (divided into 3a and 3b), 3a is a molecule that can clear the dormant liver stage hypnozoite, whilst 3b targets gametocytes to block transmission.

TCP4- molecules that prevent the population from being infected (chemo-protection)

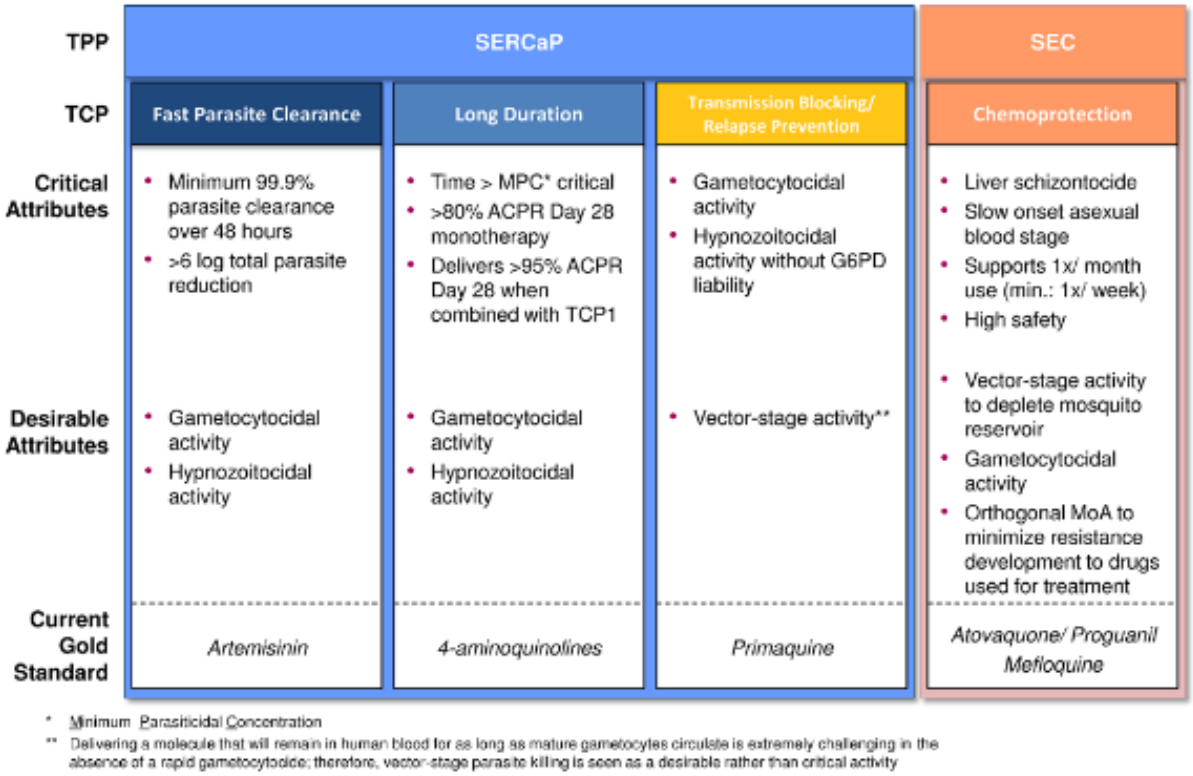


Figure 1.14: MMV Target Candidate profiles (TCP) matched to the two current Target Product Profiles (TPP)
This chart outlines the necessary attributes of a target candidate profile (TCP) under the relevant banner of the target product profile (TPP). Source: Burrows et al., (2013)

Consultation between MMV and the wider malaria communities about the potential of the new molecules currently in the MMV portfolio has led to a redefinition of the requirement for TPP1 as well as the role of the TCPs in defining these new clinical entities (Table 1.5 and Figure 1.15). In broad terms, TPP1 (for patient treatment) has been refined to be a new medicine to rapidly decrease the parasite biomass, block transmission and prevent relapse. Whilst TPP2 (chemo-protection, for example as a prophylactic or in mass drug administration) has been updated to include two molecules; one to clear the dormant liver form and the other to clear the erythroctytic stage in case of emerging infections (Figure 1.15).

Profile	Intended use
TPP-1	Case management; treatment of acute uncomplicated malaria in children or adults. Uses a combination of two or more molecules with TCP-1 activity, plus TCP-5 for reducing transmission and TCP-3 for relapse prevention, when such molecules become available For severe malaria, a parenteral formulation of a single fast-acting TCP-1 would be appropriate
TPP-2	Chemoprotection: given to subjects migrating into areas of high endemicity, or during epidemics. Uses a combination of TCP-4 activity, potentially with TCP-1 support for emerging infections
TCP-1	Molecules that clear asexual blood-stage parasitemia
TCP-2	(profile retired, see body of text)
TCP-3	Molecules with activity against hypnozoites (mainly *P. vivax*)
TCP-4	Molecules with activity against hepatic schizonts
TCP-5	Molecules that block transmission (targeting parasite gametocytes)
TCP-6	Molecules that block transmission by targeting the insect vector (endectocides)

Table 1.5: An outline of new TPPs and TCPs for new clinical entity for malaria
Source: Burrows *et al.*, (2017)

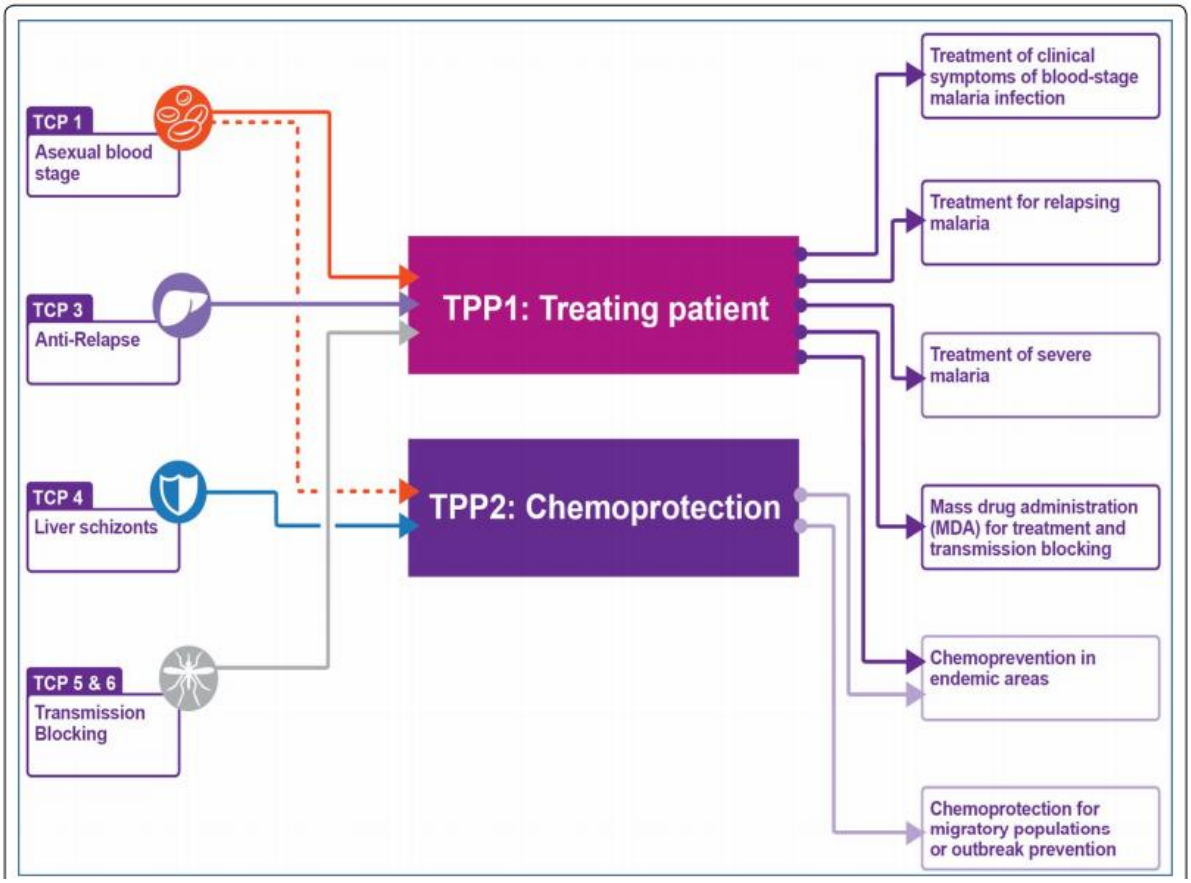


Figure 1.15: Interplay between the newly proposed TPPs (centre) and TCPs (left).
The uses of each TPPs are outlined in the panel to the right, the former TCP 1 and TCP2 have been combined to form a new more stringent TCP1, an ideal molecule that kills rapidly and is capable of maintaining over the long-term a plasma concentration above the Minimal Inhibitory Concentration (MIC) (White et al., 2017). The former TCP2 has been withdrawn. This new TCP1 recognises a key limitation of artemisinin - that whilst it has a profoundly rapid cytocidal action, it also has a very short serum half-life. Source: Burrows et al., (2017)
The former TCP3a now forms the new TCP3 and the former TCP3b is redesigned as TCP5. A new TCP, TCP6, has been introduced and this will comprises of molecules that are capable of killing the Anopheles mosquitoes that feed on an infected individual.

1.11 The search for new antimalarial drugs: Mass drug screening for new antimalarial agents

Thousands of chemical starting points are now available for further characterisation for hit to lead identification. Four research groups: GlaxoSmithKline (GSK, Gamo *et al.*, 2010), St. Jude Children's Research Hospital (Guiguemde *et al.,* 2010), Novartis (Plouffe *et al.,* 2008) and Esikits (Avery *et al.,* 2014) have all disclosed the results of the antimalarial phenotypic screening of their large/massive chemical libraries (Table 1.6). Access to these data, and open

access agreements for sub-library compound sets (see below) are steps introduced to accelerate antimalarial drug discovery.

Organisation	Compounds screened	Primary hits generated	Confirmed hits	References
St. Jude Children Research Hospital	309,474	1,300	11,341	Guiguemede *et al* ., 2010
GlaxoSmithKline	2 million	19,451	13,533	Gamo *et al* ., 2010
Novartis	1.7 million	17,000	6,549	Meister *et al* ., 2011
Eskitis	256,263	3,209	1,985	Avery *et al* ., 2014

Table 1.6: Phenotypic high throughput screening for antimalarial agents

1.11.1 Tres Cantos Antimalarial Compound Set (TCAMS)

The TCAMS library comprises 13,533 chemical compounds, originally screened by GSK, with the objective of serving as the starting point for antimalarial lead identification and optimization. The studies that generated this resource was borne out of the observation that since 1996 no new antimalarial drug had been developed (Ekland & Fidock, 2008), and evidence of emerging resistance to the current front line artemisinins (Andriantsoanirina *et al*., 2009; Bonnet *et al*., 2009; Carrara *et al*., 2009). Approximately 2 million compounds in the chemical library of GSK were screened in 384-well plate format using Lactate Dehydrogenate (LDH) assay at a single concentration of 2μM against the *P. falciparum* 3D7 strain. 19,451 molecules that inhibited the growth of the parasite by ≥80% were categorised as the primary hits. These were re-screened at the same concentration in another two separate experiments using the Dd2 malaria parasite strain. 13,533 compounds that inhibited the growth of the parasite by more than 80% in at least two of the experiments were considered as the confirmed hits which can serve as the antimalarial drug development chemical starting point (Gamo *et al.*, 2010).

Also, the confirmed hits were tested for cytotoxicity against human hepatoma HepG2 cells at 10μM, and only 1,982 of the compounds showed a selective index above the limit of human tolerance. The 50% inhibitory concentration (IC_{50}) of most of the compounds were below the

micromolar range and all but one class of antimalarial were detected during the screening (Gamo *et al*., 2010). The full compounds set have been made available to the community through Material Transfer Agreements for further characterization and optimization.

1.11.2 Medicine for Malaria Venture (MMV) - Malaria Box

The last decade had witnessed the extensive high-throughput screening of large chemical libraries leading to the generation of more than 20,000 antimalarial hits (Van Voorhis *et al*., 2016). These chemotypes could serve as starting points in the hit-to-lead generation, and also have the ability to kill other pathogens because they could share similar biological pathways targeted by these compounds (Spangenberg *et al.,* 2013). Against this background, the Medicine for Malaria Venture (MMV) had prioritized hits to generate a smaller compound set called Malaria Box. This was made freely available for the research community, as a manageable resource for drug discovery and assay development purposes. The set contained 400 compounds that were active against the asexual blood stage of *P. falciparum*. 200 compounds were selected from the hits, having the rule-of-5-complaint physicochemical properties and termed drug-like compounds. While another set of 200 compounds that represent the largest range of structural diversity were also selected and named probe-like compounds (Spangenberg *et al*., 2013) (Figure 1.16).

The open access Malaria Box has been distributed to some 200 researchers across 30 different countries throughout the world (van Voorhis *et al*., 2016). 236 screens have been performed on the Malaria Box compounds, and they were found to be active against other pathogens such as fungi, bacteria, protozoa, helminths, human cancer cells and the mosquito vector of dengue fever (Van Voorhis *et al*., 2016). In addition, the cytotoxicity test against 73 human cell line and developing zebrafish embryo at 10µM and 5µM respectively were carried out (van Voorhis *et al*., 2016). All the tests carried out on malaria box compounds will assist in the selection of

compounds for further characterisation and optimization in the drug discovery and development programs.

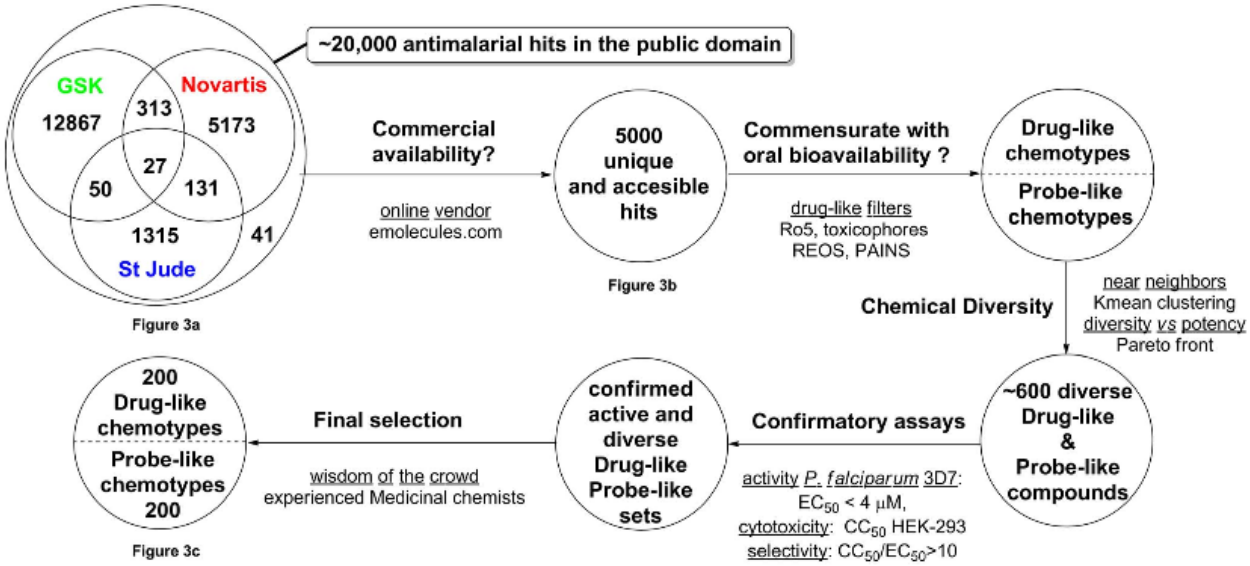


Figure 1.16: Process for selection of the MMV Malaria Box open access compound library *The schematic reports the process by which MMV prioritized approximately 20,000 hits to generate a smaller set of 400 compounds assembled in the Malaria Box. Source: Spangenberg et al., (2013)*

1.11.3 Medicine for Malaria Venture - Pathogen Box

The MMV Pathogen Box comprises of 400 different drug-like compounds that were assembled as an open access resource based on the Malaria Box model. Compounds were selected by examining and prioritizing chemical molecules from the European Bioinformatics Institute's open access database (ChEMBL17). Also, compounds were donated by the academic and pharmaceutical collaborators. This led to the generation of a library containing chemo-types that were active against malaria, tuberculosis, and neglected tropical diseases such as kinetopastids, cryptosporidiosis, onchocerciasis, lymphatic filariasis, wolbachia, schisotosomiasis, trichuriasis, hookworm, toxoplasmosis and dengue. The Pathogen Box also contains reference compounds, drugs currently used in the treatment of these diseases

1.12 The search for new antimalarial drugs: the importance of a rapid rate of kill

Determining the rate of kill of compounds early in the antimalarial drug discovery pipeline is important. Clinically, a drug should rapidly reduce parasite biomass. This has the effect of reducing the morbidity and mortality of infection. The success of artemisinin is based, in part, on this ability. This observation was demonstrated when intravenous artesunate was shown to be preferred to quinine in the treatment of severe malaria. In two large multicentre randomised malaria controlled trials carried out in Asia (Dondorp *et al.,* 2005), SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), and in Africa (Dondorp *et al.*, 2010), AQUAMAT (African Quinine Artesunate Malaria Trial), artesunate was shown to prevent more death due to severe malaria than quinine. This led to an advice that artesunate should become a treatment of choice for severe malaria, the success is attributed to rapid killing rate and its action on rings stage of malaria parasites. In addition, fast-acting compounds slow the onset and spread of resistance (Corey *et al.,* 2016) with the rapid loss in parasite numbers apparently preventing the opportunity for resistance mutants to evolve and become fixed in a parasite population.

The killing rate of antimalarial drugs is usually estimated *in vivo* using a severe combined immune deficiency (SCID) mouse model or humanised mouse (Le Bihan *et al*., 2016). This approach gives information about the predictive therapeutic index required to completely clear the parasites. This is normally estimated using two parameters. The parasite reduction ratio (PRR) is the ratio of parasite count at the start of antimalarial treatment divided by the count after 48 hours corresponding to one erythrocytic cycle of *Plasmodium falciparum* growth. The second parameter is the parasite clearance time (PCT), and is the time taken to clear 99.9% of the parasite load with infections typically no longer detected in the blood film following microscopic examination. However, using animal models to clinically evaluate how fast a compound works takes a long time and is unsuitable for high throughput screening in the drug development process. The challenge is to have a rapid *in vitro* rate of kill assay that can be used

as a filter to select the most efficacious chemo-types during the early process of drug discovery and development.

1.12.1 *In vitro* Parasite Reduction Ratio (PRR) and Parasite Clearance Time (PCT) Assays

The first *in vitro* assay that precisely measured the antimalarial killing rate was developed by Sanz *et al.,* (2012). The assay measured the speed of action of the antimalarial drug on parasite viability as opposed to the traditional techniques that utilized metabolic activities as a surrogate for the parasite growth. Importantly, the assay could differentiate between antimalarial agents on the basis of their mode of action with drugs having the same rate of kill showing the same mode of action. However, there are issues with the use of the technique in high throughput screening of large chemical compounds. Figure 1.17 illustrates how the assay works, briefly, asynchronous parasite culture (mostly 80% rings) at 2% haematocrit and 0.5% parasitaemia was exposed to test compound at concentration of fold-EC_{50} value. An aliquot of 10^5 parasite culture was removed at 0 hour and every 24 hours for up to 120 hours' time point. Limiting serial dilution was performed on the aliquot in 96 well plate and fresh erythrocytes and culture media were added. The parasite culture was maintained for up to 28 days to allow any well with viable parasite to resume growth. The parasite growth was monitored using tritriated [^{3}H]-hypoxanthine incorporation technique and number of viable parasite were estimated. The result of the assay takes longer time due to the extensive culturing steps required over 21 to 28 days.

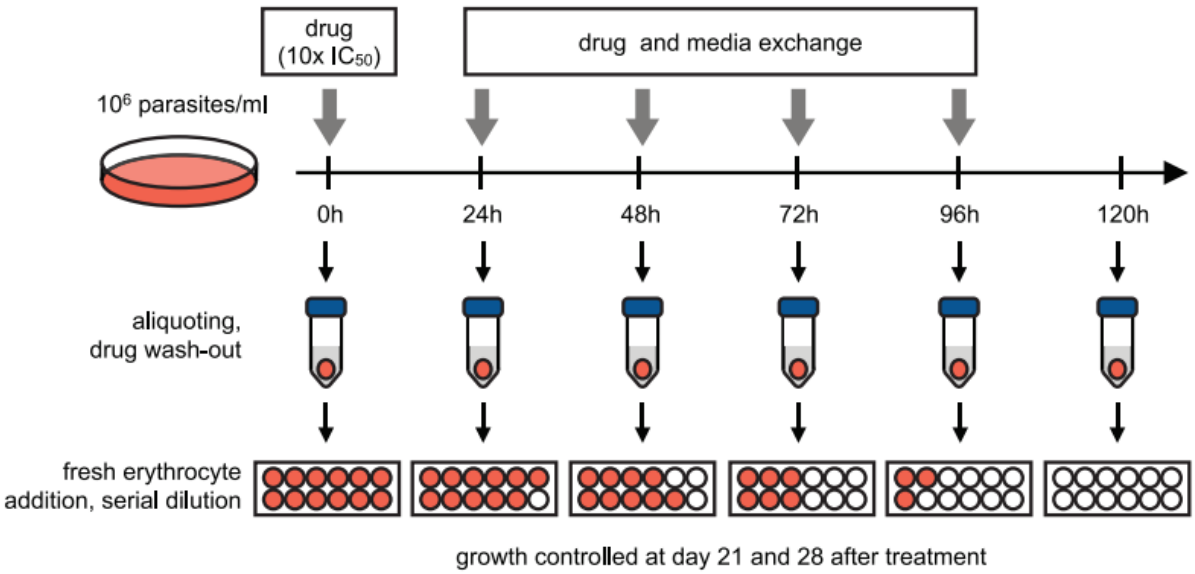


Figure 1.17: Diagrammatic representation of the in vitro PRR assay
The assay was based on limiting serial dilution of drug treated parasite and growth of any viable parasite was monitored for up to 28 days.
Source: Sanz et al., (2012)

1.12.2 *In vitro* IC_{50} speed and stage specificity killing rate assay

Le Manach *et al*. (2013) developed the second *in vitro* killing rate assay that was based on the modification of a standard [^{3}H] hypoxanthine incorporation technique. The assay utilized two approaches; the 'IC_{50} speed assay' and 'stage specificity' assay which could not be performed independently (figure 1.18). Briefly, the *in vitro* IC_{50} speed assay was set up by exposing parasite culture to the test compound and incubated for three different time points; 24 hours, 48 hours and 72 hours. The parasite growth was evaluated by using the tritriated [^{3}H]-hypoxanthine assay. Radioactive hypoxanthine was added 24 hours and 48 hours after incubation for the 48 hours and 72 hours assay respectively. Whereas, [^{3}H]-hypoxanthine was added 16 hours after incubation for the 24 hours assay and IC_{50} values were subsequently determined for five benchmark antimalarial; chloroquine, artesunate, atovaquone and pyrimethamine.

The stage-specifity assay was carried out by exposing the synchronous culture (early rings and schizonts) of NF54 parasite line to 1.6-100 X IC_{50} of antimalarial compounds in a two-fold serial dilution and incubated at 37^0C for 24 hours. After incubation, the plates were washed 4X yielding a greater than 1,000-fold dilution of the antimalarial compounds. Subsequently, radioactive hypoxanthine was added and the plates were incubated for another 24 hours before either frozen down at -20^0C or processed. One limitation of this assay is that it takes about four to seven days to obtain result.

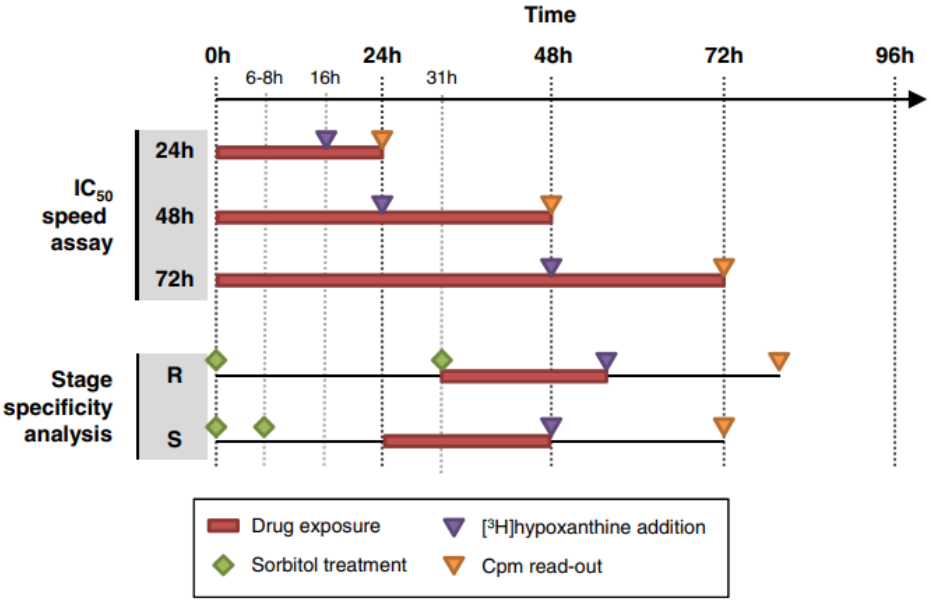


Figure 1.18: Schematic diagram of "IC50 speed" and "stage-specificity" in vitro assay
The time points indicate the incubation period, sorbitol treatment, drug exposure, addition of hypoxanthine and the final readout are depicted in the diagrammatic representation
Source: Le Manach et al., (2013)

1.12.3 Reinvasion parasite viability killing rate assay

Another *in vitro* parasite viability fast killing assay that was based on an erythrocyte invasion method was developed by Linares *et al*., (2015). Briefly, asynchronous 3D7 parasite culture (≥80% rings) was exposed to 10X IC_{50} concentration of the antimalarial drug. The plates were incubated at 37^0C for 24 or 48hours. Tested drug was renewed by washing the plate every 24 hours and adding the same volume of drug. After 24 or 48hours incubation, drug was removed

and pre-labelled non-infected erythrocyte was added to the culture and incubated at 37^0C for another 48hours (see figure 1.19 for details). The final incubation will allow viable parasite to invade labelled erythrocyte and the new infection was detected by two-colour flow cytometry. However, this technique does not readily discriminate between two fast acting drugs such as artemisinin and chloroquine. The results require 3 to 4 days to complete and the availability of flow cytometer is another limitation.

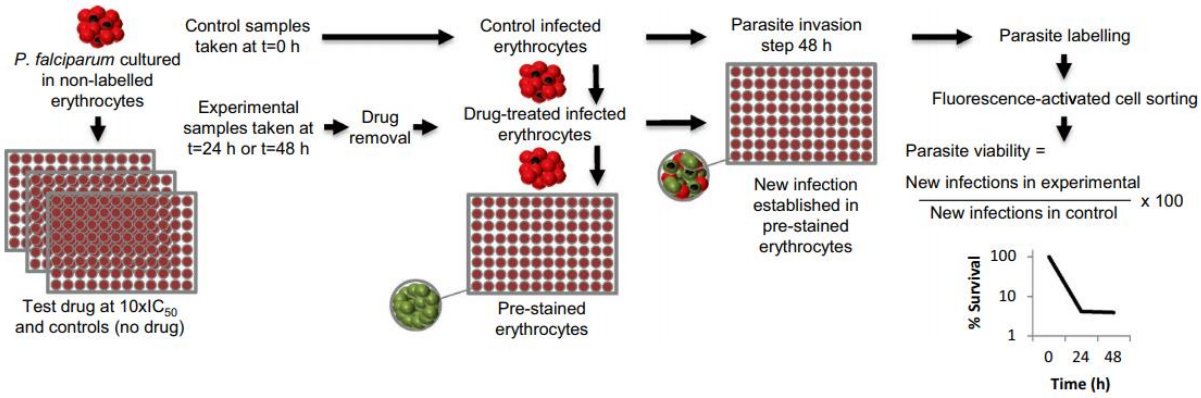


Figure 1.19: Schematic Summary of reinvasion parasite viability killing rate assay.
First, parasite culture was exposed to the antimalarial drug for 24 or 48 hours. Following drug removal, the culture was added to pre-labelled erythrocytes to allow re-invasion of viable parasites. Two-colour flow cytometry was used to detect new infection and the percentage of parasite viability was calculated (see the formula in the schematic diagram)
Source: Linares et al., (2015)

1.12.4 Bioluminescence Relative Rate of kill (BRRoK) assay

The most recent *in vitro* innovation was a rate of kill assay developed in our laboratory using *P. falciparum* genetically modified to express luciferase (Wong *et al*., 2011; Hasenkamp *et al*., 2013). Hasenkamp *et al.*, (2013) showed that $Dd2^{luc}$ provides the same IC_{50} data as Sybr Green 1 assays. This study also showed that luciferase is a more dynamic assay of parasite viability due to the rapid turn-over of the luciferase reporter protein. Ullah *et al*., (2017) showed that loss of bioluminescence following drug perturbation correlated with the *in vitro* PRR and PCT data developed for a range of benchmark antimalarials (Sanz *et al*., 2012) (Figure 1.20). Based on this work, Ullah *et al.,(2017)* then developed the Bioluminescence Relative Rate of Kill

(BRRoK) assay. In this study, they showed that effect of the drug on bioluminescence at four concentrations of test compound equivalent to the 0.33, 1, 3 and 9 x IC_{50} and their effect over 6 hrs. They then showed how these concentration-response data could provide a rank of loss of bioluminescence – where adding benchmark drugs allows this surrogate measure of rate of kill to be mapped against (relative to) antimalarial compounds with well-described pharmacodynamics data. Importantly, and only otherwise available from the *in vitro* PRR assay – the BRRoK assay discriminates between compounds that meet the minimal threshold for rate of kill – at least as fast as chloroquine – and those that meet the ideal criteria as faster than artemisninins. This innovation provided a rapid (6 hours) assay, compared to the 21-28 days for the *in vitr*o PRR assay, that was simple to complete in a multiwall plate with minimal processing steps that was robust enough for scale up (Ullah *et al.*, 2017). Table 1.7 provides a summary of the relative benefits and issues available *in vitro* rate of kill assays.

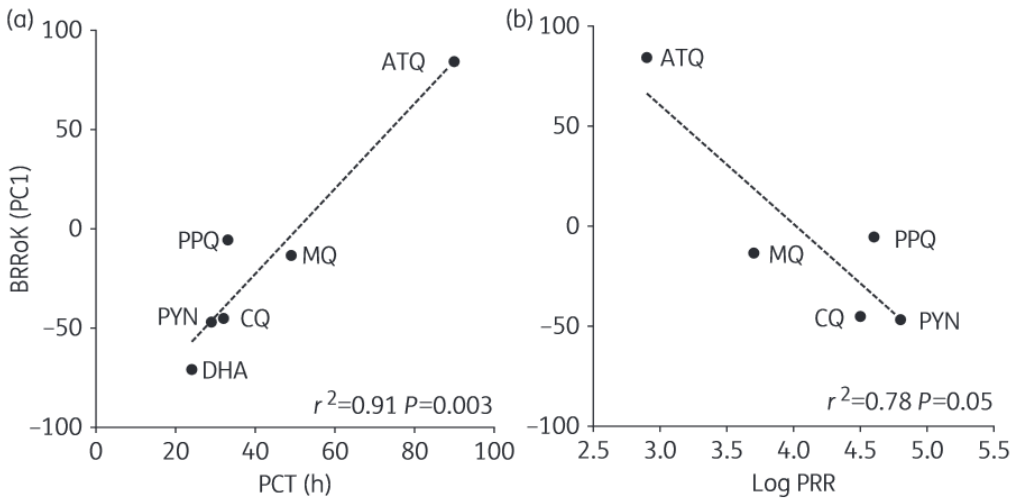


Figure 1.20: Comparing the BRRoK (PC1) with in vitro (PCT) and (b) log PRR of antimalarial drugs

The y-axis shows the zero-meaned PC1 data from Ullah et al., (2017), while the in vitro PCT (h) and log PRR data (x-axis of (a) and (b) respectively) are from Sanz et al., (2012). The broken lines represent the linear regression. DHA, dihydroartemisinin; PYN, pyronaridine; CQ, chloroquine; PPQ, piperaquine; MQ, mefloquine; ATQ, atovaquone. Source: Ullah et al., (2017)

Assay	Method	Merits	Demerits	References
In vitro PRR	serial dilution of treated parasite and and monitoring re-growth	(i) directly measure killing rate (ii) differentiate antimalarials based on mode of actions	(i) Results takes four weeks (ii)many liquid handling steps (iii)unsuitable for highthrougput	Sanz *et al.,* 2012
qRT-PCR analysis	quantification of mRNA level	Discriminate between cidal and static drug	re-growth monitoring for 8days after drug treatment for 48hours	Bahamontes-Rosa *et al.,* 2012
IC_{50} speed assay Stage specificity analysis	modified [^{3}H] hypoxanthine	(i) discriminate fast and slow antimalarials (ii) differentiate stage-specificity of anti-malarials	(i) results take up to one week (ii) usage of radioactive material (iii) initial IC_{50} determination	Le Manach *et al.,* 2013
parasite viability fast assay	re-infect-ion of pre-labelled RBCs	(i) takes only 48hours (ii) direct measure of parasite viability	(i)cannot differentiate two fast acting compounds (ii) cannot identify the slow acting compounds	Linares *et al.,* 2015
BRRoK assay	Measuring Luciferase Signal	(i) takes only 6 hours (ii) can discriminate fast and slow drug	(i)use GM parasites (ii) initial determination of IC_{50} values	Ullah *et al.,* 2017

Table 1.7: Comparison of in vitro assays of antiplasmodial intraerythrocytic killing dynamics

1.13 Addressing the knowledge gap

Keeping in mind, the shortcomings of the various *in vitro* rate of kill assays, the BRRoK assay suffers from one significant drawback. In the screening of the relative rate of kill of the MMV Malaria Box compounds, Ullah *et al.,(*2017) faced a bottleneck in the assay process in that whilst it took 6 hrs to measure the rate of cytocidal action – the EC_{50} needed to be determined for each compound in a standard 48hr standard Sybr Green I potency assay. This requirement to use variable concentrations of compounds for a BRRoK assessment significantly limits the potential to scale up this *in vitro* assay format to screen large or even massive chemical libraries to prioritise those that potentially meet the TCP1 development criteria. In this thesis I will describe an improvement in the BRRoK assay format in the development of a modified BRRoK (mBRRoK) assay that uses a much simpler format of only two fixed concentrations of test compound. The hypothesis that underpins this approach is explained fully in the introduction

to Chapter 3. The overall aim of this study is to provide a simple, robust and rapid *in vitro* tool suitable to screen thousands of compounds to support the drug discovery effort for a new SERCaP clinical entity. To achieve this aim, the following targets were addressed in this thesis;

1. Validate the hypothesis that loss of bioluminescent signal in an mBRRoK assay is proportional to potency and rate of kill using a series of benchmark antimalarial drugs with known pharmacodynamics properties.
2. Validate the mBRRoK assay against the BRRoK assay data available for a range of MMV Malaria Box compounds – use this data to establish the specificity and sensitivity of the mBRRoK assay
3. Establish the potential of the mBRRoK assay against a new MMV Pathogen Box resource to provide novel rate of kill data for an important open access resource.
4. In collaboration with GSK, utilize the mBRRoK assay to screen the TCAMS library to provide a validated short list of novel rapid acting and potent antiplasmodial compounds

This work will then be concluded with a discussion on the perspectives gained from this study on the future potential of the assay in the development of potential leads and scaling up to screen multimillion compound libraries.

2 CHAPTER 2: MATERIALS AND METHODS

2.1 Materials

2.1.1 45% glucose solution

Glucose solution (45% w/v) was prepared by adding 45g of D-glucose to distilled water to a total of 100mL. The glucose suspension was dissolved by either placing it in a water bath at 37^0C for 30 minutes or with the help of a magnetic stirrer. The solution was vacuum filtered (0.45µm pore) and stored as 10mL aliquots at 4^{o}C until use.

2.1.2 1000X Hypoxanthine solution

A total of 680mg of hypoxanthine was dissolved in 50mL of 1M sodium hydroxide solution (Sigma, UK). The hypoxanthine solution was vacuum filtered (0.45µm pore) and stored as 0.5mL aliquots at -20^{o}C.

2.1.3 10% Giemsa solution

10mL of Giemsa solution (Fluka, UK) was added to 90mL of distilled water. This solution was syringe filtered (0.45µm pore) prior to use as a stain.

2.1.4 5% Albumax

25g of albumax powder was added to 500 mL of RPMI (Roswell Park Memorial Institute) 1640 medium (Sigma, UK). The albumax suspension was dissolved by incubating at 37^0C for up to 1hr. The solution was vacuum filtered (0.45µm pore) and 40mL aliquots stored at -20^{o}C.

2.1.5 5% Sorbitol

5g of D-sorbitol powder (Sigma, UK) was added to a total volume of 100mL of distilled water. The solution was vacuum (0.45µm) pore and 15mL aliquots stored at 4^{o}C.

2.1.6 10mg/ml Blasticidin S Hydrochloride (BSD)

5mL of incomplete medium was added to 50mg of Blasticidin S HCl powder (Invitrogen, UK); the solution was stored as 0.5mL aliquots at -20^{0}C. 125µL of 10mg/ml BSD solution was added to complete medium and stored at 4^{o}C for up to 2 weeks.

2.1.7 WR99210

A 25mM concentrated stock was prepared by adding 0.05g of WR99210 powder (Jakobus Pharmaceutical, USA) to 1mL of DMSO and stored at -20^{0}C. A 25µM working solution was prepared by a 1:1000 dilution of the 25mM stock into 1mL of incomplete medium and stored at 4^{0}C. 100µl from the 25µM working solution was added to 500mL of complete medium to give the required final concentration of 5nM.

2.1.8 Glycerol freezing solution

Glycerol freezing solution was prepared by taking 142.5g of glycerol, 4g sodium lactate, 0.075g potassium chloride, 0.311g of disodium phosphate (Na_2HPO_4) and 0.129g monosodium phosphate (NaH_2PO_4) and adding distilled water to a total volume of 230mL. 10M NaOH was used to adjust the pH to 6.8, and the final volume was made up to 250mL with distilled water. The glycerol freezing solution was vacuum filtered (0.45µM pore) and stored at 4^{o}C until use.

2.1.9 Cell culture medium for *P. falciparum* culture

Complete growth medium was prepared by supplementing 500ml of RPMI1640 medium with 18.75mL of 1M HEPES (N-(2-Hydroxyethyl)piperazine-N^1-(2-ethanesulfonic acid)) buffer (Sigma, UK), 2mL of 45% glucose solution, 2.5mL of 1M sodium hydroxide solution (Sigma, UK), 5mL of 200mM L-Glutamine solution (Sigma, UK), 1.25mL of 10mg/mL Gentamicin solution (Sigma, UK), 500µL of 1000X hypoxanthine solution, 20mL of heat-inactivated pooled human plasma (National Blood and Transfusion Service, UK), 20mL of 5% albumax-

II. Incomplete medium lacks the pooled human plasma and albumax components. Depending upon the *P. falciparum* strain, complete media would be supplemented with BSD or WR99210 for drug selection of the luciferase reporter cassette.

2.1.10 Malaria Sybr Green 1 Fluorescence (MSF) lysis buffer

A 10X MSF lysis buffer stock comprises 200mM Tris pH 7.5, 50mM EDTA, 0.08% w/v saponin and 0.8% v/v Triton X-100. The 10XMSF stock is stored at room temperature. A 1XMSF working solution was prepared by diluting one volume of the 10X MSF stock solution in 9 volumes of distilled water.

2.1.11 Antimalarial compounds

Antimalarial drugs were purchased from Sigma-Aldrich and dissolved in appropriate solvent (Table 2.1). The stock solution were prepared as recommended by the supplier and stored at -20^{o}C until further use. The MMV Malaria Box compounds were provided by the Medicines for Malaria Venture (www.mmv.org) as 20µL of 10mM stock solution in DMSO. Similarly the Pathogen Box compounds were provided by the Medicines for Malaria Venture as 10µL of 10mM stock solution in DMSO. The compounds were diluted to 1mM working concentration in 9 volumes of DMSO as recommended by the Medicines for Malaria Venture and stored at -20^{o}C until use.

Table 2.1 Drug stock preparation

Name	Class	Solvent	Stock concentration
Artemether (ART)	Endoperoxide	Dimethyl sulfoxide (DMSO)	50mM
Dihydroartemisinin (DHA)	Endoperoxide	Methanol	10mM
Chloroquine (CQ)	4- aminoquinoline	Distilled water	100mM
Quinine (QN)	Aryl-alcohol	Ethanol	100mM
Atovaquone (ATQ)	Naphthoquinone	DMSO	20mM
Pyronaridine (PYN)	4- aminoquinoline	Acetic acid	5mM
Amodiaquine (AQ)	4- aminoquinoline	Methanol	10mM
Mefloquine (MQ)	Aryl-alcohol	DMSO	10mM
Piperaquine (PPQ)	4- aminoquinoline	Ethanol	10mM
Doxycycline (DOX)	Antibiotics	Distilled water	100mM
Malaria box compounds	Varied	DMSO	1mM
Pathogen box compounds	Varied	DMSO	1mM
TCAMS compounds	Varied	DMSO	1mM

2.2 Methods

2.2.1 Preparation of 50% haematocrit

Human blood group O Rhesus positive was supplied by the National Blood and Transfusion Service (UK). All work with human materials was carried out according to the provisions of the Institution's Human Tissue Authority (HTA) Licence (#12349). Human blood was passed through a leukocyte filter provided with the donation and aliquoted into pre-labelled 50ml tubes and stored at 4ºC in a HTA-approved refrigerator until use. A 50% haematocrit stock was prepared by aspirating the serum with careful removal of any residual buffy coat layer. One volume of incomplete medium was added to the red cell pellet and centrifuged at 1520g for eight minutes at room temperature. The supernatant was carefully aspirated and one volume of incomplete growth medium was added for subsequent washes and collected by centrifugation. After a third wash, the supernatant was carefully aspirated and one volume of incomplete growth medium added to make up a 50% haematocrit stock. The 50% haematocrit erythrocytes were stored at 4ºC for up to two weeks.

2.2.2 *Plasmodium falciparum* in continuous culture

All work in the category III cell culture facility was carried out according to a Code of Practice approved by the Health and Safety Executive. Ethical approval for the use of these materials for *in vitro* culture and *in vitro* assessment of antiplasmodial activity is in place. The genetically-modified *P. falciparum* strains used were registered with Keele University Genetic Modification Safety Sub-Committee.

The genetically modified Dd2^{luc} *P. falciparum* clone (Wong *et al*., 2011) was typically used throughout this study. In this clone, a luciferase reporter gene under the control of a trophozoite stage-specific expression cassette has been integrated into chromosome 7 along with a BSD drug selectable marker gene. A second genetically modified NF54^{luc} *P. falciparum* clone

(Hmoud, 2019) was provided by a PhD colleague from our laboratory. In this parasite, the same trophozoite stage-specific luciferase reporter is present on an episomal plasmid bearing a *DHFR* drug selection marker (selected using the antifolate WR99210) and a *rep*20 *P. falciparum* telomere associated repeat element (O'Donnell *et al*., 2002).

Parasites were continuously cultured in accordance with the method based on that originally described by Trager and Jensen (1976) and later modified by Freese *et al*., (1988). Routine culturing of parasites was done at a 2% haematocrit and the growth medium typically changed daily together with the preparation of thin blood smear for determination of parasitaemia and staging. Cultures were maintained by re-suspending the infected erythrocyte pellet in fresh complete medium, fresh uninfected erythrocytes and gassed under 1% oxygen, 3% carbon dioxide and 96% nitrogen (BOC, UK) before incubation at 37^{o}C.

2.2.3 Synchronisation of *P. falciparum* culture

P. falciparum culture with predominately early ring stages was synchronised according to the method originally described by Lambros and Vanderberg (1979). Packed infected erythrocytes were collected by centrifuging the culture suspension at 1520g for five minutes at room temperature. The supernatant was carefully aspirated and five volumes of pre-warmed 5% sorbitol solution was added and incubated for five minutes at 37^{o}C. The suspension was centrifuged at 1520g for five minutes at room temperature, and the supernatant carefully aspirated. The infected erythrocytes were re-suspended in fresh complete medium and an appropriate volume of uninfected erythrocytes was added. The cultured flask was gassed and incubated at 37^{o}C.

2.2.4 Freezing of *P. falciparum* culture for long-term storage

The parasites to be stored should ideally be at parasitaemia of at least 3% and predominantly contain ring stage parasites. The parasite culture is collected by centrifugation for 5 minutes at

1520g at room temperature. The supernatant was aspirated, leaving about 500µL of media on top. The erythrocyte pellet was re-suspended gently in this 500µL of media and the total volume used to define one volume. 1.5 volumes of inactivated human plasma was added and mixed gently to ensure proper resuspension of the parasite culture. Then 2.5 volumes of glycerolyte freezing solution was added dropwise while mixing gently. This parasite suspension/glycerolyte solution was then transferred as 1mL aliquots into a labelled cryogenic vial (StarLab) and stored in liquid nitrogen for long-term storage.

2.2.5 Thawing of frozen *P. falciparum* culture

A frozen vial of parasite culture was removed from the liquid nitrogen and placed at 37ºC to thaw. The parasite culture was then transferred from the vial into a 50mL sterile tube and 0.2 volumes of a 12% NaCl solution was gently added in a dropwise fashion. The tube was incubated at room temperature for 5minutes, then, 10 volumes of 1.6% NaCl was slowly added whilst continuously gently rotating to mix the tube's contents. After 5 minutes incubation at room temperature, this process was repeated with 10 volumes of 0.9% NaCl in 0.2% glucose. The parasite suspension was centrifuged at 850g for 5 minutes at room temperature. The supernatant was gently aspirated and the infected erythrocyte pellet cultured as described in section 2.2.2.

2.2.6 Determining parasitaemia and staging of *P. falciparum* culture by light microscopy

A thin smear of infected erythrocytes was prepared and fixed with absolute methanol for one minute. The slide was dried and then flooded with 10% Giemsa stain for 5 minutes. The stain was washed off the slide with water, air dried and one drop of immersion oil was applied before imaging under a x100 objective lens. The parasitaemia was estimated by counting the parasites in ten fields of infected erythrocytes and the number of erythrocytes per field estimated from counts of three fields. The parasitaemia was determined as:

$$\left(\text{Mean count of parasites from 10 fields} / \text{Mean count of erythrocytes from 3 fields}\right) x100$$

2.3 Fixed concentration, single time point estimation of relative rate of kill – the modified Bioluminescent Relative Rate of Kill (mBRRoK) assay

2.3.1 Preparation of mastermix

A thin smear of infected erythrocytes of *P. falciparum* culture was prepared to check for the staging to ensure early trophozoite, 18-24hours post infection, and a parasitaemia of greater that 2% was available. A mastermix was prepared at 4% HCT, 2% parasitaemia with 7mL of mastermix prepared per 96-multiwell plate being assessed.

2.3.2 96-multiwell plate set up

The assays were set up in 96 multiwell plates (Sarsted, UK) with 200µL of incomplete medium added to the outermost wells to reduce the edge effect resulting from evaporation. 125µL of complete medium was dispensed into the wells to which a final 10µM concentration of compound is being prepared. 100µL was added to the adjacent wells that, after dilution, will have a final 2µM concentration of compound as well as the control wells (no compound) (Figure 2.1). 2.5µL of 1mM compound solution was added to the 10µM wells and mixed by repeated pipetting. 25µL was transferred into the adjacent wells to provide a final 2µM of compound, mixed by repeated pipetting and finally discarding 25µL, creating a 1/5 dilution. Two positive control columns were set up on each plate, these had no compound inhibitor and represent 100% growth achieved in the absence of an inhibitor. 2.5µL of DMSO (to create a 2.25% solvent control) was added to the first positive column for a 10µM compound control and mixed by repeated pipetting. 25µL was moved to the second positive column for 2µM control (0.45% DMSO solvent control), mixed and 25µL was discarded. 100µL of mastermix was added to all the test wells and mixed by pipetting. The plate was incubated for 6 hours at

37ºC in a gassed chamber. Each compound was tested in duplicate on each plate, with three biological repeats providing a total of n=6 samples for each compound at each concentration.

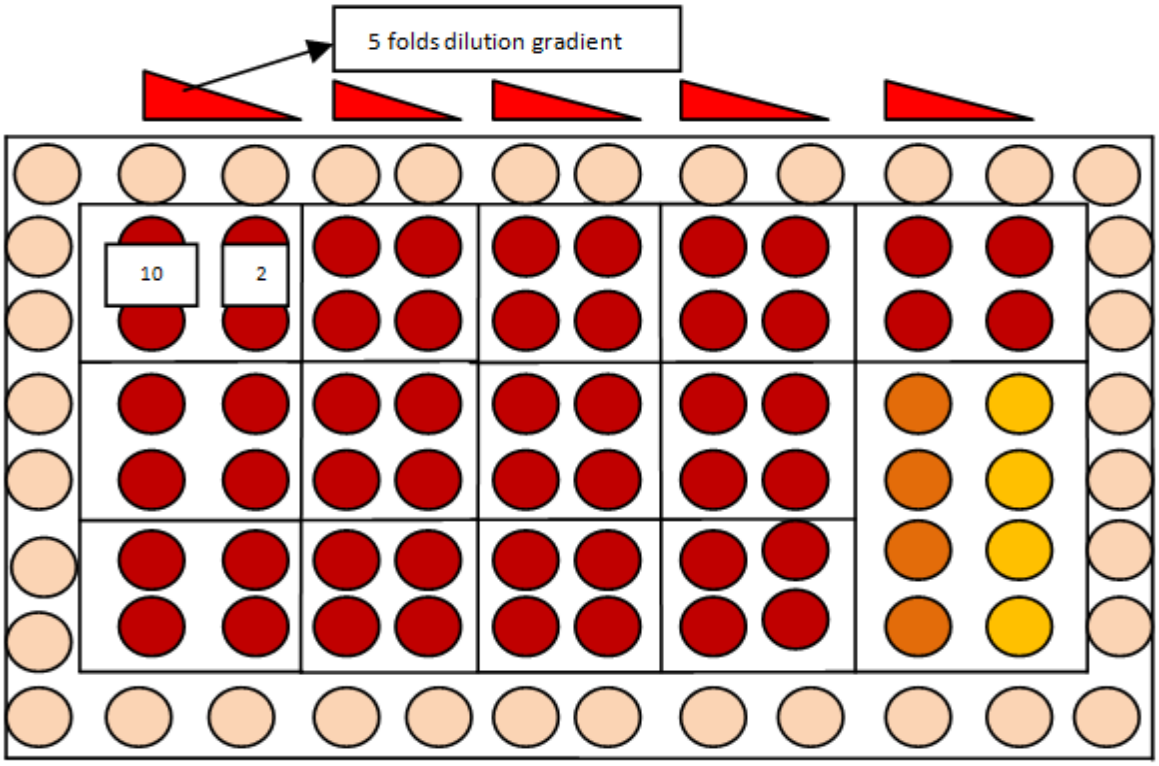


Figure 2.1: Schematic representation of the assay plate set up for modified bioluminescent relative rate of kill (mBRRoK) assay using fixed concentrations
The outermost wells (light brown) represent incomplete medium used to minimise edge effects from evaporation. Up to thirteen compounds were tested on each plate in duplicate at two concentrations (dark red). Controls representing no compounds but with DMSO content reflective of the carrier solvent for 10µM compound (2.2% DMSO, orange) and 2µM compound (0.45% DMSO, yellow) were provided as untreated controls.

2.3.3 Determination of luciferase signal

A single-step lysis protocol was carried out as described by Hasenkamp *et al*., (2012). In brief, after six hours of incubation, 40µl of cultured parasites were transferred from each well onto a white 96 multiwell plate (Greiner, UK) containing 10µl of 5X passive lysis buffer (Promega, UK). The well contents was homogenised by gentle shaking and 50µl of luminogenic substrate (Promega, UK) added to the lysed parasites. The resulting bioluminescence signal, in relative

light units, was measured for two seconds on a Glomax Multi Detection System (Promega, UK).

2.3.4 Data analysis

The relative light unit data was exported into an Excel sheet using the Instinct^{TM} software (Promega). The mean of the 2.2% and 0.45% DMSO controls were used to define 100% of the relative signal (no compound control) for the 10µM and 2µM compound treated wells, respectively. The mean and standard deviation of n=6 relative signals were plotted in GraphPad Prism v5.0 (GraphPad Software, Inc., San Diego, CA, USA).

2.4 Determination of 50% inhibitory concentration (IC_{50})

This protocols was carried out based on a protocol that originally described by Smilkstein *et al*., (2004) and revised as described below.

2.4.1 Preparation of mastermix

The same procedure was used as described in the section 2.3.1 except that the final mastermix was at a 1% trophozoite parasitaemia. The protocol used is to prepare a serial two-fold dilution series.

2.4.2 96 multiwell plate set up

The same 200µL of incomplete medium was added to the outermost wells to reduce edge effects. 200µL of complete medium was added to the compound loading wells in column 2 (Figure 2.2). The compound dilution wells (columns 3 to 10) each contained 100µL of complete medium. Two types of controls were set up on each assay plate in column 11. The top three wells contained 100µL of complete medium with no compound and represent the normalised 100% growth in the absence of an inhibitor (positive control). The bottom three wells contain 100µL of complete medium with a supra-lethal dose of 10µM chloroquine to

represent a total kill with 0% relative growth (negative control). Appropriate volumes of test compound were added to the loading wells and mixed by repeated pipetting. 100µL of this mix was then moved across the dilution wells before 100µLis discarded to provide a two-fold serial dilutions of the compound of interest. 100µL of mastermix was added to all wells and the multiwall plate incubated for 48 hours at 37^{o}C in a gassed box.

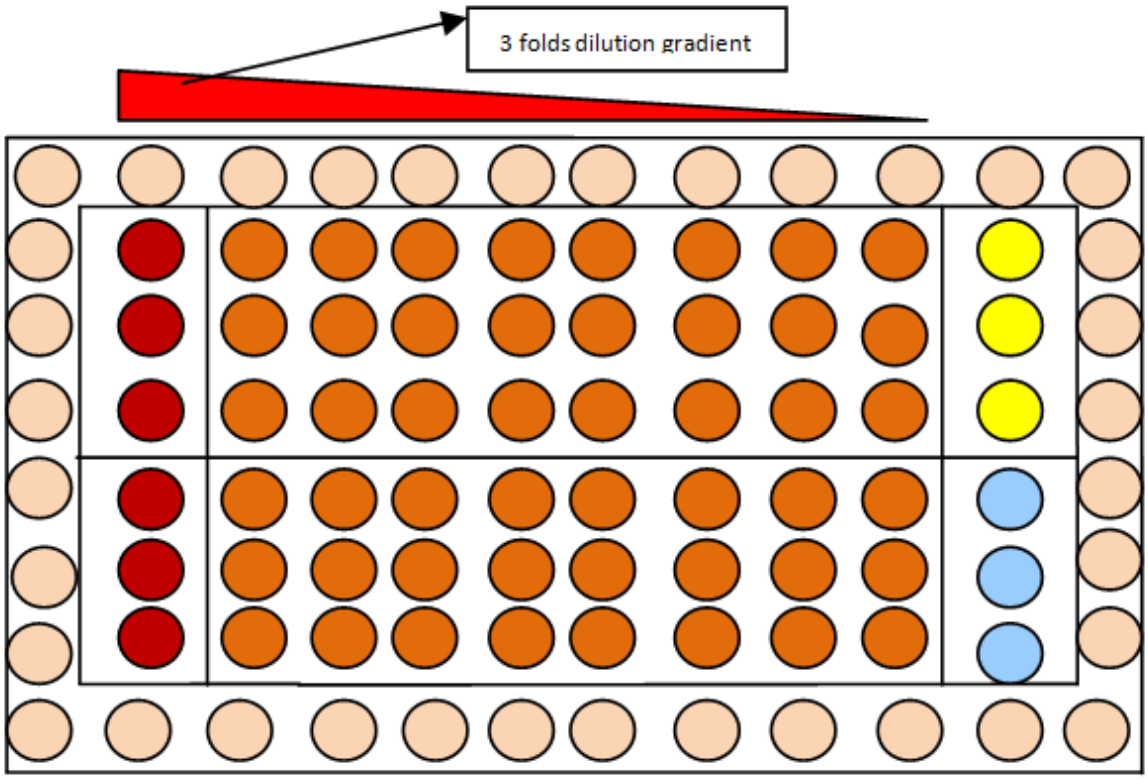


Figure 2.2 Schematic representation of 96 multiwell plate set up to determine a 50% inhibitory concentration
The outermost wells (light brown) represent incomplete medium. Two compounds were tested on each plate with the leftmost column (column 2, dark red) represents the loading wells (n=3 for each compound). The next wells (columns 3 to10, orange) represent the dilution wells. The rightmost column (column 11); yellow wells represent the positive control (no drug, 100% relative growth) and light blue wells represent the negative control (10µM CQ, 0% relative growth)

2.4.3 Sybr Green I fluorescence assay

Sybr Green I (x5000, Invitrogen) was diluted into 1X Malaria Sybr Green I Flourescence (MSF) lysis buffer (20mM Tris HCl, 5mM EDTA, 0.008% Saponin and 0.08% Triton X100). 100µL

of the MSF buffer-dye suspension was added to the corresponding well on a black 96 multiwell plate (Greiner, UK). To these, 100µL of the malaria parasite culture was added and mixed by repeated pipetting. The multiwell plate was incubated at room temperature in the dark for one hour before the fluorescence signal (in relative fluorescence units, RFU) was measured using a Glomax MultiMax (Promega, UK) fitted to use the blue fluorescent module (excitation 490nm: emission 510-570nm).

2.4.4 Data analysis

Fluorescent signal data was exported into an Excel spreadsheet using the Instinct™ software (Promega). This data was converted to a normalised % growth using the formula below:

$$\left(\left(\sum \text{signal of interest} - \sum\beta\right) \Big/ \left(\sum\alpha - \sum\beta\right)\right) x100$$

Signal of interest in the mean of n=9 wells exposed to the same concentration of compound

α are the 100% growth controls using n=9 wells with no inhibitor added

β are the 0% growth controls using n=9 wells with 10µM CQ supralethal dose

The mean values from three biological repeats, each of three technical repeats provide the n=9 samples used here. The means and their standard deviation were plotted against $\log_{10}$-transformed compound concentration using Graphpad Prism v5.0 (GraphPad Software, Inc., San Diego, CA, USA). A log concentration-normalised response regression analysis was performed to estimate the IC_{50} and provide the reported 95% confidence interval.

2.5 Bioluminescence Relative Rate of Kill (BRRoK) assay

The assay was carried out according to the protocol originally described by Ullah *et al*., (2017) with revisions as described below.

2.5.1 Preparation of mastermix

A 4% HCT and 2% trophozoite stage mastermix was prepared as described in section 2.3.1.

2.5.2 96 multiwell plate set up

The assays were set up in 96 multwell plates (Sarsted, UK) with 200µL of incomplete medium added to the outermost wells to minimize edge effects (Figure 2.3). 150µL of complete medium was added to the compound loading wells (columns 2 and 7) and 100µL of complete medium was added to the three adjacent compound-dilution wells. A volume of drug/compound corresponding to $9xIC_{50}$ of each compound was added to the loading wells on each plate. The content in the loading wells was mixed by repeated pipetting and 50µL moved across the dilution wells with mixing and finally discarded to produce a 3-fold dilution. 100µL of mastermix was added to all the wells (thus diluting the compounds to produce 9x, 3x, 1x and $0.33xIC_{50}$ over the four wells). Six wells without any drug served as the 100% normalised growth (positive) control. The plate was incubated at 37^{o}C for 6 hours in a gassed box.

2.5.3 Determination of luciferase signal

This was carried out as described in section 2.3.3

2.5.4 Data analysis

This was carried out as detailed in the section 2.3.4 except that with only one (positive) control was used to calculate the signal of interest as a proportion of the untreated control.

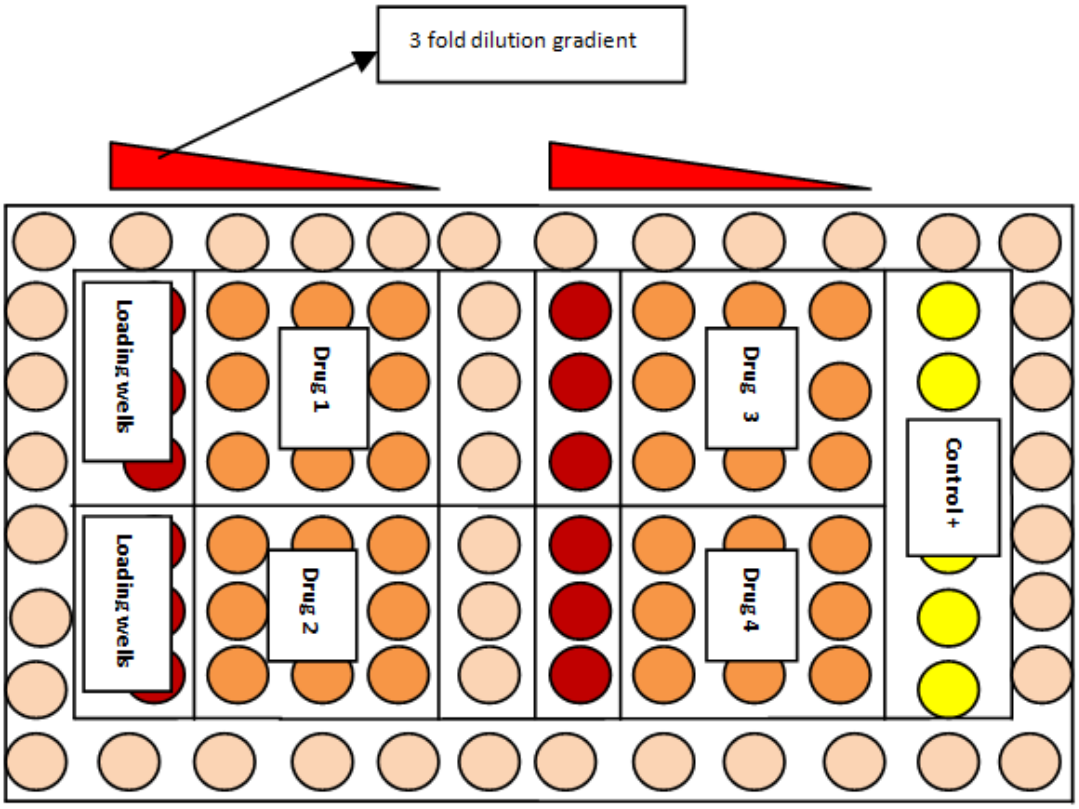


Figure 2.3 Assay plate set-up for Bioluminescence Relative Rate of Kill (BRRoK) determination
The outermost (light brown) wells contain 200µL of incomplete medium. Compound loading wells (final 9xEC_{50}) are indicated in dark red with the plate setup allowing up to 4 compounds to be evaluated. The dilution wells are indicated in orange (providing a 3 fold dilution series). The positive (yellow) wells contain no compound, with all bioluminescent signals measured determined as a percentage of their mean RLU count.

2.6 A modified Bioluminescence Relative Rate of Kill (mBRRoK) assay adapted for high-throughput screening of the Tres Cantos Antimalarial Compound set

2.6.1 Preparation of master mix

A mastermix was prepared according to the protocol detailed in the section 2.3.1 except that the total volume was based on the requirement for 7.7mL per plate (based on 20µl per test well on a 384 multiwell plate).

2.6.2 384 well plate set up

The assay was set up in 384 well plates (Sarsted) that were pre-loaded by GlaxoSmithKline (GSK, Tres Cantos, Spain) with 0.02µl or 0.04µl of 10mM and 1mM fixed concentrations of the TCAMs compounds (figure 2.4) respectively (separate plate for each fixed concentration). Upon resuspension in 20µl of parasite culture, this provides for either a 10µM or a 2µM fixed concentration in that well. 20µl of 2%HCT was dispensed into the first eight wells (negative control i.e. 0% growth) of column 6 (blank), while 20µl of the master mix (positive control i.e. 100% growth) was added to the remaining eight wells. 10µM and 2µM fixed concentration of four known antimalarial (dihyroartemisinin, chloroquine, mefloquine, and atovaquone) were added in triplicates to column 18 (blank). Then, 20µl of master mix was added to the remaining wells containing the test compound and antimalarial. The plates were gently mixed and incubated at 37^{o}C in gassed modular chamber for six hours.

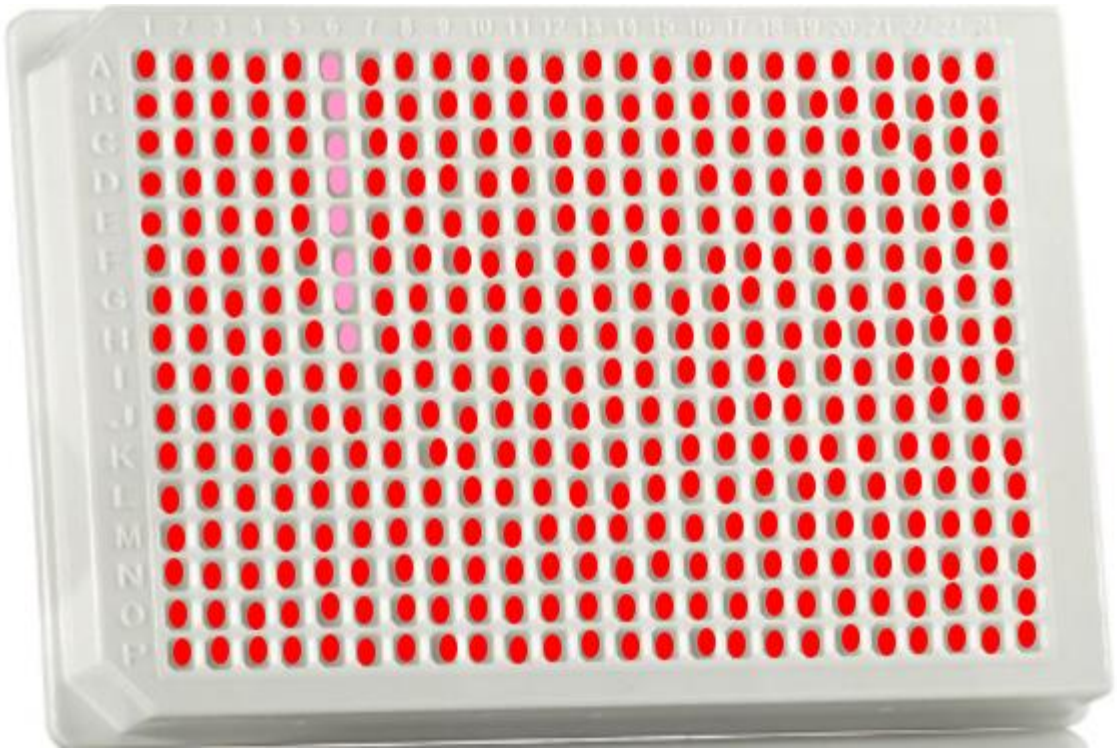


Figure 2.4: Assay plate set-up for modified Bioluminescence Relative Rate of Kill determination.
Red indicates 2% parasite culture added to all the wells except the first 8 wells in column 6 (pink) where 2%HCT was added as negative control (0% growth). The remaining 8 wells in column 6 contained 2% parasite culture without drug (100% growth).

2.6.3 Luciferase assay

A single lysis procedure described by Hasenkamp *et al.*, (2012) was used throughout. After six hours of incubating the assay plates, 5X passive lysis buffer (Promega) and luciferase substrate (Promega) were reconstituted in ratio of 1 to 2 respectively. An equal volume (20µl) of the reconstituted reagent was added to the culture in each wells using a repeating dispenser (Sarsted, UK) and gently mixed. The luciferase signal was measured in relative light units on a Glomax Multi Detection System (Promega, UK).

2.6.4 Data analysis

Data generated was exported into an excel sheet using the Instinct software (Promega). The mean of the eight wells with only master mix (positive control) was used to define 100% of signal (no compound) for the 10µM and 2µM compound treated plates. The one data point for

each fixed concentration were plotted in Graphpad prism V 5.0 (GraphPad Software, Inc. San Diego, CA, USA).

Principle component analysis (PCA) of the subsequent confirmatory BRRoK data using both $Dd2^{luc}$ and $NF54^{luc}$ strains was performed by Dr. Raman Sharma, LSTM. PCA was performed on the 0.3x, 1x, 3x and 9xIC_{50} variables for the 6 hrs bioluminescence assay endpoints using the KNIME analytics platform to reduce the dimensionality of these data set, allowing the concentration rate relationship to be captured in one parameter. Correlation of the PC1 components with relative bioluminescence data, with accompanying statistical analyses, was carried out using GraphPad Prism v5.0.

2.6.5 Assessment of mBRRoK assay quality parameters

20µl each of non-infected erythrocytes (negative signal control) and parasite-infected erythrocytes (positive signal control), were added to the first 8 wells and last 8 wells of column 6 respectively on each assay plate. The data generated were used to calculate the metrics for assessing the quality of high throughput assays such as the Z` score, % maximum and minimum coeffeicient of variation ($\%CV_{max}$ and $\%CV_{min}$) and the signal/background (S/B) ratio as described by Zhang *et al.*, (1999). The Z` was calculated by using the formula: $Z` = 1 - [(3\sigma_{(+)} + 3\sigma_{(-)}) / \mu_{(+)} - \mu_{(-)}]$, in which $\sigma_{(+)}$ and $\mu_{(+)}$ are the mean and standard deviation of positive signal control respectively, while $\sigma_{(-)}$ and $\mu_{(-)}$ are the mean and standard deviation of negative signal control respectively. $\%CV_{max}$ was evaluated: $100x [\sigma_{(+)} / \mu_{(+)}]$ and $\%CV_{min}$: $100x [\sigma_{(-)} / \mu_{(-)}]$. The S/B was calculated: $\sigma_{(+)} / \sigma_{(-)}$.

3 CHAPTER 3: Validation of a modified Bioluminescence Relative rate of Kill (mBRRoK) assay

3.1 Introduction

Rate of kill is an important pharmacodynamics property of antimalarial compounds that is typically evaluated at the preclinical and phase IIa of clinical trials. Determining this parameter early in the drug development process offers the opportunity to reduce the attrition rate later in the 10-15 years of discovery and clinical trials (Tamimi and Ellis, 2009). Towards this aim, Ullah *et al*., (2017) developed and validated a rapid in *vitro* bioluminescence-based rate of kill assay (BRRoK) that allows the determination of the initial cytocidal effect of antimalarial agents within six hours. The assay utilizes a genetically modified parasite clone ($Dd2^{luc}$) that expresses a strong luciferase signal under the control of *Pfpcna* flanking sequence during the S-phase of the trophozoite stage (Wong *et al.,* 2011). Expression of this strong luciferase signal at trophozoite stage has been attributed to the temporal control of *Pfpcna* 5´ and 3´flanking sequences on the luciferase reporter gene (Hasenkamp *et al.,* 2012). The $Dd2^{luc}$ parasite was generated using the *bxb1*integrase system (Wu *et al.,* 1995) where the luciferase reporter, flanked by *Pfpcna* 5´ and 3´ un-transcribed regulatory sequences, was inserted into chromosome 7 of *P. falciparum*.

Earlier work in Horrocks' laboratory has demonstrated the optimization of a bioluminescence assay on a 96 wells plate format. Hasenkamp *et al.,* (2013) showed a proof of principle that cytocidal action of antimalarial drugs could be measured in the $Dd2^{luc}$ parasite strain through the loss of luciferase signal following drug exposure. The loss of luciferase signal was both concentration and time dependent and has been attributed to luciferase being an unstable reporter with a half-life of approximately 1.5 hr in *P. falciparum* (Hasenkamp *et al.,* 2013). Building on this, Ullah *et al.,* (2017) developed and validated a microplate-based bioluminescence relative rate of kill (BRRoK) assay to determine the initial rate of kill of

benchmark antimalarial drugs. Briefly, the relative concentration-dependent effect of six WHO-approved antimalarial drugs were initially compared by using fold changes in EC_{50} concentrations. $Dd2^{luc}$ parasites were exposed to equal concentrations of drug that corresponds to a range of 81-0.33x EC_{50} using 3-fold dilution in a microtiter plate and incubated for six hours. The residual bioluminescence signal was read, normalized against the untreated control, and plotted against the drug concentrations (Figure 3.1). The result shows that all the drugs, except atovaquone, attain their initial maximal rate of kill at a concentration that corresponds to >9x EC_{50}. This observation agrees with the findings of Sanz *et al.*, (2012) who had earlier reported that cytocidal drugs reach their optimum killing rate at a concentration of 10xEC_{50}. The killing rate of drugs were ranked as artemisinin>chloroquine>4-methanol quinolines>atovaquone which is in agreement with what has been reported *in vivo* and *in vitro* about their relative ranking order (White *et al.*, 1997; Pukrittayakamee *et al.*, 2000 (Bahamontes-Rosa *et al.*, 2012; Le Manach *et al.*, 2013).

Subsequently, Ullah *et al.,* (2017) used the BRRoK assay to determine the initial cytocidal effects of 372 compounds of the MMV Malaria box after measuring their EC_{50} values. The $Dd2^{luc}$ parasite was exposed to fold-EC_{50} concentrations (0.33x to 9x) of the compounds. Loss of bioluminescence signal for these compounds in concentration and time dependent manner was used to compare against those for a panel of benchmark antimalarial dugs. The BRRoK assay provided a relative ranking order and not a true rate of kill, although these data are ranked with benchmarks for which the true rate of kill has been determined. This ranking also aligns with the description of minimal essential and ideal criteria for a TCP1 candidate molecule in the future SERCaP drug defined by MMV (Burrows *et al.*, 2013). As such, the BRRoK assay provides a fast and simple way of exploring the immediate cytocidal rate of kill effect of these compounds.

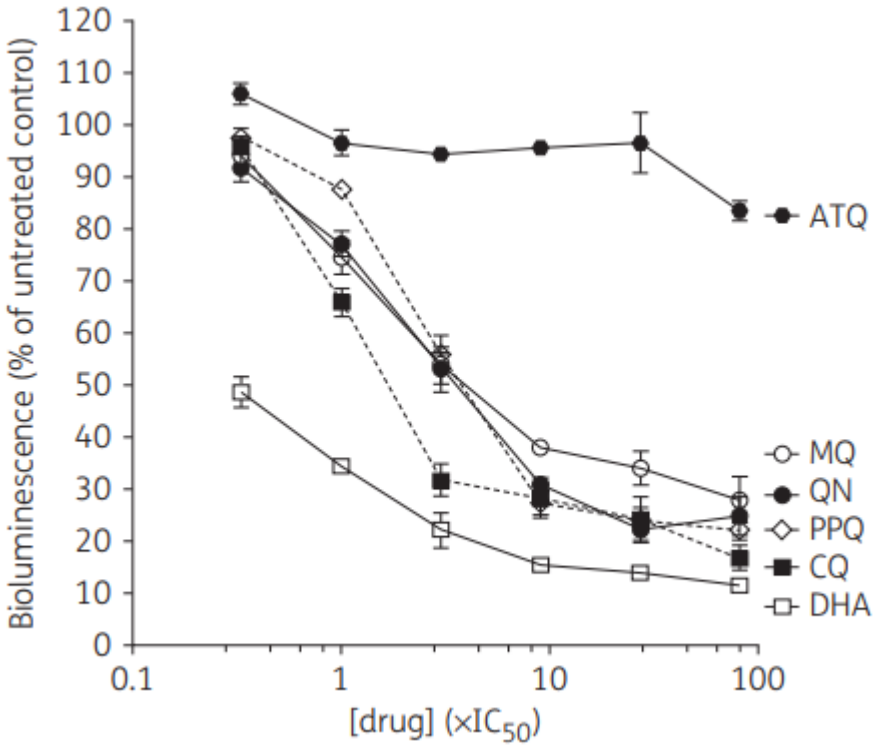


Figure 3.1: Concentration-dependent bioluminescence signal loss following fold EC_{50} of benchmark antimalarial drugs perturbation

Mean fraction of residual bioluminescence signal normalized against an untreated control after 6 hours of exposure to fold-IC_{50} of the antimalarial drugs (RLU±stdev (n=6)). ATQ, atovaquone; MQ; mefloquine; QN, quinine; PPQ,piperaquine; CQ,chloroquine;DHA, dihydroartemisinin. (Source: Ullah et al., 2017).

Moving forward, a Principle Component Analysis (PCA) was performed on the BRRoK data for four equipotent concentrations at 3 and 6 hrs endpoints to reduce the dimensionality to a single value that can be easily explore and managed. The concentration rate relationship was compressed into a new variables called principle components. The first principle component (PC1), accounted for majority of the variance (89%) in the 6 hour dataset. Subsequently, the percentage of explained variance reduced across the second principle component (PC2), third principle component (PC3) and fourth principle component (PC4) (Table 3.1). The PC1 was used to rank the initial cytocidal effect of 372 MMV Malaria Box compounds (figure 3.2), with smaller value indicating a faster acting compound, that is the lower the PC1 values, the greater the cytocidal effect. Consequently, the ranking of initial cytocidal activities of the MMV compounds was informed by comparison against the initial cytocidal effect determined for the known antimalarial drugs. This provides a surrogate information with regards to immediate

cytocidal effects of MMV compounds. Using the PC1 value estimated from BRRoK data, 53 MMV compounds were shown to exert an initial rate of kill at least as fast as chloroquine, of these, 17 compounds were shown to be at least as good as dihydroartemisinin.

Table 3.1: Estimated variance in the principle components of BRRoK data derived after 3 and 6hrs of compound exposure

	Variance Explained	Cumulative Variance Explained
	3-HOURS	
PC1	0.89	0.89
PC2	0.08	0.97
PC3	0.02	0.99
PC4	0.01	1.00
	6-HOURS	
PC1	0.86	0.86
PC2	0.11	0.97
PC3	0.02	0.99
PC4	0.01	1.00

Source: (Ullah, 2016 PhD thesis)

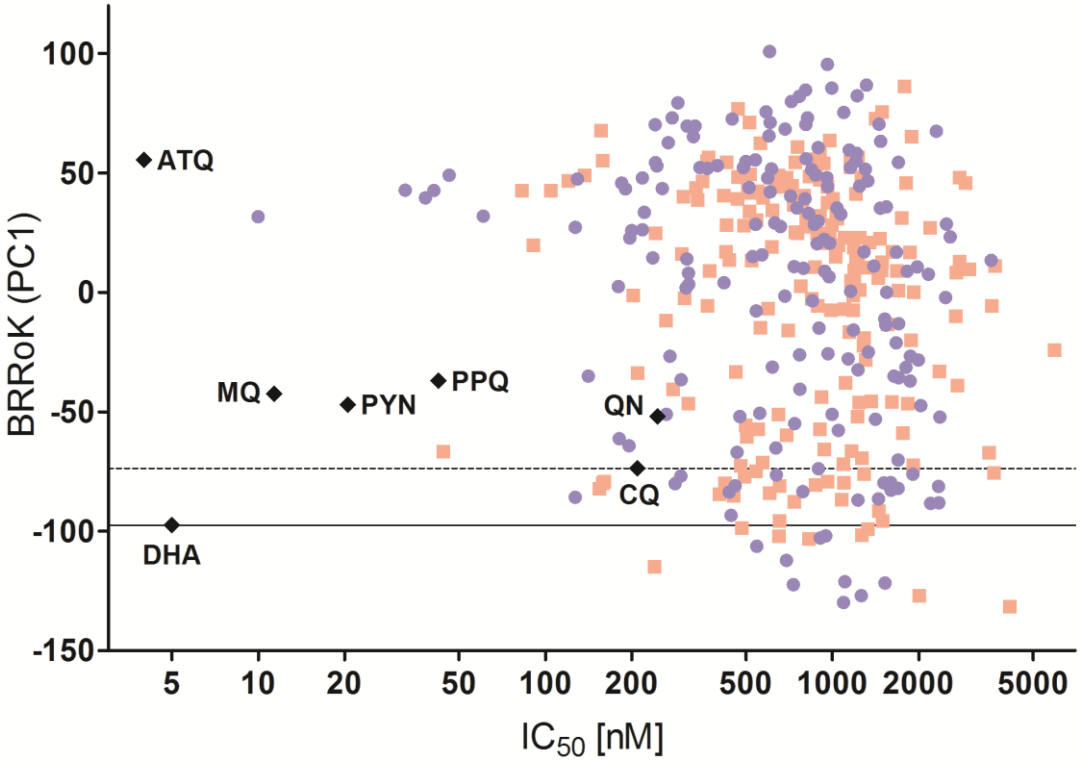


Figure 3.2: Scatter plot of BRRoK (PC1) against IC_{50} values of 372 MMV Malaria Box compounds and 7 known antimalarial drugs.
The Malaria Box compounds are indicated as pink squares and blue circles for drug-like and probe-like respectively. Benchmark antimalarial drugs are represented with black diamonds. The continuous and broken horizontal lines indicated the ideal (for dihydroartemisinin) and minimal (for chloroquine) thresholds respectively, as reported by BRRoK assay for TCP1 candidates. ATQ, atovaquone; CQ; chloroquine; DHA, dihydroartemisinin; MQ, mefloquine; PPQ, piperaquine; PYN, pyronaridine; QN, quinine. (Source, Ullah et al., 2017).

Moreover, Ullah *et al.,* (2019) provided a proof-of-principle that the Rok of antimalarial compounds is linked to their mechanism of action. This was demonstrated by comparing the BRRoK data with the predicted mode of action for the MMV compounds. This resulted in a relative ranking of PfATP4 > parasite haemoglobin catabolism > DHFR-TS > DHODH > bc1 complex targets, in order of fast to slow RoK. Also, MMV compounds were clustered together based on their related core scaffold and compared against the BRRoK data and revealed that compounds with similar chemical structures, and therefore likely targets, clustered together. This analyses showed an intrinsic rapid cytocidal action for the diamino-glycerols and 2-(aminomethyl) phenol and slow action for the 8-hydroxyquinolines, 2-phenylbenzimidazole and triazolopyrimidines scaffolds (Ullah *et al.,* 2019).

The BRRoK assay is a valuable tool to support drug discovery due to its ease of use, it can be readily scaled for high-throughput screening, and it is rapid, robust and offers an ability to differentiate between minimal and ideal TCP1 candidates. However, there are limitations in the use of this assay. Firstly, is the need to use genetically modified parasite (GM) lines that express the luciferase reporter gene. However, in Horrocks' laboratory, there is now access to another GM parasite line that express the luciferase, under the control of *Pfpcna* flanking sequences, in the more drug-sensitive NF54 line (Hmoud, 2019). The second limitation is that the temporal (trophozoite) expression of luciferase GM parasites, with poor levels of reporter expression in rings and schizonts stages. However, this could readily be addressed in transgenic parasites line using a new reporter construct with a luciferase flanked by regulatory sequences that will afford temporal expression at all/other erythrocytic stages. The third limitation which is a major setback of the BRRoK assay is the need to know the EC_{50} values. This data takes a longer time (48hrs) to measure than the BRRoK assay (6hrs), and may not be available for large compound sets or the *P. falciparum* clone being investigated. This limits the utilization of the assay for

high throughput screening of large compound set such as TCAMS library – a gap that is addressed in this thesis.

Developing a much higher throughput assay to identify rapid acting compounds is key to quickly triage thousands of antimalarial hits currently available to malaria community. In addition, the assay should incorporate a second property of potency in the triage process for rapid acting compounds. Ideally, bringing these two properties (potency and rate of kill) together can be achieved using fixed concentrations – offering a much simpler assay set-up at the same time. There is an understanding that the loss of bioluminescence when parasites are exposed to a concentration of compound relates to both the potency of compounds (in terms of access or binding to target) and RoK (intrinsic due to mechanism of action). Potency is expressed as EC_{50} and more importantly as the multiples of which are achieved in fixed concentrations (i.e. the more potent a compound, the more fold EC_{50} achieved at a fixed concentration). Sanz *et al.,* (2012) and Ullah *et al.,* (2017) reported that maximal *in vitro* RoK is achieved at 10x and 9x $EC_{50,}$ respectively.

An ideal criteria for potency for a compound of interest set here as less than 200nM, with 10x EC_{50} will be equivalent to **2µM**. A minimum criteria was set at 1µM maximum potency, with 10x EC_{50} will be equivalent to **10µM.** Therefore, two fixed concentration of 2µM and 10µM were employed here to screen for rapid and potent antimalarial compounds. The assay is now termed the modified Bioluminescence Relative Rate of kill (mBRRoK) as it utilizes two fixed concentrations of test compounds against the trophozoites stage of *P. falciparum* for six hours.

To support the development and validation of the mBRRoK assay, I provide here;

1. proof-of-principle in the use of fixed concentration assays of benchmark antimalarial (known potency and RoK determined using a range of *in vitro* RoK assays) to demonstrate the application of the mBRRoK assay.

2. validate the mBRRoK assay with larger set of compounds from MMV Malaria Box (with known BRRoK assay data for comparison).

3. explore the performance of mBRRoK assay in a second genetically modified parasite strain ($NF54^{luc}$).

3.2 Results

3.2.1 Initial proof of concept using known antimalarial drug benchmarks

In vitro rate of kill data is available for a number of antimalarial drugs (Sanz *et al.*, 2012; Ullah *et al.*, 2017; Ullah *et al.*, 2019) and are summarised in Table 3.2. These benchmarks represent a range of chemo-types with several modes of action. Using the relative rate of kill (PC1), parasite reduction ratio (PRR) and parasite clearance time (PCT) data from these *in vitro* studies, a broad classification of rate of kill can be described. A rate of kill equivalent or better than chloroquine (CQ) is defined here as **rapid** – this is in line with the target candidate profile description for a rapid acting compound by the Medicine for Malaria Venture (Burrows *et al.*, 2013). These rapid acting compounds include the endoperoxides, artemether (ART) and dihydroartemsinin (DHA). Compounds Slower than chloroquine, but with a PC1 <0 (as reported in Ullah *et al*., 2017), are described here as having a **moderate** rate of kill. These include the 4-aminoquinolines, amodiaquine (AQ) is included in this group after the initial mBRRoK data analysed as no previous data available, and piperaquine (PPQ) as well as the aryl alcohols mefloquine (MQ) and quinine (QN). Compounds with a PC1 >0 are defined here a **slow** acting, and include the napthoquinone, atovaquone (ATQ) and the antibiotic doxycycline (DOX is included in this group after the initial mBRRoK data analysed as no previous data available).

The initial proof of concept experiment was designed to explore whether an mBRROK assay would provide data that reports the correct relative order for rates of kill for these benchmark drugs as well as how the mBRRoK assay data correlates with available BRRoK data (the PC1 data reported in Ullah *et al.*, 2017). *P. falciparum* Dd2^{luc} was exposed to these benchmark drug at 2µM and 10µM for 6 hours and the residual bioluminescence signal normalized to the mean of an untreated control. All experiments were carried out as technical duplicates, with three independent biological repeat performed.

The mean and ± standard deviation of n=6 is reported in Figure 3.3A.Taking the mean normalized bioluminescence signal after exposure at 2µM and 10µM and plotting them against each other provides a standard representation used in this thesis for mBRRoK data (Figure 3.3B). Data typically falls on a diagonal from a slope of 1, or above this diagonal i.e. a compound does not typically produce a greater kill at the lower 2µM concentration exposure. Whilst, the loss of bioluminescence signal is a result of both the intrinsic rate of kill of a compound, it will also reflect the fold EC_{50} achieved at the 2 µM and 10µM - reported in Table 3.2 where the majority of compounds tested achieve at least a 10-fold EC_{50} at both concentrations tested here. Fast acting compounds typically fall towards the lower left as there is minimal residual bioluminescence after 6hr exposure at either concentration. Slower acting compounds (or those with a long lag phase) are towards the top right as they do not report a loss of bioluminescence in the 6hr assay done here. For the eight benchmarks tested here – the understanding of their relative order of rate of kill is certainly reported in this study where artemisinins> quinolines> napthoquinones. Differentiating between 4 amino-quinolines and aryl alcohols is not possible at this point. The reduced efficacy of chloroquine in the chloroquine-resistant (CQR) strain Dd2 raises the EC_{50} and consequently reduces the fold-EC_{50} that can be achieved. This is certainly compared to those for the other 4 amino-quinolines and aryl alcohols, and this may account for this rapid acting compound falling further up the slope. There is no available rate of kill data available for amodiaquine and doxycycline from these two studies. Amodiaquine shares the same apparent mBRRoK data as other 4-aminoquinolines and is termed moderate here. Doxycycline shares the same space as the slow atovaquone. This position, however, may also reflect the low EC_{50}-fold achieved at both 2 µM and 10µM (Table 3.2).

To further explore how the mBRRoK assay performs, the mean normalized bioluminescence signal at 10µM and 2µM was compared to the PC1 parameter reported in previous 6hr bioluminescence assays using this Dd2^{luc} strain (Ullah *et al.,* 2017; Ullah *et al.,* 2019). These analyses (Figure 3.3C and D), respectively, report significant levels of good linear correlation (R^2>0.9). This is expected as the relative order of their rate of kill is maintained in both assay systems. Together, these initial findings appear to provide a proof-of-principle that indicates that the mBRRoK assay will report loss of bioluminescence based on both the relative rate of kill and potency of a compound.

Table 3.2: Comparison of in vitro rate of kill data for benchmark antimalarials used in this study

Name	Abbreviation	Class	EC_{50} Dd2^{luc}	PC1[a]	Log PRR[b]	PCT[b] (hrs)	Lag phase[b]	Rate of Kill Classification	x EC_{50} at 2µM	x EC_{50} at 10µM
Artemether	ART	Endoperoxide	8.4nM	.	8	24	0	Rapid	238	1190
Dihydroartemisinin	DHA	Endoperoxide	5nM	-97.4	.	.	.	Rapid	400	2000
Chloroquine	CQ	4-aminoquinoline	200nM	-73.7	4.5	32	0	Rapid	10	50
Amodiaquine	AQ	4-aminoquinoline	26nM	.	.	.	.	Moderate	77	385
Piperaquine	PPQ	4-aminoquinoline	43nM	-37	.	.	.	Moderate	47	235
Quinine	QN	Aryl alcohol	246nM	-52	.	.	.	Moderate	8	41
Mefloquine	MQ	Aryl alcohol	11nM	-42.4	3.7	43	0	Moderate	176	880
Doxycycline	DOX	Antibiotic	3µM	.	.	.	.	Slow	0.7	3
Atovaquone	ATQ	Naphthoqui-none	4nM	55.4	2.9	90	48	Slow	500	2500

***a**, Ullah et al.,(2017); **b**, Sanz et al., (2012); **.**, no data available from these studies*

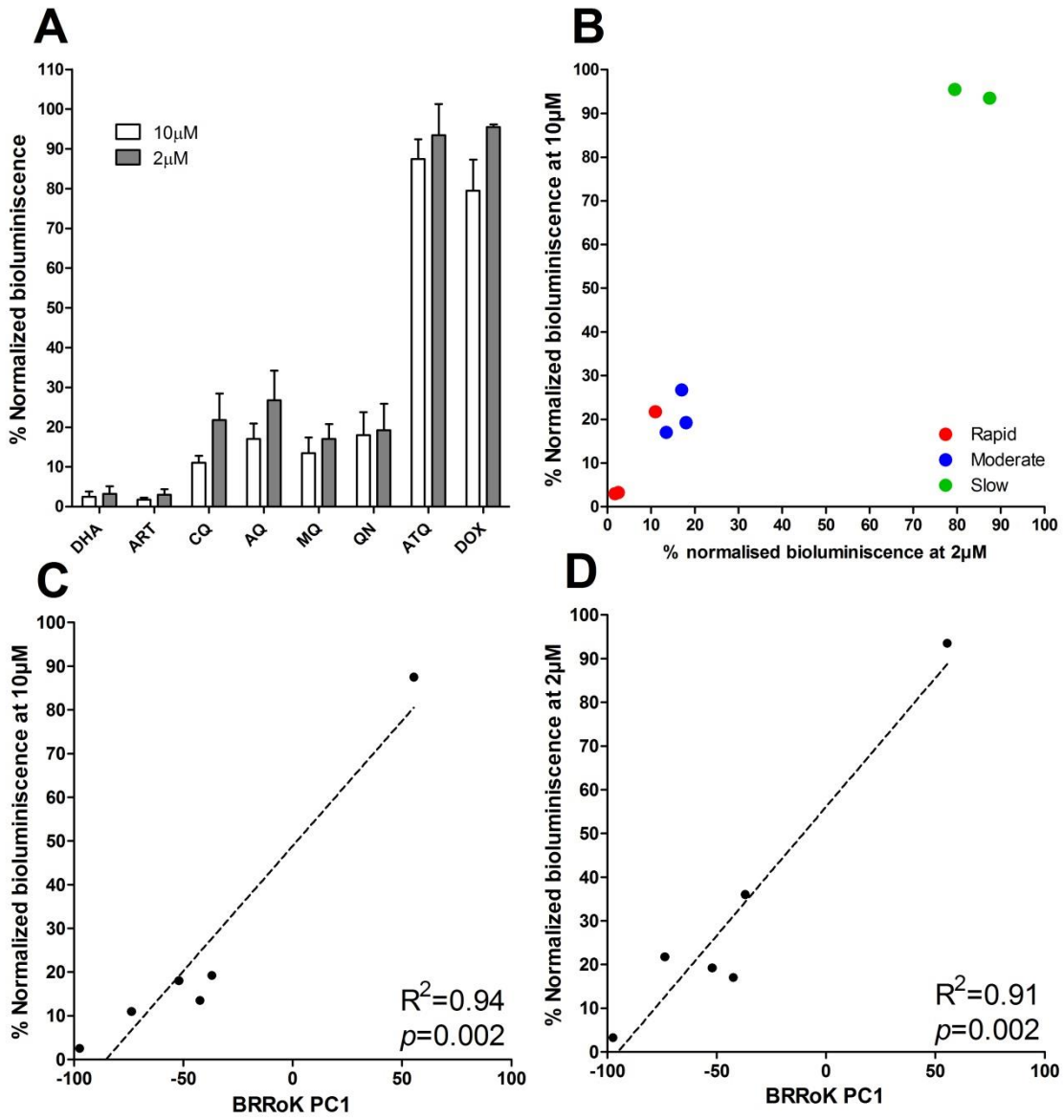


Figure 3.3: Establishing a proof of concept for mBRRoK using benchmark antimalarial drugs.

(A) Bar chart reporting the mean and stdev (n=6) of normalized bioluminescence signal after 6 hrs exposure to the indicated compound at 10μM (clear) and 2μM (grey). (B) Comparison of the mean normalized bioluminescence signal at 10μM and 2μM to provide a standard representation of mBRRoK data in this thesis. The position of benchmark antimalarial is shown using a key based on their relative in vitro rate of kill (see Table 3.2). Linear regression analyses of mean normalized bioluminescence signal at 10μM (C) and 2μM (D) against the available BRRoK PC1 parameter for six benchmarks antimalarial tested here. Abbreviations for compounds are reported in Table 3.2.

3.2.2 MMV Malaria Box compounds: validation of the mBRRoK assay

The initial proof of concept was expanded with the pool of compounds tested within the BRRoK assay. Ullah *et al*., (2017) reported the relative rate of kill for 372 compounds in the MMV Malaria Box. Here, 100 compounds from the MMV Malaria Box were selected based on a range of characteristics, including; predicted rate of kill (rapid, moderate and slow from PC1 data reported in Ullah *et al.*, 2017) and groups of compounds related by chemo-type as well as predicted mode of action (Ullah *et al.*, 2019). The selection also recognised that samples that were running out could not be used as sufficient repeats of data would not be generated for analysis. A summary table for these 100 MMV Malaria Box compounds is provided in Appendix 1.

Using the same experimental approach as described above, a comparison of mean normalized bioluminescence signal of n=6 (technical duplicates with three independent biological repeats) after exposure to 10µM and 2µM is reported in Figure 3.4. Each MMV Malaria box compound is shown as a grey filled circle, with the mBRRoK antimalarial benchmarks, colour-coded for their rate of kill, overlaid.

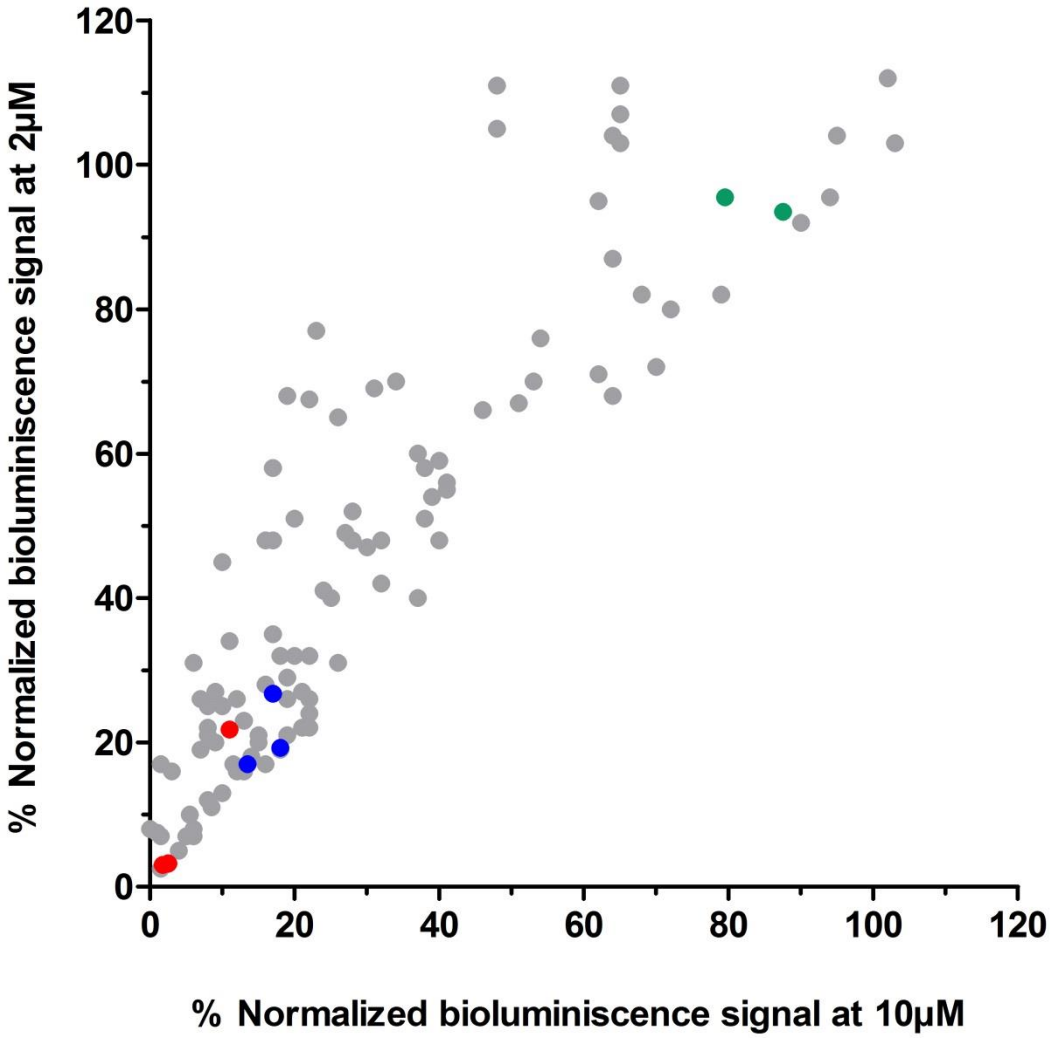


Figure 3.4: mBRRoK graph for 100 MMV Malaria Box compounds
Comparison of the mean normalized bioluminescence signal at 10µM and 2µM from mBRRoK assay data of 100 MMV Malaria box compounds (grey filled circles). The position of benchmark antimalarials is shown using a key based on their relative in vitro rate of kill (see Table 3.2 and Figure 3.3B). Each data point represents the mean (n=6).

As expected based on the range of PC1 data available, the MMV Malaria Box compounds are distributed over this "mBRRoK graph". The position of the antimalarial benchmarks provides position markers within this dataset to start making predictions of a compounds' *in vitro* rate of kill. To explore this prediction, the 100 MMV Malaria Box compounds were assigned a rapid, moderate or slow rate of kill classification based on the PC1 parameters defined above. Just over half were designated moderate (PC1 falls between -73 and 0), with 31 rapid (PC1<-73)

and 17slow (PC1>0) (Figure 3.5A). The mBRRoK graph for these data with colour coding was plotted (Figure 3.5B).

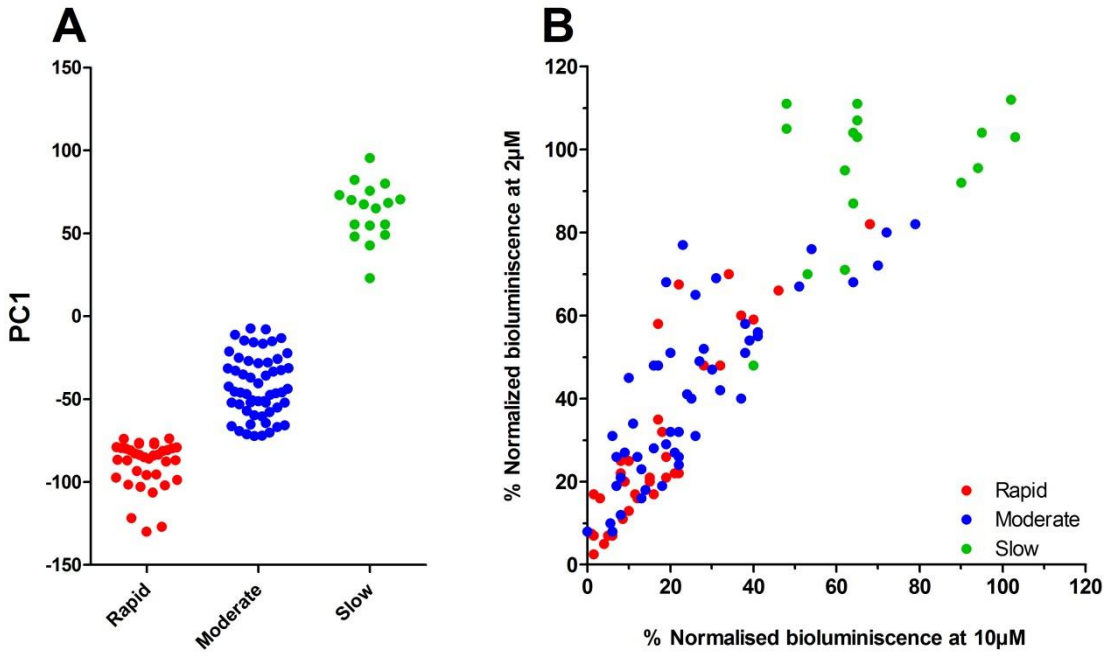


Figure 3.5: Exploring predictions of rate of kill mBRRoK graph
(A) Dot plot reporting the PC1 (and thus classification of rate of kill) for the 100 Malaria Box compounds used in this study. (B) Replotting the mBRRoK graph from Figure 3.4 with the class of rate of kill for each MMV Malaria box compound reported on the graph. Note: the antimalarial drug benchmarks have been removed from this representation of Figure 3.4.

With the larger set of data, there appear to be some interesting observations;

1 The slow acting MMV malaria Box compounds are almost exclusively clustered in the top right, within the region demarked using the ATQ and DOX benchmarks.
2 The majority of rapid acting compounds fall in the lower left region, along with the artemisinin benchmarks. There are, however, about one third of compounds that are position further up the gradient.
3 Moderately acting compounds occupy most of the gradient, albeit with a focus on the centre. These compounds are more likely to overlap with the rapid compounds rather than the slow acting compounds.
4 There are singleton examples of rapid and slow acting compounds that appear in the wrong position on this mBRRoK graph based on PC1 data.

As with the antimalarial drugs, the mean normalized bioluminescence signal at 10µM and 2µM was compared to the reported MMV Malaria Box compound PC1 parameter (Ullah *et al.*, 2017; Ullah *et al.,* 2019). These analyses (Figure 3.6A and B), respectively, report significant linear correlations, although the level of correlation (R^2 of 0.5-0.54) are much lower than those for the antimalarial benchmarks (Figure 3.3C and D). This likely reflects that the mBRRoK mean normalized bioluminescence signals at 10µM and 2µM represent both the rate of kill and potency of a compound, whereas the PC1 data is from a BRRoK assay that only explores the rate of kill. The generally lower potency of the MMV Malaria Box compounds compared to antimalarial drugs means that the 10µM and 2µM concentrations likely do not achieve at least a 10-fold EC_{50} for most of the MMV Malaria Box compounds – and this effect of lower potency compounds contributes to the lower correlation with PC1 than achieved using the antimalarial benchmarks.

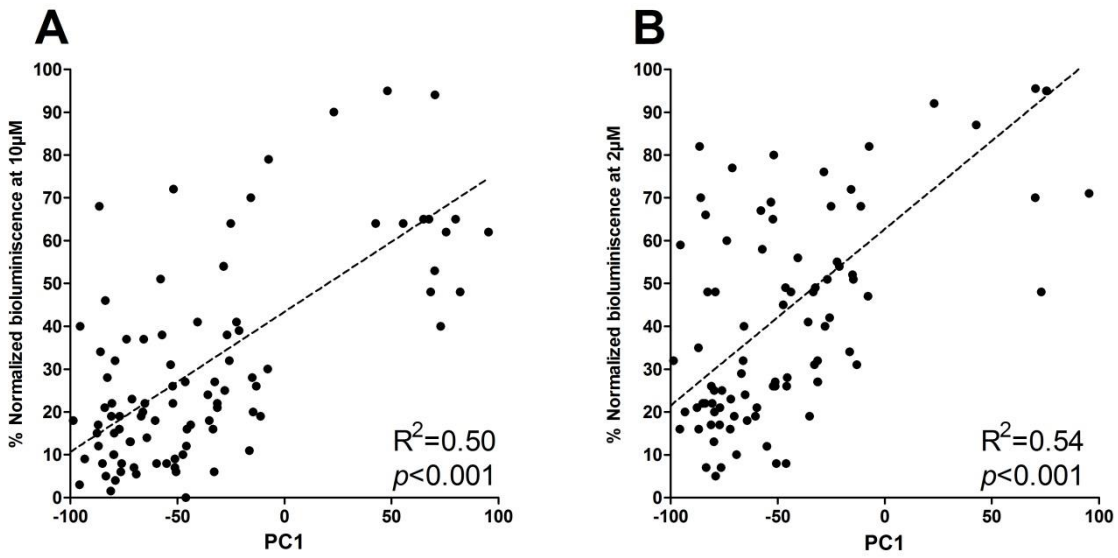


Figure 3.6: Correlating mBRRoK and BRRoK data for the MMV Malaria Box compounds *Linear regression analyses of mean normalized bioluminescence signal at 10µM (A) and 2µM (B) against the available BRRoK PC1 parameter for the 100 MMVMalaria Box compounds tested in this study.*

3.2.3 Determination of the sensitivity and specificity of the mBRRoK assay

Sensitivity and specificity are two metrics that are employed to ascertain the validity of results yielded by a screening test. Sensitivity is typically defined as the ability of a screening test to correctly identify true positives, whilst specificity is typically defined as the ability of the assay to correctly identify true negatives to a reference standard (Trevethan, 2017). Here, the sensitivity and specificity of the mBRRoK assay was determined to provide a rational approach in defining the thresholds of the bioluminescence signal that will be used as cut off points later in other drug discovery libraries. Sensitivity in the context of this study is defined as a measure of the correct identification of a fast rate of kill compound, whilst specificity is a measure of the correct elimination of slow compounds.

The objective here is to define the thresholds of normalized bioluminescence signal after exposure to 2 µM and 10µM to enable a plot of box on the mBRRoK graph within which

candidates that are considered likely to have a rapid rate of kill will occupy. To complete this task the following approach was undertaken;

1. Using the mean normalized bioluminescence signal at either 2 µM or 10µM, thresholds were applied at 10 to 50% at 10% increments. These then defined lists of MMV Malaria Box compounds and four benchmark controls that fell on either side of these thresholds. Those below the increment threshold were regarded as an mBRRoK prediction as a fast acting compound.
2. Two definitions of the true fast rate of kill compounds were used here to explore differences between a high threshold of discovery and a low threshold of discovery. The first high threshold criteria is based on the PC1 value for chloroquine (PC1 of -73.7). This threshold establishes whether the mBRRoK assay correctly defines a compound activity as falling in the TCP1 criteria- i.e. at least as fast as chloroquine. A second, lower threshold is based on a PC1 value of -47. This PC1 value encompasses the initial rate of kill data for the quinoline drugs (mefloquine, amodiaquine and quinine) included in the selected benchmarks and shown to not be clearly resolved from CQ in the initial mBRRoK analysis. Of note, is that all of these quinoline drugs are judged as having a rapid rate of kill using the 48 hours invasion assay of Linares *et al.*, (2015).
3. Using the two lists of compounds provided for each 10% increment for both the 2 µM or 10µM concentrations, these lists of compounds were then compared against the BRRoK PC1 values (high and low threshold). Using these data, the following approach was used to determine sensitivity and specificity when compounds were assorted into one of four cells;
    - True positive – below the bioluminescence threshold and with PC1 data lower than the high (<-73.7) or low (<-43) PC1 threshold

- False positive - below the bioluminescence threshold and with PC1 data greater than the high (<-73.7) or low (<-43) PC1 threshold
- True negative - above the bioluminescence threshold and with PC1 data greater than the high (<-73.7) or low (<-43) PC1 threshold
- False negative - above the bioluminescence threshold and with PC1 data lower than the high (<-73.7) or low (<-43) PC1 threshold

The following formulae were used; Sensitivity = $[N_{TP}/(N_{TP} + N_{FN})]$ *100 and Specificity = $[N_{TN}/ (N_{TN} + N_{FP})]$ *100. The effect of where the cut-off for the normalized bioluminescence signals in determining the sensitivity and specificity of the mBRRoK assay are plotted in Figure 3.7. Figures 3.7A and B use the higher threshold of PC1<-73.7 to define a true fast acting compound (with A using the 2µM and B the 10µM bioluminescent data), Figures 3.7C and D use the lower threshold of PC1<-47 to define a true fast compound. All graphs report that as the remaining bioluminescence signal after 6hr of action is increased, the assay is more likely to correctly identify fast acting compounds (increase in sensitivity, filled circles and dotted line) but is also likely to include more compounds that are not fast (false positives)and thus the specificity of the assay falls (open circles). This is the same whichever threshold of determining a true positive is used as well as the concentration of the compound being tested.

To take the assessment of the mBRRoK assay forward, the bioluminescence signal at which the specificity and sensitivity intersected on Figures 3.7A to D were taken to define the regions of interest on the mBRRoK graphs (Figure 3.7E). The rationale being that these intercepts reflect the position where each quality is optimum compared to the other. Thus, a 20x25 box was defined as capturing the mBRRoK fast acting hits based on the higher (chloroquine or better) threshold and a 25x45 box defines the mBRRoK fast acting hits based on the low (quinoline or better) threshold. Table 3.3 reports the numbers of compounds each box contains, as well as the

sensitivity and specificity of those criteria based on the BRRoK PC1 data. In addition, a True Discovery Rate was determined ($TDR=[N_{TP}/(N_{TP}+N_{TN})]*100$)

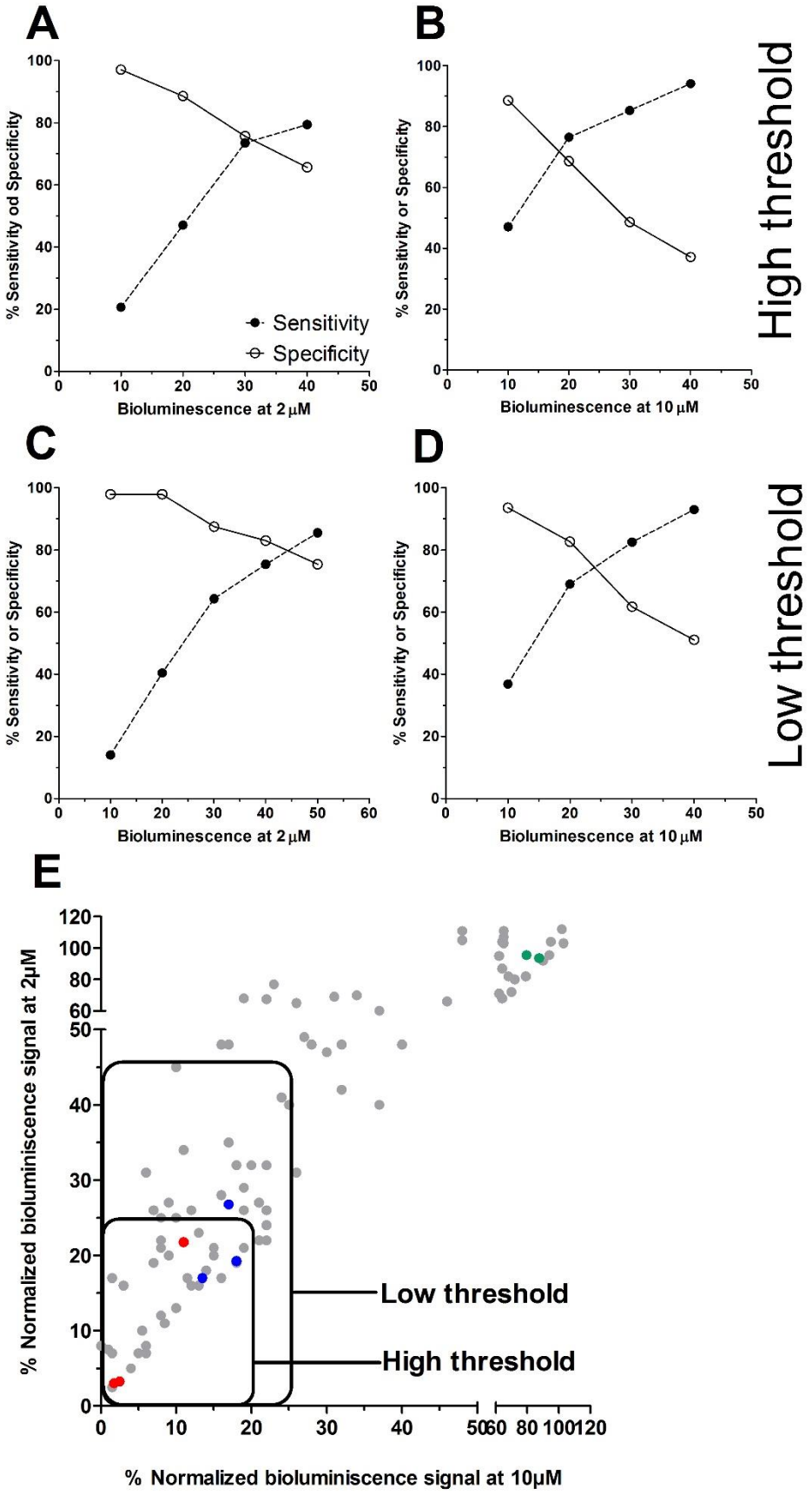


Figure 3.7: Exploring the sensitivity and specificity of mBRRoK assay.

Using increments of 10% of the normalized bioluminescent signal after exposure to 2µM (A and C) and 10µM (B and D) of the 100 MMV Malaria Box compounds and four antimalarial benchmark drugs, the sensitivity and specificity of the mBRRoK assay under those conditions were plotted. The threshold for a true hit used two definitions; a high threshold based on the compounds being at least as fast a CQ in the BRRoK assay (A and B) or a low threshold where compounds were at least as fast as the quinolone class of drugs (C and D). Using these parameters, boxes that identify regions of interest on a mBRRoK graph (this is an adapted version of Figure 3.3) based on these two thresholds. The numbers of compounds identified, specificity, sensitivity and true discovery rate for each box is shown in Table 3.3

Table 3.3: mBRRoK assay parameters at high and low threshold cut-offs

	# Hits[a]	% Sensitivity	% Specificity	% True Discovery Rate
mBRRoK high threshold[b]	37	75	82	81
mBRRoK high threshold[b]	50	84	70	73

a, out of 104 compounds; b, see Figure 3.7E

Therefore, as the "hits" box on the mBRRoK graph is made larger, more compounds are identified as potentially being fast acting. The analysis presented in Table 3.3, which uses the *in vitro* rate of kill for CQ or better as the definition of a true hit, suggests that the inclusion of the additional hits as the "hits" box gets larger does capture fast-acting compounds and so the sensitivity (ability to identify true hits) increases. However, the trade-off is that many of the additional compounds are not true hits, thus, the true discovery rate falls off and the specificity (ability to discriminate true negatives) declines.

3.2.4. Exploring the performance of mBRRoK in a NF54^{luc} transgenic line

To date, all BRRoK and mBRRoK data were derived using the Dd2^{luc} transgenic line. Another PhD student in the Horrocks laboratory has introduced the same luciferase expression cassette used in Dd2^{luc} into the NF54 parasite line (Hmoud, 2019 PhD thesis). The *pcna* 5' untranslated region (UTR)-luciferase-*pcna* 3'UTR cassette is present in NF54^{luc} as an episomal plasmid, using WR99210 antifolate as a selection drug. Of note is that NF54^{luc} is a Chloroquine sensitive (CQS) strain yet has the same trophozoite-specific expression of the luciferase reporter as does the CQR Dd2^{luc} line. NF54^{luc} was made available to this study to enable a comparison of the mBRRoK assay performance in a second genetically-distinct line. Ullah *et al.,* (2017) have previously shown a concentration dependent loss of bioluminescence signal following exposure of Dd2^{luc} parasite clone to fold EC_{50} concentrations of benchmark antimalarials (see figure 3.1). To extend this observation to NF54^{luc} (CQS), EC_{50} data were developed for four benchmark antimalarial drugs (dihydroartemisinin, chloroquine, mefloquine and atovaquone) by using 48 hours MSF assay described in section 2.4. The EC_{50} values were determined from log dose-response curves (Figure 3.8). Subsequently, the relative initial cytocidal effect of the four antimalarial drugs were determined using BRRoK assay developed by Ullah *et al.,* (2017). Here, NF54^{luc} parasites were exposed to a 3-fold serial dilution of 9xEC_{50} to 0.33xEC_{50} concentration series for 6 hours. The mean ± stdev bioluminescence signal was normalized to an untreated control and plotted against drug concentrations (Figure 3.9). Comparison of the data indicates the expected relative ranking order of dihydroartemisinin > chloroquine > mefloquine > atovaquone and agrees with the relative order of rate of kill described for the same drugs *in vivo* and *in vitro* (White *et al.,* (1997; Pukrittayakamee *et al.,* 2000; Bahamontes-Rosa *et al.,* 2012; Sanz *et al.,* 2012; Le Manach *et al.,* 2013; Linares *et al.,* 2015; Ullah *et al.,* 2017).

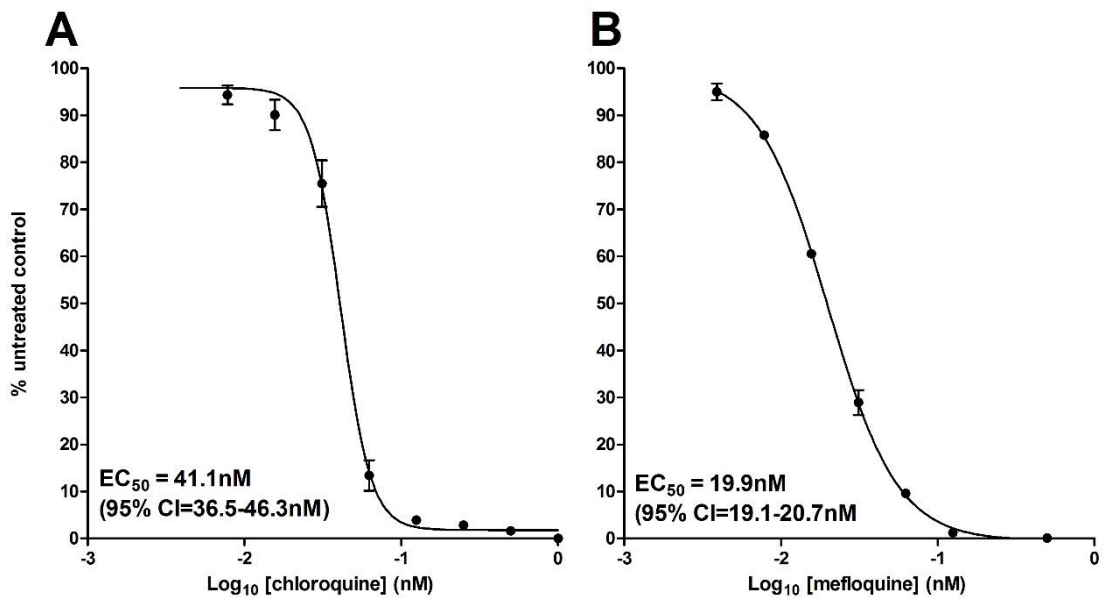


Figure 3.8: Exemplars of log concentration- response curves for the benchmark antimalarials, chloroquine and mefloquine against NF54^{luc} parasite clones.
Each data point represents the mean with standard deviation (from three biological repeats, n=9) indicated by error bars.

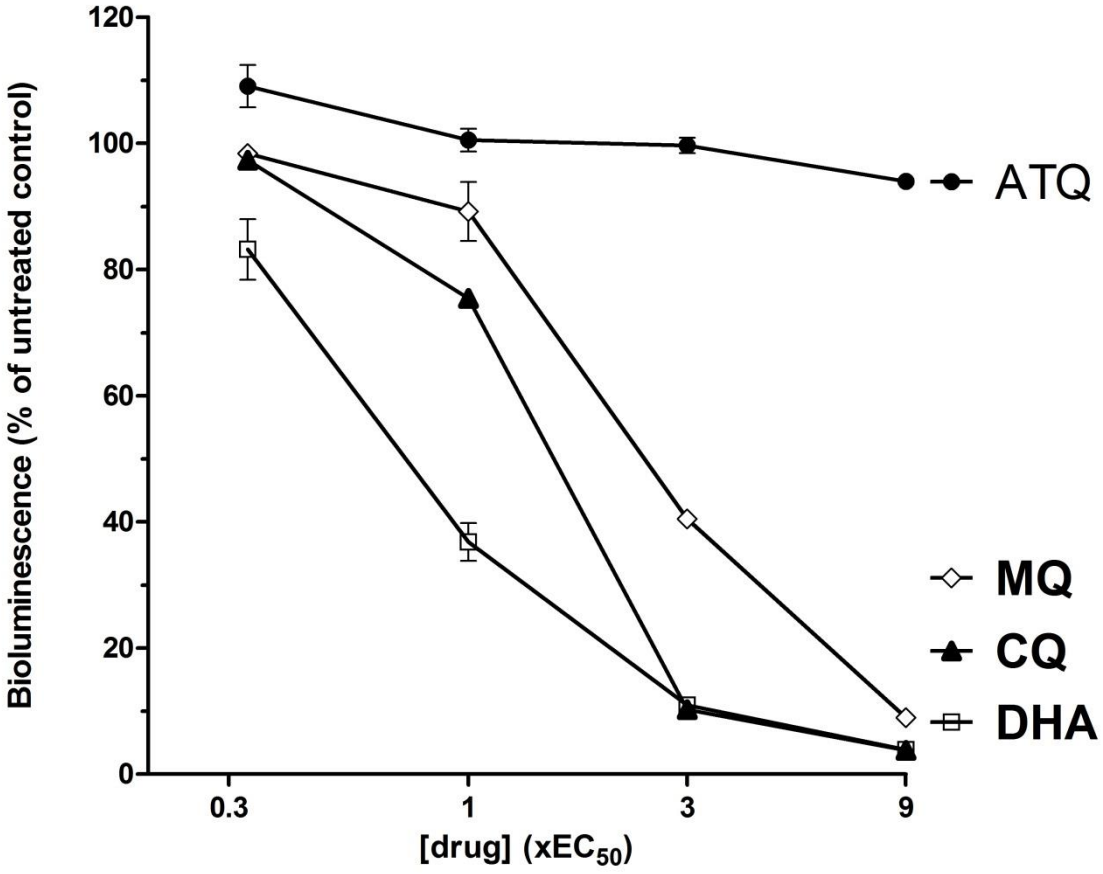


Figure 3.9: BRRoK assay of benchmark antimalarials in NF54^{luc}.
The mean bioluminescence signal (normalized against an untreated control) remaining after a 6 hours exposure of P. falciparum NF54^{luc} to the indicated fold-EC$_{50}$ of each drug is plotted. Error bars represent mean ± SDs from three biological replicates. ATQ, atovaquone; CQ, chloroquine; DHA, dihydroartemisinin; MQ, mefloquine.

Moving forward, the performance of mBRRoK assay against NF54^{luc} parasite line was undertaken. For this comparison, 66 of the 100 compounds from the MMV Malaria Box has sufficient materials remaining for this analysis. NF54^{luc} was exposed to two fixed concentrations (10µM and 2µM) of the test compounds for 6 hours. The mean and stdev of the normalized bioluminescent signals (n=6, technical duplicates and three biological repeats) are recorded in appendix 2. The percentage normalised bioluminescence signal at 10µM and 2µM concentrations were plotted to produce the standard mBRRoK plot (Figure 3.10A). Here the 66 MMV Malaria Box compounds (grey circles) with the rate of kill colour-coded antimalarial benchmarks are shown. As for Dd2^{luc}, the antimalarial benchmarks are projected into the

expected space based on their rate of kill. Interestingly, CQ, in this CQS strain achieves the necessary fold EC_{50} at 10µM and 2µM to move further down to the left and separates from the moderate rate of kill aryl alcohols of QN and MQ. Removing the antimalarial benchmarks, and colour-coding the MMV Malaria Box compounds for a rate of kill classification based on their $Dd2^{luc}$ BRRoK data (PC1 values) allows us to produce Figure 3.10B. Critically, the key features of this chart relating to the relative position of fast and slow acting compounds holds. What is evident, however, is that there are a number of fast acting compounds, predicted in this mBRRoK assay to be slow, and this issue will be picked up in the discussion.

As expected, there were significant correlation between the screening data for the two parasite strains at 10µM (figure 3.10C) and 2µM (figure 3.10D) concentrations. The 10µM data reflect a greater discriminating power at excluding the slow-acting compounds. Furthermore, using the most stringent sensitivity and specificity threshold of 20% x 25% bioluminescence cut off, compounds were divided into four groups (see figure 3.7 for details). A total of 35 compounds (more than half) were identified to have initial RoK at least as fast as chloroquine in $Dd2^{luc}$ and $NF54^{luc}$ with 31 compounds common to both parasite strains (see appendix 2 for details). This results shows that the initial RoK for the MMV Malaria Box compounds appears to be similar for the two parasite strains. This concept will be explained further in chapter 5 of this thesis.

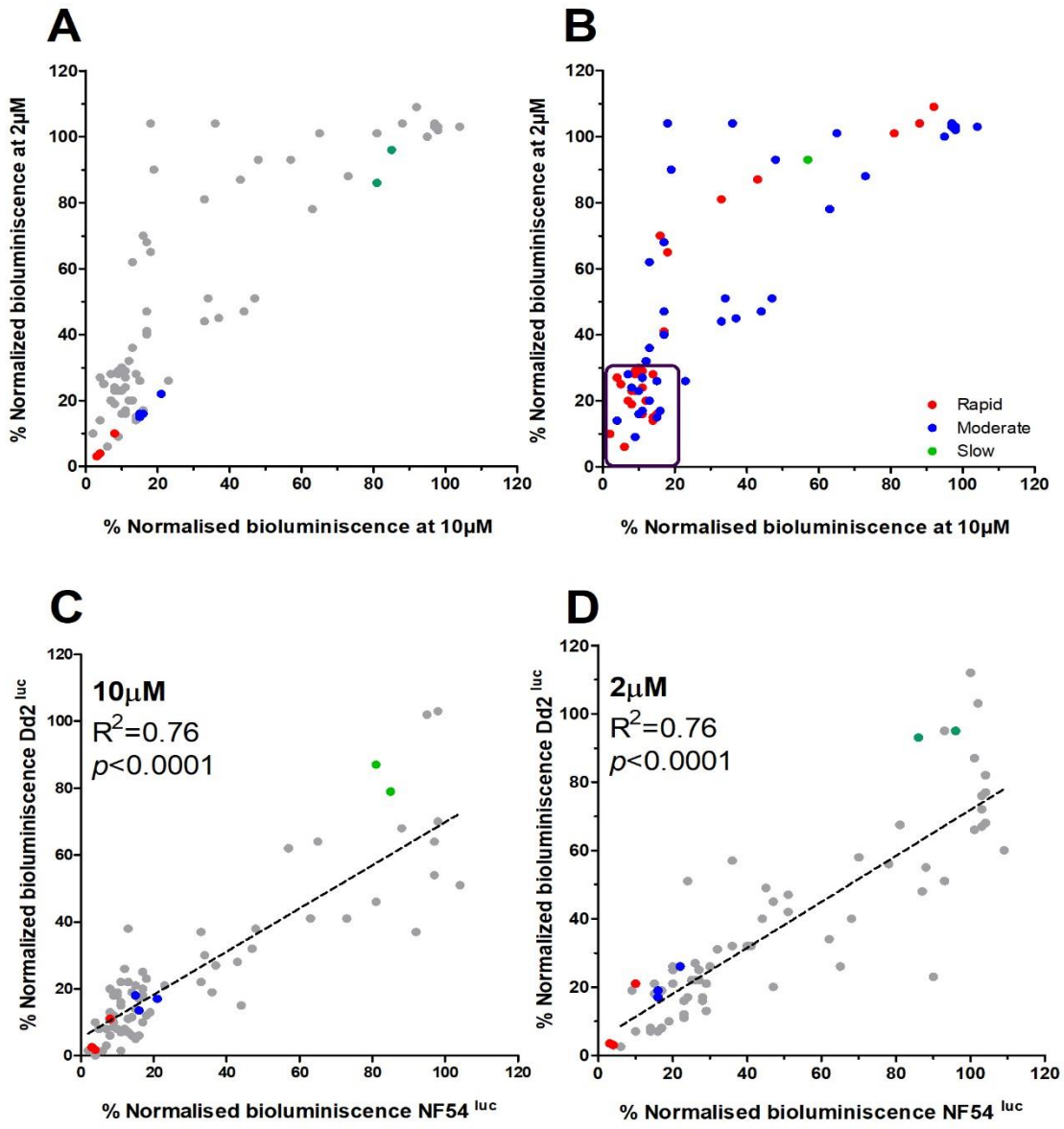


Figure 3.10: Exploring the performance mBRRoK assay in NF54^{luc} parasite line.
(A) Represent mBRRoK graph for mean (n=6) normalized bioluminescence signal at 10µM and 2µM for 66 MMV Malaria Box compounds (grey filled circles) against the NF54^{luc} parasite clone. Benchmark antimalarial drugs are shown using a key based on their relative in vitro rate of kill (see table 3.2 and figure 3.3B). (B) Replotting the mBRRoK graph from (A) with class of rate of kill for each MMV Malaria Box compounds reported on the graph (note that the benchmark antimalarial drugs have been removed from the plot). Linear regression analyses for correlating the mean normalized bioluminescence signal at 10µM (C) and 2µM (D) of mBRRoK Dd2^{luc} data against NF54^{luc} data for the 66 MMV Malaria Box compounds tested against NF54^{luc} parasite line.

3.3 Discussion

A rapid *in vitro* screening assay to quickly triage the thousands of antimalarial hits for fast-acting chemo-types offers an opportunity to triage compound libraries based on both their potent and rate of initial cytocidal action. One such assay is the BRRoK assay developed by Ullah *et al.,* (2017). The assay can determine the initial cytocidal effect of antimalarial compounds after six hours of parasites exposure. One major drawback that limits the scaling of the assay for high throughput screening is the need to know the EC_{50} values of the test compounds (48 hours MSF assays) before commencing with the determination of the speed of action. To enable scale-up, a modified BRRoK assay that utilizes two fixed concentrations was developed here to meet this challenge. The mBRRoK assay explores a compound's RoK and potency together in a format that is much more amenable to a high throughput screening of large compound libraries. The principle is that loss of bioluminescence signal following parasites exposure to the test compound will be proportional to the rate of kill (greater in fast acting compounds) and potency (indicated as reaching at least 10x EC_{50} in either of the fixed concentration).

An initial proof of concept of this simpler approach was demonstrated by exposing the parasites to two fixed concentration of the eight benchmarks antimalarial with available EC_{50} and RoK data. The mBRRoK assay described here was able to rank the drugs' initial rate of kill in the order of endoperoxides > quinolines > naphthoquinone/antibiotics as expected (see Figure 3.3 B). These findings are in agreement with what has been reported in the literature about the *in vitro* cytocidal action of these antimalarial drugs (Sanz *et al.*, 2012; Ullah *et al.,* 2017; Ullah *et al*., 2019). Interestingly, analysis of this first set of data suggested that bioluminescence signal loss for quinine and mefloquine were greater than that of chloroquine at 2µM. This illustrates that the mBRRoK assay considers RoK and potency together in the loss of bioluminescence (whereas BRRoK compensates for the potency by using equi-potent EC_{50} concentrations). This

suggests that sufficient EC_{50} folds for the optimum rate of kill for chloroquine (EC_{50} *c*. 200nM) were not achieved at 2 µM as against that of mefloquine (EC_{50} of *c*. 40nM) and this represents a limitation in the mBRRoK when attempting to estimate a RoK for a low potency compound. Also of note is that whereas Linares *et al.,* (2015) could not differentiate between two fast-acting compounds (artemisinin and chloroquine) in their flow cytometry based assay, mBRRoK, like BRRoK, assay could demonstrate a difference between these two important benchmark drugs. Also, it was shown that whilst doxycycline and atovaquone have a vast difference in X EC_{50} achieved for each drug using the fixed concentrations as atovaquone is some 500X more potent than doxycycline, both, as expected have a negligible immediate cytocidal effect. Both drugs have lag times and are not initially cytocidal. Ullah *et al.,* (2017) observed similar killing profile for atovaquone in which 6 hours window of parasites exposure to the drug did not affect loss in bioluminescence signal. Though multiples of EC_{50} folds concentration was achieved for atovaquone, the temporal peak luciferase expression at trophozoites stage in $Dd2^{luc}$ parasites (Wong *et al.,* 2011; Hasenkamp *et al.,* 2013), limit the possibility of extending the assay readout time. Although, Sanz *et al.,* (2012) *in vitro* PRR assay demonstrated that atovaquone was able to reach its optimum killing rate at a concentration corresponding to x10 EC_{50}, however, this was only after 90 hours of exposure. The lag time observed with doxycycline likely reflect that the drug is an antibiotic, likely targeting apicoplast function, and is used as prophylactic rather than for treatment of an infection. A similar very slow killing rate profile was reported for azithromycin (another antibiotic drug used as a malaria prophylactic drug) by Linares *et al.,* (2015).

To further establish this concept, the loss of bioluminescence signal at 10µM and 2µM (modified BRRoK assay) indicated a strong correlation with PC1 values (Ullah *et al.,* 2017) for the benchmark antimalarial (Figure3.3 C and D), although there do appear to be some limitations in the discrimination between the quinolines; chloroquine, mefloquine and quinine.

Overall, this simpler assay appears to work well in discriminating and ranking the benchmark antimalarials but provides data distinct to the standard BRRoK or *in vitro* PRR assays as the effect of potency also affects the loss of bioluminescence signal. That said, this modified BRRoK assay takes only 6 hours and performed as well as that of Linares *et al.*, (2015) which also did not discriminate between quinolines but required 2-4 days to complete. This initial proof of concept indicates that the hypothesis of loss of bioluminescence signal directly correlates with potency and RoK for the fast-acting antimalarial. The modified BRRoK assay based on two fixed concentration is a simpler way to quickly identify the fast-acting compounds (TCP1 candidates) based on their initial rate of kill.

To access the performance of mBRRoK with reference to the standard BRRoK assay, the percentage normalized bioluminescence signal at 10µM (A) and 2µM (B) were compared with the PC1 (BRRoK) data (Figure 3.6). There was a significant correlation between the two parameters, however, this correlation was less than that of benchmark antimalarials reported in Figure 3.3. The difference might be due to two reasons. First, the benchmark antimalarial are all potent, having EC_{50} values less than 250nM (except for doxycycline that has an EC_{50} of 3µM) and will therefore always be used at a concentration of close to, or greater than, 10x EC_{50} at both concentrations tested and therefore all likely be maximally active *in vitro*. In the BRRoK assays, issues with variations in EC_{50} are not apparent based on how the concentrations are equipotent. Secondly, the BRRoK PC1 values were based on four different concentrations of data, covering fold-EC_{50} concentrations range between 0.33 to 9 x EC_{50} for all matched compounds. This represents a wider range of data over more sampling points as opposed to 10µM and 2µM data representing only two concentrations and different fold-EC_{50} for different compounds.

In order to further explore the performance of the modified BRRoK assay in relation to the standard BRRoK assay, the PC1 values of the 100 MMV Malaria Box compounds were

explored. Compounds were ranked based on a rapid, moderate, slow criteria and then screen in mBRRoK and how these compounds distributed within the space specifically explored. Importantly, it was confirm that rapid compounds are typically found in the bottom left of the distribution. Of a note is that slow compounds almost exclusively are found in the top right and the moderate compounds have a wider distribution. Whilst simple to categorise the shift from bottom left to top right as just a measure of RoK (fast to slow), this is not straight forward as the impact of potency (and thus how many fold EC_{50} are achieved) will affect this. This is perhaps shown best when comparing the red (rapid) and green (slow) compounds. One of the 16 slow compounds falls at the 50% boundary of the x and y axis, with the remainder all above and to the right. Whilst for some compounds, a 10 fold EC_{50} may not be achieved to reach its maximal RoK, the intrinsic RoK is slow anyway and will therefore always fall to the top right as minimal loss of bioluminescence is observed. About one third of the rapid (red compounds), however, do fall above the same 50%-50% axis split. Here, rapid compounds are likely seen, but also less potent compounds – where the mBRRoK output is less than maximum kill against an intrinsic rapid RoK and thus a less than maximal loss of bioluminescence.

To further explore the correlation between mBRRoK and BRRoK, the sensitivity (ability to correctly identify rapid acting compounds) and specificity (ability to disregard slow acting compounds) was employed. Two thresholds of "fast acting" were explored – defined as a PC1 of chloroquine (-73.7) or less or a PC1 of a quinolone (i.e. < 43 based on the PC1 for mefloquine). Different mBRRoK parameters were tested and a final future selection criteria selected. This criteria defines a 20x25 box on the mBRRoK plot (high stringency box on Figure 3.7E) that shows high sensitivity (75%) and specificity (82%) and a true discovery rate of 81%. Importantly, by reducing the complexity of the BRRoK assay to the mBRRoK assay for a high throughput screen, 81% of true fast acting RoK compounds can still be identified in a high throughput format.

To understand why some 20% were missed, it was considered whether these were likely compounds that whilst having a rapid RoK, they were also less potent. Using the same low and high threshold parameters from Figure 3.7, compounds were designated to fall either inside (in) or outside (out) of the hits box. As expected, and irrespective of the stringency of the threshold to define rapid kill, the PC1 of hits inside the box were significantly lower than of those outside (Figure 3.11 A and C). The PC1 of compounds outside of the box extend to the full range of PC1. Using an hypothesis that compounds that were designated rapid in BRRoK, and not discovered in the mBRRoK (red boxes on chart) may not be identified as rapid in mBRRoK as they are less potent and therefore do not achieve the fold EC_{50} to effect the maximal kill effect. Interestingly, exploring this with either the low or high threshold for defining rapid action in the BRRoK assay, there were no significant differences (ANOVA with Dunnets post-test, all $p>0.05$) between the EC_{50} of the different groups of compounds (Figure 3.11 B and D).

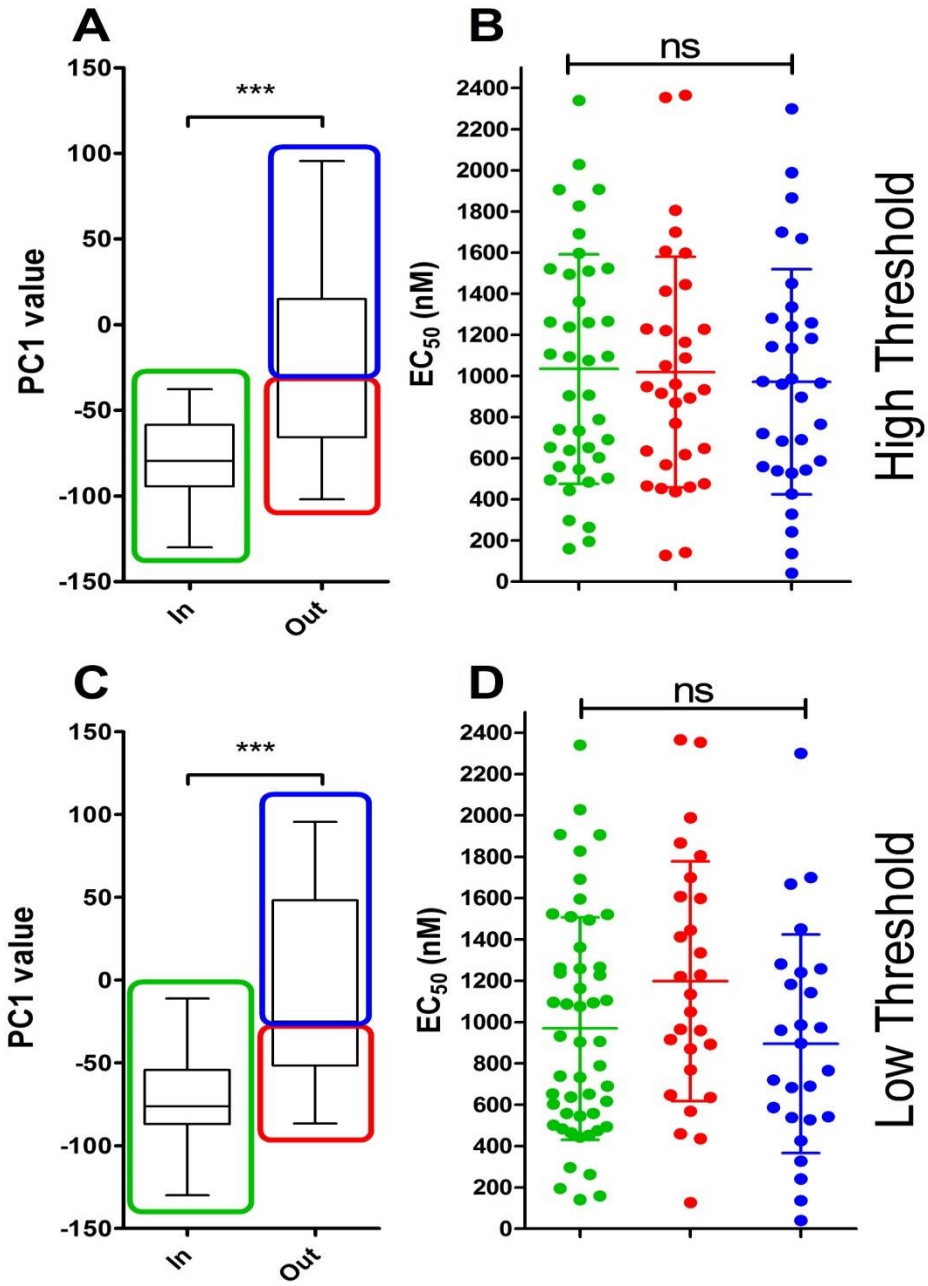


Figure 3.11: Box and whiskers plots showing the distribution of MMV Malaria Box
Compounds predicted to have chloroquine-like (high threshold) and quinoline-like activities (low threshold).The plots A and C show the distribution of PC1 data from BRRoK assay (Ullah et al., 2017), using the parameters of mBRRoK assay. B and D show the comparison of EC_{50} values for compounds with chloroquine-like and quinoline-like activities, respectively. Data shown in B and D are from compounds marked in the same coloured boxes in A and C, respectively – thus a comparison on the relative potency of compounds grouped by their rate of kill is shown.

Ullah *et al.,* (2019) showed that relative RoK for the MMV Malaria Box compounds provided a link to their antimalarial mode of action and information on their core scaffolds. To explore how compounds with a shared MoA and structure appear on an mBRRoK plot clusters were plotted (Figure 3.12). Predicted MoA for 36 compounds are available across four MoA with the known following rank of RoK; PfATP4 > haemoglobin catabolism >DHODH > bc1 (Figure 3.12A). These clusters fall as anticipated from how we are starting to understand RoK on the mBRRoK plot. Importantly the majority of the fast PfATP4 compounds are towards the bottom left and the slow DHODH/bc1 targeting molecules are exclusively towards the top right.

Compounds that share related core scaffold were also clustered based on their mBRRoK data (Figure 3.12B). A ranking order of initial RoK for these scaffols has been reported (Ullah *et al.*, 2019) with iso-Quinolines > Diamino-Glycerol = 2-Phenoxy-Benzylamine > triazolo-pyrimidine, with the mBRRoK plot recapitulating this known order. The details of the selected MMV Malaria Box compounds with their predicted mode of action and core scaffolds are reported in appendix 1 of this thesis.

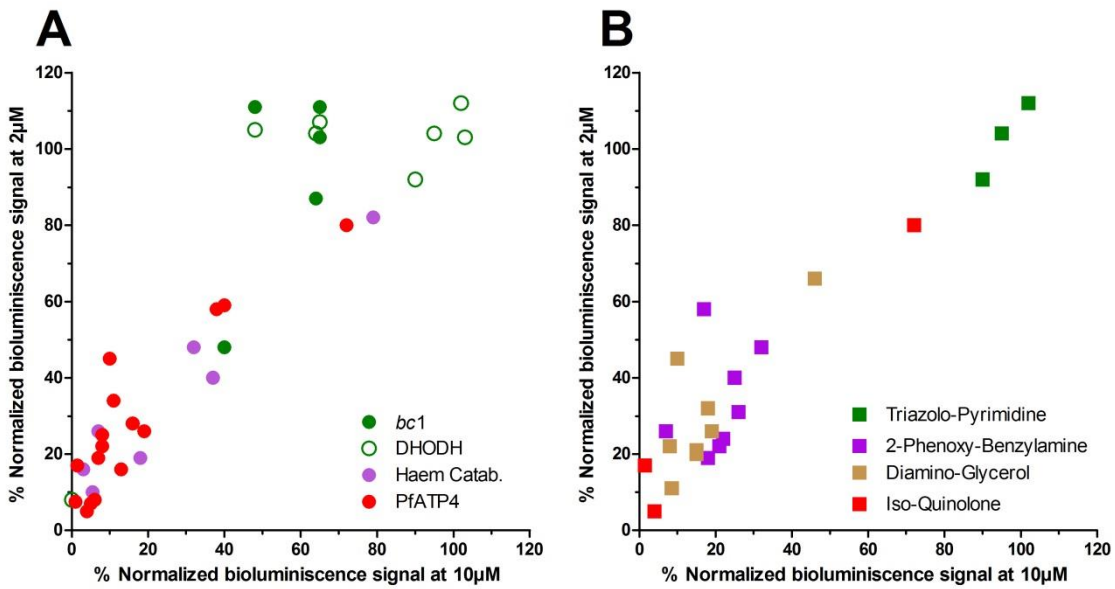


Figure 3.12: Correlating mode of action of MMV Malaria Box compounds with mBRRoK six hours data.
(A) Represent normalized bioluminescence signal at 10µM and 2µM for MMV compounds that target bc1 complex, DHODH, parasite haemoglobin catabolism and PfATP4. Whilst (B) indicates normalised bioluminescence signal at 10µM and 2µM for MMV compounds clustered based on their related core scaffolds for Triazolo-Pyrimidine, 2-Phenoxy-Benzylamine, Diamino-Glycerol and iso-Quinoline.

Given that the above comparison between BRRoK and mBRRoK assay were done only in $Dd2^{luc}$ parasite line, understanding the relationship between intrinsic RoK and MoA in another genetically distinct parasite clone was highly desirable. Against this backdrop, MMV compounds predicted by mBRRoK assay to be rapid acting for $Dd2^{luc}$ (chloroquine-resistant) and $NF54^{luc}$ (chloroquine-sensitive) parasite line were structurally examined to explore similarities in RoK based on related core scaffolds. Compounds sharing five core scaffolds were identified to have similar initial rapid RoK in both parasite lines. Three compounds from Diamino-Glycerol scaffold, two iso-Quinolines, two 2-Phenoxy-Benzylamine, two acridines and two quinoxaline (Figure 3.13 for their structures and MMV identifiers) showed similar rapid intrinsic RoK in both parasite lines (Figure 3.14).

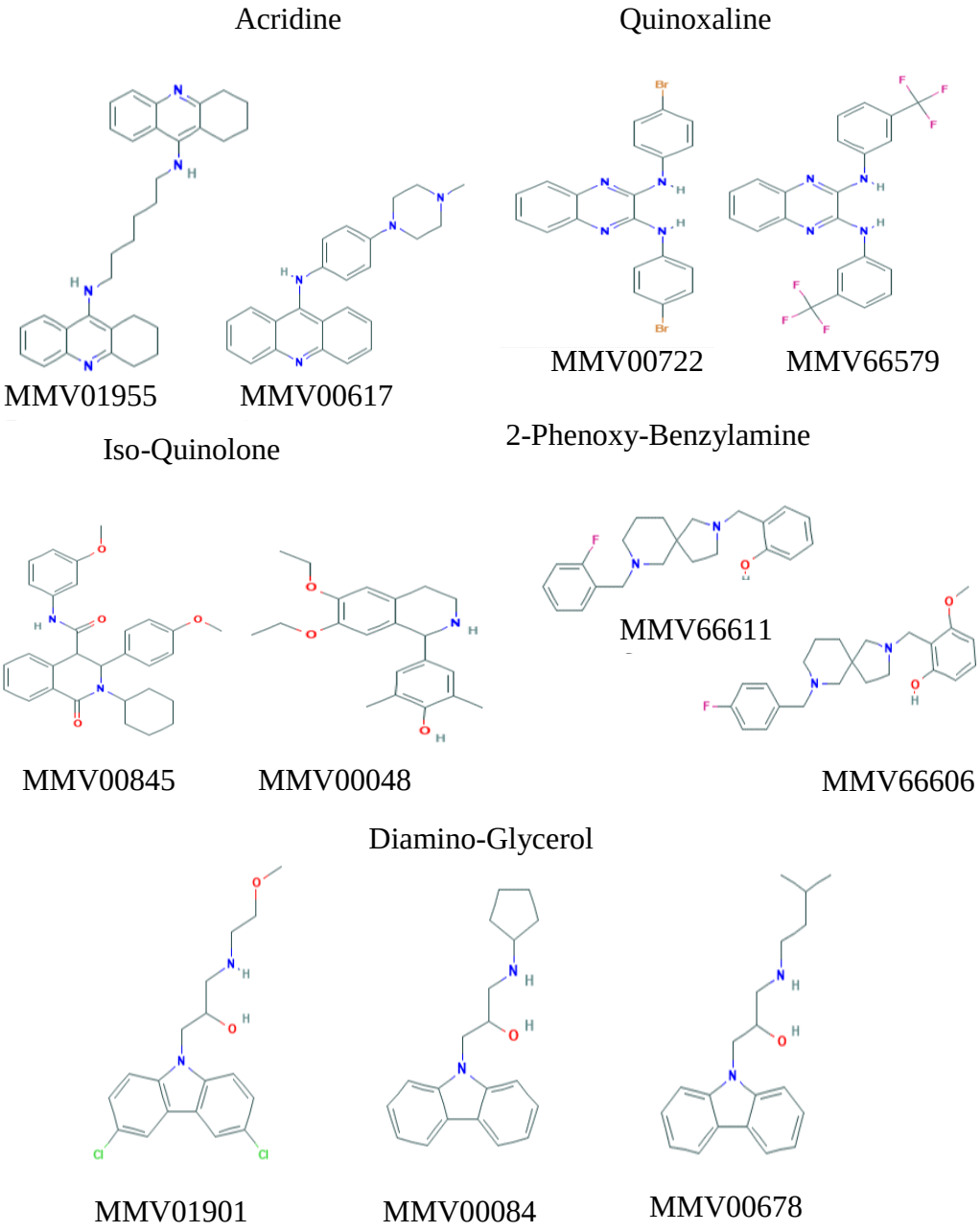


Figure 3.13: Chemical structures of MMV compounds clusters with related initial rapid RoK in Dd2^{luc} and NF54^{luc} parasite lines

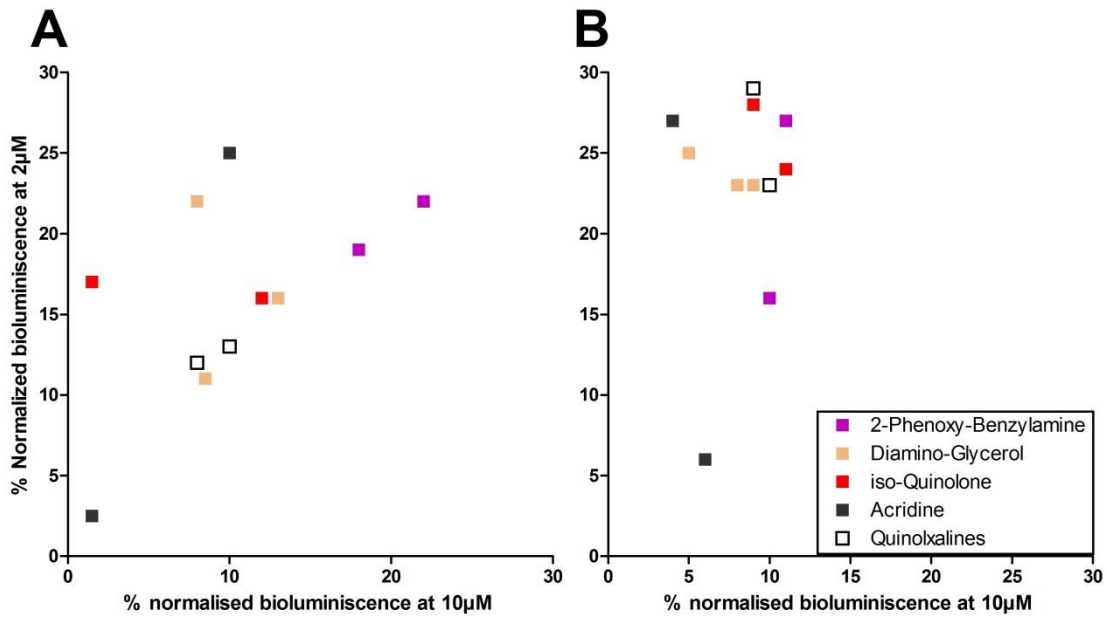


Figure 3.14: mBRRoK plots illustrating structural related compounds in the Malaria Box that share a similar rapid rate of kill in Dd2^{luc} and NF54^{luc} parasite lines.
(A) Represents Dd2^{luc}, whilst (B) represents NF54^{luc} parasites lines. The key provides information on the core scaffolds reported in Figure 3.13.

Interestingly, three compounds from Diamino-Glycerol group were reported by Allman *et al.*, (2016) and Ullah *et al.*, (2019) as PfATP4 inhibitors as was one (MMV008455) of the iso-Quinolines. The second iso-Quinolines was reported by Allman *et al.*, (2016) and Ullah *et al.*, (2019) to target parasite haemoglobin catabolism. Also, the two 2-Phenoxy-Benzylamine were reported by Allman *et al.*, 2016 and Ullah *et al.*, (2019) as targeting haemoglobin inhibitors. Mode of actions are yet to be assigned to the remaining compounds.

Moving forward, understanding how compounds move across the mBRRoK plot in the two parasite strains could provide an insight to potential strain variations – such as the differences in drug resistance between these two strains (Hasenkamp *et al.*, 2013). A question here is whether compounds that are moving in similar directions in the different mBRRoK plots would have structural similarities related to the known drug resistance profilers. To understand this, changes (Δ) in percentage normalized bioluminescence signal at 10µM and 2µM was calculated for mBRRoK data of the two parasite strains. The data was plotted as scatter plot and overlaid

with chemical structures of some MMV Malaria Box compounds (Figure 3.15). Compounds indicated in green had a greater killing effect in NF54^{luc} compared with Dd2^{luc} parasite strains and they were not structurally related. Whilst, compounds indicted with blue colour has a reduced killing effect in NF54^{luc} compared to Dd2^{luc}. Of note is that MMV000704 and MMV666079 (compounds 4 and 5 on Figure 3.15) are quinolines and may be perhaps expected to be more potent in NF54^{luc} compared to Dd2^{luc} as they would be able to achieve a greater fold EC_{50} at the tested concentrations. Unfortunately there was some two years between mBRRoK testing in NF54^{luc} and Dd2^{luc} and this may account more for any differences than their sensitivity to classes of compounds. This effect will be explored again later in this thesis with a more contemporary testing of these samples against each other.

Taking these observations together, the mBRRoK assay is a simpler way of moving the standard BRRoK assay forward for scaling up for high throughput screening. Overall, the mBRRoK assay would appear to be best placed at the initial screening stage for an antimalarial drug discovery campaign to quickly triage compounds with fast cytocidal action and good to moderate potency. However, given some apparent limitations around the 81% true discovery rate and a need to better understand how the RoK and potency parameters operate, particularly outside of the "hit box" would suggest a moving forward for further validation using an additional larger compound library resource for which there was no pre-existing data on their initial *in vitro* RoK action.

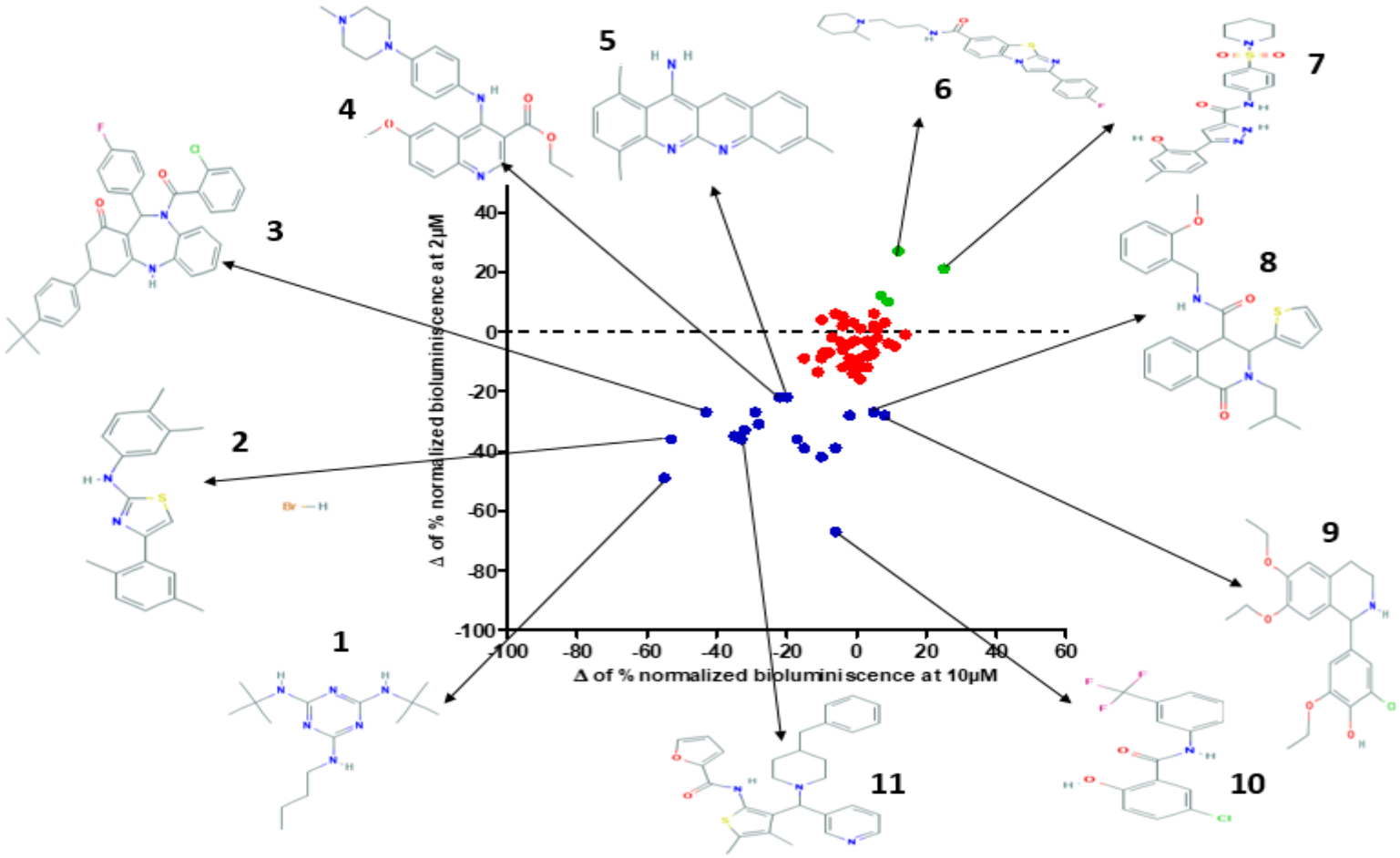


Figure 3.15: Plot for changes in percentage normalised bioluminescence signal of mBRRoK data for Dd2^{luc} and NF54^{luc} parasite stains

Compounds indicated in figures 1 to 11 are MMV665864, MMV007654, MMV011436, MMV000704, MMV666079, MMV000634, MMV665906, MMV000648, MMV000481, MMV665807, MMV396663 respectively.

4 CHAPTER 4: The use of the modified BRRoK assay to screen the MMV Pathogen Box compound collection

4.1 Introduction

The landscape for drug discovery for Neglected Tropical Diseases has been continually changing over the last decade with a transition from traditional pharmaceutical industries, with their confidential practices, to a more open-access drug discovery process (Duffy *et al.,* 2017). Open-access drug discovery has contributed immensely towards the identification and optimization of potential chemo-types that have biological activities against a range of Neglected Tropical Diseases (Maurer *et al.,* 2004; DeLano, 2005; Munos, 2006; Gunther *et al.,* 2008; Singh, 2008; Orti *et al.,* 2009; Mazanetz *et al.,* 2012; Ardal and Rottingen., 2012; Davies *et al.,* 2015; Reichman and Simpson, 2016). Drug discovery in malaria represents an exemplar of this open-access drug discovery approach (Wells *et al.,* 2016; Lucantoni *et al.,* 2013; Bowman *et al.,* 2014; Duffy and Avery, 2013; Ruecker *et al.,* 2014; and Hain *et al.,* 2014) but has also impacted on other diseases such as tuberculosis (Bhardwaj *et al.,* 2011 and Ballell *et al.,* 2013), schistosomiasis (Todd and Coaker, 2015), toxoplasmosis (Boyom *et al.,* 2014), cryptosporidiosis (Bessoff *et al.,* 2014) and kinetoplastid diseases (Kaiser *et al.,* 2015). Critical to this success was the development and release of open-access compound libraries such as the Malaria Box and Pathogen Box by the Medicine for Malaria Venture. These resources are distributed to researchers worldwide with the requirement that results generated from such libraries will be made publically available to the larger community (Wells *et al.,* 2016).

Ullah *et al.,* (2017) were one of the over 200 research groups that received the Malaria Box (van Voorhis *et al.,* 2016). 236 *in vitro* screens against different *Plasmodium spp*. strains as well as other cell/pathogen based systems have been reported for the Malaria Box with Meta-analyses of these data reported by van Voorhis *et al,* (2016). The results from these collaborated efforts have led to the setting up of some 30 new projects in which the compounds have shown

biological activity for diverse disease-causing organisms including cancers (Celik *et al.*, 2015). Building on this great achievement of Malaria Box, the MMV has provided a second open-access drug discovery compound set- termed the Pathogen Box (http://www.pathogenbox.org/). This new set comprises of 400 diverse, drug-like compounds that have biological activities against a number of Neglected Tropical Diseases (MMV, 2015). One-third of the compound set (33%) have activity in malaria screens, followed by tuberculosis with 30%, 18% have activity against kinetoplastid pathogens, helminths (8%), cryptosporidiosis (about 3%) and toxoplasmosis (about 4%). Dengue has the least number of compounds (about 1%) while about 7% of the set are reference compounds – compounds that are or have been used in the treatment of one or more of these diseases (Figure 4.1)

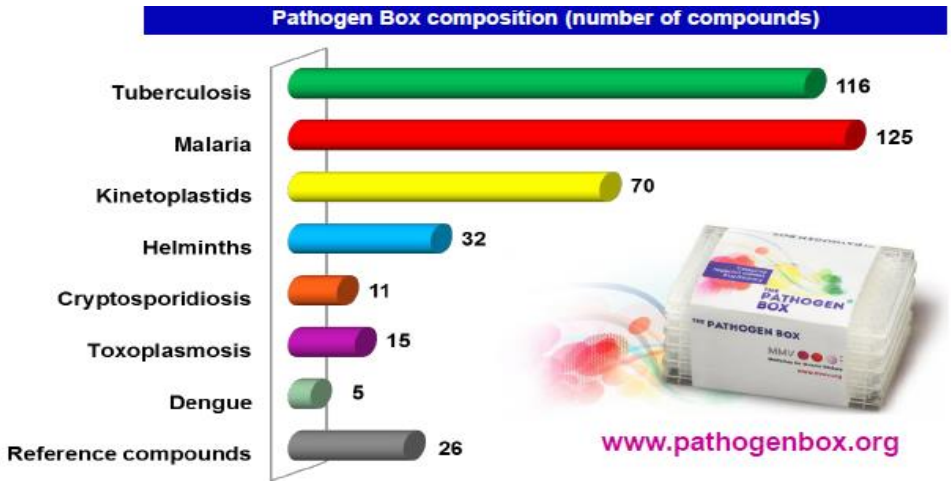


Figure 4.1: Disease targets for the 400 compounds in the MMV Pathogen Box.
The bar chest represents the number of compounds with activity demonstrated against the indicated disease (Source – www.pathogenbox.org*)*

The MMV Pathogen Box compound set was triaged from the European Bioinformatics Institute's open-access database (https://www.ebi.ac.uk/chembl/) in collaboration with specialists from other disease areas (MMV, 2015). Then, professionals from the medicinal chemistry formed a Scientific Selection Committee that reviewed the resulting compounds set.

At this point, fresh solid samples were sourced and their biological activity confirmed with cytotoxicity tests performed to demonstrate each was 5-fold less toxic against human cell line than the indicated pathogen (MMV, 2015). A summary of the selection process is illustrated in Figure 4.2.

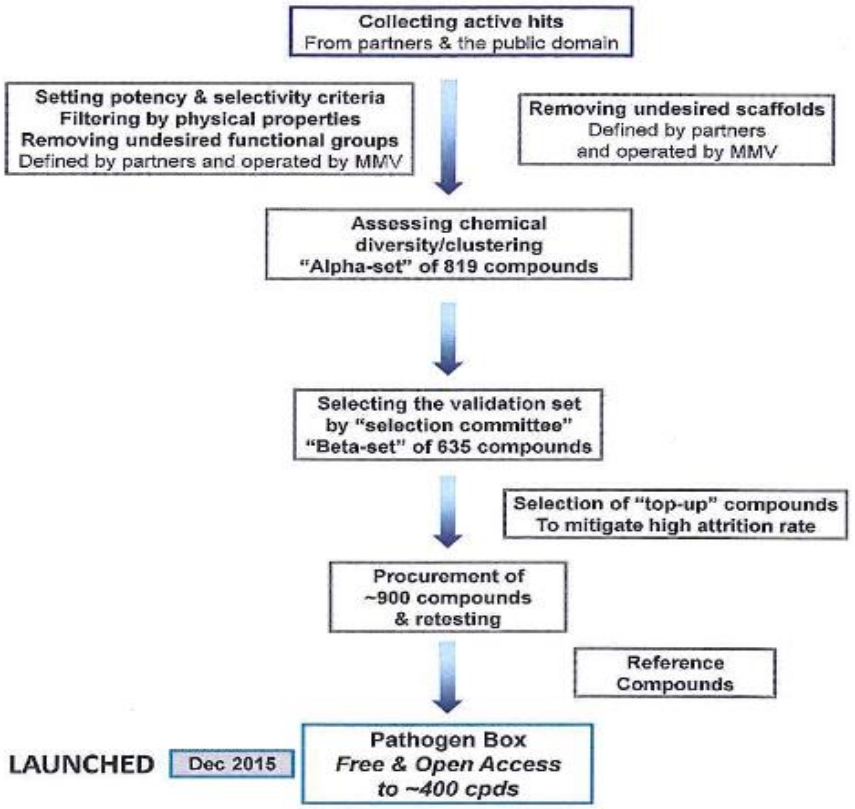


Figure 4.2: Flow chart for the selection of compounds in the MMV Pathogen Box
The schematic illustrates the major steps that were involved in the filtering process to generating the 400 compounds in the Pathogen Box library. (Source: www.mmv.org)

The MMV Pathogen Box also comes with an excel spreadsheet that states the plate layout, details of the compounds such as structure, trivial names, salt form, and cLogP. The biological activities of the compounds were also included in this supporting information. Some screens have been performed on the Pathogen Box to provide the first new leads. The first was the identification of Tolfenpyrad (MMV688934), a pyrazole-5-carboxamide based insecticide that demonstrated activity against the helminth Barber's pole worm (Preston *et al*., 2016). 30 major

publications (as at the time of writing up this thesis), from different research groups that have exploited the potential of this compounds set against diverse pathogens are available on the MMV website (https://www.mmv.org/newsroom/publications).

The potential of the MMV Pathogen Box as an open-access drug discovery resource to catalyse the discovery of drugs against malaria and some neglected diseases have been demonstrated. I decided to screen the MMV Pathogen Box using the mBRRoK assay for two purposes;

(1)To explore the performance of the mBRRoK assay against a larger compound set than had previously been tested, but also a compound set for which there was no available *in vitro* rate of kill data.

(2)To support the utility of the Pathogen Box resource for antimalarial drug discovery by being able to provide initial *in vitro* data on their apparent initial cytocidal action with a view to identify those that offer potential as TCP1 candidates.

4.1 Results

4.1.1 Scaling up of the modified-BRRoK assay to screen the MMV Pathogen Box for potent and fast-acting antimalarial chemo-types.

The use of the validated mBRRoK assay to identify fast-acting cytocidal compounds in Dd2^{luc} parasites was explored using the MMV Pathogen Box compounds set. *P. falciparum* Dd2^{luc} cultures were exposed to fixed concentrations (10µM and 2µM) of the compound library in a 96 micro well plate assay for 6 hours and then the residual bioluminescence signal measured and normalized to the mean of untreated controls as described in section 2.3. All experiments were carried out as technical duplicates with three independent biological replicates performed. The mean of n=6 samples was plotted to provide the characteristic mBRRoK plot described in the previous chapter (Figure 4.3). Nine benchmark antimalarial drugs: DHA, ART, CQ, AQ, PPQ, MQ, QN, ATQ and DOX (EC_{50} and RoK data available in Table 3.2) were included in the plot to act as signposts to mark the activity spaces of the compounds in these mBRRoK plots.

Interestingly, the majority of compounds that appear to have the greatest effect at 10µM and 2µM (bottom left) are compounds selected from screens for anti-plasmodial activity (Figure 4.3A). For compounds with other disease indications, there appeared to be none that were as active at 10µM and 2µM. Two compounds included in the Pathogen box as reference compounds, did appear to have activity at both 10µM and 2µM. The first, mefloquine (MMV000016), was expected and its position relative to the mefloquine benchmark control included is indicated by two arrows in Figure 4.3B. The other reference compound identified was pentamidine (MMV000062). Known to be a potent compound in *P. falciparum* with EC_{50} between 50-130nM (Bell *et al*., 1990), this is the first indication that its action is also likely to be rapid. The entire screening data for the 400 MMV Pathogen Box compounds using mBRRoK assay is reported in appendix 3 at the end of this thesis.

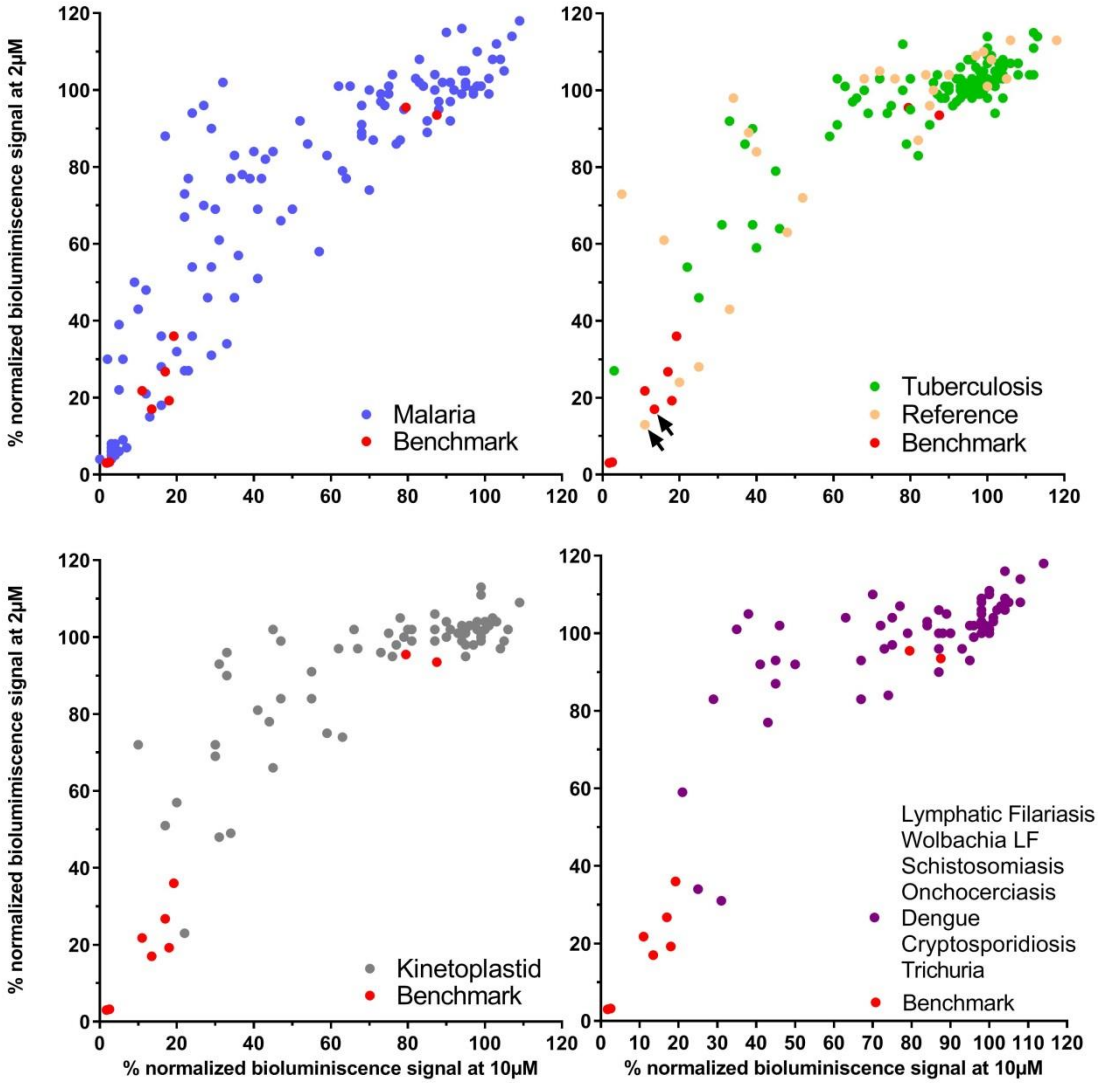


Figure 4.3: mBRRoK graph for 400 MMV Pathogen Box compounds
Comparison of the mean normalized bioluminescence signal at 10µM and 2µM from mBRRoK assay data of 400 MMV Pathogen box compounds, the keys provides information of each disease set. The position of benchmark antimalarial is shown using a key based on their relative in vitro rate of kill (see Table 3.2 and Figure 3.3B). Each data point represents the mean (n=6).

To rationally define cut off bioluminescence signals at 10µM and 2µM for the compounds of interest whose potency and RoK will be confirmed, the sensitivity and specificity criteria described for the Malaria Box compounds in section 3.2.2 were used to rank the compounds' mBRRoK data into a chloroquine (CQ)-like and quinoline-like activity space (Figure 4.4). As indicated on the graphs in Figure 3.7E, the meeting points for sensitivity and specificity at 2µM and 10µM for chloroquine-like and quinoline-like are 20 by 25 and 25 by 45 respectively. These

were used to define boxes for the compounds of interest to be taken forward for potency and RoK confirmation. The fast-acting (chloroquine CQ-like) and moderate-acting (quinoline-like) are located in the lower left quadrant. These identify 21 and 36 compounds, respectively.

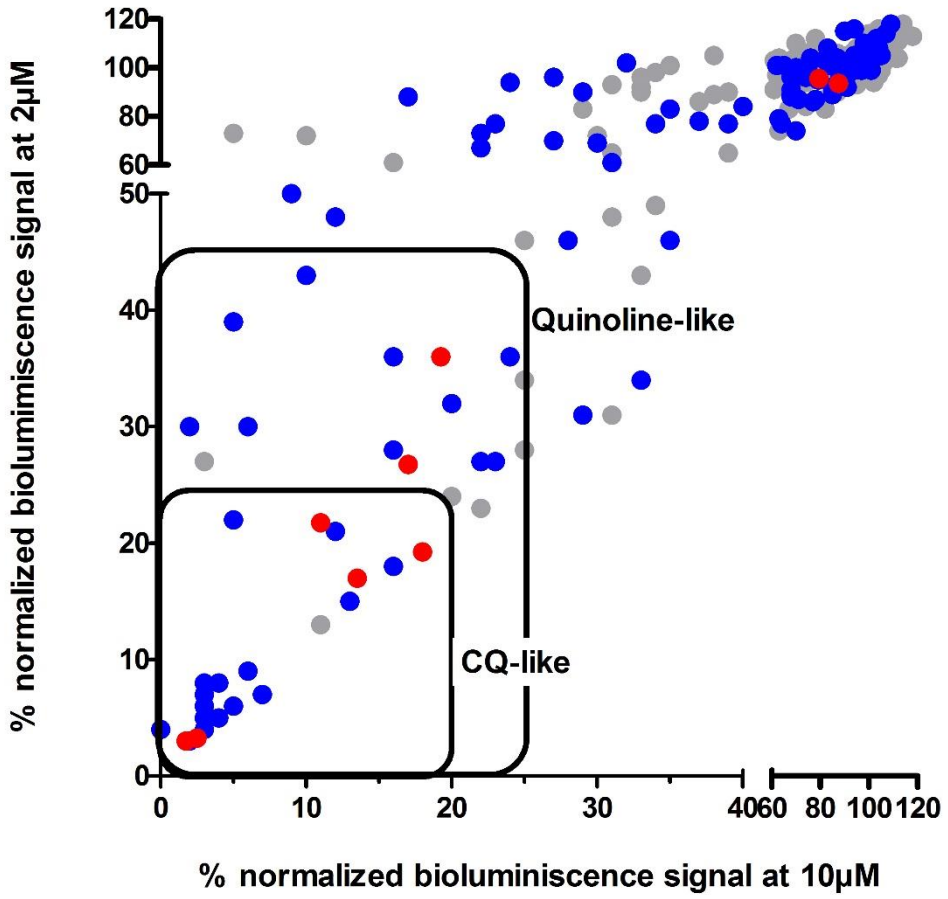


Figure 4.4: Prioritising MMV Pathogen Box Compounds from an mBRRoK plot.
The same mBRRoK plot as Figure 4.3 is shown here, although with variations in the axes to highlight the area with greatest loss of bioluminescence signal. Benchmark antimalarial are shown in Red and the compounds selected from a malaria screen in blue (as per Figure 4.3). Remaining compounds based on disease dataset or reference compounds are all shown in grey. Each data point represents the mean (n=6).

4.1.2 Confirmation of potency (EC_{50}) and Rate of kill (RoK) of the identified hits from MMV Pathogen Box compounds.

A total of 36 compounds that exert an initial rapid relative rate of kill comparable to quinolines (Figure 4.4) were identified for follow up 50% effective concentration (EC_{50}) prior to a BRRoK evaluation to confirm a rapid rate of kill independent of the potency of the compound. For these, sufficient material from the MMV Pathogen Box provided was available to determine the EC_{50}/BRRoK data for ten compounds. Figure 4.5 illustrates how these compounds (shown in blue) are positioned compared to the benchmark antimalarials. For comparison, four compounds that collocate with the known slow benchmark antimalarials, atovaquone and doxycycline (shown in black filled circles on Figure 4.5) were also selected for analysis.

Using a 48 hours MSF assay described in section 2.4, EC_{50} data were first developed in $Dd2^{luc}$ parasite line for these compounds (Figure 4.6A). Using this data, BRRoK assays were then done using the standard 6 hours experiment (Ullah *et al*., 2017; Ullah *et al*., 2019) and their plots shown next to their respective concentration-response curve (Figure 4.6B, shown over two pages). Table 4.1 reports the MMV identification number, disease targets, EC_{50} values and initial rate of kill of the identified hits (relative to established benchmarks included in the assay). Of the ten mBRRoK "hits", nine were derived from anti-plasmodial screens and one (MMV637229) in a trichuriasis screen (https://www.mmv.org/mmv-open/pathogen-box/pathogen-box-supporting-information). Two of the four predicted slow compounds (MMV020537 and MMV024397) were derived from anti-plasmodial screens, with one from a kinetoplastid screen (MMV659004) and the last a reference compound (MMV021057-Azoxystrobin).

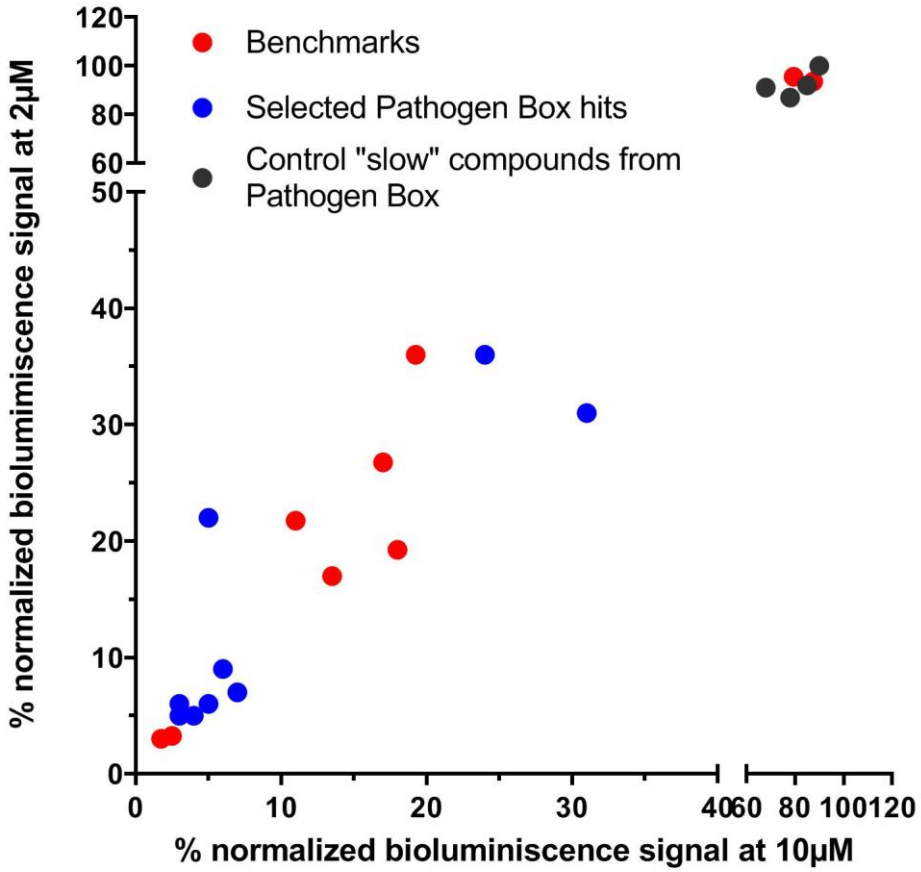
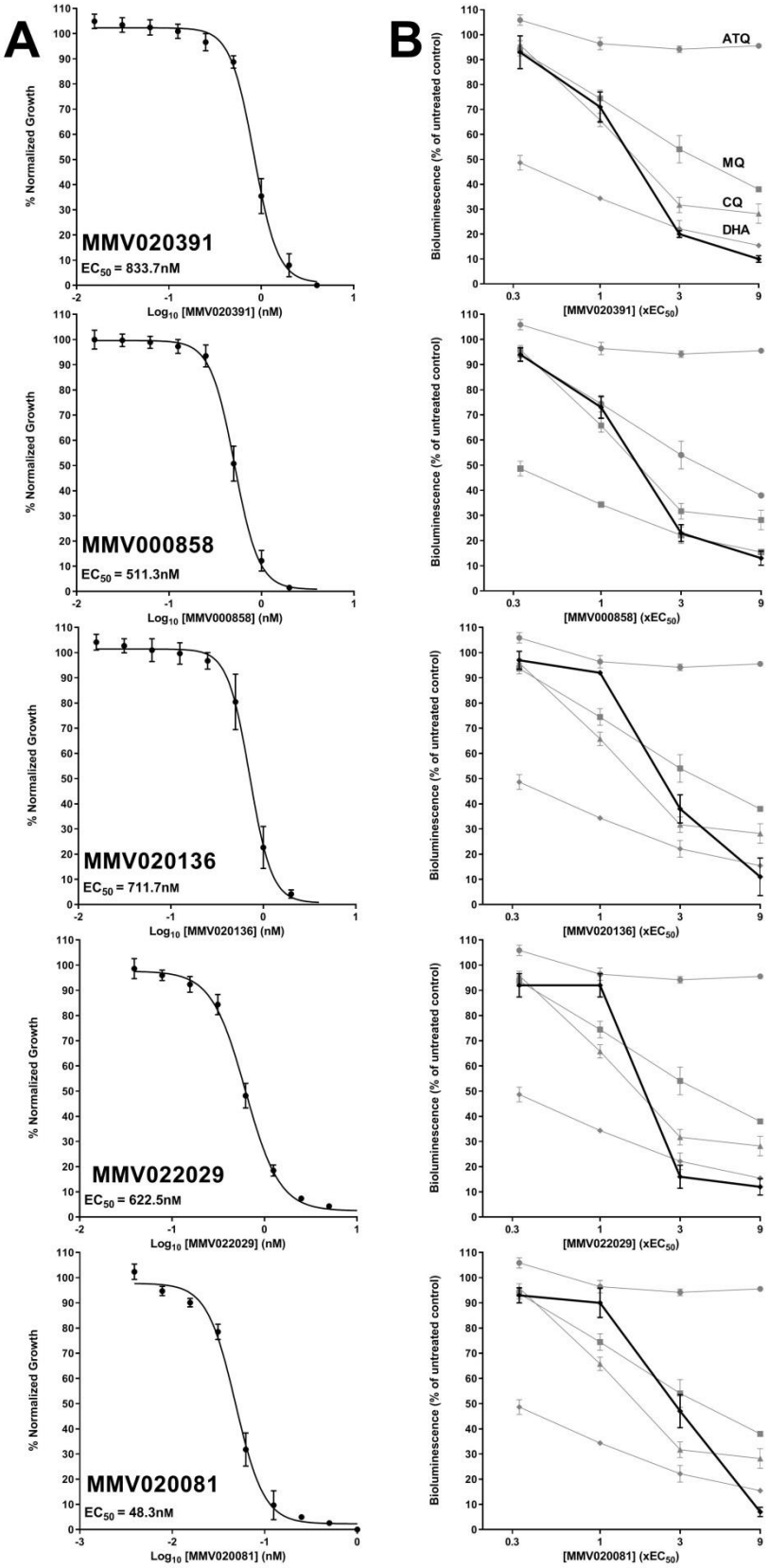


Figure 4.5: mBRRoK plot showing selection of MMV Pathogen Box Compounds for follow up studies.
The same mBRRoK plot as Figure 4.4 is shown here, although with variations in the axes to highlight the area with greatest loss of bioluminescence signal. Benchmark antimalarial are shown in Red and the compounds selected based on predictions they are rapid and potent (i.e. "hits "are shown blue with Black identifying compounds predicted to be slow based on their colocation with doxycycline and atovaquone.

As expected, all the ten "hit" compounds are potent to moderately potent with EC_{50} values ranging from 48.3nM to 883.7nM (these potency results are in agreement with data from MMV Pathogen_Box_Activity_Biological_Data_Smiles at https://www.pathogenbox.org/about-pathogen-box/composition). From the BRRoK assays, six would likely be compounds of interest to meet TCP1 criteria based on their curves position compared to chloroquine or better, with the remaining four all within the mefloquine (quinoline –like) control.


A
B
% Normalized Growth
MMV020391
EC50 = 833.7nM
Log10 [MMV020391] (nM)
MMV000858
EC50 = 511.3nM
Log10 [MMV000858] (nM)
MMV020136
EC50 = 711.7nM
Log10 [MMV020136] (nM)
MMV022029
EC50 = 622.5nM
Log10 [MMV022029] (nM)
MMV020081
EC50 = 48.3nM
Log10 [MMV020081] (nM)
Bioluminescence (% of untreated control)
ATQ
MQ
CQ
DHA
[MMV020391] (xEC50)
[MMV000858] (xEC50)
[MMV020136] (xEC50)
[MMV022029] (xEC50)
[MMV020081] (xEC50)

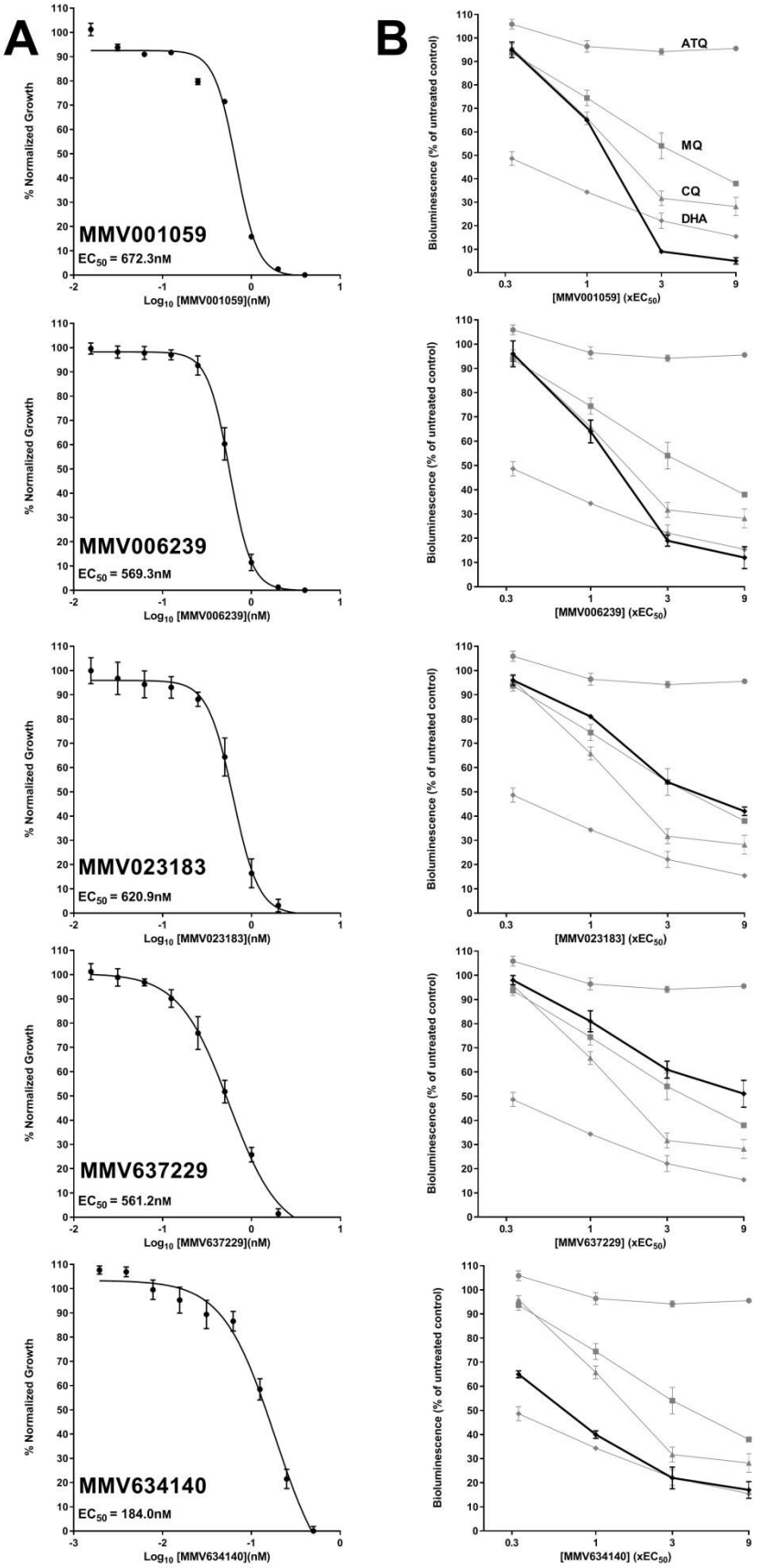

A
B
% Normalized Growth
MMV001059
EC50 = 672.3nM
Log10 [MMV001059](nM)
MMV006239
EC50 = 569.3nM
Log10 [MMV006239](nM)
MMV023183
EC50 = 620.9nM
Log10 [MMV023183](nM)
MMV637229
EC50 = 561.2nM
Log10 [MMV637229](nM)
MMV634140
EC50 = 184.0nM
Log10 [MMV634140](nM)
Bioluminescence (% of untreated control)
ATQ
MQ
CQ
DHA
[MMV001059] (xEC50)
[MMV006239] (xEC50)
[MMV023183] (xEC50)
[MMV637229] (xEC50)
[MMV634140] (xEC50)

Figure 4.6: Concentration-response curves and BRROK charts of the MMV Pathogen mBRRoK hits (previous two pages).
Log_{10} concentration-normalised response graphs (48 hours MSF assay) (A) and standard BRRoK (6 hours) fold EC_{50}-normalized response (B) graphs for the indicated compounds selected from the MMV Pathogen Box. On A, the curve represents the non-linear regression (mean ±stdev n=9) used to estimate the EC_{50} reported. For B, the BRRoK response for the indicated compound is shown using a black line) with the same data reported for four benchmark antimalarials (DHA, dihydroartemisinin; CQ, chloroquine; MQ, mefloquine and ATQ, atovaquone) shown in gray for comparison.

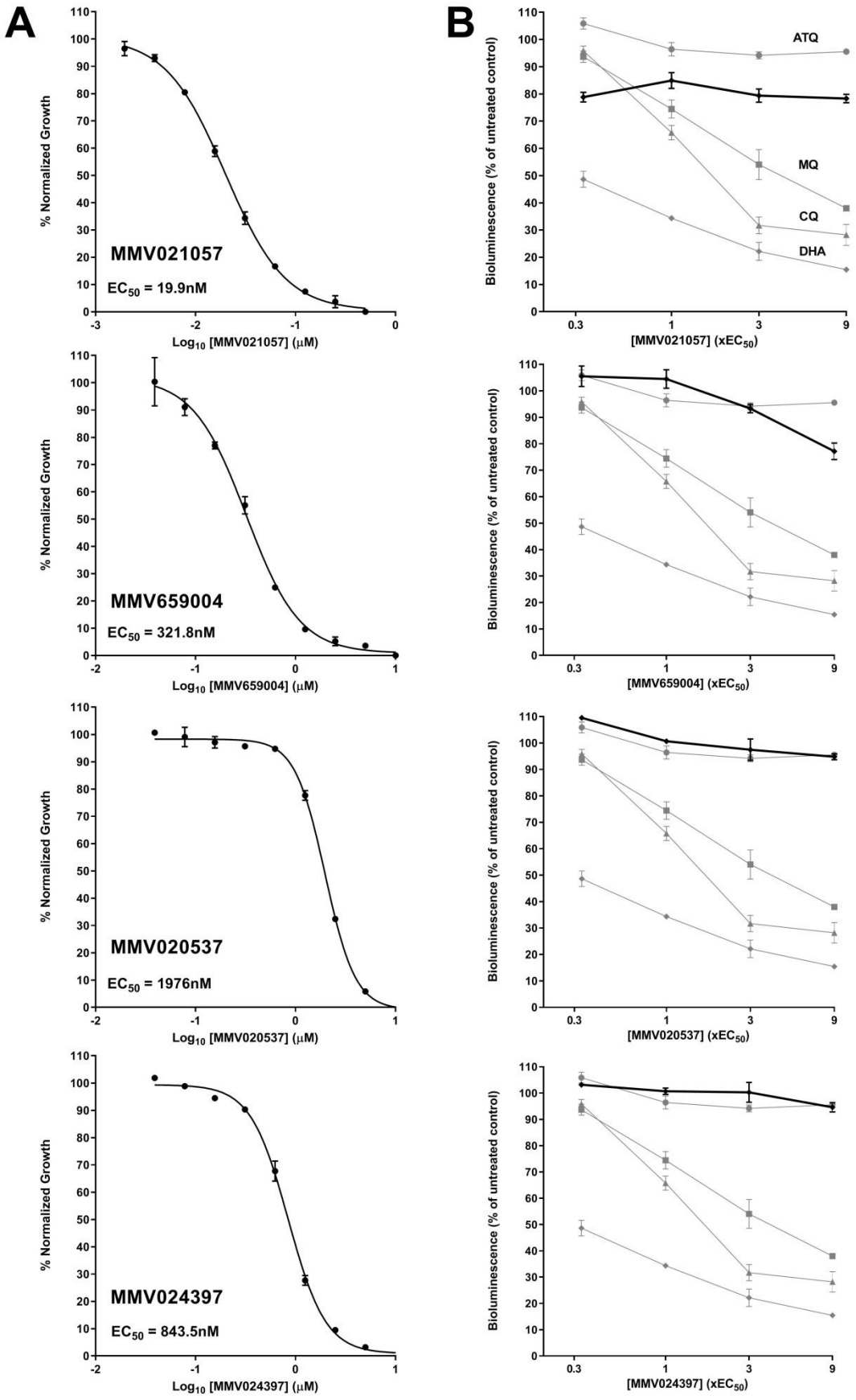
Table 4.1: List of Pathogen Box compounds predicted to be potent and rapid in cytocidal action

MMV ID	**Indicated disease set**	**EC_{50}(nM) (95% Confidence interval)**	**Relative initial rate of kill**
MMV020391	Malaria	883.7 (758.8-916.0)	Chloroquine-like
MMV000858	Malaria	511.3 (483.4-540.8)	Chloroquine-like
MMV006239	Malaria	569.3 (554.3-584.7)	Chloroquine-like
MMV022029	Malaria	622.5 (562.2-689.2)	Chloroquine-like
MMV001059	Malaria	672.3 (527.5-857.0)	Chloroquine-like
MMV634140	Malaria	184 (89.6-377.8)	Chloroquine-like
MMV023183	Malaria	620.9 (560.1-688.2)	Mefloquine-like
MMV020136	Malaria	711.7 (662.0-765.2)	Mefloquine-like
MMV020081	Malaria	48.3 (41.9-55.7)	Mefloquine-like
MMV637229	Trichuriasis	561.2 (467.4-673.9)	Mefloquine-like

The potency and relative rate of kill of four compounds predicted to be less potent and/or slow-acting were similarly confirmed using a MSF 48 hours assay and BRRoK assay (Figure 4.7 A and B, respectively). The concentration-response curves report that three of the compounds (MMV021057, MMV659004 and MMV024397) are within the minimal threshold for potency (EC_{50} below 1µM) but display an initial killing rate comparable to atovaquone. MMV0210537 appears to be both slow acting and with a low potency.

Together, these findings provide proof of concept that the mBRRoK assay can be employed with a compound set for which no information about their initial cytocidal action is known and (i) identify "hits" that show good to moderate potency and initial cytocidal activity as well as (ii) apparently exclude slow-acting compounds irrespective of their potency.

Figure 4.7: Concentration-response curves and BRROK charts of the MMV Pathogen mBRRoK compounds that are not identified as hits (following page).
Log_{10} concentration-normalised response graphs (A) and standard BRRoK fold EC_{50}-normalized response (B) graphs for the indicated compounds selected from the MMV Pathogen Box. On A, the curve represents the non-linear regression (mean ±stdev n=9) used to estimate the EC_{50} reported. For B, the BRROK response for the indicated compound is shown using a black line) with the same data reported for four benchmark antimalarials (DHA, dihydroartemisinin; CQ, chloroquine; MQ, mefloquine and ATQ, atovaquone) shown in gray for comparison.


A
B
% Normalized Growth
MMV021057
EC50 = 19.9nM
Log10 [MMV021057] (μM)
MMV659004
EC50 = 321.8nM
Log10 [MMV659004] (μM)
MMV020537
EC50 = 1976nM
Log10 [MMV020537] (μM)
MMV024397
EC50 = 843.5nM
Log10 [MMV024397] (μM)
Bioluminescence (% of untreated control)
ATQ
MQ
CQ
DHA
[MMV021057] (xEC50)
[MMV659004] (xEC50)
[MMV020537] (xEC50)
[MMV024397] (xEC50)

4.2 Discussion

The MMV Pathogen Box is a set of 400 structurally diverse compounds that have been identified from a number of screens against pathogenic organisms. Of these 400 compounds, 125 have been identified on the basis of their inhibitory effect on the proliferation of intra erythrocytic *P.falciparum*. Here, this compound library offered the opportunity to evaluate the ability of the mBRRoK assay to be used in a fixed-concentration screen to identify potent and rapidly acting compounds in a compound library that has not been evaluated for their rate of kill activity. The ease of use of mBRRoK assay without the prior determination of EC_{50} values underlines the opportunity for a quick and simple screening tool for antimalarial drug discovery. Screening of the MMV Pathogen Box compounds identified 21 compounds to fall within the "hit" box defined for this assay in Chapter 3. Figures 4.8 and 4.9 report their structures.

Analysis of the biophysical properties of these 21 best compounds show there was no correlations seen across a range of biophysical properties when compared to compounds that were not hits. These key biophysical properties included molecular weight (MW), lipophilicity of ionized form (logD), lipophilicity of neutral form (logP), polar surface area (PSA), the number of rotatable bonds (RB), and the number of hydrogen bond acceptors (HBA) or donors (HBD), basic and acidic pKa. Whilst this may be due to the relatively small number of compounds in each disease set, it is apparent that no simple biophysical feature accounts for the selection of the predicted 21 Pathogen Box hits.

Comparing these hits against their predicted mechanism of actions offers an opportunity to integrate this mBRRoK data with additional datasets generated by others also investigating the Pathogen Box compounds. One such study on the Pathogen Box compounds is a study for compounds that disrupt malaria parasite ion and volume homeostasis by Dennis *et al.,* (2018). The study identified eleven Pathogen Box compounds that apparently exert their effect through direct interaction with PfATP4 protein. This led to the alteration of Na^+ export/H^+ import

function, thereby causing an increase in Na^+ influx and cytosolic pH. Of the eleven compounds identified by Dennis *et al.*, (2018) as PfATP4 inhibitors, ten (Figure 4.8) were identified as "hits" in the mBRRoK assay here. Of note is MMV006239 which shares a structure with the spiroindolones KAE609 (cipargamin) and NITD246 which have both been validated as PfATP4 inhibitors (Rottmann *et al.*, 2010, Spillman and Kirk, 2015). Also of note is MMV085210, the only predicted PfATP4 in the Pathogen Box not identified in this screen – with this compound being the least potent of the 11 as well as affecting the least change in Na^+ influx in the Dennis *et al.*, (2018) study. Of the ten PfATP4 "hits", six were subsequently investigated using the BRRoK assay and had a rapid RoK confirmed independent of their potency (Figure 4.10). Also of note is that the potency of these six compounds is similar to that reported in Dennis *et al*. (2018) where they report a range of 110-720nM compares to 48-883nM in this study.

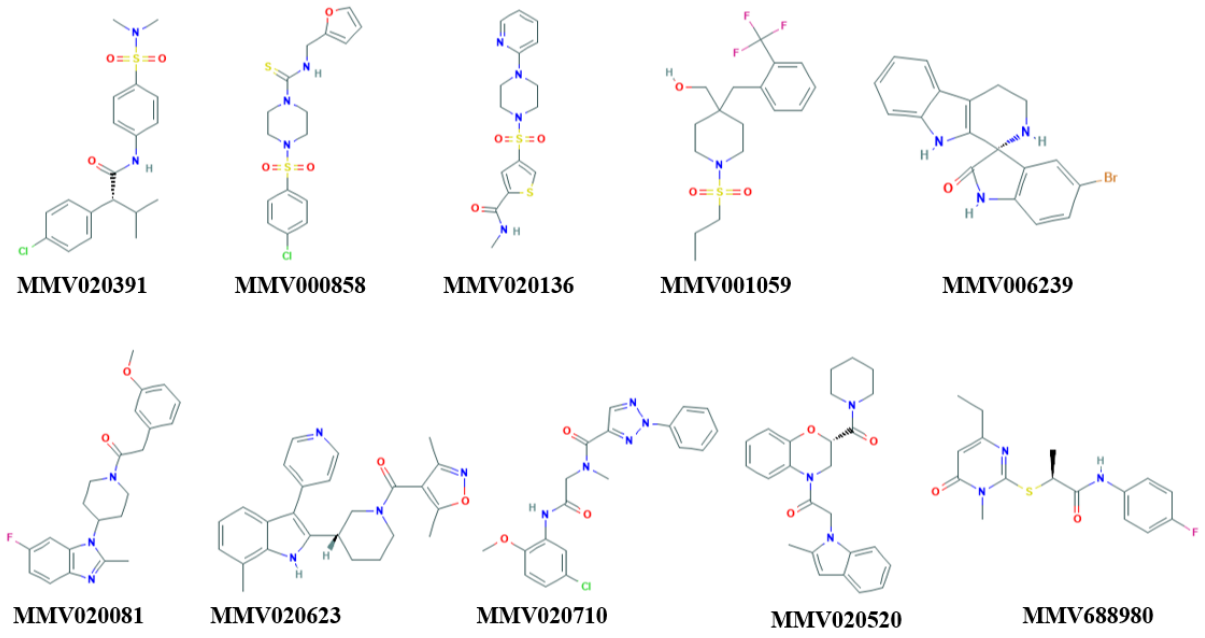


Figure 4.8: Structures and MMV identifiers for MMV Pathogen Box "hit" compounds that have predicted action against PfATP4

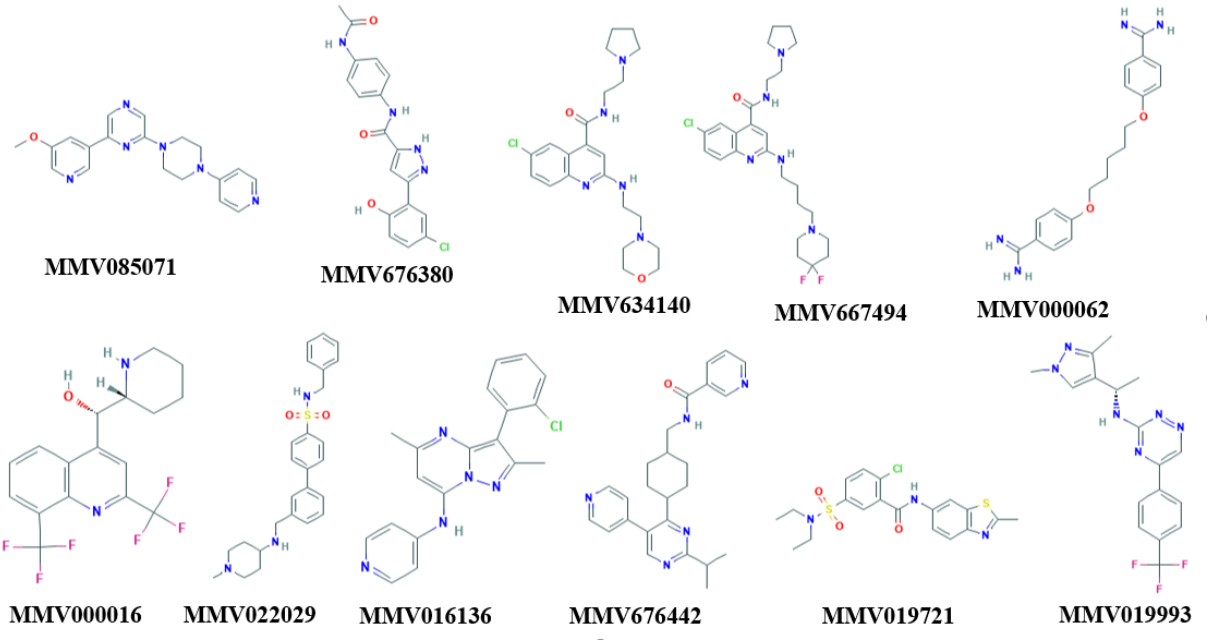


Figure 4.9: Structures and MMV identifiers for MMV Pathogen Box "hit" compounds

Table 4.2: Summary of 21 best compounds from the MMV Pathogen Box

MMV ID	Disease set	10µM	2µM	Predicted MoA
MMV020391	Malaria	3	5	PfATP4
MMV000858	Malaria	3	6	PfATP4
MMV020136	Malaria	4	5	PfATP4
MMV001059	Malaria	6	9	PfATP4
MMV006239	Malaria	3	6	PfATP4
MMV020081	Malaria	5	6	PfATP4
MMV020623	Malaria	4	8	PfATP4
MMV020710	Malaria	2	3	PfATP4
MMV020520	Malaria	3	4	PfATP4
MMV688980	Malaria	3	8	PfATP4
MMV085071	Malaria	7	7	Digestive vacoule
MMV676380	Malaria	0	4	Digestive vacoule
MMV634140	Malaria	7	7	PfeEF2
MMV667494	Malaria	3	5	PfeEF2
MMV000062	Ref compound	11	13	NA
MMV000016	Ref compound	20	24	Haemozoin synthesis
MMV022029	Malaria	5	22	NA
MMV016136	Malaria	12	21	NA
MMV676442	Malaria	16	18	NA
MMV019721	Malaria	13	15	NA
MMV019993	Malaria	3	7	NA

NA: not available

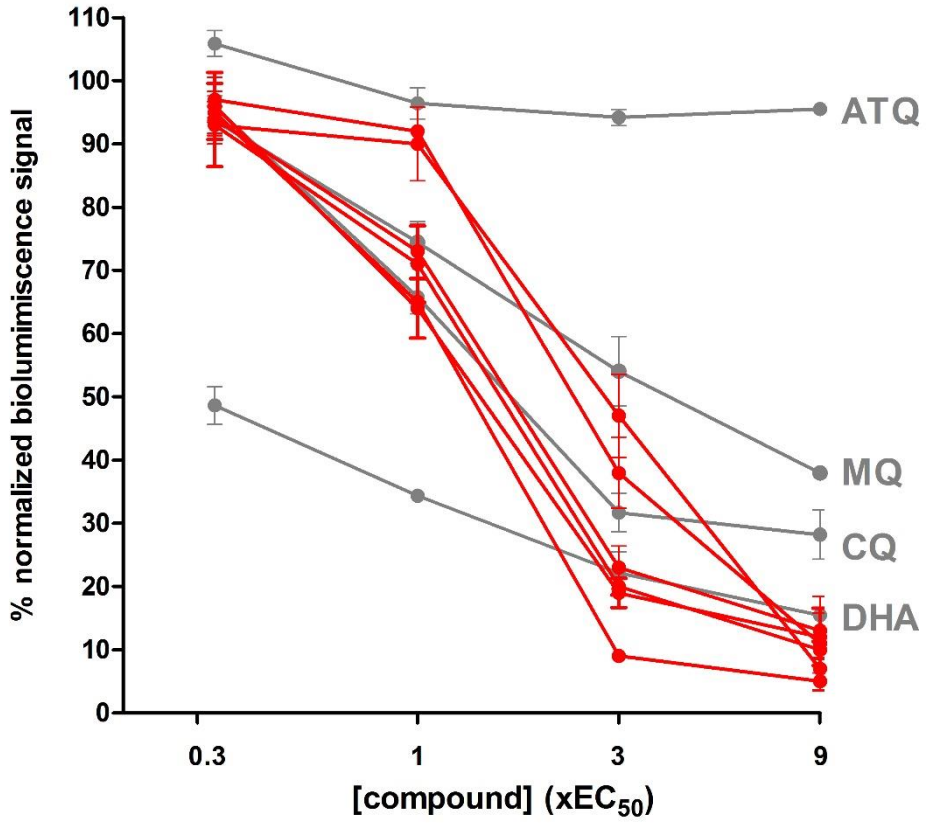


Figure 4.10: BRRoK chart of the MMV Pathogen mBRRoK "hits" identified as PfATP4 inhibitors.
Standard BRRoK fold EC_{50}-normalized response graphs from Figure 4.6 selecting six compounds identified in Dennis et al., (2018) as PfATP4 inhibitors. The BRRoK response curves for the PfATP4 inhibitors are shown in red with the same data reported for four benchmark antimalarials (DHA, dihydroartemisinin; CQ, chloroquine; MQ, mefloquine and ATQ, atovaquone) shown in grey for comparison.

From Figure 4.9, MMV085071 and MMV676380, whilst structurally unrelated, were reported by Tong *et al*., (2018) as two of three hits in a screen for compounds that permeabilize the parasite's digestive vacuole (DV). The screen was prompted by the work of Ch'Ng *et al*., (2011) who showed that exposure to the sub-micromolar concentration of chloroquine permeabilized the DV and led to an efflux of calcium ions that precedes mitochondrial outer membrane potential (MOMP) collapse and then DNA degradation. Interestingly, of the ten compounds

identified in the Pathogen Box that cause calcium efflux from the DV, MOMP and DNA damage, only three did not also inhibit β-haematin formation (which CQ does), with MMV085071 and MMV676380 as two of these three compounds. Whilst these compounds were not tested in BRRoK here, Tong *et al.,* (2018) reported a rapid *in vitro* killing rate for MMV085071 and moderate to fast cytocidal action for MMV676380 – coincident to the >90% loss of bioluminescence even at 2µM shown here.

MMV634140 and MMV667494 share a structural similarity to DDD107498, a compound originally reported by Baragana *et al.,* (2015) as a novel multi-stage inhibitor of protein synthesis through targeting the *P. falciparum* translation elongation factor 2 (*Pfe*EF2; Jackson *et al.,* 2011). MMV634140 was confirmed in this study to have a rapid initial cytocidal action, comparable to DHA, as well as a good potency at 184nM (Figure 4.6). These compounds potentially represent a new characterisation of the RoK for another target, protein translation, which elicits a rapid rate of kill.

Compound MMV000062 and MMV000016 are reference compounds pentamidine and mefloquine, respectively. Pentamidine is used for the treatment of the hemolymphatic stage of Human African Trypanosomiasis (HAT) as well as leishmaniasis (Werbovetz, 2006; Kaiser *et al.*, 2011). Pentamidine has previously been reported to show activity against *P. falciparum*, but suffers from the setback of not being orally bioavailable as well as serious side effects such as renal toxicity and cardiotoxicity (Feddersen and Sack, 1991; Bray *et al.*, 2003; Antoniou and Gough, 2005). Duffy *et al.,* (2017) reported an EC_{50} of 0.01µM for pentamidine against the intra erythrocytic stage of 3D7 *Plasmodium* strain. The rapid killing rate displayed by this drug in the 6 hours mBRRoK assay likely resulted from the multiples of fold-EC_{50} concentrations achieved at the two fixed concentrations (1000 x EC_{50} folds at 10µM and 200 x EC_{50} folds at 2µM). MMV000016, mefloquine, a blood schizonticide with some neurological side effects in some patients (Nevin and Byrd, 2016). As expected from the use of this compound as a

benchmark compound, mefloquine showed a high loss of bioluminescence in the mBRRoK assay, a reflection of its previously reported *in vitro* pharmacodynamics killing rate (Sanz *et al.,* 2012; Linares *et al.,* 2015; Ullah *et al.,* 2017) as well as its high potency (Hasenkamp *et al,* 2012).

The remaining five "hits"; MMV022029, MMV016136, MMV676442, MMV019721, and MMV019993 have, to date, no reported biological target in *P. falciparum*. Importantly, these compounds, all structurally diverse from one another, may offer some opportunity to the malaria drug development community for further hit-to-lead optimization. Of these, however, MMV019993 may be the most interesting hit due to its likely rapid parasiticidal effect based on the high levels of bioluminescence signal loss in a potent compound (200nM, available for Dd2 by MMV). The summary of the predicted fast and potent compounds (with their predicted mode of action) from the MMV Pathogen Box compounds is presented in table 4.2.

Figure 4.11 has been developed here to better explore how compounds with the same MoA can be seen to be displayed across the mBRRoK plot. Rapid acting compounds that target PfATP4 function and haemoglobin catabolism (Ullah *et al.,* 2019), digestive vacuole integrity or PfeEF2 function (reported here) all are typically clustered towards the bottom left (highest level of bioluminescence loss at both concentrations). There are some compounds reported to target PfATP4 in the Pathogen Box that do not fall towards the bottom left. This observation in terms of the variation in the initial RoK has been reported for predicted PfATP4 inhibitors from the MMV Malaria Box (Ullah *et al.,* 2017; Ullah *et al.,* 2019). MMV011229 is an imidazopyrimidine selective inhibitor of DHODH (Marwaha *et al.,* 2012) with three additional DHODH inhibitors (MMV020591, MMV020537, MMV020289) reported by Ross *et al.,* (2018). As expected for DHODH inhibitors (Phillips *et al.,* 2015; Phillips *et al.,* 2016; Ullah *et al.,* 2017; Ullah *et al.,* 2019) they cluster towards the upper right (minimal loss of bioluminescence at both concentrations).

Three compounds; MMV024101, MMV010576 and MMV085499 show a moderately fast initial RoK in mBRRoK plot (Figure 4.11). MMV024101 is a 1, 5-naphthyridine identified by Kandepedu *et al.,* (2018) as a novel *P. falciparum* Phosphatidylinositol-4-Kinase (PfPI4K) inhibitor from the screening of MMV Pathogen Box compounds. MMV010576 was identified by Younis *et al.*, (2013) from a phenotypic screen of the SoftFocus kinase library as a potent and selective *in vitro* inhibitor of *P. falciparum*. The third compound, MMV085499 was reported by Vaele (2019) to share similar structure with UCT943 (2-aminopyrazine). UCT943 was reported by Brunschwig *et al.,* (2018) to also be a PfPI4K inhibitor with potential to be a component in a SERCaP drug for the treatment, prevention and transmission-blocking of malaria parasites. Another two compounds; MMV010545 and MMV023985 predicted by Vaele (2019) to be PfPI4K inhibitors are clustered together towards the upper left of the mBRRoK plot. The prediction was based on their structural similarity with imidazopyridazine compounds identified by McNamara *et al.,* (2013) as PfPI4K inhibitors.

Five compounds, (MMV032967, MMV676260, MMV393144, MMV392832 and MMV007920) that show moderate initial RoK in mBRRoK plot were predicted by Vaele (2019) to likely target the *P. falciparum* equilibrative nucleoside transporter type 1 (PfENT1). The first three compounds are 2-arylimidazopyridines and the fourth, a pyrrolopyridine that closely resemble similar scaffolds reported by Lougiakis *et al*., (2016) and Gavriil *et al*., (2018) as fungal nucleobase transporter (FcyB) inhibitors and human NK_3 tachykinin receptor blockers (Geldenhuys *et al*., 2010). PfENT1 mediate the salvage of purines necessary for parasite proliferation from host erythrocyte and offers a potential drug target against *P. falciparum* (Deniskin *et al*., 2016; Sosa *et al*., 2020). A group of compounds identified and developed by Frame *et al*., (2015) and Deniskin *et al.,* (2016) as PfENT1 inhibitors closely resemble the fifth compound predicted by Vaele (2019) as a putative PfENT1 inhibitor. Details of the predicted

mode of action for some of the malaria compounds inside the MMV Pathogen Box compounds are presented appendix 4 at the end of this thesis.

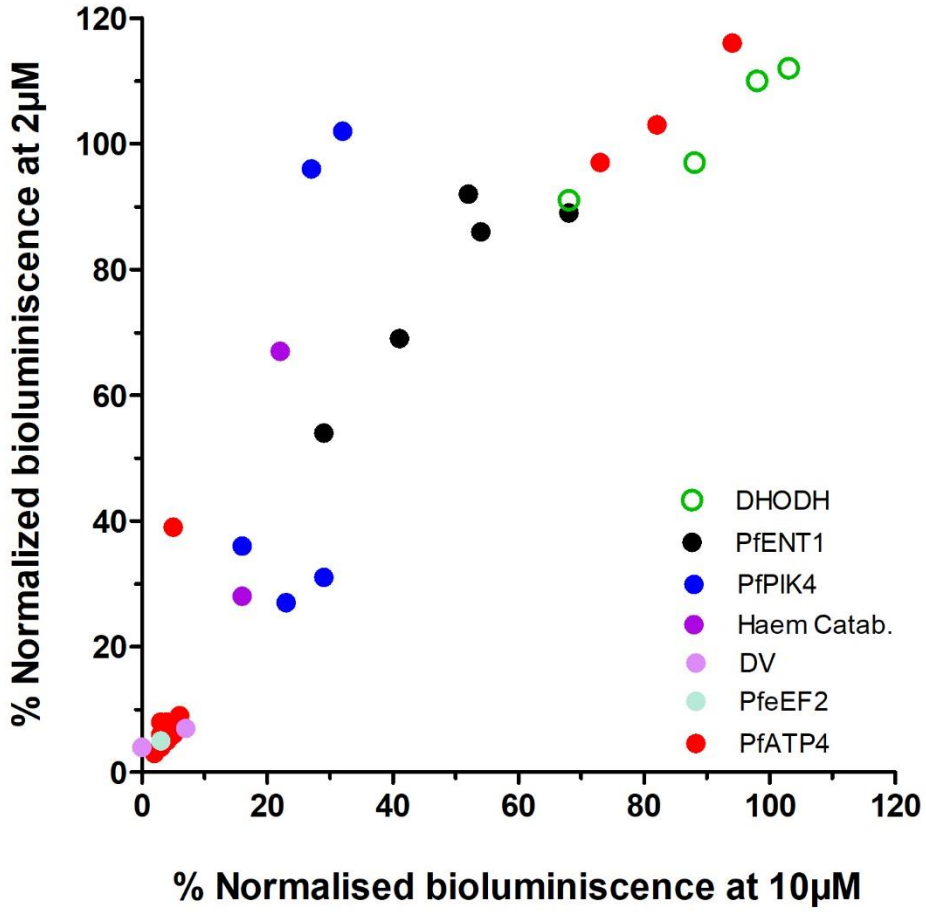


Figure 4.11: mBRRoK plot to explore potential MoA information for the MMV Pathogen Box compounds
A standard mBRRoK plot comparing the mean normalized bioluminescence signal at 10µM and 2µM.The key reports the colour codes used for the putative MoA.

With the mBRRoK data for 400 compounds now plotted, understanding why compounds are located in different parts of the plot is important if analyses of MoA and potency are to be of use (see Figure 4.12). Compounds in the lower left appear to be rapidly acting and potent as hypothesised (Figure 4.12 B red box) and target PfATP4 or DV disruptors that are known rapid RoK targets. Compounds in the upper right appear to have compounds within them that are slow or have a delayed death phenotype – such as antibiotics, DHODH and bc1 inhibitors (Figure 4.12B blue box). The slow acting compounds are arrayed in this space due to the apparent absence of initial cytocidal action, irrespective of the potency of the compound. Therefore as one moves from lower left to upper right, it can be predicted that the rate of kill is getting slower.

Moving towards the upper left on the mBRRoK plot is less well understood. The plot doesn't go beyond the point where there is a slope of 1 and the slope intercepts the y axis at x=0 and y=0 (termed here the minimum line) – this is because a compound should not cause a greater loss of bioluminescence at 2µM than at 10µM. Taking the intra erythrocytic potency where reported for each of the 400 MMV Pathogen Box compounds (www.mmv.org), these data can be plotted (Figure 4.12A) for three different strains of *P. falciparum*. There appears no obvious pattern when a quartile analysis of the potency of the compounds (see key for the 3D7 data) is plotted. However, when the most potent (Figure 4.12B) and least potent (Figure 4.12C) are plotted and a linear regression done, it is clear that the linear regression for the most potent compounds is closer to the minimum line. This would be expected as these more potent compounds can better achieve a >10 fold EC_{50}, or at least close to it, at either 2 or 10µM – for these compounds, the position of the slope absolutely informs you of their relative rate of kill. The regression of the least potent compounds moved towards the upper left and deviates away from a slope of 1. For these compounds, the lack of potency suggests they move away from the minimum line and for these compounds their position is based on the interaction between the

fold EC_{50} they achieve and the impact this has on them achieving ***their maximal rate of kill,*** whether this is slow or rapid – and is not simple to predict.

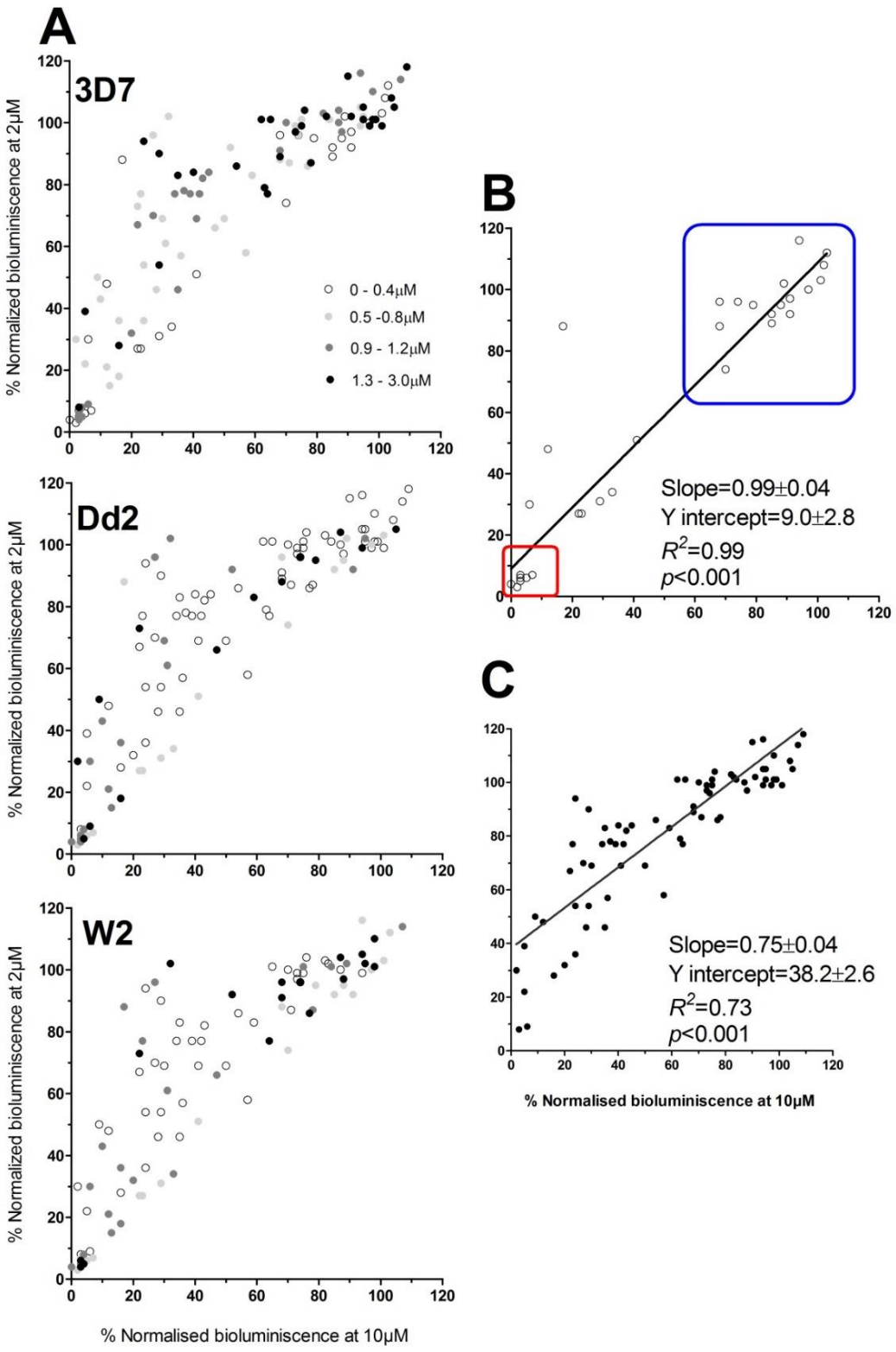


Figure 4.12: Exploring the regions of a mBRRoK plot – the impact of potency (previous page) *(A) Standard mBRRoK plot comparing the mean normalized bioluminescence signal at 10µM and 2µM for the 400 MMV Pathogen Box compounds. The three plots show the potency (see key on the 3D7plot) in three different P. falciparum strains. Using this data, plots of the most potent (B; 0-0.4µM) and least potent (C; 1.3 µM or above) are shown with a linear regression plotted for data on graphs B and C. Blue box represents compounds with known slow acting MoA and red box compounds with known rapid acting MoA.*

Overall, the mBRRoK assay appears to be good at predicting fast-acting compounds and excluding slow acting compounds with their initial RoK data appearing to correlate with the known or proposed modes of action. Together, these findings appear to validate the utility of the mBRRoK assay to rapidly prioritize fast and potent compounds from a library of unknown rate of kill - and even for a resource as reasonably well described as the MMV Pathogen Box, new insights around novel hits and information around rates of kill for new potential MoA have been achieved.

5 Chapter 5

5.1 Introduction

The search for new classes of antimalarial has been greatly improved through the application of technological innovations such as robotic automation and liquid handling together with miniaturization of screening assays to provide ultra-high throughput (HTS) screening of massive compound libraries (Lackovic *et al.*, 2014). Moreover, development in the field of chemoinformatics for the analysis, filtering and interpretation of the large datasets from such ultra-HTS provide an indispensable tool in the field of drug discovery (Duffy *et al.*, 2012). These innovations build on two fundamental approaches for screening commonly utilized in drug discovery; phenotypic, or "whole-cell" screens, and target-based screens. Phenotypic screening allows for the interrogation of all the possible targets of a test compound on the target cell (here typically *P. falciparum* and often the asexual stage within an erythrocyte) within a biological context that is "close" to its use as a drug. Whilst target-based screening instead involves direct evaluation of the compound effect on a specific target, often the purified protein target (Swinney, 2013).

An advantage of the phenotypic screen is that compounds that do not access the target cell – here not penetrate the infected erythrocyte's multiple membrane layers – can be excluded from further characterisation. It is also often considered that the effect of the test compound is examined in an unbiased manner in these "whole-cell" assays and that no previous knowledge of the target of the compound is required to develop the assay strategy (Swinney, 2013 and Katsuno *et al.*, 2016). Compounds that exert synergistic effect or have many targets within the same cell are gathered together in this "whole-cell" (Hovlid and Winzeler, 2016). A major shortcoming of any phenotypic screen, however, is the difficulty in scaling and optimization of the identified hits because some knowledge of the probable target is required (Plouff *et al.*, 2008). As target-based screens already have defined target, lead optimization and scaling of

meaningful screens is a lot easier. Thus, there appears to be some advantage to understanding the target for the drug being developed and approaches for resolving targets such as selection of resistant mutants and biochemical affinity-based methods may offer some answers (Plouffe *et al* 2008). Although, again, the task of performing these target identification strategies do pose difficulties and can be time-consuming (Plouffe *et al.,* 2008). Nevertheless, with automation and miniaturization of cellular screens, large amount of data for a particular chemo-type can now be rapidly gathered from arrays of different cellular screens (Plouffe *et al*., 2008; van Hooris *et al*., 2016).

As compounds which show similar activity against a particular target or pathway will probably have the same profile across different screens, this open up the utility of *in silico* activity profiling of antimalarial compounds as demonstrated by Plouffe *et al*., (2008). Data generated from a fluorescence-based screen of 1.7 million compounds yielded some 17,000 compounds with potent antimalarial activities following a screen across 131 different cellular and enzymatic screens. Plouffe *et al*., (2008) was able to show the cellular pathway and/ or protein target for some of the selected compounds. Since this initial HTS work, several other examples of screens against asexual intraerythrocytic stages of *P. falciparum* using fluorescence-based assays have been reported (Banieck *et al*., 2007; Guiguemde *et al*., 2010; Avery *et al*., 2014; Baragana *et al*., 2015). One study reported the screen of nearly 2 million compounds from GlaxoSmithKline (GSK) performed by Gamo *et al.,* (2010). All compounds were tested *in vitro* at a 2µM fixed concentration against the *P. falciparum* 3D7 strain. 19,451 compounds were found to inhibit parasite growth by more than 80% over 48hrs. Subsequently, fresh samples of these primary hits were re-tested against the multidrug resistant Dd2 parasite strain at 2µM concentration and nearly 8000 compounds (80%) inhibited the parasite growth by at least 50%. As expected, compounds that were less potent against Dd2 were predominantly quinolines or had structures similar to antifolates. This finding agrees with the report of Yuan *et al.,* (2009) that showed a

number of these related chemotypes were less active against the multi-drug resistant Dd2 parasites. A final selection of 13,533 compounds of confirmed hits in Dd2 and 3D7 is collectively termed the Tres Cantos (the GSK research site near Madrid) Antimalarial Compound Set (TCAMS) library was based and included compounds that inhibit parasite growth by more 80% in at least two of the screening experiments performed. In addition to antiplasmodial activity, evidence of cytotoxicity and interference with luciferase reporter assays was observed for some 1,982 compounds (15%) when assayed at 10µM against in HepG2 cells and were excluded. For many of the compounds within the TCAMS library, when complete concentration-response assays have been done, most have thus far been reported to have potency within sub-micromolar range (Gamo *et al.,* 2010). For these compounds in TCAMS library, a structural analysis of the different chemo-types by molecular framework (Bernis and Murcko, 1996) or finger print analysis has been done. These molecular framework and finger print clusters describe a core scaffold and minor substituent pattern, respectively (Gamo *et al.*, 2010). This analysis was reported to provide 416 molecular frameworks, 857 clusters and 1,978 singletons, with the intention to use these structural data to support discovery of possible mechanism of action. This was based on an assumption that compounds clustered together may share the same mode of action (Gamo *et al.,* 2010) such as protein kinases and host-pathogen interaction related targets suggested for some of these compounds.

There has been progress in screening the TCAMS library against other parasite stages, where screening of *P. falciparum* gametocytes identified 373 compounds with dual activity against both intraerythrocytic and gametocyte stages (Almela *et al.,* 2015). Secondary confirmation and cytotoxicity assays of the primary hits resulted in 98 compounds that were progressed for further analysis. Filtering these 98 compounds using physicochemical properties resulted in the prioritization of 56 compounds for additional follow-up. In a second study, Miguel-Blanco *et al*., (2017) screened the TCAMS library against *P. falciparum* stage V female gametocytes.

More than 400 compounds that showed activities against female gametocytes at 2µM fixed concentration were identified. These hits were chemically grouped into 57 clusters and 33 singletons. Subsequently, four compounds from three different scaffold clusters were selected for *in vitro* transmission-blocking confirmation (Miguel-Blanco *et al*., 2017). Recently, Delves *et al*., (2019) screened the TCAMS library for transmission-blocking compounds in an *ex vivo P. berghei* ookinete formation assay. 437 compounds were reported to inhibit parasite ookinete formation with an IC_{50} of less than 10µM. Cytotoxicity testing identified 273 compounds that showed more than 10-fold parasite selectivity when compared with activity against HepG2 cells. The remaining hit compounds were classified into 49 chemicals clusters and transmission-blocking activities were confirmed for six compounds selected from six different scaffold clusters (Delves *et al.,* 2019). The TCAMS library has also been used for screening against intrahepatic stages of *P. falciparum* using a forward chemical genetic (Raphemot *et al*., 2016) approach that led to the identification and confirmation of 103 compounds with dual-stage malaria parasite inhibitors in liver and erythrocyte host cells.

GSK has mined the TCAMS library to identify potential compounds that could serve as starting points for lead optimization (Calderon *et al*., 2011).13,533 TCAMS compounds have been filtered down to 47 series using an agglomerative structural clustering analysis informed by their physicochemical properties. The top 5 important series are indolines, aryl carboxamides, alkyl prazoles, thienopyrazoles and 4-aminopiperidines (Calderon *et al*., 2011). These chemical starting points have been presented by GSK for an open innovation in Malaria drug discovery. First of these series to be exploited for lead optimization developments were the cyclopropyl carboxamides (Rueda *et al*., 2011; Sanz *et al*., 2011). This series readily inhibits both drug-resistant and dug-sensitive *P. falciparum* strains *in vitro* and display *in vivo* oral efficacy in a mouse model. However, selection for resistant mutant was relatively easy and this prevented their further development (Sanz *et al*., 2011). The second series to be exploited were the

indolines, but their interaction with serotonin antagonist receptors (Calderon *et al*., 2012) blocked their development. However, a new lead was generated by using a double-divergent structural activity relationship analysis (Calderon *et al*., 2012). The spiroindolone (KAE609) is an example of an antimalarial candidate that was identified from the antiplasmodial screening of TCAMS library. This molecule is currently undergoing further clinical trials and may represent the first new antimalarial chemotype to be introduced in two decades of drug discovery research (Flannery *et al*., 2013).

Given the development and validation of the mBRRoK assay in the previous two chapters, this chapter sets out to demonstrate the optimization of a moderate miniaturization of this mBRRoK assay and the application of this assay to screen the TCAMS library for compounds that show both potent and fast-acting activity. The TCAMS library being selected based on its provenance in antiplasmodial activity and the work already available in terms of structural and cytotoxicity data. This work represented an open access collaboration with GSK, who, based on the evidence provided to them on the validation of the mBRRoK assay, agreed to provide 12,514 compounds from the TCAMS library printed onto 384-well plates sufficient to provide a 10µM or 2µM concentration.

5.2 Results

5.2.1 Optimization and miniaturization of the mBRRoK assay to a 384-well plate format

The TCAMS library was provided on a series of seventy-six 384-well microplates. Of these, 38 were set up to deliver a 10µM concentration and the remaining 38 (mapped identically to the first 19 plates) to deliver a 2µM concentration when solubilised in a 20µL volume of infected erythrocyte culture. Thus, each of the 12,514 compounds were provided at two concentrations for a n=1 sample count at each concentration. Blank wells were available on all plates to allow controls (untreated culture, supralethal kill (10 µM of CQ), and benchmark antimalarials) to be included. As all previous assays with BRRoK and mBRRoK used a 2% haematocrit, the same haematocrit was used throughout here.

The first parameter evaluated was to ensure that using 20µL volume of infected erythrocyte culture ($Dd2^{luc}$) would provide for a linear response in loss of parasitaemia (or viable parasites). Therefore, in triplicate on a 384-well plate, a 2% trophozoite stage infected erythrocyte culture was diluted in a two-fold series with a 2% HCT erythrocyte culture. This reduces the parasitaemia but does not affect the overall haematocrit. The samples were processed by the addition of 20µL of a 5X passive lysis/luciferase reagent and after mixing the luciferase signals measured. The measurements were repeated using three measurement times; 2sec, 1 sec and 0.5sec. These data are integrated by the bioluminometer and counts/sec are reported – there was no difference between the parasitaemia *v.* bioluminescence – the linear regression of these data (Figure 5.1) overlapped exactly and so the data only for 0.5sec of measurement is shown. However, using a 0.5sec measurement instead of a 2sec measurement, changed the time to measure the signals over a 384-well plate from almost 13 minutes to just over three minutes. Data presented in Figure 5.1 also shows a linear response between bioluminescence signal and parasitaemia to at least 0.0625% parasitaemis – i.e. over a range that would enable a 96.875% kill to be measured over a 6hr assay. This is greater than the estimated maximum performance

of the assay – this would assume that a 100% kill is affected immediately and that the luciferase ½ life is 1.5 hrs (Hasenkamp *et al*., 2012) – over 6 hrs in these conditions a 93.75% signal loss would be achieved.

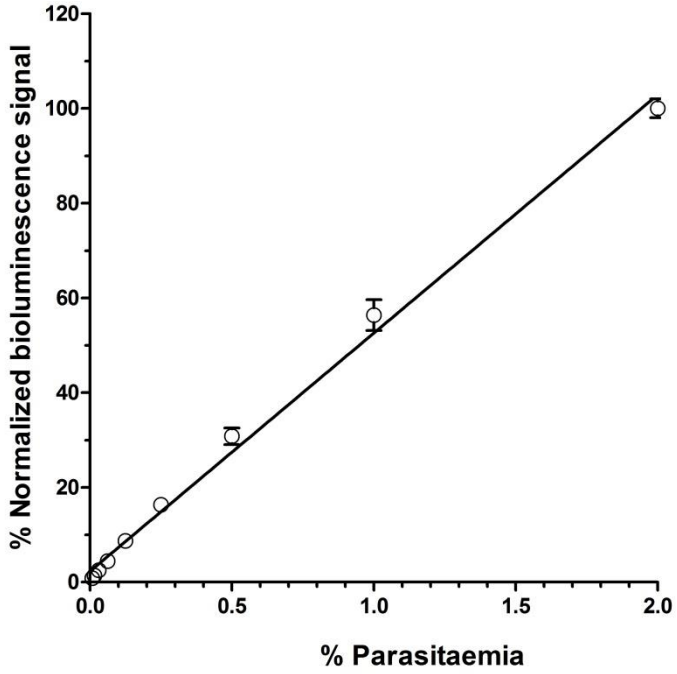


Figure 5.1: Exploring the linear correlation between parasitaemia and bioluminescence signal on a 384-well microplate
The bioluminescence signal from the indicated parasitaemia of trophozoite stage Dd2^{luc} was plotted (n=3, mean ±stdev) and *a* linear *regression done. The data plotted is from a measurement of 0.5sec/well – with data from 1sec and 2sec/well exactly overlapping data shown here.*

Given the time to record the signal over the whole plate, it was decided to next compare the measurement of the effect of compounds when seeded at the top (Rows A to D) or bottom of a plate (Rows M to P) that was read over its entirety (wells are measured A1 to A24, then B1 to B24 etc.). Ninety compounds were assessed, comprising seven benchmark antimalarials, 16 Malaria Box compounds and 67 Pathogen Box compounds. These were assessed on different plates at either 10µM or 2µM, with three replicates being prepared. Bioluminescence signals were measured after 6hrs of exposure and normalized to the mean of six untreated controls placed at the top and bottom of each plate. A comparison of the signal (mean, n=3) measured

at the top and bottom of the plate reveal a strong linear correlation between the same effects measured at the top and bottom of the 384-well plate (Figure 5.2). This would indicate that over the time course of measuring a plate that the position of the well would not affect the outcome. Of note is the greater killing effect achieved at 10µM providing a greater range of effects to enable a greater correlation to be established (Figure 5.2A), whereas the lack of measured kill at 2µM for some 50% of the compounds produces a bias in the distribution of data (Figure 5.2B).

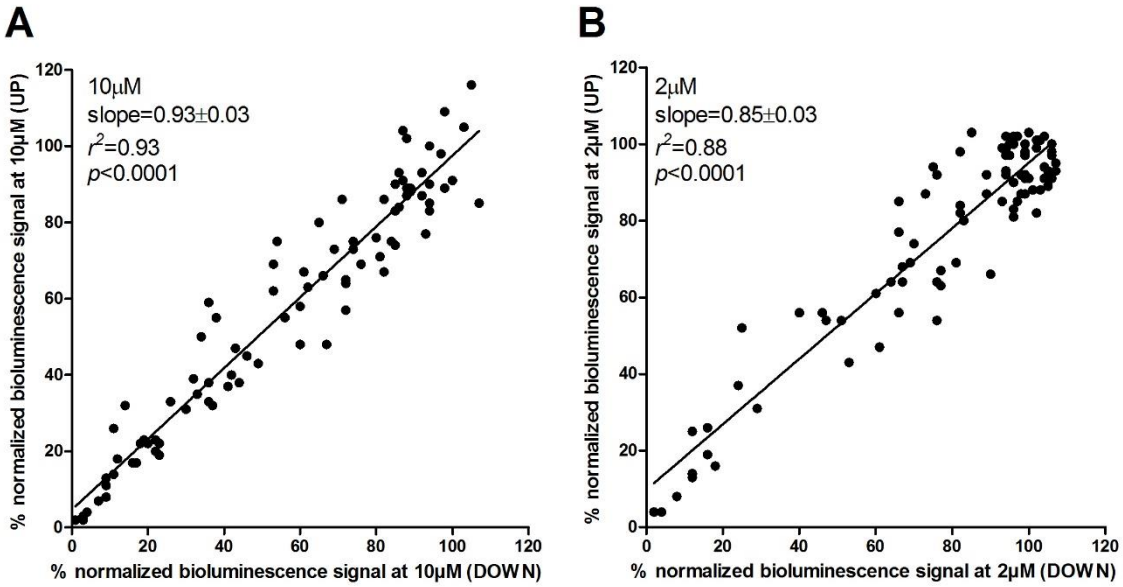


Figure 5.2: Exploring the effect of plate positioning on bioluminescence signal on a 384-well microplate.
*The p*lots represent the mean normali*zed bioluminescence signal (n=3) after exposure to* (*A) 10µM or* (*B) 2µM of 90 compounds positioned either at the top (y-axis) or bottom (x-axis) rows on a 384-well plate. The insert text provides the parameters for a linear regression analysis.*

As a final validation of the adaptation into the 384-well mBRRoK assay, a comparison of the 384 *vs* 96 well microplate assays was done. Using the same 90 compounds chosen for the analysis of plate-position effect above, the mean of the data developed for both the top and

bottom of the 384-well plates (i.e. n=6 datasets) was compared to available data developed for these same compounds as described in chapters 3 (benchmarks and Malaria Box compounds) and 4 (Pathogen Box compounds). Thus, for the MMV Compound sets, n=6 datasets at 10µM and 2µM were available from a 96-well plate format, with the mean of at least n=9 experiments used for the benchmark antimalarials. These data are compared in Figure 5.3. Comparison of these signals shows a good correlation (slope close to 1 and r^2 of ≥0.76) between the datasets developed for the same concentration of each compound. This, and the previous data, indicated a position to move forward with the GSK plate screening.

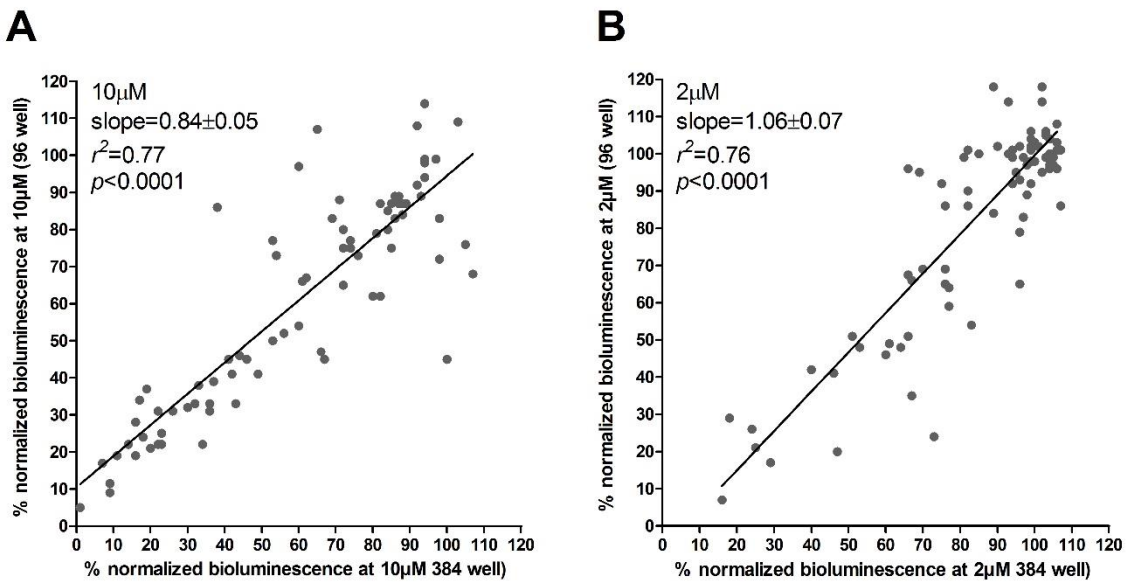


Figure 5.3: Comparison of mBRRoK assay performance between 96-well and 384-well microplate assay formats.
The plots represent the mean normalised bioluminescence signal (n≥6) after exposure to (*A) 10µM or* (*B) 2µM of 90 compounds assayed on 96-well plates (y-axis) or 384-well plates (x-axis). The insert text provides the parameters for a linear regression analysis.*

5.2.2 Screening the TCAMS library in a 384-well mBRRoK assay

As described earlier, each of the 76 plates provided by GSK has empty wells provided for the controls to monitor assay performance during the screen. These controls fell into two groups. The first was the addition to 25 pairs of plates wells of 1 well with either 10µM or 2µM (based on the concentration of the TCAMS library on that plate) of four bechmarks; DHA (rapid), CQ (rapid), MQ (moderate) and ATQ (slow). The second control, on all plates, was the addition of eight wells with no compound added (the mean of these also acting as the normalization for all data on that plate) and eight wells with a 2% erythrocyte haematocrit to act as a negative control due to no parasite materials in the culture. These two sets of eight wells allows for each plate the following high throughput assay quality parameters (Zhang *et al*., 1998) to be determined: Z' score, signal/background ratio, coefficient of variation around the maximum ($\%CV_{max}$) and minimum ($\%CV_{min}$) signals (see section 2.6.5 on how to determine them, and Table 5.1 for a report of all values).

Plotting the 25 pairs of benchmark antimalarial controls (Figure 5.4) provides a "cloud" of data points for each of the four compounds in spaces already demonstrated previously in this thesis to be occupied by these antimalarial compounds in $Dd2^{luc}$. The "cloud" illustrates the minimal variation in the actual data determined for a series of n=1 measurements, and suggest a consistent assay performance, at least for these 25 plates. These data also provide key markers on the 384-well mBRRoK plot to provide relative data.

Plotting the Z' and S/B ratio across all 76 384-well plates is shown in Figure 5.5. The robustness of the assay was demonstrated by high Z' scores (0.74-0.98) over all plates, with a minimum of 0.5 indicated as a good parameter for high throughput screening (Zhang *et al*., 1998). The sensitivity of the assay was maintained, even using the reduced volumes of parasite culture and assay reagents, with high S/B ratios (160 to 475) over all plates. As expected for this

bioluminescence assay, there is a low maximum coefficient of variation (CV_{max}, 1% to 9%) which illustrates the consistency in maximum signal across all untreated control samples used to normalise all other data on the plate. The high minimum coefficient of variation (CV_{min}, 8% to 35%) in bioluminescence assays has previously been described by Hasenkamp *et al*., (2013) due to the very low background (between 50-80 counts) signals obtained, so low that they are not used as a background correction in these assays.

Overall, these assay performance parameters indicate a robust and sensitive assay performed across all 76 384-well plates used in this high throughput study.

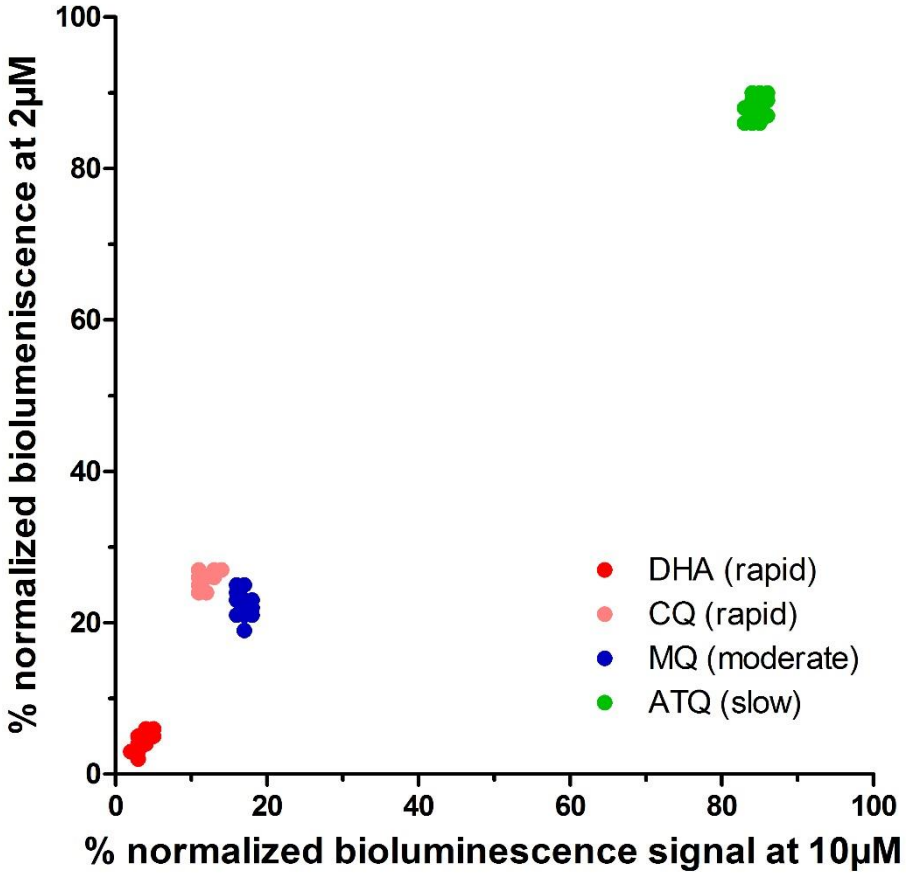


Figure 5.4: Marking benchmark antimalarial data "clouds" on a 384-well mBRRoK plot.

The normalised bioluminescence signal from corresponding pairs of 384-well plates (based on the TCAMS compounds arrayed on them – see Table 5.1) for 10µM and 2µM of benchmark antimalarials are plotted on this mBRRoK plot. Each data point represents one of 25 sets of data – producing the data "cloud" for that particular antimalarial benchmark. ATQ, atovaquone; CQ, chloroquine; DHA,

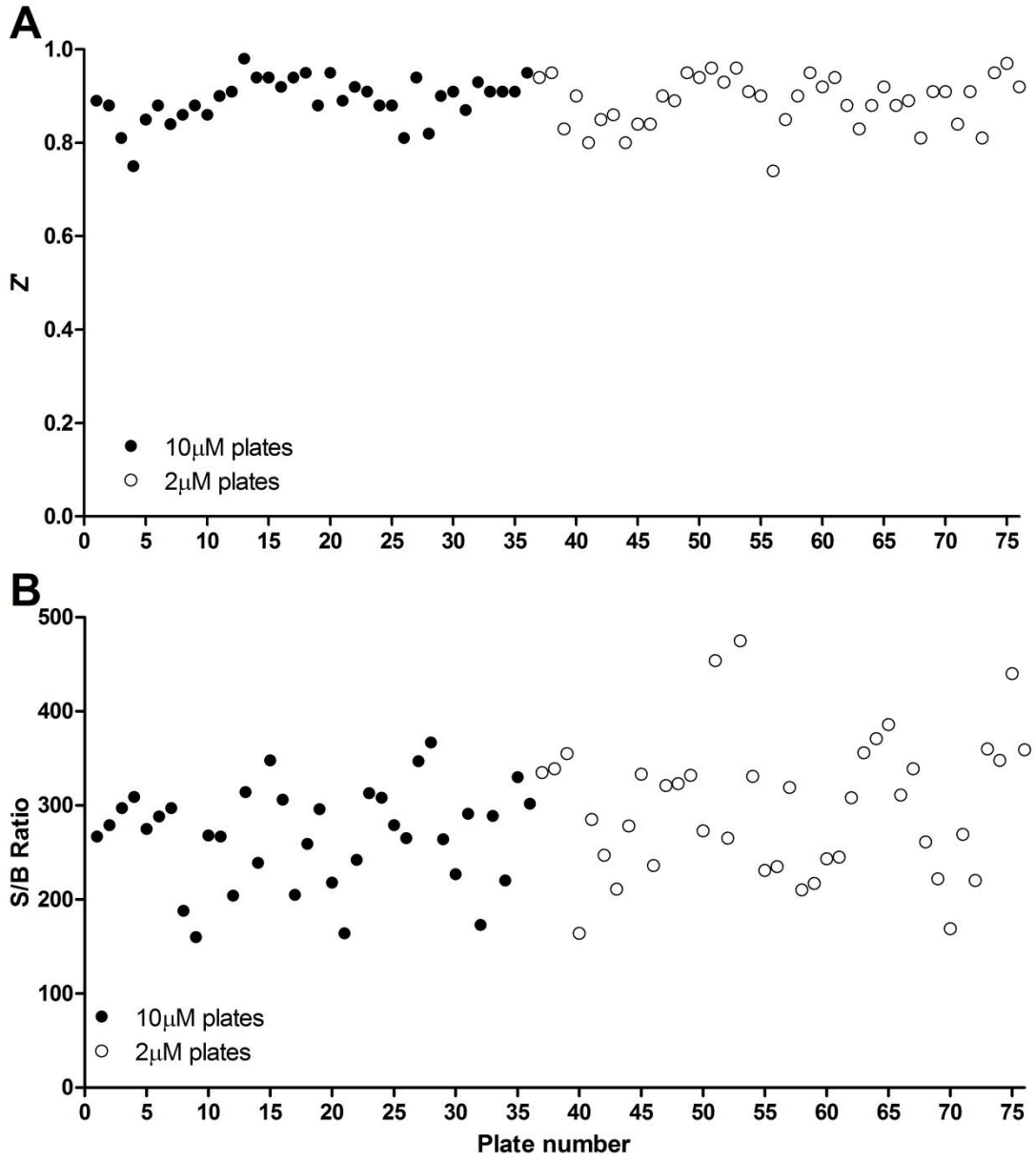


Figure 5.5: Monitoring of assay performance parameters for the mBRRoK of TCAMS library
(A) The Z' score (ideally above 0.5 for a HTS, Zhang et al., 1998). The first 38 plates represent compounds plated at 10μM, with the next 38 plates the same compound plates (in order, see Table 5.1) with 2μM of compound plated.
(B) The mean signal/background (S/B) for the untreated control vs the no-parasite (erythrocyte only) control.

Table 5.1: mBRRoK assay performance parameters for TCAMS screen.
Each row reports a pair of plates that contain the same compounds at the indicated concentration.

	10µM plate					2µM plate			
TCAMS Plates ID	**Z' score**	**S/B**	**%CV$_{max}$**	**% CV$_{min}$**	**TCAMS Plates ID**	**Z' score**	**S/B**	**%CV$_{max}$**	**% CV$_{min}$**
U004O3V	0.89	267	4	28	U004KV7	0.83	355	6	19
U004O47	0.88	279	4	24	U004KV8	0.9	164	3	21
U004O3S	0.81	297	6	31	U004KVC	0.8	285	7	14
U004FAT	0.75	309	8	23	U004KUN	0.85	247	5	23
U004O3W	0.85	275	5	30	U004KUL	0.86	211	5	19
U00403U	0.88	288	4	32	U004KV1	0.8	278	7	17
U004O3Q	0.84	297	5	35	U004KUW	0.84	333	5	14
U004O40	0.86	188	5	23	U004KUT	0.84	236	5	8
U004O3Z	0.88	160	4	13	U004KUQ	0.9	321	3	14
U004FAS	0.86	268	4	30	U004KV4	0.89	323	4	20
U004O3R	0.9	267	3	30	U004KV9	0.95	332	2	16
U004O41	0.91	204	3	21	U004KUV	0.94	273	2	18
U004O42	0.98	314	1	19	U004KVB	0.96	454	2	22
U004KWJ	0.94	239	2	22	U004KV3	0.93	265	2	20
U004KW7	0.94	348	2	19	U004KUP	0.96	475	1	15
U004KWK	0.92	306	2	25	U004KVA	0.91	331	3	15
U004KWI	0.94	205	2	15	U004KV5	0.9	231	3	32
U004KW4	0.95	259	2	17	U004KUS	0.74	235	9	29
U004KWH	0.88	296	4	35	U004KUZ	0.85	319	5	19
U004KWA	0.95	218	2	23	U004KV6	0.9	210	3	25
U004KVL	0.89	164	4	26	U004KV2	0.95	217	2	22
U004KWE	0.92	242	3	25	U004KUX	0.92	243	3	25
U004O45	0.91	313	3	21	U004KUU	0.94	245	2	10
U004KWB	0.88	308	4	20	U004KUR	0.88	308	4	20
U004KWD	0.88	279	4	16	U004KUY	0.83	356	6	15
U004O44	0.81	265	3	17	U004KVD	0.88	371	4	14
U004KWL	0.94	347	2	13	U004KV0	0.92	386	3	12
U004KWF	0.82	367	6	31	U004KVE	0.88	311	4	18
U004KW9	0.9	264	3	23	U004KVM	0.89	339	4	13
U004O3T	0.91	227	3	23	U004KVK	0.81	261	6	14
U004O46	0.87	291	4	27	U004KVO	0.91	222	3	16
U004O3X	0.93	173	2	17	U004KVI	0.91	169	3	39
U004KW8	0.91	289	3	20	U004KVJ	0.84	269	5	9
U004KW3	0.91	220	3	23	U004KVG	0.91	220	3	23
U004KWG	0.91	330	3	20	U004KVF	0.81	360	6	22
U004O3Y	0.95	302	2	13	U004KUM	0.95	348	2	27
POOLCGS	0.94	335	2	13	U004KVH	0.97	440	1	17
U004O43	0.95	339	2	14	U004KVN	0.92	359	3	14

A mBRRoK plot for all the 12,514 TCAMS library compounds is shown in Figure 5.6. A complete report of all data against each compound ID is presented in a spreadsheet in appendix 5 at end of this thesis. In order to define a cut-off for compounds of interest in this screen, the sensitivity and specificity thresholds calculated in chapter 3 were applied to the screening data (20% for 10µM and 25% for 2µM). A total of 975 compounds were selected in this mBRRoK screen of the TCAMS library as compounds likely to be fast-acting and have high potency. This primary screen provides a hit rate of 7.8%, a high value that reflects the pre-selection of TCMAS library compounds based on their potency. The data was shared with GSK with the aim to resupply compounds for the confirmation of potency and rate of kill in a standard BRRoK assay.

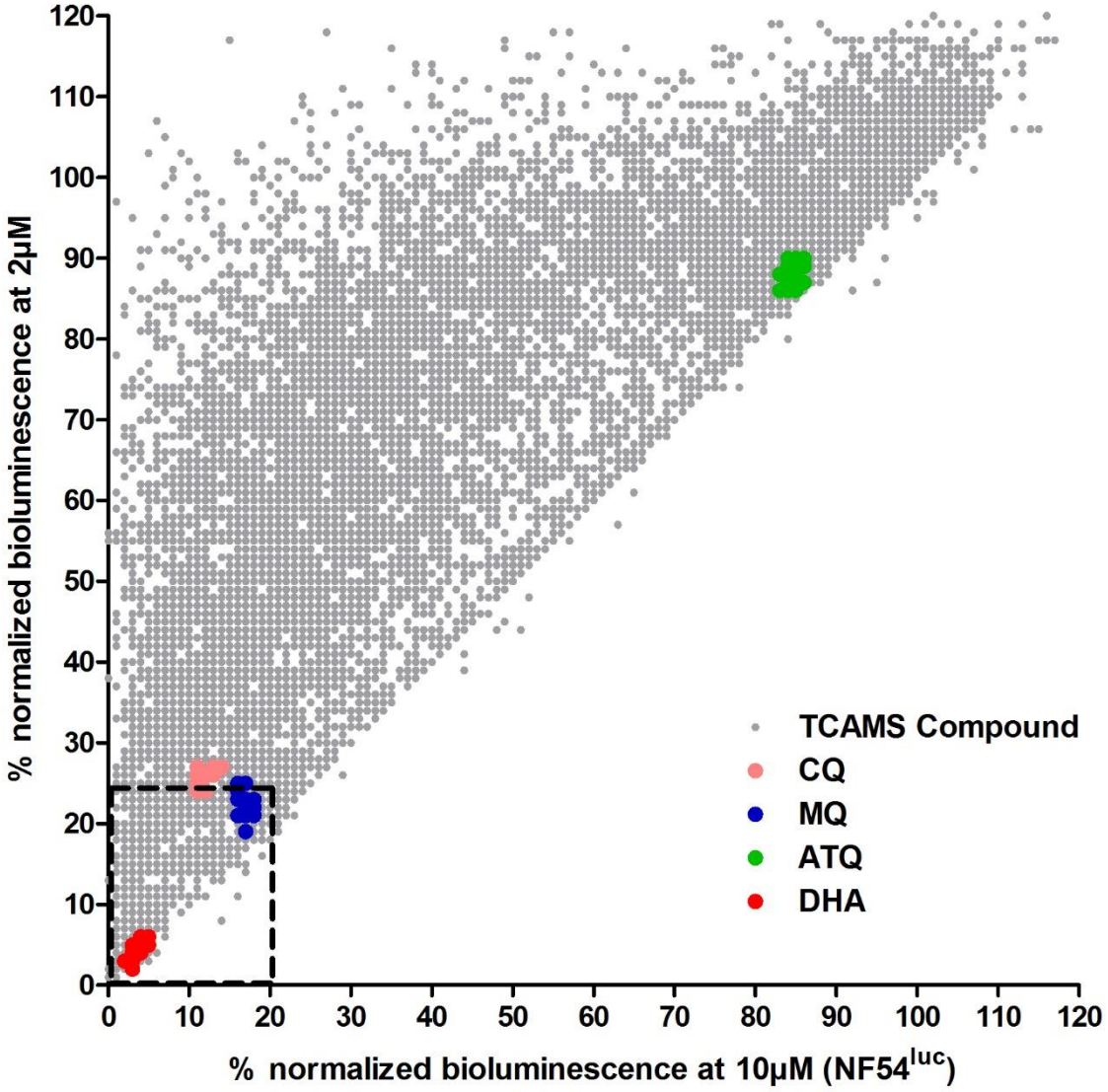


Figure 5.6: mBRRoK plot of 12,514 TCAMS library compounds.
The normalised bioluminescence signal for 12,514 TCAMS library compounds after 10µM and 2µM exposure for 6hrs.These are marked in gray (n=1 for each compound). Benchmark antimalarials are plotted on this mBRRoK plot. Each data point represents one of 25 sets of data. ATQ, atovaquone; CQ, chloroquine; DHA, dihydroartemisinin;MQ, mefloquine.

5.2.3 Re-confirmation of mBRRoK hits

A total of 165 compounds were resupplied by GSK for the confirmatory assays. Of these, 136 compounds were selected to fall within the box on the mBRRoK plot predicted to identify potent and rapid acting compounds. The remaining 29 compounds fell out of this space and thus likely fail one or both of the rapid acting and potency requirements. As the previous assays had been done as single measurements, the first step of the confirmation was to repeat the mBRRoK assay. For ease of volume handling, these assays were all done in 96-well plates, with three independent repeats for 10µM and 2µM fixed concentrations used in all experiments. A second step in this confirmation was through the use of a second strain of *P. falciparum*, using the genetically-distinct NF54^{luc}, again with three independent measurements.

The scatter plots in figure 5.7A reports the distribution of the TCAMS compounds in the secondary screening in 96 well plate against Dd2^{luc} parasite strain. The sensitivity and specificity criteria for high threshold (20 x 25) in chapter 3 (section 3.2.2) was used to define the region on the plot that contain the predicted fast-acting compounds. 110 compounds (81%) out of the 136 compounds initially predicted to be potent and fast acting in the HTS of TCAMS library were re-confirmed in the secondary screening. Plotting the compounds that were inside the box of n=1 screen (Figure 5.7A in red) and outside the box (in blue), highlight that where some initial hits were not reconfirmed as being within the predicted rapid acting and potent area, no slow/low potency compounds were found to move into the hit box in the subsequent screen.

Using the same experimental approach with the NF54^{luc} strain, a total of 109 compounds occupied the hit box (Figure 5.7B). As would perhaps be expected for the majority of the compounds, there was good correlation (slope, r^2 and significance of the linear relationship) between the screening data between the two parasite strains when used at 10µM (Figure 5.7C)

or 2µM (Figure 5.7D) concentrations. Interestingly, of the 109 compounds within the NF54^{luc} hit box, 97 of these were also found within the Dd2^{luc} hit box, with the remainder (except one) just falling outside the box. This suggests that the use of the n=3 mBRRoK assay in the two different strains has now taken the compounds of interest from the n=1 screen down from 81% based on a n=3 screen of one strain (Dd2^{luc}) down to 72%.

The initial relative rate of kill data were developed for 58 compounds out of the 165 compounds re-supplied by the GSK using the standard BRRoK assay. This would allowed the determination of their rate of kill without the issue of the potency of the compound contributing to the loss of bioluminescence signal. These 58 compounds were predicted from the mBRRoK in 96-well plate as follows:

Dd2^{luc} screen: 29 compounds in the hit box for speed and potency and 29 outside

NF54^{luc} screen: 31 compounds in the hit box for speed and potency and 27 outside

Thus, compounds that appear to have differences in mBRRoK activity in the two genetically distinct strains have been identified.

BRRoK assays require EC_{50} data to enable the fold-EC_{50} concentrations to be determined. As these could be different in the Dd2^{luc} and NF54^{luc} strains, an initial experiment was determined on nine compounds to explore the variation in EC_{50} in Dd2^{luc} and NF54^{luc} compared to the available data (Gamo *et al*., 2010) for these compounds prepared in 3D7 (another CQS strain), although noting these were only reported in µM and to 1 significant figure. The log concentration-normalised response curves used to estimate the EC_{50} in each strain is shown in Figure 5.8 with a comparison of these between the three strains in Table 5.2. Based on the similarity of these data between the strains, it was decided to test the activity of all these

compounds in both $Dd2^{luc}$ and $NF54^{luc}$ strains using the available 3D7 EC_{50} data (Gamo *et al.*, 2010) in BRRoK assay format.

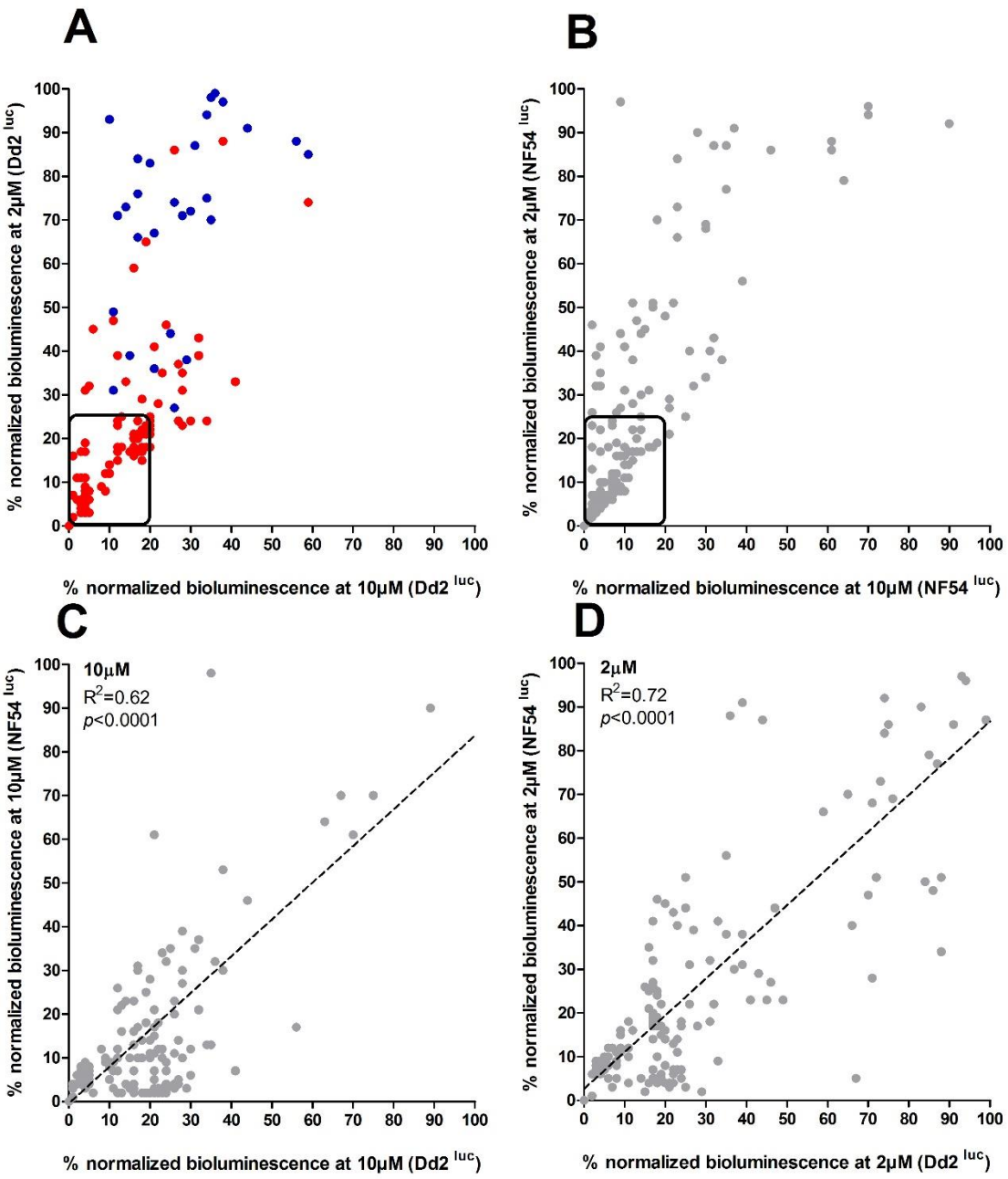


Figure 5.7: Confirmation mBRRoK assay data in Dd2^{luc} and NF54^{luc} strains
Standard mBRRoK plots of bioluminescence signals in A Dd2luc and B NF54luc for 165 compounds from the TCAMS library resupplied by GSK. For A, data in red are compounds that were initially identified as falling within the hit box for rapid acting and potent compounds in the original n=1 screen, with data in blue compounds that fell outside this box in the original screen. C and D report a linear correlation of remaining bioluminescence in Dd2^{luc}(x axis) and NF54^{luc} (y-axis) after exposure to 10µM and 2µM, respectively. Each data points represent mean of n=6 measurement (three biological repeats as technical repeats).

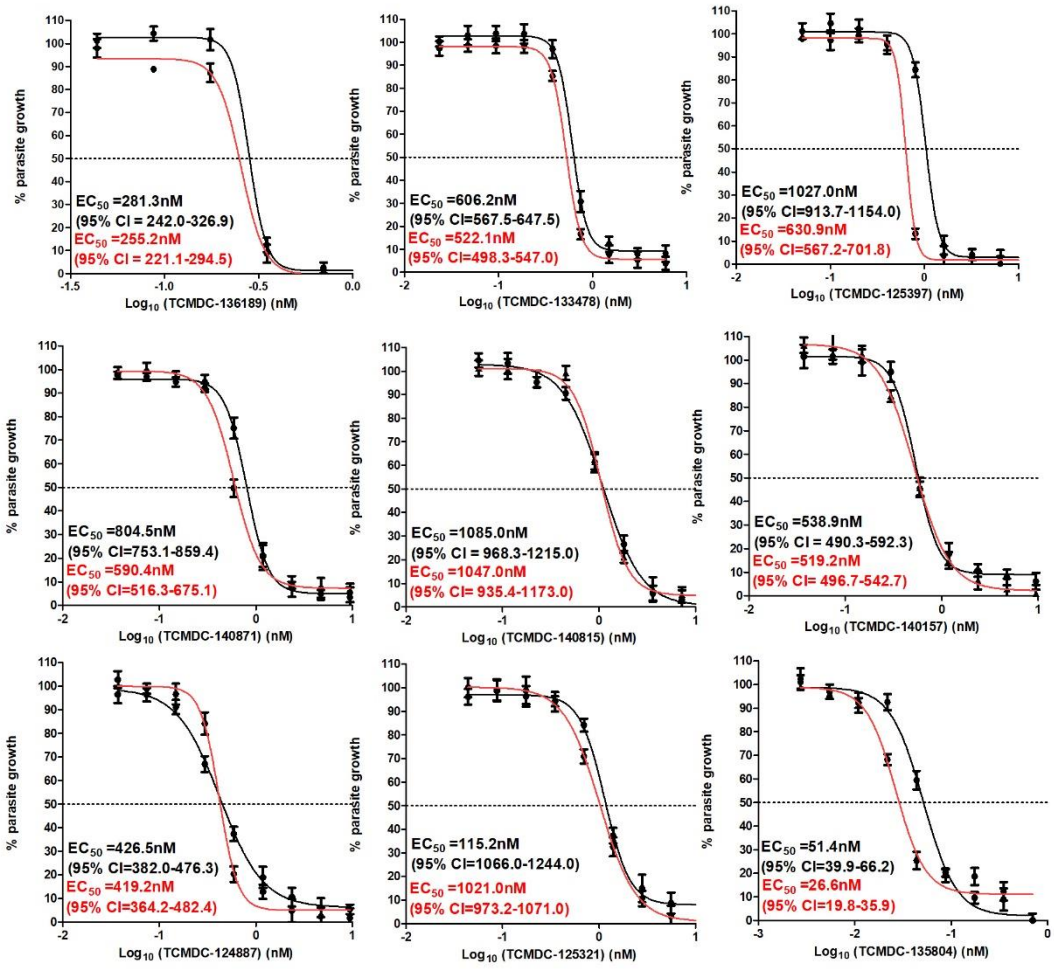


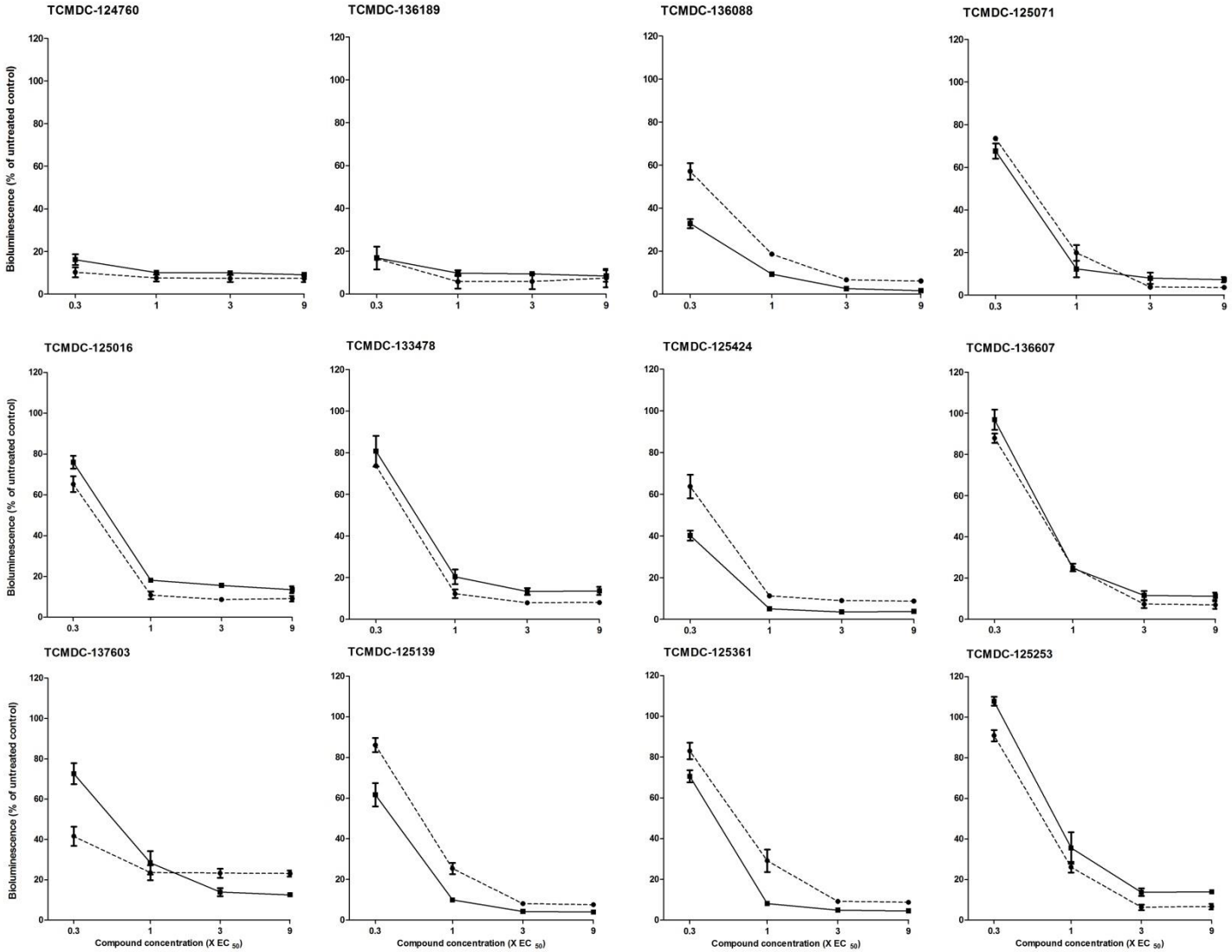
Figure 5.8: Concentration-normalised response curve for selected TCAMS compounds
Log_{10} concentration-normalised response graphs for the indicated compounds selected from the TCAMS library. $Dd2^{luc}$ and $NF54^{luc}$ EC_{50} curves are represented in black and red colour respectively. The curves represent the non-linear regression (mean ±stdev n=6) used to estimate the EC_{50} reported on each chart (see Table 5.2).

Table 5.2: List of selected TCAMS compounds and their EC_{50} determined in 3D7, $Dd2^{luc}$ and $NF54^{luc}$

TCMAS ID	EC_{50} (µM) in 3D7[1]	EC_{50} (µM) in $Dd2^{luc}$	EC_{50} (µM) in $NF54^{luc}$
TCMDC-136189	0.7	0.3	0.3
TCMDC-133478	0.4	0.5	0.2
TCMDC-125397	0.7	1.0	0.6
TCMDC-140871	0.6	0.8	0.6
TCMDC-140815	0.8	1.0	1.0
TCMDC-140157	0.6	0.5	0.5
TCMDC-124887	0.5	0.4	0.4
TCMDC-125321	0.7	1.2	1.0
TCMDC-135804	0.04	0.05	0.02

[1] 3D7 EC_{50} values are from Gamo *et al.*, (2010).

The standard BRRoK assay was performed against the two parasite lines for all 58 compounds. The standard BRRoK graphs representing the concentration-dependent loss of bioluminescence over 6hrs are reported for all the compounds in Figure 5.9. These data were developed in three biological repeats, each with three technical repeats (n=9 total). This figure is presented over five panels, labelled A to E. In table 5.3 a list of the compound ID, the panel on which the data is reported and an interpretation of the curve is shown. The interpretations of the relative rate of kill are based on the shape of the curves compared to existing data on available benchmarks in $Dd2^{luc}$ and $NF54^{luc}$ (Chapter 3). Fast highlights compounds that are at least as fast as CQ and therefore would meet the minimum *in vitro* threshold for activity. Moderate highlights those compounds that fall around the relative rate of kill activity described for aryl alcohols such as mefloquine and quinine – and up to the moderate rate of kill for folate inhibitors such as pyrimethamine. Slow represents compounds that are similar to the atovaquone benchmark. Different represents compounds that the rate of kill data appears different between $Dd2^{luc}$ and $NF54^{luc}$.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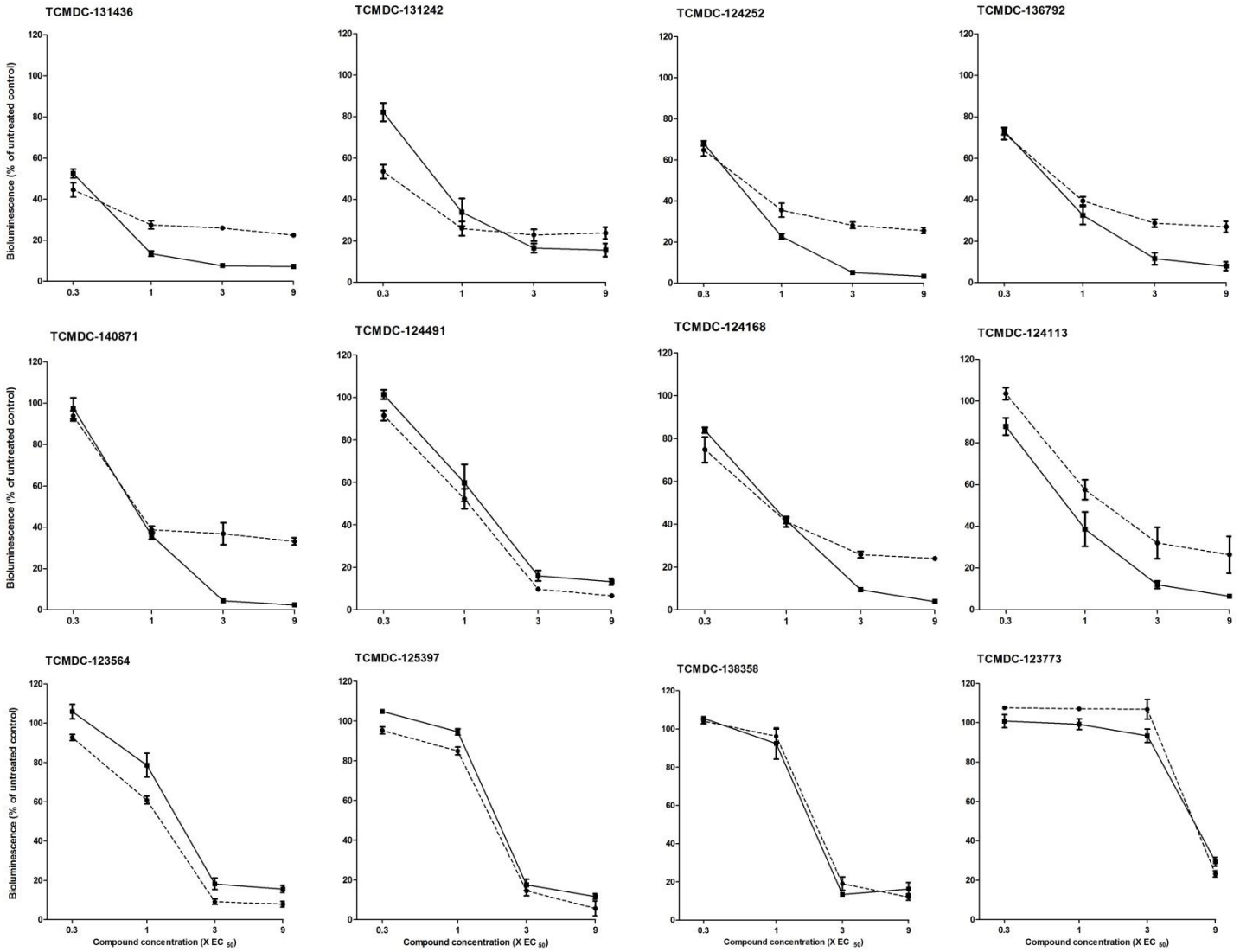
TCMDC-136189
TCMDC-136088
TCMDC-125071
TCMDC-125016
TCMDC-133478
TCMDC-125424
TCMDC-136607
TCMDC-137603
TCMDC-125139
TCMDC-125361
TCMDC-125253
Bioluminescence (% of untreated control)
Compound concentration (X EC 50)
0.3
1
3
9
0
20
40
60
80
100
120

A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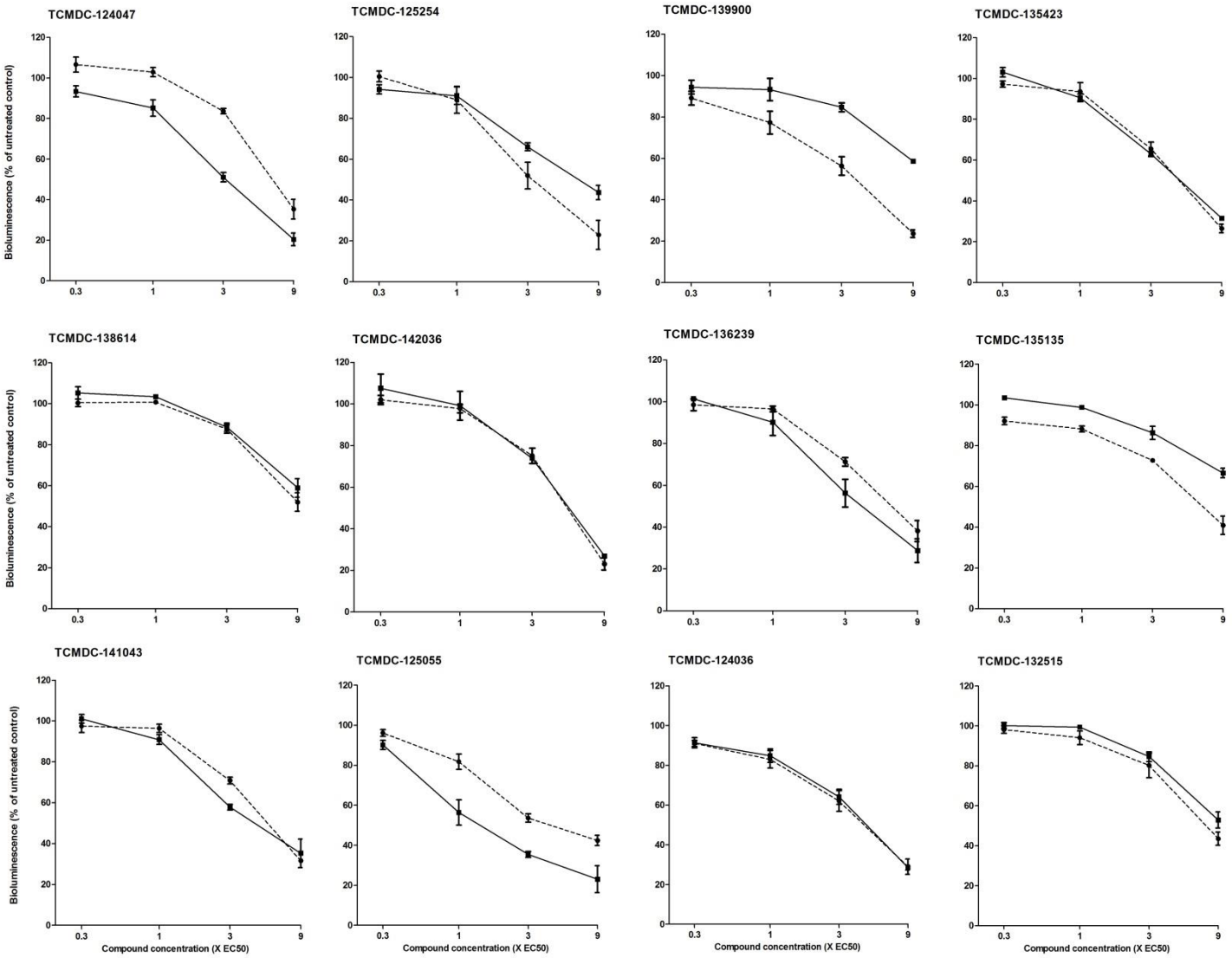
TCMDC-131242
TCMDC-124252
TCMDC-136792
TCMDC-140871
TCMDC-124491
TCMDC-124168
TCMDC-124113
TCMDC-123564
TCMDC-125397
TCMDC-138358
TCMDC-123773
Bioluminescence (% of untreated control)
Compound concentration (X EC 50)
0.3
1
3
9

B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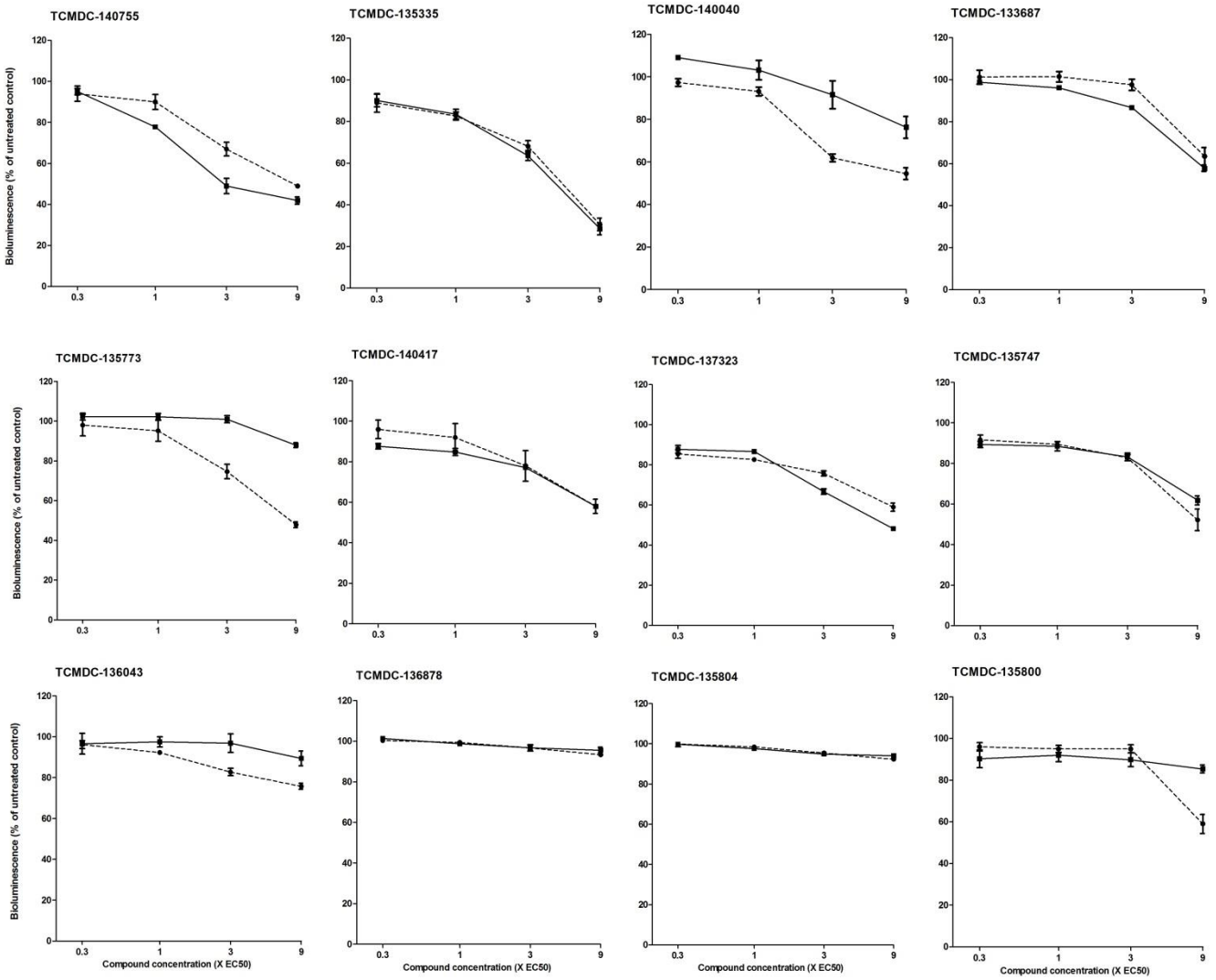
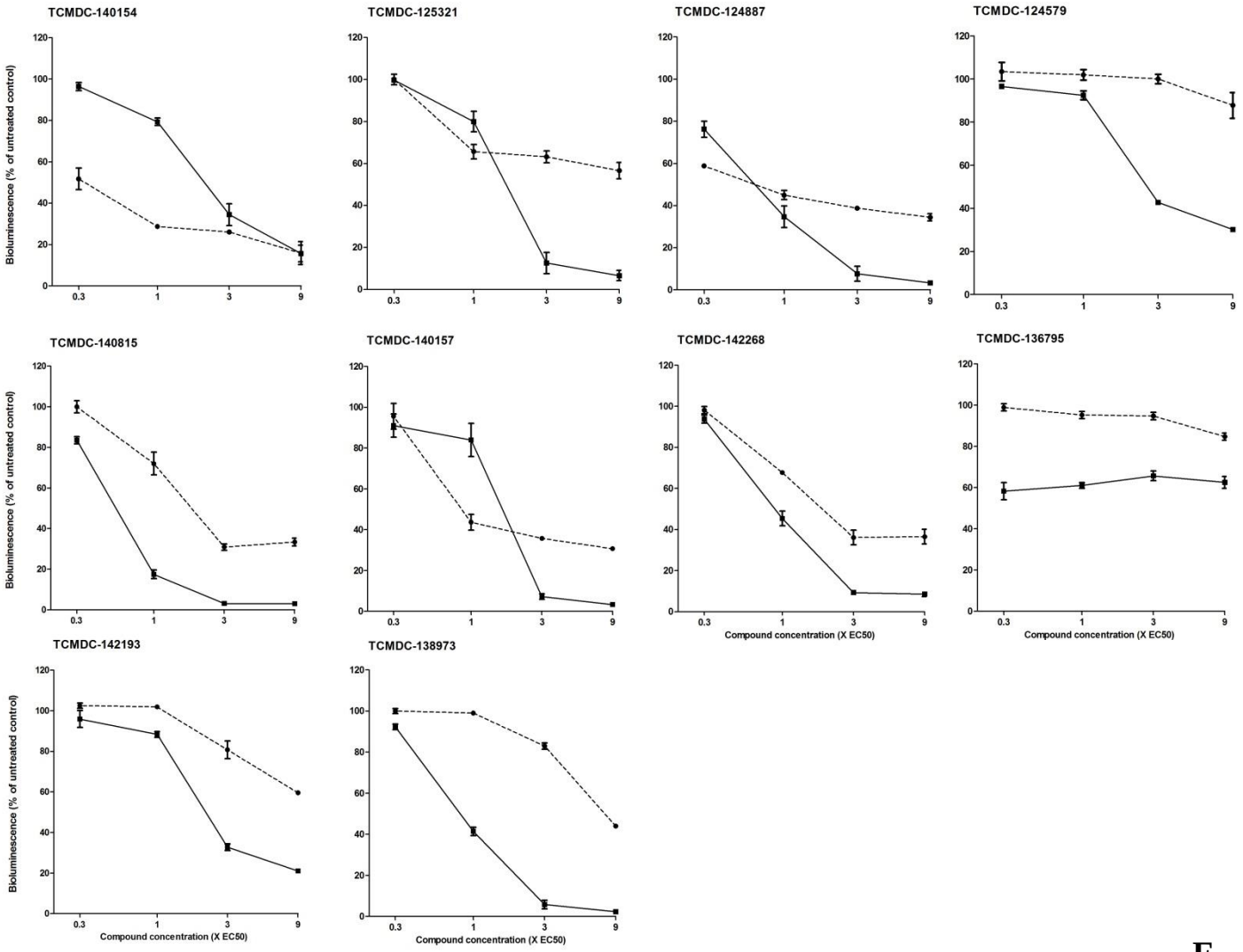
TCMDC-125254
TCMDC-139900
TCMDC-135423
TCMDC-138614
TCMDC-142036
TCMDC-136239
TCMDC-135135
TCMDC-141043
TCMDC-125055
TCMDC-124036
TCMDC-132515
Bioluminescence (% of untreated control)
Compound concentration (X EC50)
0.3
1
3
9
0
20
40
60
80
100
120

C


TCMDC-140755
TCMDC-135335
TCMDC-140040
TCMDC-133687
TCMDC-135773
TCMDC-140417
TCMDC-137323
TCMDC-135747
TCMDC-136043
TCMDC-136878
TCMDC-135804
TCMDC-135800
Bioluminescence (% of untreated control)
Compound concentration (X EC50)
0.3
1
3
9
0
20
40
60
80
100
120

D


TCMDC-140154
TCMDC-125321
TCMDC-124887
TCMDC-124579
TCMDC-140815
TCMDC-140157
TCMDC-142268
TCMDC-136795
TCMDC-142193
TCMDC-138973
Bioluminescence (% of untreated control)
Compound concentration (X EC50)
0.3
1
3
9
0
20
40
60
80
100
120

E

Figure 5.9: Confirmation BRRoK plots of 58 selected TCAMS compounds (previous pages)
Panels A to E each report standard concentration v. bioluminescence signals for 6hr BRRoK assays for 58 selected compounds resupplied from the TCAMS library. Solid filled line and broken line represent $NF54^{luc}$ and $Dd2^{luc}$ BRRoK data, respectively. Each data point represents the mean ±stdev of n=9 data. Information on the interpretation of the rate of kill is reported in Table 5.3.

Table 5.3: Mapping of TCAMS compounds to panels on Figure 5.9 and interpretation of their relative rate of kills.

Panel	TCAMS ID	Relative Rate of Kill	Panel	TCAMS ID	Relative Rate of Kill
A	TCMDC-124760	Fast	D	TCMDC-140755	Moderate
A	TCMDC-136189	Fast	D	TCMDC-135335	Moderate
A	TCMDC-136088	Fast	D	TCMDC-140040	Slow
A	TCMDC-125071	Fast	D	TCMDC-133687	Slow
A	TCMDC-125016	Fast	D	TCMDC-135773	Slow
A	TCMDC-133478	Fast	D	TCMDC-140417	Slow
A	TCMDC-125424	Fast	D	TCMDC-137323	Slow
A	TCMDC-136607	Fast	D	TCMDC-135747	Slow
A	TCMDC-137603	Fast	D	TCMDC-136043	Slow
A	TCMDC-125139	Fast	D	TCMDC-136878	Slow
A	TCMDC-125361	Fast	D	TCMDC-135804	Slow
A	TCMDC-125253	Fast	D	TCMDC-135800	Slow
B	TCMDC-131436	Fast	E	TCMDC-140154	Different
B	TCMDC-131242	Fast	E	TCMDC-125321	Different
B	TCMDC-124252	Fast	E	TCMDC-124887	Different
B	TCMDC-136792	Fast	E	TCMDC-124579	Different
B	TCMDC-140871	Moderate	E	TCMDC-140815	Different
B	TCMDC-124491	Moderate	E	TCMDC-140157	Different
B	TCMDC-124168	Moderate	E	TCMDC-142268	Different
B	TCMDC-124113	Moderate	E	TCMDC-136795	Different
B	TCMDC-123564	Moderate	E	TCMDC-142193	Different
B	TCMDC-125397	Moderate	E	TCMDC-138973	Different
B	TCMDC-138358	Moderate			
B	TCMDC-123773	Moderate			
C	TCMDC-124047	Moderate			
C	TCMDC-125254	Moderate			
C	TCMDC-139900	Moderate			
C	TCMDC-135423	Moderate			
C	TCMDC-138614	Moderate			
C	TCMDC-142036	Moderate			
C	TCMDC-136239	Moderate			
C	TCMDC-135135	Moderate			
C	TCMDC-141043	Moderate			
C	TCMDC-125055	Moderate			
C	TCMDC-124036	Moderate			
C	TCMDC-132515	Moderate			

5.3 Discussion

The development and validation of a modified BRRoK assay in chapters 3 and 4 led to this test of the large TCAMS compound library using a 384-well microplate format. The 384-well assay was shown to be robust with Z' scores ranges between 0.74 to 0.98 (with ideal being >0.5) and a CV_{max} from 1% to 9%. The high signal to background ratio from 160 to 475 illustrates the sensitivity of the assay at the small assay volumes used. As such, it can be concluded that the 384-well mBRRoK assay is a reliable and robust assay that offers the opportunity to rapidly screen a large compound libraries. Potential future work in adapting to a 1536-well microplate format to provide screens of massive compound libraries, in excess of 100,000 compounds, may be possible given the sensitivity of the bioluminescence assay used. Comparing these 384-well assay quality parameters with other *in vitro* antimalarial HTS assays reported (Che *et al.*, 2012; Lucantoni *et al.*, 2016; Swann *et al.*, 2016; Baniecki *et al.*, 2007; Plouffe *et al.*, 2016) is extremely favourable to the bioluminescence format used here – particularly with respect to the high signal to background ratio.

The screen of the 12,516 TCAMS compounds identified 975 compounds within the "hits" box, i.e. compounds that would be predicted to be both potent and rapid acting. The 7.8% hit rate is high for a high throughput screen, where typically the top 1-2% of hits would be identified for follow up work. The high hit rate here presumably is the result of the TCAMS library containing compounds pre-selected for their *in vitro* antiplasmodial activity. 165 compounds were selected for follow up analysis after a resupply of materials from GSK. These contained 136 compounds from the hit box. A two-step process was followed – both using a 96-well mBRRoK assay with n=3 technical repeats done, but done in two different *P. falciparum* strains. This approach led to 97 of the 136 compounds (71.3%) being a hit in both screens. This suggests that doing a 96-well mBRRoK assay in both strains does add value to a screening approach – and this will be picked up further in the final discussion for the thesis.

The potential to use mBRRoK data generated for Dd2^{luc} and NF54^{luc} parasite lines to explore potential strain-specific variation has been discussed earlier in this thesis. Calculating the change (Δ) in the percentage normalized bioluminescence signal at 10µM and 2µM between the two strains (Dd2^{luc} is used as the zero-point) allowed this concept to be explored with this screen of the 165 follow on compounds. In figure 5.10, the variation in bioluminescence signal data was plotted and overlaid with chemical structures of 9 compounds that appear to show the largest variation between the Dd2^{luc} and NF54^{luc} parasite lines. Four of these compounds; TCMDC-142036, TCMDC-138973, TCMDC-142193, and TCMDC-142105) shown in green on Figure 5.10, have a greater effect in NF54^{luc} compared to Dd2^{luc} in the mBRRoK assay. Interestingly, these four compounds are quinolines and would therefore likely have a higher EC_{50} in Dd2^{luc} due to its quinoline resistance profile (Hasenkamp *et al*., 2012), although this was not confirmed here due to the lack of material. As the mBRRoK assay uses a fixed concentration, the Dd2^{luc} parasites may have been exposed to a reduced fold-EC_{50} concentration of these compounds that affected the killing effect. Looking at the BRRoK data, although noting that these were all developed using the 3D7 EC_{50} data (a CQ-sensitive strain like NF54^{luc}) in Figure 5.9, data for three compounds are available. One, TCAM-142036 has a moderate killing effect in both strains – typical for quinolines and aryl alcohols. The most telling data is that of TCMDC-138973 and TCMDC-142193 (last two compounds on panel E of Figure 5.9) where the killing effect of these compounds was greater in NF54^{luc} than for Dd2^{luc} – strongly suggesting that they are less potent in the Dd2^{luc} CQ-resistant strain. Two additional structurally-related compounds were picked out in this analysis. Compounds TCMDC-135800 and TCMDC-135804 appear to be two of four compounds that have a greater killing effect in Dd2^{luc} than in NF54^{luc} (identified in blue on Figure 5.10). Currently, the overall RoK for TCMDC-135800 and TCMDC-135804 is that they exert a slow killing effect (Figure 5.9) and thus any differences in their relative potency would not be readily apparent in a BRRoK plot.

However, that this simple comparison approached offer up new data regarding differences in activities in different strains, and that at least for some there is a ready explanation, suggests that the use of mBRRoK assays extends beyond rapid screening of potent and fast-killing compounds – the potential use of this will also be picked up in the final discussion.

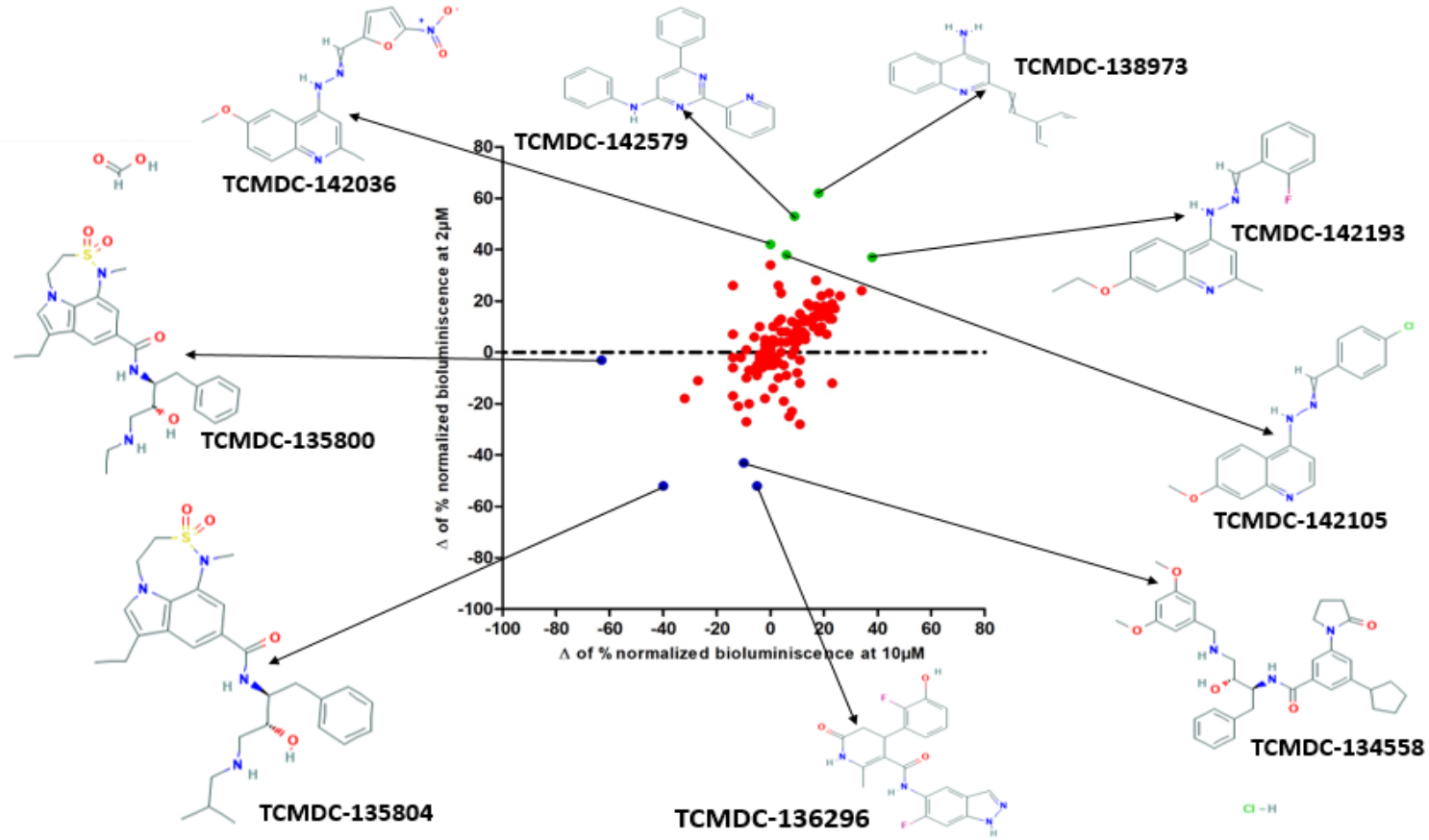


Figure 5.10: Exploring differences between mBRRoK data developed in Dd2^{luc} and NF54^{luc} parasite strains

The scatter plot shows the differences between percent normalised bioluminescence signals developed in each strain at 10μM and 2μM (where the difference reported is that of NF54l^{uc} to Dd2^{luc}). The mean from n=3 measurements in each strain is reported here for 165 compounds. Compounds that show an apparent greater killing effect in NF54^{luc} are highlighted in green and are towards the top right quadrant, compounds with an apparent greater killing effect in Dd2^{luc} are shown in blue and fall towards the left lower quadrant. All others are shown in red. Highlighted structures are shown around the plot.

The mBRRoK explores both potency and rate of kill within the apparent killing effects observed. To understand the rate of kill of compounds relative to each other, the original BRRoK assay is used as it uses the same fold-EC_{50} concentrations. The move to mBRRoK here was in part driven by the fact that the measurement of an EC_{50} takes longer than the rate of kill determination. For the TCAMS compounds, EC_{50} data is available from measurements done using the 3D7 parasite line (Gamo *et al.*, 2010). Data in Figure 5.8 and Table 5.2 showed that for the majority of the nine compounds assessed (selected as most of these were made available by GSK) that there was little difference in the EC_{50} for the three strains tested. It was therefore decided to use the available 3D7 data to prepare BRRoK plots for 58 compounds for which there was sufficient material to enable the three independent assays to be done. A summary of the key finding is shown in Table 5.3 and adds new relative rate of kill for discovery antimalarial compounds – of note is that there appear to be at least 16 compounds that would meet the TCP1 criteria of at least as fast as chloroquine and of particular note are compounds TCMDC-124760 and TCMDC-136189 would readily meet the ideal criteria for at least as fast as artemisinins. Using the threshold criteria for each graph that compared the concentration-dependent loss of bioluminescent signal compared to antimalarial benchmarks (see chapter 3), the compounds were determined as either fast (greater than or around chloroquine), moderate (aryl alcohol to pyrimethamine/folate inhibitor) or slow (slower than pyrimethamine/similar to atovaquone). Grouping the concentration-dependent loss of bioluminescent signal curves by these categories (Figure 5.11) readily shows how they can provide a relative indication of the rates of kills of these compounds, with the rapid acting (Figure 5.11A) clearly more distinct in their activities at 3x and 9xEC_{50} compared to the moderate and slow compounds (Figures 5.11 B and C) – supporting the use of the 10xEC_{50} threshold in the mBRRoK assay to determine the 10µM and 2µM when screening for the rapid acting compounds.

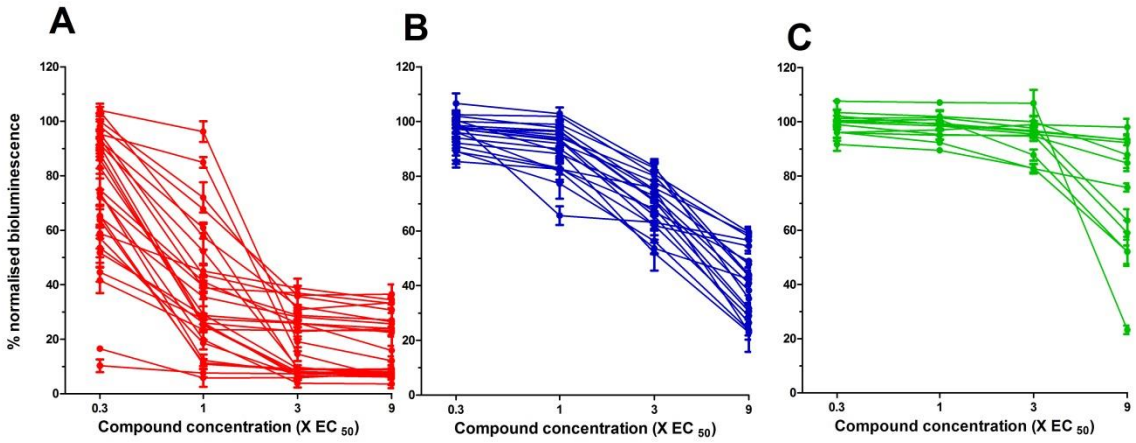


Figure 5.11: Grouping the concentration dependent-loss of bioluminescence curves for compounds determined to be (A) rapid, (B) moderate and (C) slow acting in their BRRoK assays *The BRRoK curves reported here are all adapted from data reported in Figure 5.9 and classified in Table 5.3*

With the large datasets available for the 12,516 compounds screened, the opportunity to better understand how the position of a compound on the mBRRoK plot relates to its potency and rate of kill was explored again. Previous observations in chapters 3 and 4 highlights that rapid acting and potent compounds do fall in the lower left of the mBRRoK plot and slow acting compounds fall to the upper right of the plot. Given that most of the benchmark antimalarials show the same loss in bioluminescence signal at both 10µM and 2µM, then falling close to this position where the slope is 1 and intercept on y-axis is 0 (below which no compound should theoretically lay) would perhaps result from their potency as the compounds readily achieve at least a 10-fold EC_{50} at both 10µM and 2µM. It was considered if moving away from this point towards the top left of the chart, where compounds have greater activity at 10µM than 2µM, and are thus likely to be able to achieve a lower fold EC_{50} at 2µM than at 10µM that there would be a trend of increasing EC_{50} data as one moves towards the top left. To explore this, five bands of compounds moving across the dataset were determined (Figure 5.12A) – with the hypothesis that as one moved from band 1 to 5, that there would be an increase in the mean EC_{50} data as we move away from the slope with the intercept on y-axis at 0. The available EC_{50} data from

3D7 for the compounds in each band was determined and a box and whisker plot for these data in each band prepared (Figure 5.12B). Interestingly, using non-parametric tests for significance (ANOVA with Bonferroni post-tests) in the distribution of the data, no significance was seen between any of the groups. Any slight variation perceived in the box-and-whisker plot most likely reflects the numbers of compounds within each band (with the most in band 1 and least in band 5). This suggests that potency cannot be attributed to a compound based on its position on an mBRRoK plot beyond the exiting observation of potent and rapid acting compounds in the lower left of the plot. More work in understanding the impact of the rate of kill, and therefore much more data from BRRoK plots are needed.

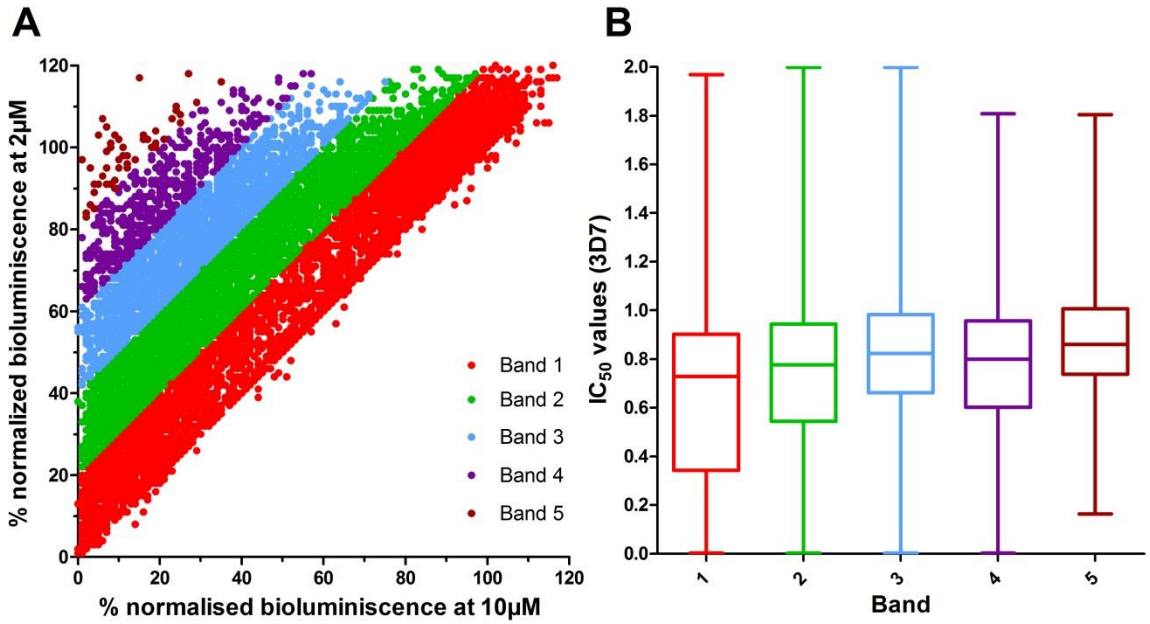


Figure 5.12: Rainbow plot for TCAM library compounds
Represents the stratification of mBRRoK plot for TCAMS library compounds into five coloured bands using their corresponding 3D7 EC_{50} data. (B) Indicates the box plots for the TCAMS EC_{50} values.

In chapters 3 and 4, compounds with the same MoA were shown to display similar RoK in the mBRRoK plot. Using the available data for 195 TCAMS compounds (see appendix 6 for detail), mBRRoK plots for inhibitors of PfATP4, haemoglobin catabolism, folate biosynthesis, DHODH and bc_1 complex were all plotted (Figure 5.13). As expected, compounds that target the PfATP4 and haemoglobin catabolism clustered towards the bottom left of the mBRRoK plot with some of the PfATP4 inhibitors displaying moderate to negligible killing effect (an observation reported here as well as in Ullah *et al.*, 2017 and 2019). As expected, compounds that target DHODH and the bc_1 complex clustered towards the upper right, typical of a negligible killing effect over 6 hour due to the lag phase. As would be expected for compounds that target folate biosynthesis pathway, they display a moderate killing effect on the mBRRoK plot. The benchmark for this class of inhibitors would be pyrimethamine which shows a slower *in vitro* rate of kill than aryl alcohols and up to a 24 hour lag period (Sanz *et al.*, 2012). Given that the folate inhibitor WR99210 is used as a drug selective marker for the generation of the

Dd2^{luc} strain, the action of folates hasn't been specifically explored in the BRRoK and mBRRoK assays – not least as these compounds are not likely to be rapid acting based on the Sanz *et al.,* (2012) data and that shown here in Figure 5.13.

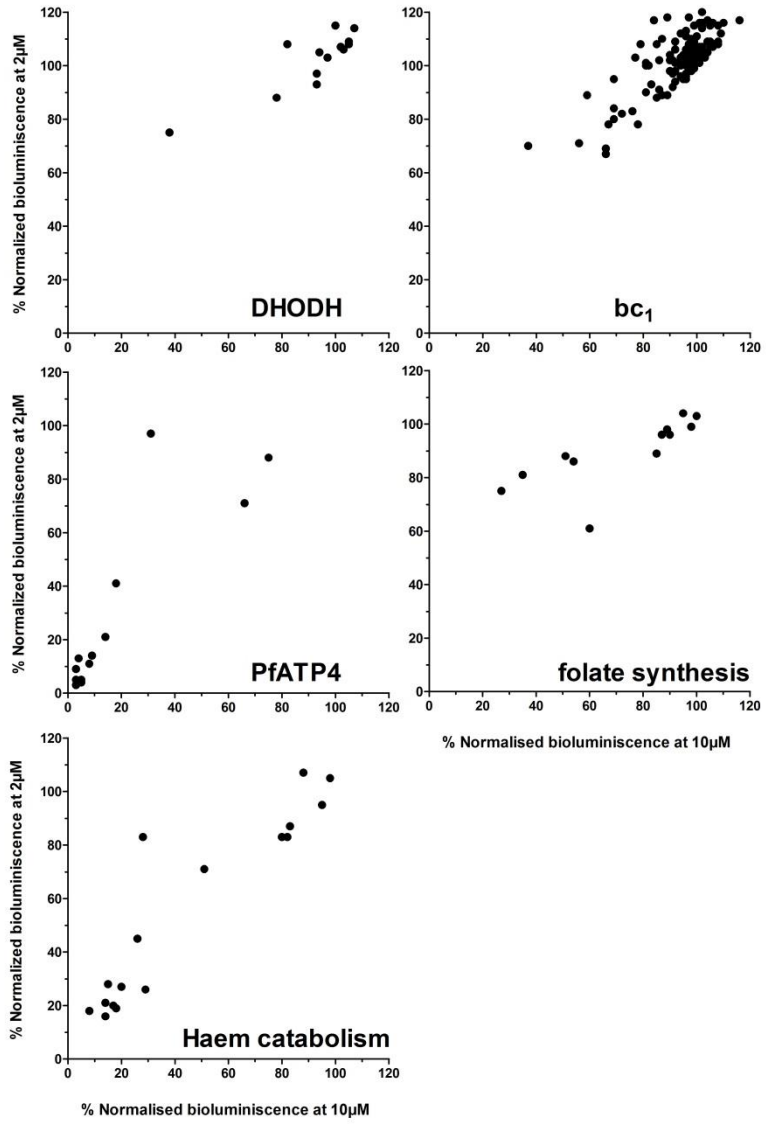


Figure 5.13: Correlating mode of action of TCAMS library compounds with mBRRoK six hour data.
Each data point represents normalized bioluminescence signal at 10µM and 2µM for TCAMS library compounds that target DHODH, bc1 complex, PfATP4, folate biosynthesis and haemoglobin (haem) catabolism.

6 Chapter 6: Discussion

Emergence of resistance to the frontline artemisinin combination therapies underscores the urgent demand for alternative antimalarial drugs to treat active malaria cases. Thousands of compounds with potent antiplasmodial activity have been identified in whole-cell phenotypic screens of compound libraries by GSK (Gamo *et al.,* 2010), Novartis (Plouffe *et al.,* 2008) and St. Jude Children's Hospital (Guiguemde *et al.,* 2010). These hits are available for hits-leads optimization and characterization. As part of this process, an *in vitro* determination of their rate of kill would assist in screening for fast-acting compounds as knowing this pharmacodynamic property could inform decisions to proceed to *in vivo* or even clinical studies. The BRRoK assay was developed in the Horrocks lab to address issues with other *in vitro* rate of kill assays (Bahamontes-Rosa *et al.,* 2012; Le Manach *et al.,* 2013; Linares *et al.,* 2015; Sanz *et al.,* 2012; Ullah *et al.,* 2017), with BRRoK being able to differentiate between compounds that met minimal essential and ideal TCP1 criteria using a simple and robust moderate throughput assay. However, whilst BRRoK has many strengths as an assay, the need to know the EC_{50} values of the test compounds before performing the assay limits the assay to a medium throughput. To enable a scale up in the provision of a robust assay to prioritise the screening for rapidly cytocidal antiplasmodial compounds, this thesis addressed the "EC_{50} bottleneck" through the development, validation and use of a modified BRRoK assay, termed the mBRRoK assay.

Through the "proof-of-concept" using benchmark antimalarials, to a validation using a medium throughput screen of the MMV Pathogen Box to the application of the mBRRoK to screen 12,514 TCAMS library compounds a number of key features have been defined for this assay;

(i) this 6 hours assay offers a simple, quick, robust and reliable tool for screening antimalarial compounds that are both potent and show a rapid initial cyctocidal action

(ii) the assay performance parameters have been defined and, using the 20x25 “hit box” appears to provide a 81% true discovery rate for compounds that are at least as rapid acting as chloroquine.

(iii) the assay also appears particularly effective in excluding compounds that affect a slow initial cytocidal action, irrespective of their potency

(iv) the assay is readily scalable to a 384-well microplate format, retaining its robust assay characteristics

Of particular note is the understanding of how compounds fall on the mBRRoK plot which can be used to provide information about their potency and rate of cytocidal action (Figure 6.1). These have been well described for rapid and potent compounds as well as for compounds that are slow (have a lag phase of > 6hrs) irrespective of their potency. Interestingly, at each stage of development of the mBRRoK assay, compounds with known mode of action with well understood rates of kill have been able to be plotted to the mBRRoK plot in defined spaces. Examples of this include the rapid rates of action for haemoglobin catabolism and for PfATP4 inhibitors, and slow rates of kill for DHODH and bc_1 complex inhibitors (Ullah *et al.,* 2019). Compounds with moderate potency and/or moderate rates of cytocidal action, however, do not fall on the mBRRoK plot in a predictable manner. Analyses of how EC_{50} affects the position of a compound on the mBRRoK plot have been less successful. One key hypothesis explored is that as compounds move towards the top left of the plot they would be less potent. This would be exemplified on Figure 6.1 by CQ and MQ – these compounds share a similar rate of kill (albeit lying either side of the definition for fast and moderate) with CQ being less potent in Dd2 (c 200nM) than MQ (c 40nM). Exploring this hypothesis in this thesis has failed to demonstrate any significant difference in compounds as they move towards the upper left corner. However, to do this properly a large number of related compounds that target the same mode of action would be needed. This would remove the confounder effect of the rate of kill

and allow only the effect of potency to be judged. As more data is developed on the modes of action, this would be an interesting analysis to complete.

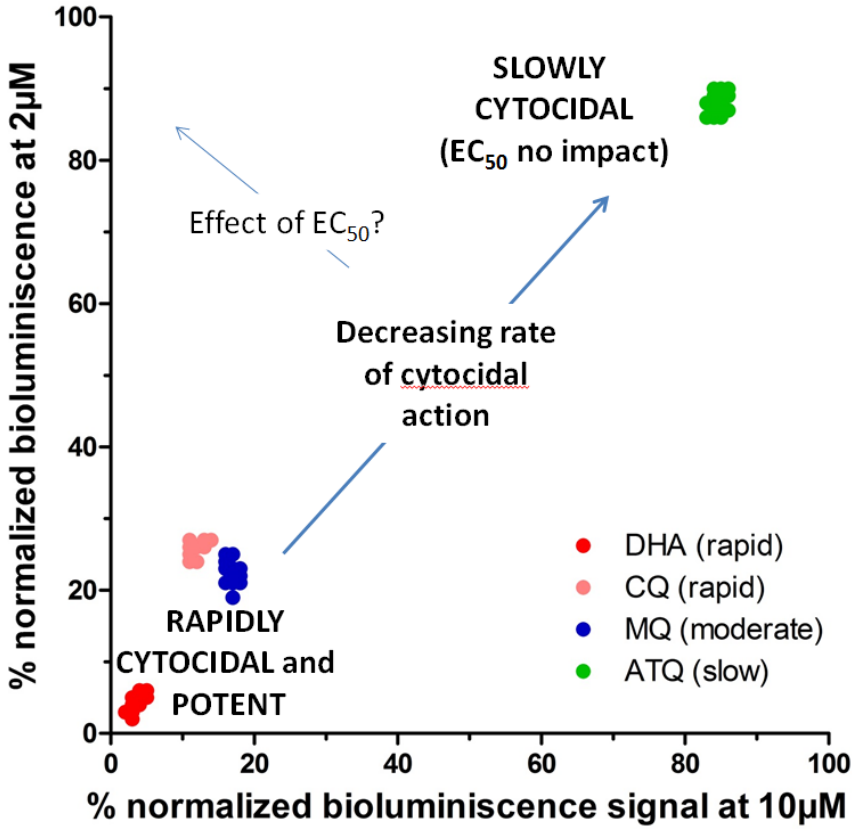


Figure 6.1: Exploring the distribution of compounds on a mBRRoK plot based on their potency and initial rate of cytocidal action.
Figure adapted from Chapter 5.

After completing the screening of the first new compound library using the mBRRoK assay on the MMV Pathogen Box, the utility of even this small scale screen was highlighted in the potential new leads identified. Of particular interest were MMV634140 and MMV66749, both structurally related to DD107498 (a novel PfeEF2 inhibitors) and here predicted to elicit a rapid relative rate of kill – a novel observation for a new class of molecules. Thus, in terms of a novel mode of action that shows a rapid rate of cytocidal action, I would suggest that PfeEF2 inhibitors would be of interest for further optimization and characterization. Also of note from the MMV Pathogen Box screen were five compounds (MMV022029, MMV016136,

MMV676442, MMV019721 and MMV019993) all predicted to show a rapid rate of initial cytocidal activity – albeit with no predicted mode of action, and thus potentially of interest as they may have a novel mode of action. This work highlights how understanding the rate of kill adds a new dimension to existing potency data when reviewing the data from a compound library. These data have all been shared with MMV in accordance with the requirements for the supply of the materials. There has been no follow up on mBRRoK assays beyond those reported here due to the limited amount of material the MMV Pathogen Box provides. However, a priority list is available to now discuss with MMV as part of ongoing projects our laboratory is providing to this organisation.

This thesis also first described the use of a second genetic strain in the BRRoK/mBRRoK assay. NF54^{luc} was developed using the same *Pfpcna*-luciferase expression cassette – although here the reporter plasmid is likely maintained as an episomal plasmid (Muqdad Hmoud, PhD Thesis 2019). The initial benchmark RoK data developed for Dd2^{luc} and NF54^{luc} using BRRoK assay were essentially the same except for the differences in drug resistance profile for the quinolines compound as would be expected. There was a considerable overlap of the number of predicted fast-acting compounds against Dd2^{luc} and NF54^{luc} when the hits from the n=1 TCAMS library screen were followed up after the resupply of 165 compounds from GSK. Here, I was able to repeat all the mBRRoK data with n=3 measurements as well as do BRRoK assays for some 58 of the compounds in the two genetically distinct lines. 110 and 109 compounds were predicted to demonstrate a rapid initial RoK in Dd2^{luc} and NF54^{luc} respectively. There was a great overlap between the two parasite strains, with 97 compounds predicted to be fast-acting against Dd2^{luc} share the same RoK with NF54^{luc}. In chapter 3 the potential for comparing mBRRoK data from two strains was first explored and then used again for the data developed from the 165 TCAMS compounds. This comparison plot reveals not only the divergence (Δ % normalised bioluminescence) of the data at 10µM and 2µM between the strains, but also a vector for the

data that would suggest in which strain the greater inhibitory effect is produced. The potential for this comparison information was shown where;

(i) of the 14 compounds predicted to have a reduced killing effect in $Dd2^{luc}$ compared with $NF54^{luc}$, five of these compounds are quinolines. This observation agrees with the report of Gamo *et al*., (2010) concerning the quinolines in the TCAMS library that show less activity against Dd2 parasites.

(ii) of the 12 compounds predicted to have a greater killing effect against $Dd2^{luc}$ compared with $NF54^{luc}$, two pairs of compounds show similarities in their core scaffold (figure 6.2). These are compounds with no designated mode of action information.

These findings appear to support the potential of mBRRoK assay to explore drug resistance profiles in genetically distinct parasite strains when used in this assay. For example, the mBRRoK assay could perhaps be used in future to study the effect of antimalarial compounds against artemisinin-resistant and artemisinin-sensitive parasite strains as the first step in triaging compounds that are both potent and rapid – recognising that searching for compounds active against artemisinin resistant parasites that will likely dominate the future of antimalarial treatment for the next thirty years.

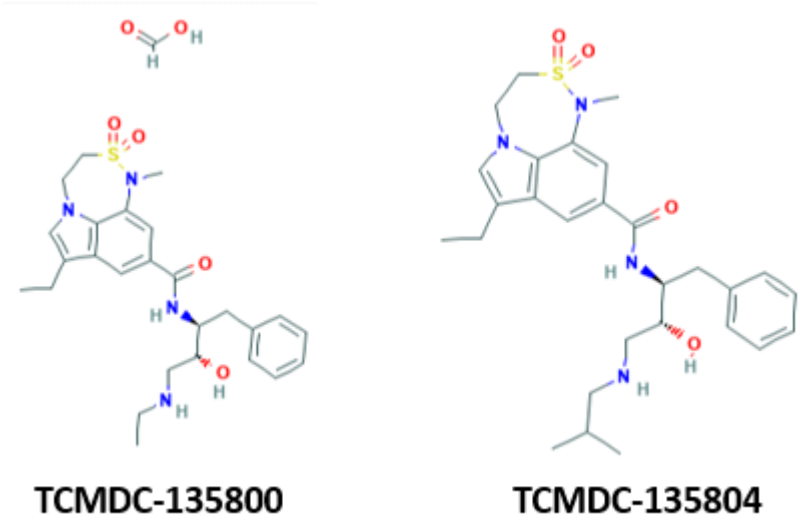


Figure 6.2: Chemical structures of two compounds that show greater killing in Dd2^{luc} compared with NF54^{luc}
The compounds show similarities in their core scaffolds.

With the new BRRoK assay data developed here for Dd2^{luc} , a repeat Principle Components Analysis (PCA) was carried out in collaboration with Dr Raman Sharma of the Liverpool School of Tropical Medicine who completed the analysis with the MMV Malaria Box data (Ullah *et al.*, 2017; Ullah *et al.*, 2019). PCA offers the potential to reduce the dimensionality of the data into a single parameter (first principle component, PC1) that can easily be included in analyses as a measure of the relative rate of kill, where a smaller PC1 – reflecting low bioluminescence signals after exposure to compound– reports rapid initial cytocidal activity. A new PCA was done using the 6hr BRRoK assay data, this analysis included the previous Dd2^{luc} data for benchmark antimalarials and 376 compounds from the MMV Malaria Box – but also included here data on 14 compounds from the MMV Pathogen Box in Dd2^{luc} as well as 58 compounds from the TCAMS library done in Dd2^{luc} and NF54^{luc}. These data are all provided in appendix 7. Taking both the potency of compounds (expressed in nM) and the relative rate of kill data (expressed as zero-mean PC1 values) a new view of available potency *versus* rate of kill data in the Dd2^{luc} parasite is now available (Figure 6.3). This analysis allows me to explore the interplay between the potency and initial cytocidal action of MMV Malaria Box,

MMV Pathogen Box and TCAMS library compounds. Compounds that are potent (low EC_{50}) and exert an initial rapid RoK occupy the bottom left quadrant of the plot (activity space of dihydroartemisinin, DHA). The distribution of the MMV Pathogen Box and TCAM library compounds appear to follow similar pattern reported for the MMV Malaria Box by Ullah *et al.*, (2017). Using the TCP1 ideal threshold, i.e. compounds that are at least as fast a DHA (PC1<-85), 11 TCAMS compounds were identified. However, only one compound, TCMDC-124760 (N-(5-Chloro-2,4-dimethoxyphenyl)-2-(2-methylpropyl)-1-oxo-3-thiophen-2-yl-3,4-dihydroisoquinoline-4-carboxamide), appears to meet the potency criteria (EC_{50} <200nM).

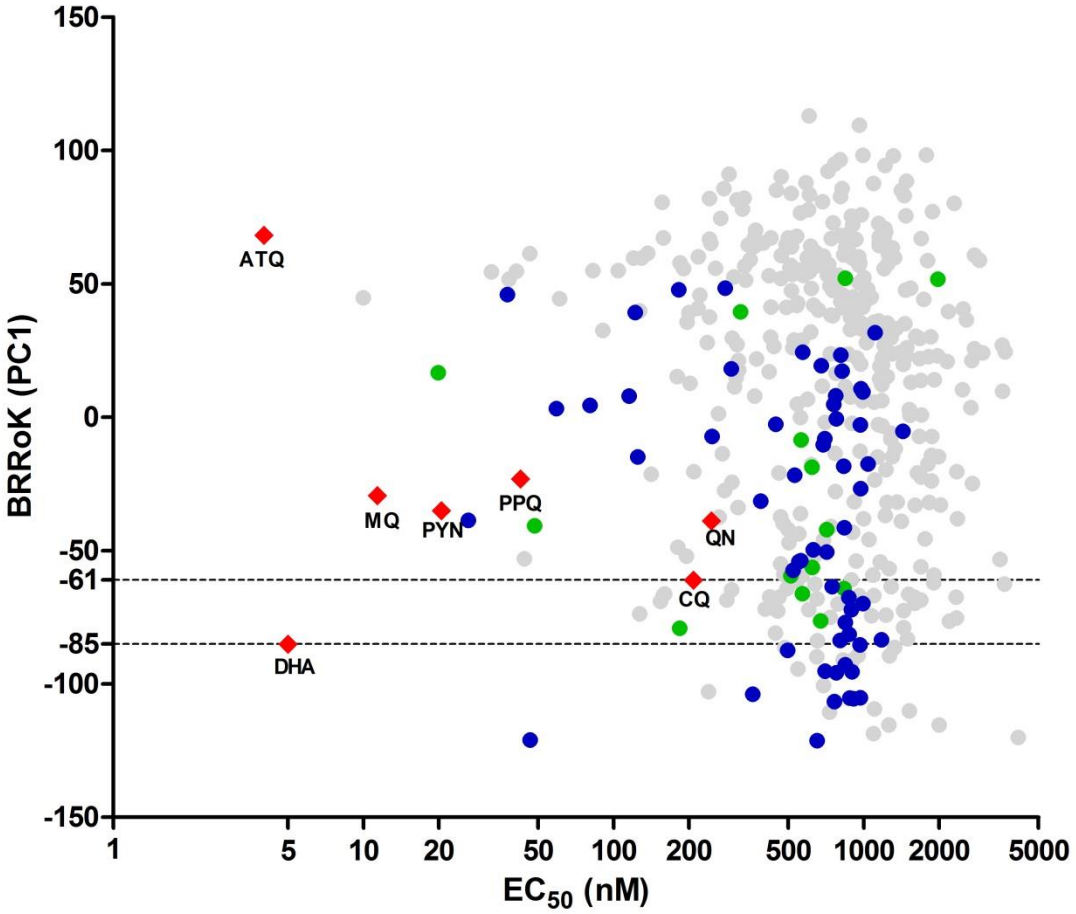


Figure 6.3: Plot of all available BRRoK (PC1) data against EC_{50} for the MMV Malaria Box, Pathogen Box and TCAMS library compounds against the Dd2luc parasites.
Malaria Box compounds are indicated as grey circles, Pathogen Box compounds are represented by green circles and TCAMS library compounds by blue circles. The 7 benchmark antimalarial drugs are indicated with red filled diamonds. The TCP1 ideal and TCP1 minimal thresholds are set based on the PC1 values (BRRoK data) for dihydroartemisinin and chloroquine, respectively, and are shown as dashed lines. DHA, dihydroartemisinin, CQ, chloroquine, MQ, mefloquine, PYN, pyronaridine, PPQ, piperaquine, QN, quinine, ATQ, atovaquone.

As would perhaps be expected, no compounds from the MMV Pathogen Box appear to meet the TCP1 ideal criteria because the compounds were selected for diversity to support drug discovery campaign against Neglected Tropical Diseases. However, four compounds do meet the minimal threshold of at least as fast as chloroquine. Importantly, new data on a key pharmacodynamics property has been shown to be developed quickly and with a process of analysis that allows for a ready triage of the most potent and rapid compounds, with additional functionality available when comparing two different strains. So, for the first time, the same type of plot has been prepared using available potency *versus* rate of kill data in the $NF54^{luc}$ parasite for the 58 TCAMS compounds screened (Figure 6.4). Plotting the TCAMS library BRRoK data for $NF54^{luc}$ shows a similar distribution pattern observed in the same plot for $Dd2^{luc}$ parasite line. 19 compounds, however, likely meet the TCP1 ideal threshold, with two of these (TCMDC-124760 and TCMDC-142268) appearing to look promising for hit-lead optimization, although TCMDC-124760 shows the same potency and relative rate of kill in $Dd2^{luc}$ parasites.

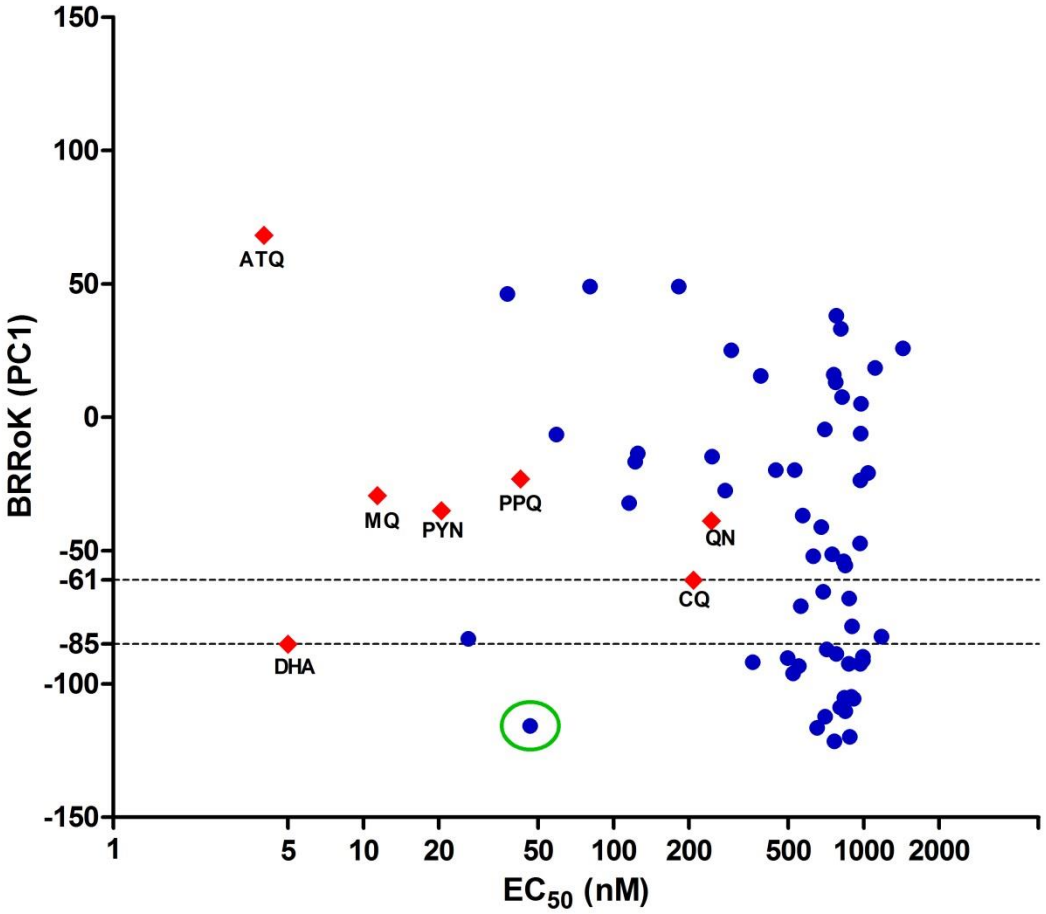


Figure 6.4: Plot of available BRRoK (PC1) data against EC_{50} for the TCAMS library compounds against $NF54^{luc}$ parasites.

TCAMS library compounds are in indicated in blue circles with TCMDC-124760 shown inside a green circle. The seven benchmark antimalarial drugs are indicated with red filled diamonds. The TCP1 ideal minimal thresholds are set based on the PC1 values (BRRoK data) for dihydroartemisinin and chloroquine, respectively, using broken lines. DHA, dihydroartemisinin, CQ, chloroquine, MQ, mefloquine, PYN, pyronaridine, PPQ, piperaquine, QN, quinine, ATQ, atovaquone.

Taking the best TCAMS hits from both plots, a comparison of the PC1 values shows some variation (Table 6.1) between classifications as meeting the minimum or ideal TCP1 threshold. That said, the top ranking compounds in both strains align well and show a trend in the TCAMS n=1 screen that suggests that they would all have been identified with a more stringent selection criteria i.e. a 10x10 hit box (this would reduce the overall number of hits from the 12514 compounds from 975 to 191). This same criteria would also exclude two compounds that meet the ideal TCP1 criteria in both strains and a mixed ideal/minimum TCP1criteria for at least six compounds. This would suggest that whilst applying a much more stringent criteria would reduce any expected subsequent workflow – the BBRoK data developed in the two strains here would suggest that a significant number of compounds (i.e. 50%) of interest would be missed out.

Table 6.1: Comparison of BRRoK PC1 data against the original TCAMS screening data

		PC1 value		TCAMS screen in Dd2 (n=1)		High
Compound name	**EC_{50} (nM)**	**$Dd2^{luc}$**	**$NF54^{luc}$**	**10µM**	**2µM**	**threshold**
TCMDC-136189	651	-121.2	-116.5	1	1	Yes
TCMDC-124760	46	-121.0	-115.8	6	4	Yes
TCMDC-136088	763	-106.6	-121.4	7	12	No
TCMDC-125071	912	-105.5	-105.5	3	5	Yes
TCMDC-125424	878	-105.3	-119.8	3	9	Yes
TCMDC-125016	971	-105.1	-92.5	2	4	Yes
TCMDC-133478	360	-103.8	-91.8	3	4	Yes
TCMDC-136607	777	-95.8	-88.7	4	9	Yes
TCMDC-125253	899	-95.5	-78.4	4	6	Yes
TCMDC-125139	701	-95.2	-112.3	1	2	Yes
TCMDC-125361	843	-92.8	-110.2	3	8	Yes
TCMDC-137603	497	-87.4	-90.3	17	19	No
TCMDC-140154	967	-85.3	-47.4	17	24	No
TCMDC-131436	804	-83.6	-108.7	14	22	No
TCMDC-131242	1177	-83.4	-82.2	20	22	No
TCMDC-124491	874	-81.4	-67.9	7	9	Yes
TCMDC-123564	844	-76.9	-55.6	3	10	Yes
TCMDC-124252	893	-72.1	-104.7	16	20	No
TCMDC-124168	991	-69.8	-89.8	14	21	No
TCMDC-136792	873	-67.6	-92.5	18	23	No
TCMDC-140815	836	-41.4	-105.1	14	16	No
TCMDC-124887	521	-57.4	-96.1	14	19	No
TCMDC-140871	550	-54.1	-93.2	13	21	No
TCMDC-138973	993	9.5	-91.1	9	90	No

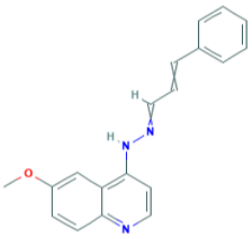
The validated mBRRoK assay is intended to quickly triage 12,516 TCAMS library for compounds that affect rapid relative rate of kill with good potency. The top 100 TCAMS compounds (based on their ranking in residual bioluminescence activity) from the n=1 TCAMS screen were clustered manually into structural related scaffolds (Figure 6.5). Ullah *et al.*, (2019) provided a proof-of-principle that compounds which share similar core scaffolds show the same relative rate of kill in the BRRoK assay. Here, the mBRRoK assay data appear to provide similar information – as would be expected if an assumption that the related scaffolds affect kill through the same rapid mechanism. Of the 100 compounds, 80 fall into one of nine distinct core scaffolds;

- eight 4-aminoquinolines a known rapid acting class of compound
- four closely related compounds with an isoquinoline core

- Five acridines – a class of compound shown in Ullah *et al.*, (2017) to have a rapid mode of action
- Twelve quinazolines, with three subclusters within this group – no data exists on this group of compounds
- Seven compounds sharing a sulphonamide moiety
- Ten triazoles, with eight closely related to one another
- Eight diverse compounds that share a core pyrimidine moiety
- Eleven diverse compounds that share a core benzamide moiety
- Fourteen 2-phenyl-benzimidazole compounds, with the same class identified as generally having a moderate rate of kill in Ullah *et al.*, (2019). Interestingly, the same study reported one of these compounds had a rate of kill that was greater than that of DHA. Understanding what substitutions around the 2-phenyl-benzimidazole core would be of particular interest.

Currently, these data are all shared with GSK. The next step in working with this data will be to use chemical informatics to prioritise examples of structurally-related compounds that share the same rapid rate of kill. BRRoK assays in $Dd2^{luc}$ and $NF54^{luc}$ can then be used to confirm this rapid activity. Data from other screens on this compound library would offer the opportunity to select classes of molecules that are of particular development interest or are novel.

Quinoline clusters



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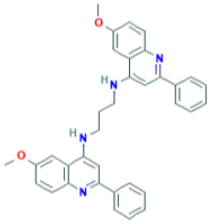

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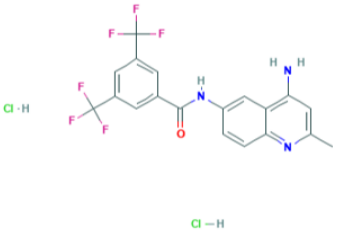

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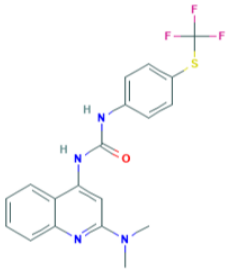

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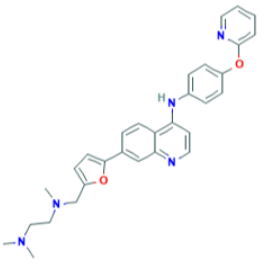

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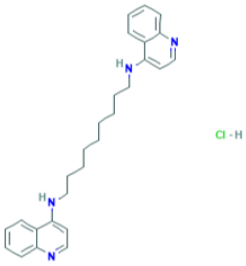

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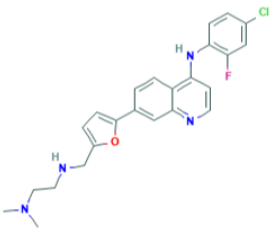

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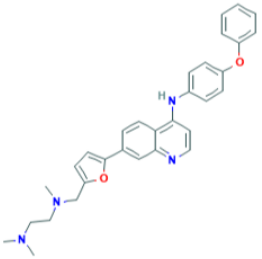

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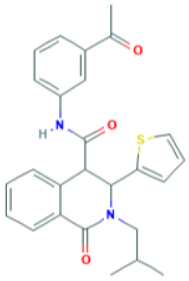
Isoquinoline clusters



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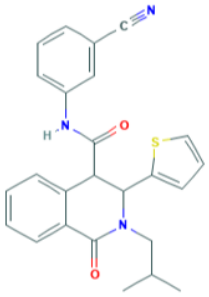

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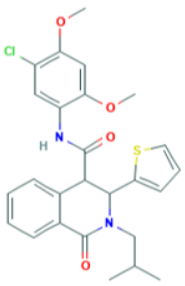

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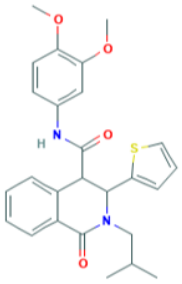

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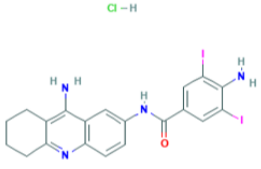
Acridine clusters



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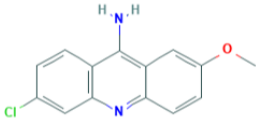

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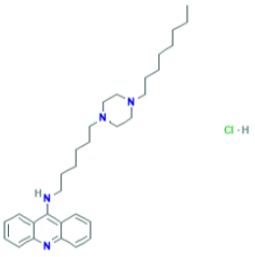

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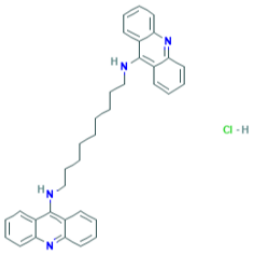

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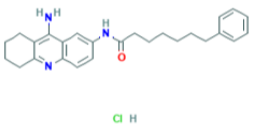

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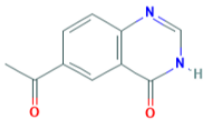
Quinazolines



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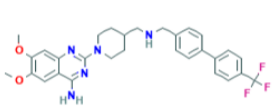

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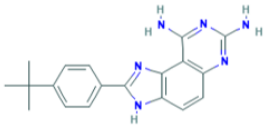

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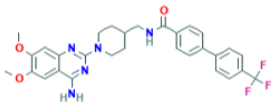

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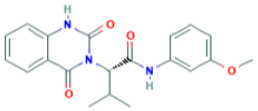

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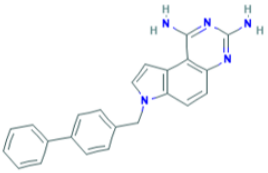

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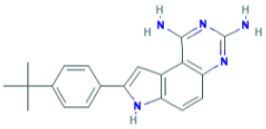

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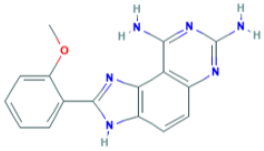

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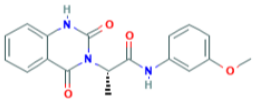

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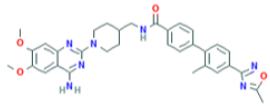

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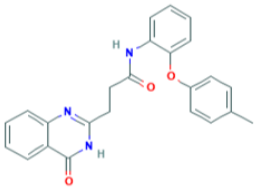

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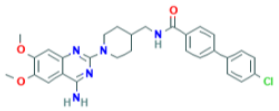

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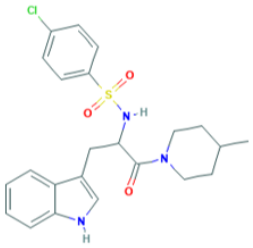
Sulfonamide clusters



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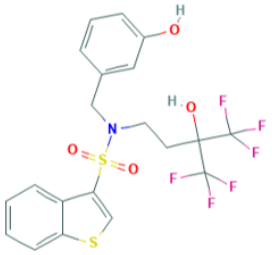

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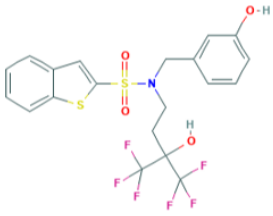

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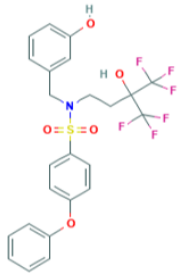

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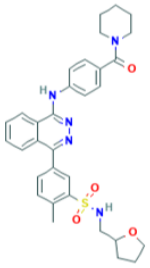

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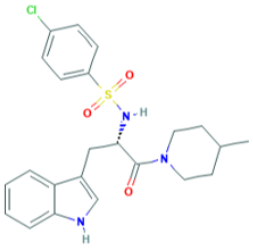

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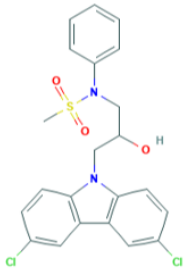

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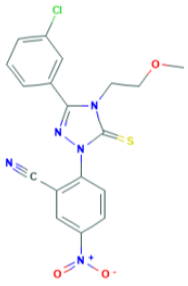
Triazole clusters



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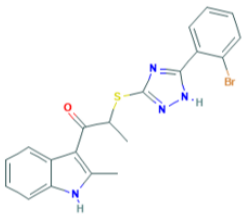

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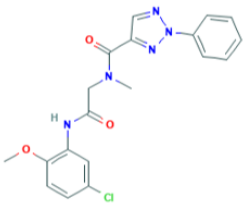

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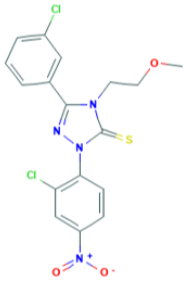

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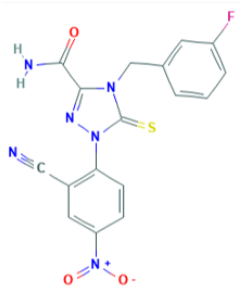

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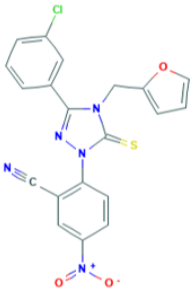
Triazole clusters continued



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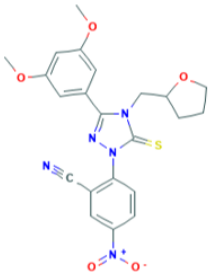

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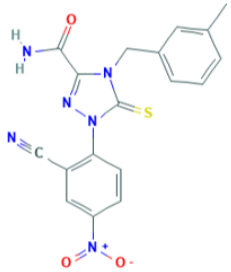

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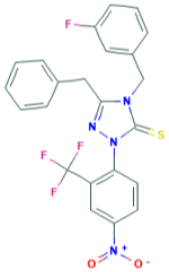

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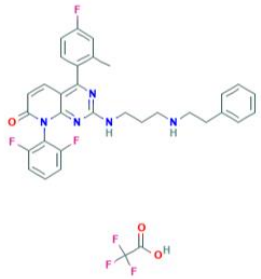
Pyrimidine clusters



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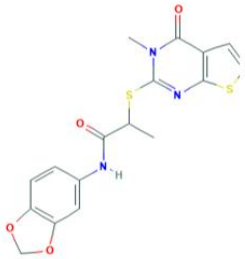

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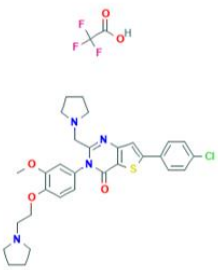

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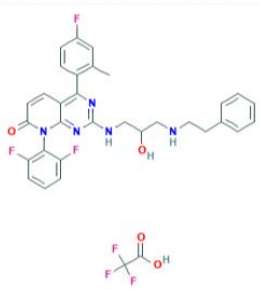

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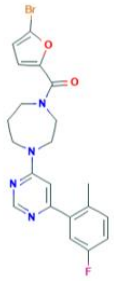

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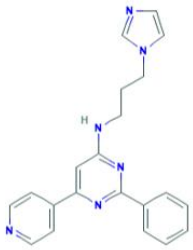

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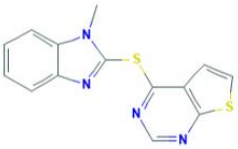

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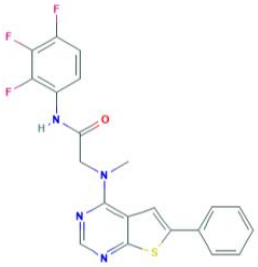

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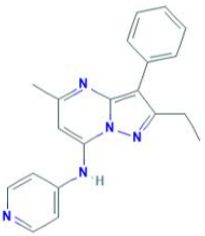

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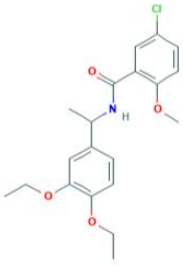
Benzamide clusters



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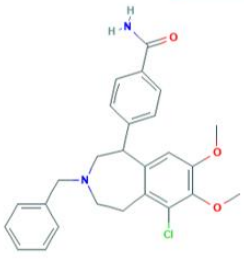

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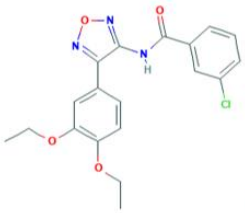

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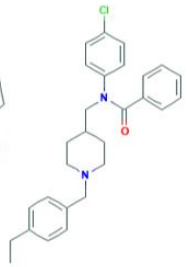

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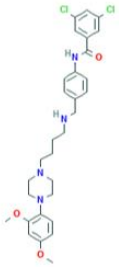

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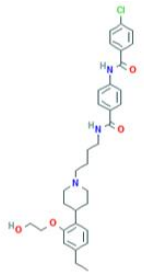

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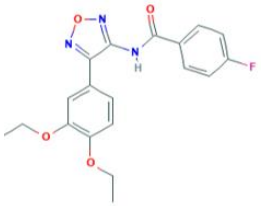

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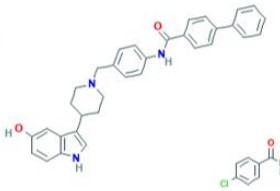

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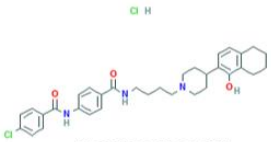

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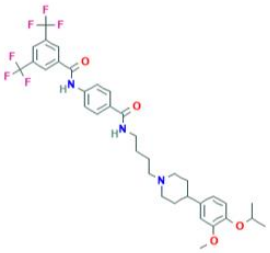

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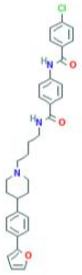

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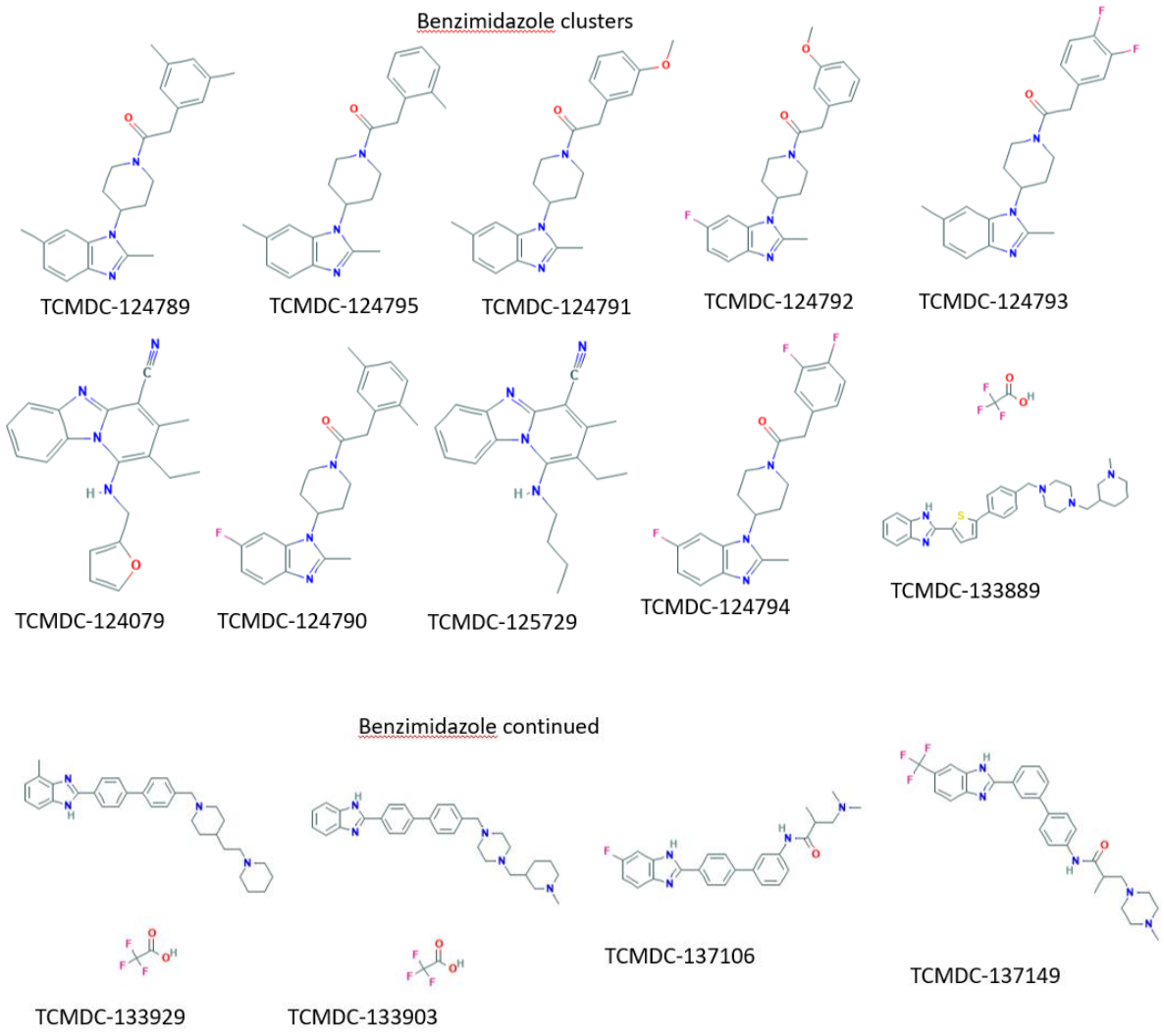

Figure 6.5: Chemical structures of the top 100 TCAMS compounds predicted to have initial rapid rate of kill in the mBRRoK screen of the TCAMS library

There appear to be two routes forward for development of the mBRRoK assay format. The first is the idea of expanding into a 1536-microwell assay format suitable for screening of >100,000 compound libraries. This could be done using the two strains to provide comparative data that would underpin a chemical informatics analysis of the data. This would have the main aim of searching for and developing novel classes of compound that are both potent and rapid acting. The second opportunity would be to look at changing the nature of the luciferase expression cassette. Currently the mBRRoK assay utilizes two genetically modified parasite lines that express peak luciferase signal at the trophozoite stage. The performance of mBRRoK assay

against other erythrocytic stages (rings and schizont) could be explore by replacing the current *Pfcna* luciferase cassette with one that could constitutively express reporter gene at other stages. Data on genes that are constitutively expressed are readily available from studies of developmental gene expression and are reported through the PlasmoDB site. As an alternative strategy, work is ongoing in the generation of a transgenic parasite that will express reporter gene at the ring stage. Regulatory sequences flanking the gene expressing the knob associated histidine rich protein (kahrp) (Lanzer *et al.*, 1992) could replace the luciferase expressing cassette in the existing base plasmid (MH1 in Figure 6.6).

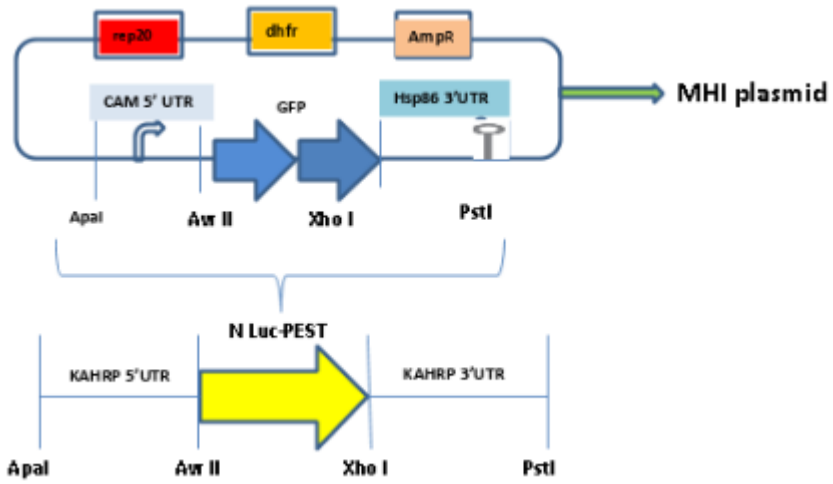

Figure 6.6: Subcloning strategy for generating Nanoluc-PEST transgenic parasites
Three sections of the existing plasmid will be replaced: Green fluorescent protein (GFP) reporter will be replaced with nanoluc-PEST, CAM5´UTR and Hsp86 3´UTR will be replaced with kahrp 5´ and 3´UTR respectively. The restriction sites are indicated with restriction enzymes: ApaI, AvrII, XhoI, PstI. Drugs selection (dhfr and AmpR),rep^{20}, DNA repeat sequence, Amp^{R}, Ampicillin.

This approach also envisages reducing the size of the reporter plasmid through the use of a nanoluc-PEST transgene – a highly unstable version of the bioluminescence reporter, with work done in *Leishmania mexicana* showing a ½ life measure of some 8 minutes (Berry *et al.*, 2018). Comparison of mBRRoK data in rings and trophozoite stages would enable the triage process to select compounds that are likely to exert a cytocidal action over the 48hr life cycle and effect a more effective and timely reduction in parasitaemia irrespective of when the treatment is

initiated. Clearly, taking the opportunity to develop stage-specific mBRRoK assay to explore antimalarial activities of drugs or compounds in artemisinin-resistant (ART^R) and artemisinin-sensitive (ART^S) strains of *P. falciparum* offers the opportunity to focus on work with smaller compound libraries (e.g. the 975 compounds that have already been highlighted in the screening of the TCMAS library) or for libraries of 300-500 compounds synthesised around lead series of interest.

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Appendix 1(Chapter 3)

This table reports full dataset of the MMV Malaria Box compounds with the predicted mode of action and core scaffolds

Compound ID	IC_{50} in Dd2 (nm)(1)	6hr PC1(1)	Designation	10μM	2μM	Related core Scaffold (1)	Ullah et al (1)	Allman et al (2)	Lehane et al (3)	Creek et al (4)
MMV009015	1093.0	-129.9	Probe like	11.5	17.0					
MMV666021	1259.0	-126.9	Probe like	1.5	7.0					
MMV665809	1523.0	-121.7	Probe like	17.0	58.0	2-Phenoxy-Benzylamine				
MMV019555	545.3	-106.3	Probe like	1.5	2.5					
MMV006787	906.6	-102.8	Probe like	8.5	11.0	Diamino-Glycerol				
MMV007092	948.3	-101.9	Probe like	22.0	67.5					
MMV665826	1266.0	-101.5	Drug like	1.0	7.5		PfATP4	Cellular Homeostasis/PfATP4	PfATP4	
MMV665806	483.5	-98.6	Drug like	18.0	32.0	Diamino-Glycerol				
Dihydroartemisinin	5.0	-97.4	Benchmark	2.5	3.3					
MMV000483	653.5	-95.7	Drug like	3.0	16.0		Hemoglobin Catabolism	Hemoglobin Catabolism		
MMV007617	1494.0	-95.5	Drug like	40.0	59.0		PfATP4	Cellular Homeostasis/PfATP4	PfATP4	
MMV667491	443.2	-93.3	Probe like	9.0	20.0					
MMV396736	733.6	-87.6	Drug like	15.0	21.0	Diamino-Glycerol				
MMV667490	1227.0	-87.0	Probe like	17.0	35.0					
MMV001049	1076.0	-86.8	Drug like	12.0	16.0					
MMV666079	1445.0	-86.5	Probe like	68.0	82.0					
MMV665831	127.2	-85.9	Probe like	34.0	70.0					ART-Like
MMV000848	452.7	-85.0	Drug like	8.0	22.0	Diamino-Glycerol	PfATP4	Cellular Homeostasis/PfATP4		
MMV019127	603.2	-83.9	Drug like	21.0	22.0	2-Phenoxy-Benzylamine				
MMV665882	436.4	-83.6	Probe like	46.0	66.0	Diamino-Glycerol				
MMV006764	789.1	-83.4	Probe like	5.0	7.0		PfATP4		PfATP4	
MMV007591	1598.0	-82.8	Probe like	28.0	48.0					
MMV008455	2340.0	-81.2	Probe like	1.5	17.0	Iso-Quinolone	PfATP4		PfATP4	
MMV019017	651.8	-80.9	Drug like	19.0	26.0	Diamino-Glycerol	PfATP4	Cellular Homeostasis/PfATP4		
MMV006545	870.5	-80.6	Drug like	22.0	22.0					
MMV007224	1511.0	-79.8	Probe like	10.0	13.0					
MMV006172	1596.0	-79.6	Probe like	10.0	25.0					Quinoline-like
MMV000839	1096.0	-79.5	Drug like	15.0	20.0	Diamino-Glycerol				
MMV011795	959.3	-79.1	Drug like	32.0	48.0	2-Phenoxy-Benzylamine	Hemoglobin Catabolism	Hemoglobin Catabolism		
MMV006429	160.0	-79.0	Drug like	4.0	5.0	Iso-Quinolone	PfATP4	Cellular Homeostasis/PfATP4	PfATP4	ART-Like
MMV396794	493.5	-77.1	Drug like	16.0	17.0					
MMV007181	296.5	-76.9	Probe like	19.0	21.0					
MMV007113	638.0	-76.4	Probe like	6.0	7.0					
MMV665949	1906.0	-76.1	Probe like	8.0	25.0		PfATP4		PfATP4	
MMV665864	892.6	-73.8	Probe like	37.0	60.0					
Chloroquine	208.8	-73.7	Benchmark	11.0	21.8					
MMV396633	1908.0	-72.2	Drug like	13.0	16.0		PfATP4	Cellular Homeostasis/PfATP4		
MMV665807	1088.0	-71.9	Drug like	13.0	23.0					
MMV019862	569.1	-71.2	Drug like	23.0	77.0					
MMV666124	1692.0	-70.2	Probe like	7.0	19.0		PfATP4		PfATP4	
MMV396669	1262.0	-69.2	Drug like	5.5	10.0		Hemoglobin Catabolism	Hemoglobin Catabolism		
MMV006303	464.9	-66.9	Probe like	19.0	29.0					
MMV020505	1163.0	-66.2	Drug like	20.0	32.0					
MMV009108	932.9	-65.7	Drug like	37.0	40.0		Hemoglobin Catabolism	Hemoglobin Catabolism		
MMV666060	635.4	-65.2	Probe like	22.0	24.0	2-Phenoxy-Benzylamine				
MMV000442	195.6	-64.3	Probe like	14.0	18.0					
MMV666061	501.8	-60.4	Drug like	18.0	19.0	2-Phenoxy-Benzylamine	Hemoglobin Catabolism	Hemoglobin Catabolism		
MMV306025	691.1	-59.7	Drug like	8.0	21.0					
MMV007654	1049.0	-57.8	Probe like	51.0	67.0					

MMV665890	903.8	-57.1	Drug like	38.0	58.0		PfATP4	Cellular Homeostasis/PfATP4	PfATP4	
MMV665794	739.1	-55.0	Probe like	8.0	12.0					
MMV000986	1412.0	-53.1	Probe like	31.0	69.0					
MMV080034	2366.0	-52.2	Probe like	26.0	65.0					
Quinine	246.0	-52.0	Benchmark	18.0	19.3					
MMV665830	475.6	-52.0	Probe like	22.0	26.0					
MMV000653	1220.0	-51.9	Drug like	72.0	80.0	Iso-Quinolone	PfATP4	Cellular Homeostasis/PfATP4	PfATP4	
MMV019881	263.8	-51.1	Probe like	9.0	27.0					
MMV666116	646.7	-51.1	Drug like	7.0	26.0	2-Phenoxy-Benzylamine	Hemoglobin Catabolism	Hemoglobin Catabolism		
MMV007275	558.0	-50.6	Probe like	6.0	8.0		PfATP4		PfATP4	
MMV666025	2028.0	-47.4	Probe like	10.0	45.0	Diamino-Glycerol	PfATP4		PfATP4	
MMV665953	1828.0	-46.4	Drug like	27.0	49.0					
MMV666102	1239.0	-46.0	Drug like	0.0	8.0	2-Phenyl-Benzimidazole	DHODH	mtETC/ Pyrimidine Synthesis		
MMV000481	1607.0	-45.8	Drug like	12.0	26.0					
MMV665857	1362.0	-45.5	Drug like	16.0	28.0		PfATP4	Cellular Homeostasis/PfATP4		
MMV006706	915.5	-43.7	Drug like	17.0	48.0		Folate Biosynthesis	Folate Biosynthesis		
Mefloquine	11.4	-42.4	Benchmark	13.5	17.0					
MMV000704	769.1	-40.5	Probe like	41.0	56.0					
Piperaquine	42.5	-37.0	Benchmark	19.3	36.0					
MMV000478	1699.0	-35.8	Probe like	24.0	41.0					
MMV019406	141.3	-35.1	Probe like	18.0	19.0	2-Phenoxy-Benzylamine				ART-Like
MMV666071	459.0	-33.3	Drug like	16.0	48.0					
MMV665906	2354.0	-32.8	Drug like	6.0	31.0		Folate Biosynthesis	Folate Biosynthesis		
MMV665881	1228.0	-32.5	Probe like	27.0	49.0					
MMV000445	1805.0	-31.4	Probe like	22.0	32.0					
MMV000443	617.2	-31.3	Probe like	21.0	27.0					
MMV011436	1989.0	-28.4	Probe like	54.0	76.0					
MMV665944	1135.0	-27.9	Probe like	25.0	40.0	2-Phenoxy-Benzylamine				
MMV128432	1867.0	-26.8	Probe like	38.0	51.0					
MMV019995	965.0	-25.7	Probe like	32.0	42.0					
MMV396663	1335.0	-25.0	Probe like	64.0	68.0					
MMV019780	1281.0	-22.3	Drug like	41.0	55.0					
MMV000304	1668.0	-21.1	Probe like	39.0	54.0					
MMV000648	1143.0	-16.4	Drug like	11.0	34.0		PfATP4		PfATP4	
MMV006882	1183.0	-15.7	Probe like	70.0	72.0					
MMV006169	897.4	-15.0	Probe like	28.0	52.0					
MMV000634	558.9	-14.6	Drug like	20.0	51.0					
MMV020912	1700.0	-13.1	Probe like	26.0	31.0	2-Phenoxy-Benzylamine				
MMV666604	1521.0	-11.1	Probe like	19.0	68.0					
MMV665786	542.8	-7.8	Probe like	30.0	47.0					
MMV001038	986.6	-7.3	Drug like	79.0	82.0		Hemoglobin Catabolism	Hemoglobin Catabolism		
MMV665874	1241.0	23.1	Drug like	90.0	92.0	Triazolo-Pyrimidine	DHODH	mtETC/ Pyrimidine Synthesis		ATQ Like
MMV666023	40.9	42.7	Probe like	64.0	87.0		bc1			ATQ Like
MMV007374	691.2	48.2	Drug like	95.0	104.0	Triazolo-Pyrimidine	DHODH			
MMV011259	136.9	49.1	Drug like	102.0	112.0	Triazolo-Pyrimidine	DHODH	mtETC/ Pyrimidine Synthesis		ATQ Like
MMV666693	426.4	54.7	Drug like	103.0	103.0		DHODH	mtETC/ Pyrimidine Synthesis		ATQ Like
Atovaquone	4.0	55.4	Benchmark	87.5	93.5					
MMV008294	538.5	55.5	Probe like	64.0	104.0		DHODH			ATQ Like
MMV396680	327.7	65.1	Probe like	65.0	107.0		DHODH			ATQ Like
MMV396679	2300.0	67.5	Probe like	65.0	103.0		bc1			ATQ Like
MMV006250	684.0	68.4	Probe like	48.0	105.0		DHODH			
MMV665923	241.5	70.2	Probe like	53.0	70.0					
MMV396678	1451.0	70.4	Probe like	94.0	95.5					

MMV007127	818.2	73.1	Probe like	40.0	48.0		bc1			
MMV006861	586.7	75.6	Probe like	62.0	95.0					
MMV006457	719.8	80.0	Probe like	65.0	111.0		bc1			ATQ Like
MMV006389	766.4	82.2	Probe like	48.0	111.0		bc1			
MMV000787	961.0	95.5	Probe like	62.0	71.0	8-Hydroxy-Quinoline				

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Appendix 2 (Chapter 3)

This table reports full mBRRoK screening data of 66 MMV Malaria Box compounds against Dd2^{luc} and NF54^{luc} parasite lines (data reported in chapter 3). The compounds are categorised as red-initial RoK > CQ in Dd2^{luc} and NF54^{luc}, blue-initial RoK>CQ in only Dd2^{luc}, amber-initial RoK>CQ NF54^{luc} only, green-initial RoK <CQ in Dd2^{luc} and NF54^{luc}.

MMV ID	10µM (Dd2^{luc})	2µM (Dd2^{luc})	10µM (NF54^{luc})	2µM (NF54^{luc})
MMV306025	8.0	21.0	7	25
MMV666102	0.0	8.0	4	14
MMV666021	1.5	7.0	2	10
MMV396736	15.0	21.0	7	20
MMV019555	1.5	2.5	6	6
MMV008455	1.5	17.0	11	24
MMV006764	5.0	7.0	15	16
MMV007113	6.0	7.0	14	14
MMV007224	10.0	13.0	9	25
MMV007181	19.0	21.0	14	15
MMV000443	21.0	25.0	15	24
MMV007275	6.0	8.0	16	17
MMV396794	16.0	17.0	11	25
MMV666124	7.0	19.0	11	17
MMV666116	7.0	25.0	11	24
MMV019017	19.0	25.0	5	25
MMV665794	8.0	12.0	10	23
MMV000442	14.0	18.0	15	15
MMV019406	18.0	19.0	9	9
MMV006787	8.5	11.0	9	23
MMV000848	8.0	22.0	8	23
MMV006172	10.0	25.0	4	25
MMV000483	3.0	16.0	9	24
MMV665949	8.0	25.0	12	20
MMV009015	11.5	17.0	14	25
MMV666061	18.0	19.0	10	16
MMV000839	15.0	20.0	18	65
MMV000481	12.0	25.0	17	68
MMV665807	13.0	23.0	19	90
MMV001049	12.0	16.0	17	41
MMV396669	5.5	10.0	17	40
MMV000634	20.0	51.0	8	24
MMV011795	32.0	48.0	10	25
MMV665806	18.0	32.0	8	19
MMV019127	21.0	22.0	11	16
MMV665890	38.0	58.0	13	20
MMV007092	22.0	67.5	33	81
MMV000648	11.0	34.0	18	104

MMV009108	37.0	40.0	23	26
MMV006706	17.0	48.0	33	44
MMV666604	19.0	68.0	36	104
MMV007591	28.0	48.0	43	87
MMV020505	20.0	32.0	44	47
MMV000704	41.0	56.0	63	78
MMV006861	62.0	95.0	57	93
MMV665906	6.0	31.0	13	36
MMV019780	41.0	55.0	37	45
MMV020912	26.0	31.0	12	32
MMV665786	30.0	47.0	34	51
MMV665882	46.0	66.0	81	101
MMV665944	25.0	40.0	13	36
MMV128432	38.0	51.0	48	93
MMV665864	37.0	60.0	92	109
MMV019995	32.0	42.0	47	51
MMV011436	54.0	76.0	97	103
MMV007654	51.0	67.0	104	103
MMV666071	16.0	48.0	73	88
MMV396663	64.0	68.0	97	104
MMV011259	102.0	112.0	95	100
MMV666023	64.0	87.0	65	101
MMV000445	22.0	32.0	98	103
MMV666079	68.0	82.0	88	104
MMV666693	103.0	103.0	98	102
MMV665953	27.0	49.0	13	62
MMV666025	10.0	45.0	17	47
MMV665809	17.0	58.0	16	70

Appendix 3 (Chapter 4)

This table reports full mBRRoK screening data for the 400 MMV Pathogen Box compounds (data reported in chapter 4). The data indicate the normalized bioluminescence signal against the untreated control when the parasites were exposed to 10µM and 2µM concentrations of the test compounds.

Compound ID	Disease Set	10µM	2µM
MMV688854	CRYPTOSPORIDIOSIS	29	83
MMV689255	CRYPTOSPORIDIOSIS	67	83
MMV688853	CRYPTOSPORIDIOSIS	74	84
MMV675994	CRYPTOSPORIDIOSIS	105	108
MMV676053	CRYPTOSPORIDIOSIS	95	102
MMV676191	CRYPTOSPORIDIOSIS	101	103
MMV675993	CRYPTOSPORIDIOSIS	87	90
MMV676050	CRYPTOSPORIDIOSIS	75	97
MMV676182	CRYPTOSPORIDIOSIS	84	103
MMV675968	CRYPTOSPORIDIOSIS	41	92
MMV676599	CRYPTOSPORIDIOSIS	84	102
MMV688416	DENGUE	102	106
MMV688350	DENGUE	93	96
MMV688921	DENGUE	98	102
MMV688352	DENGUE	73	96
MMV688543	DENGUE	99	102
MMV003270	HOOKWORM	79	100
MMV688796	KINETOPLASTIDS	101	103
MMV688776	KINETOPLASTIDS	103	104
MMV688934	KINETOPLASTIDS	100	104
MMV690028	KINETOPLASTIDS	100	104
MMV688943	KINETOPLASTIDS	81	99
MMV687762	KINETOPLASTIDS	105	99
MMV688793	KINETOPLASTIDS	106	102
MMV688942	KINETOPLASTIDS	104	97
MMV688514	KINETOPLASTIDS	109	109
MMV688797	KINETOPLASTIDS	98	102
MMV202553	KINETOPLASTIDS	102	105
MMV188296	KINETOPLASTIDS	99	101
MMV688958	KINETOPLASTIDS	99	100
MMV688360	KINETOPLASTIDS	103	104
MMV099637	KINETOPLASTIDS	100	102
MMV688798	KINETOPLASTIDS	95	95
MMV652003	KINETOPLASTIDS	44	78
MMV676604	KINETOPLASTIDS	78	105

MMV690027	KINETOPLASTIDS	75	101
MMV676600	KINETOPLASTIDS	67	97
MMV676602	KINETOPLASTIDS	30	69
MMV675997	KINETOPLASTIDS	45	66
MMV595321	KINETOPLASTIDS	94	103
MMV688547	KINETOPLASTIDS	34	49
MMV689060	KINETOPLASTIDS	96	103
MMV689061	KINETOPLASTIDS	101	103
MMV689028	KINETOPLASTIDS	80	102
MMV688371	KINETOPLASTIDS	10	72
MMV688283	KINETOPLASTIDS	47	84
MMV688361	KINETOPLASTIDS	33	90
MMV689029	KINETOPLASTIDS	87	106
MMV688410	KINETOPLASTIDS	31	48
MMV676048	KINETOPLASTIDS	79	100
MMV690103	KINETOPLASTIDS	95	102
MMV676057	KINETOPLASTIDS	62	97
MMV690102	KINETOPLASTIDS	47	99
MMV689709	KINETOPLASTIDS	95	101
MMV688179	KINETOPLASTIDS	33	96
MMV689437	KINETOPLASTIDS	91	102
MMV688362	KINETOPLASTIDS	17	51
MMV687706	KINETOPLASTIDS	66	102
MMV045105	KINETOPLASTIDS	99	113
MMV688180	KINETOPLASTIDS	31	93
MMV676162	KINETOPLASTIDS	99	111
MMV688467	KINETOPLASTIDS	87	102
MMV675998	KINETOPLASTIDS	93	101
MMV659010	KINETOPLASTIDS	98	104
MMV676008	KINETOPLASTIDS	96	103
MMV688274	KINETOPLASTIDS	55	91
MMV688407	KINETOPLASTIDS	20	57
MMV659004	KINETOPLASTIDS	90	100
MMV688279	KINETOPLASTIDS	22	23
MMV688271	KINETOPLASTIDS	30	72
MMV676186	KINETOPLASTIDS	99	99
MMV688474	KINETOPLASTIDS	41	81
MMV688372	KINETOPLASTIDS	76	95
MMV658993	KINETOPLASTIDS	87	99
MMV676159	KINETOPLASTIDS	96	103
MMV004168	KINETOPLASTIDS	59	75

MMV676161	KINETOPLASTIDS	94	101
MMV688795	KINETOPLASTIDS	97	98
MMV689244	KINETOPLASTIDS	95	98
MMV689243	KINETOPLASTIDS	73	96
MMV688754	KINETOPLASTIDS	94	99
MMV001561	KINETOPLASTIDS	63	74
MMV658988	KINETOPLASTIDS	81	102
MMV688415	KINETOPLASTIDS	45	102
MMV688273	KINETOPLASTIDS	77	98
MMV1236379	KINETOPLASTIDS	90	104
MMV688550	KINETOPLASTIDS	55	84
MMV687776	LYMPHATIC FILARIASIS	77	107
MMV687775	LYMPHATIC FILARIASIS	67	93
MMV676492	LYMPHATIC FILARIASIS	104	116
MMV010764	MALARIA	105	105
MMV000907	MALARIA	45	84
MMV084603	MALARIA	35	46
MMV1028806	MALARIA	101	99
MMV676350	MALARIA	74	96
MMV026020	MALARIA	95	102
MMV006372	MALARIA	57	58
MMV011903	MALARIA	70	74
MMV020591	MALARIA	88	97
MMV020623	MALARIA	4	8
MMV020512	MALARIA	10	43
MMV020982	MALARIA	43	82
MMV020120	MALARIA	68	88
MMV676605	MALARIA	40	84
MMV007638	MALARIA	28	46
MMV021057	MALARIA	85	92
MMV020136	MALARIA	4	5
MMV020710	MALARIA	2	3
MMV020517	MALARIA	70	100
MMV019721	MALARIA	13	15
MMV020537	MALARIA	68	91
MMV019838	MALARIA	37	78
MMV020520	MALARIA	3	4
MMV019234	MALARIA	74	96
MMV016136	MALARIA	12	21
MMV676442	MALARIA	16	18
MMV020152	MALARIA	23	77

MMV024397	MALARIA	78	87
MMV019807	MALARIA	92	121
MMV560185	MALARIA	95	105
MMV019189	MALARIA	68	91
MMV020321	MALARIA	76	104
MMV019087	MALARIA	97	100
MMV676528	MALARIA	64	77
MMV020320	MALARIA	84	101
MMV085210	MALARIA	5	39
MMV006239	MALARIA	3	6
MMV000858	MALARIA	3	6
MMV006741	MALARIA	59	83
MMV019742	MALARIA	94	116
MMV009054	MALARIA	104	108
MMV006901	MALARIA	22	73
MMV020391	MALARIA	3	5
MMV676380	MALARIA	0	4
MMV008439	MALARIA	63	79
MMV020388	MALARIA	94	105
MMV022236	MALARIA	79	95
MMV1030799	MALARIA	95	101
MMV021375	MALARIA	83	102
MMV1029203	MALARIA	98	101
MMV062221	MALARIA	91	102
MMV1088520	MALARIA	90	115
MMV023370	MALARIA	102	108
MMV1019989	MALARIA	97	99
MMV1037162	MALARIA	99	101
MMV026468	MALARIA	88	95
MMV020670	MALARIA	34	77
MMV023953	MALARIA	27	70
MMV010576	MALARIA	23	27
MMV032967	MALARIA	52	92
MMV031011	MALARIA	22	67
MMV026356	MALARIA	33	34
MMV011511	MALARIA	42	77
MMV007625	MALARIA	50	69
MMV007471	MALARIA	77	86
MMV024829	MALARIA	29	90
MMV022029	MALARIA	5	22
MMV024035	MALARIA	9	50

MMV020291	MALARIA	82	103
MMV006833	MALARIA	41	51
MMV026490	MALARIA	65	101
MMV687246	MALARIA	17	88
MMV024114	MALARIA	73	99
MMV676269	MALARIA	62	101
MMV020081	MALARIA	5	6
MMV026550	MALARIA	71	87
MMV023860	MALARIA	24	94
MMV023949	MALARIA	94	99
MMV024406	MALARIA	24	54
MMV023233	MALARIA	22	27
MMV085230	MALARIA	83	122
MMV085071	MALARIA	7	7
MMV676260	MALARIA	41	69
MMV032995	MALARIA	87	100
MMV019790	MALARIA	98	101
MMV009135	MALARIA	92	100
MMV011765	MALARIA	89	102
MMV024937	MALARIA	39	77
MMV085499	MALARIA	29	31
MMV023985	MALARIA	32	102
MMV024195	MALARIA	35	83
MMV007803	MALARIA	109	118
MMV001059	MALARIA	6	9
MMV011691	MALARIA	47	66
MMV676877	MALARIA	36	57
MMV663250	MALARIA	16	28
MMV007133	MALARIA	107	114
MMV022478	MALARIA	2	30
MMV024101	MALARIA	16	36
MMV676881	MALARIA	87	104
MMV024443	MALARIA	31	61
MMV023388	MALARIA	30	69
MMV688980	MALARIA	3	8
MMV011229	MALARIA	103	112
MMV393144	MALARIA	29	54
MMV007920	MALARIA	68	89
MMV019993	MALARIA	3	7
MMV687794	MALARIA	101	103
MMV023183	MALARIA	24	36

MMV020165	MALARIA	12	48
MMV667494	MALARIA	3	5
MMV028694	MALARIA	20	32
MMV010545	MALARIA	27	96
MMV023227	MALARIA	73	97
MMV020289	MALARIA	98	110
MMV634140	MALARIA	7	7
MMV030734	MALARIA	68	96
MMV676358	MALARIA	75	99
MMV407834	MALARIA	6	30
MMV019551	MALARIA	91	97
MMV016838	MALARIA	85	89
MMV676270	MALARIA	83	108
MMV026313	MALARIA	91	92
MMV392832	MALARIA	54	86
MMV084864	MALARIA	75	101
MMV676480	ONCHOCERCIASIS	72	102
MMV001493	ONCHOCERCIASIS	75	104
MMV002817	ONCHOCERCIASIS	87	100
MMV668727	ONCHOCERCIASIS	38	105
MMV676204	ONCHOCERCIASIS	100	110
MMV675969	ONCHOCERCIASIS	108	114
MMV676064	ONCHOCERCIASIS	100	111
MMV675995	ONCHOCERCIASIS	100	100
MMV676063	ONCHOCERCIASIS	50	92
MMV675996	ONCHOCERCIASIS	87	96
MMV671636	ONCHOCERCIASIS	88	100
MMV689758	REFERENCE COMPOUNDS	86	100
MMV000062	REFERENCE COMPOUNDS	11	13
MMV002529	REFERENCE COMPOUNDS	90	104
MMV687800	REFERENCE COMPOUNDS	38	89
MMV001625	REFERENCE COMPOUNDS	97	109
MMV637953	REFERENCE COMPOUNDS	82	87
MMV000063	REFERENCE COMPOUNDS	48	63
MMV688773	REFERENCE COMPOUNDS	85	96
MMV000011	REFERENCE COMPOUNDS	84	104
MMV688774	REFERENCE COMPOUNDS	16	61
MMV688991	REFERENCE COMPOUNDS	40	84
MMV687801	REFERENCE COMPOUNDS	105	103
MMV689480	REFERENCE COMPOUNDS	68	103
MMV003152	REFERENCE COMPOUNDS	118	113

MMV000023	REFERENCE COMPOUNDS	52	72
MMV000014	REFERENCE COMPOUNDS	20	24
MMV687803	REFERENCE COMPOUNDS	72	105
MMV688994	REFERENCE COMPOUNDS	101	108
MMV687798	REFERENCE COMPOUNDS	76	103
MMV688775	REFERENCE COMPOUNDS	33	43
MMV689000	REFERENCE COMPOUNDS	34	98
MMV001499	REFERENCE COMPOUNDS	25	28
MMV002816	REFERENCE COMPOUNDS	100	101
MMV687796	REFERENCE COMPOUNDS	106	113
MMV688978	REFERENCE COMPOUNDS	5	73
MMV688990	REFERENCE COMPOUNDS	99	110
MMV688761	SCHISTOSOMIASIS	63	104
MMV676382	SCHISTOSOMIASIS	70	110
MMV688763	SCHISTOSOMIASIS	46	102
MMV676536	SCHISTOSOMIASIS	90	100
MMV688762	SCHISTOSOMIASIS	43	77
MMV688768	SCHISTOSOMIASIS	98	108
MMV688313	SCHISTOSOMIASIS	114	118
MMV1198433	SCHISTOSOMIASIS	89	105
MMV688178	SCHISTOSOMIASIS	98	105
MMV688771	SCHISTOSOMIASIS	104	109
MMV688270	SCHISTOSOMIASIS	101	104
MMV688766	SCHISTOSOMIASIS	25	34
MMV688552	SCHISTOSOMIASIS	35	101
MMV688472	TOXOPLASMOSIS	101	104
MMV688548	TOXOPLASMOSIS	95	93
MMV688471	TOXOPLASMOSIS	104	106
MMV688470	TOXOPLASMOSIS	98	102
MMV688704	TOXOPLASMOSIS	98	103
MMV688852	TOXOPLASMOSIS	67	83
MMV688509	TOXOPLASMOSIS	45	93
MMV688417	TOXOPLASMOSIS	90	100
MMV688703	TOXOPLASMOSIS	98	106
MMV688955	TOXOPLASMOSIS	108	108
MMV688364	TOXOPLASMOSIS	45	87
MMV688469	TOXOPLASMOSIS	96	102
MMV688411	TOXOPLASMOSIS	98	100
MMV688345	TOXOPLASMOSIS	98	109
MMV688330	TOXOPLASMOSIS	103	107
MMV637229	TRICHURIASIS	31	31

MMV676526	TUBERCULOSIS	78	112
MMV688553	TUBERCULOSIS	94	99
MMV676501	TUBERCULOSIS	90	100
MMV676449	TUBERCULOSIS	99	102
MMV676412	TUBERCULOSIS	104	103
MMV688889	TUBERCULOSIS	98	99
MMV676389	TUBERCULOSIS	97	102
MMV676603	TUBERCULOSIS	100	101
MMV676401	TUBERCULOSIS	61	91
MMV102872	TUBERCULOSIS	96	98
MMV676477	TUBERCULOSIS	100	101
MMV688888	TUBERCULOSIS	90	101
MMV053220	TUBERCULOSIS	99	103
MMV676584	TUBERCULOSIS	111	104
MMV676439	TUBERCULOSIS	102	101
MMV676395	TUBERCULOSIS	103	103
MMV676379	TUBERCULOSIS	104	98
MMV661713	TUBERCULOSIS	61	103
MMV688554	TUBERCULOSIS	80	103
MMV676555	TUBERCULOSIS	78	100
MMV676383	TUBERCULOSIS	68	100
MMV676444	TUBERCULOSIS	101	102
MMV676409	TUBERCULOSIS	106	107
MMV553002	TUBERCULOSIS	104	106
MMV688756	TUBERCULOSIS	100	102
MMV090930	TUBERCULOSIS	105	103
MMV676431	TUBERCULOSIS	100	98
MMV676571	TUBERCULOSIS	92	97
MMV676445	TUBERCULOSIS	89	101
MMV676589	TUBERCULOSIS	99	102
MMV676388	TUBERCULOSIS	69	94
MMV688936	TUBERCULOSIS	63	101
MMV676476	TUBERCULOSIS	100	107
MMV676377	TUBERCULOSIS	102	105
MMV676406	TUBERCULOSIS	97	101
MMV676461	TUBERCULOSIS	98	105
MMV676509	TUBERCULOSIS	97	101
MMV063404	TUBERCULOSIS	100	103
MMV676558	TUBERCULOSIS	101	102
MMV688555	TUBERCULOSIS	96	101
MMV676597	TUBERCULOSIS	91	96

MMV676588	TUBERCULOSIS	93	98
MMV676554	TUBERCULOSIS	99	100
MMV676539	TUBERCULOSIS	96	101
MMV202458	TUBERCULOSIS	97	100
MMV676474	TUBERCULOSIS	99	100
MMV461553	TUBERCULOSIS	98	100
MMV676520	TUBERCULOSIS	100	109
MMV676512	TUBERCULOSIS	99	102
MMV012074	TUBERCULOSIS	112	104
MMV676386	TUBERCULOSIS	89	98
MMV069458	TUBERCULOSIS	82	83
MMV687239	TUBERCULOSIS	96	108
MMV688122	TUBERCULOSIS	86	102
MMV687145	TUBERCULOSIS	104	106
MMV688327	TUBERCULOSIS	98	102
MMV687747	TUBERCULOSIS	93	103
MMV688466	TUBERCULOSIS	80	95
MMV687749	TUBERCULOSIS	25	46
MMV688846	TUBERCULOSIS	37	86
MMV054312	TUBERCULOSIS	101	109
MMV688508	TUBERCULOSIS	104	108
MMV687243	TUBERCULOSIS	100	114
MMV687730	TUBERCULOSIS	87	104
MMV687251	TUBERCULOSIS	100	107
MMV687254	TUBERCULOSIS	102	103
MMV687703	TUBERCULOSIS	31	65
MMV687248	TUBERCULOSIS	45	79
MMV688125	TUBERCULOSIS	46	64
MMV687188	TUBERCULOSIS	96	103
MMV688124	TUBERCULOSIS	39	65
MMV688845	TUBERCULOSIS	75	96
MMV687699	TUBERCULOSIS	99	105
MMV687146	TUBERCULOSIS	98	102
MMV687696	TUBERCULOSIS	93	101
MMV687170	TUBERCULOSIS	98	103
MMV023969	TUBERCULOSIS	21	59
MMV687138	TUBERCULOSIS	97	106
MMV688262	TUBERCULOSIS	72	103
MMV687189	TUBERCULOSIS	103	107
MMV687807	TUBERCULOSIS	93	106
MMV676478	TUBERCULOSIS	99	103

MMV021660	TUBERCULOSIS	85	91
MMV687273	TUBERCULOSIS	95	100
MMV687180	TUBERCULOSIS	95	108
MMV688891	TUBERCULOSIS	108	104
MMV687172	TUBERCULOSIS	113	114
MMV688844	TUBERCULOSIS	101	108
MMV024311	TUBERCULOSIS	94	101
MMV688941	TUBERCULOSIS	59	88
MMV687812	TUBERCULOSIS	3	27
MMV676411	TUBERCULOSIS	89	101
MMV676468	TUBERCULOSIS	108	107
MMV676470	TUBERCULOSIS	96	100
MMV688938	TUBERCULOSIS	40	59
MMV047015	TUBERCULOSIS	88	98
MMV676472	TUBERCULOSIS	74	94
MMV687765	TUBERCULOSIS	22	54
MMV676524	TUBERCULOSIS	108	107
MMV611037	TUBERCULOSIS	112	115
MMV200748	TUBERCULOSIS	100	103
MMV687700	TUBERCULOSIS	65	97
MMV676384	TUBERCULOSIS	112	111
MMV687729	TUBERCULOSIS	97	99
MMV687813	TUBERCULOSIS	66	98
MMV153413	TUBERCULOSIS	93	100
MMV688755	TUBERCULOSIS	104	104
MMV228911	TUBERCULOSIS	94	102
MMV272144	TUBERCULOSIS	33	92
MMV161996	TUBERCULOSIS	90	104
MMV146306	TUBERCULOSIS	102	94
MMV688557	TUBERCULOSIS	87	99
MMV021013	TUBERCULOSIS	79	86
MMV688939	TUBERCULOSIS	92	103
MMV393995	TUBERCULOSIS	100	111
MMV495543	TUBERCULOSIS	39	90
MMV1110498	WOLBACHIA LF	100	101
MMV407539	WOLBACHIA LF	87	106
MMV676398	WOLBACHIA LF	96	99

Appendix 4(Chapter 4)

This table reports the predicted mode of action and core scaffolds for Malaria compounds in the MMV Pathogen Box

MMV ID	10µM	2µM	Disease set	Core scaffold	Dennis *et al (1)*	Tong *et al (2)*	Vaele (3)	Wicht et al., (4)	Gemma et al (5)	Younis et al (6)	Marwaha et al (7)	Ross et al (8)
MMV676380	0	4	Malaria			Digestive Vacoule						
MMV020710	2	3	Malaria		PfATP4							
MMV022478	2	30	Malaria	Pyrazolopyrimidine			NADPH oxidase					
MMV020520	3	4	Malaria		PfATP4							
MMV020391	3	5	Malaria	Sulfonamide	PfATP4							
MMV667494	3	5	Malaria	Amido quinolines			PfeEF2					
MMV006239	3	6	Malaria		PfATP4							
MMV000858	3	6	Malaria	Sulfonamide	PfATP4							
MMV019993	3	7	Malaria									
MMV688980	3	8	Malaria		PfATP4							
MMV020136	4	5	Malaria	Sulfonamide	PfATP4							
MMV020623	4	8	Malaria		PfATP4							
MMV020081	5	6	Malaria	Benzimidazole	PfATP4							
MMV022029	5	22	Malaria									
MMV085210	5	39	Malaria	Sulfonamide	PfATP4							
MMV001059	6	9	Malaria	Sulfonamide	PfATP4							
MMV407834	6	30	Malaria									
MMV085071	7	7	Malaria			Digestive Vacoule						
MMV634140	7	7	Malaria	Amido quinolines			PfeEF2					
MMV024035	9	50	Malaria									
MMV020512	10	43	Malaria									
MMV016136	12	21	Malaria	prazolopyrimidine								
MMV020165	12	48	Malaria									
MMV019721	13	15	Malaria									
MMV676442	16	18	Malaria									
MMV663250	16	28	Malaria						Hemozoin			
MMV024101	16	36	Malaria	1,5-Naphthyridines								
MMV687246	17	88	Malaria									
MMV028694	20	32	Malaria	Benzotriazole			AMPK					
MMV023233	22	27	Malaria									
MMV031011	22	67	Malaria				Hemozoin					
MMV006901	22	73	Malaria	Quinoline								
MMV010576	23	27	Malaria							*PfPI4K*		
MMV020152	23	77	Malaria									
MMV023183	24	36	Malaria									
MMV024406	24	54	Malaria									
MMV023860	24	94	Malaria									
MMV023953	27	70	Malaria									
MMV010545	27	96	Malaria	imidazopyridazines			*PfPI4K*					
MMV007638	28	46	Malaria									
MMV085499	29	31	Malaria	2-aminopyrazine			*PfPI4K*					
MMV393144	29	54	Malaria	2-aryl-imidazopyridine			*PfENT1*					
MMV024829	29	90	Malaria									
MMV023388	30	69	Malaria									
MMV024443	31	61	Malaria									
MMV023985	32	102	Malaria	imidazopyridazines			*PfPI4K*					
MMV026356	33	34	Malaria									

MMV020670	34	77	Malaria									
MMV084603	35	46	Malaria									
MMV024195	35	83	Malaria	Thienopyrimidines			*PfPI4k*					
MMV676877	36	57	Malaria									
MMV019838	37	78	Malaria									
MMV024937	39	77	Malaria				*PfDGAT-1*					
MMV676605	40	84	Malaria									
MMV006833	41	51	Malaria									
MMV676260	41	69	Malaria	2-aryl-imidazopyridine			*PfENT1*					
MMV011511	42	77	Malaria									
MMV020982	43	82	Malaria					Hemozoin				
MMV000907	45	84	Malaria									
MMV011691	47	66	Malaria	imidazopiperazines								
MMV007625	50	69	Malaria									
MMV032967	52	92	Malaria	2-aryl-imidazopyridine			*PfENT1*					
MMV392832	54	86	Malaria	pyrrolopyridines			*PfENT1*					
MMV006372	57	58	Malaria	Pyrimido[4,5-b]indole								
MMV006741	59	83	Malaria	Aminoquinazoline			*PfPIK4*					
MMV676269	62	101	Malaria									
MMV008439	63	79	Malaria									
MMV676528	64	77	Malaria	Sulfonamide			*PfSIR2*					
MMV026490	65	101	Malaria									
MMV020120	68	88	Malaria									
MMV007920	68	89	Malaria	Benzoxazole			PfENT1					
MMV020537	68	91	Malaria									DHODH
MMV019189	68	91	Malaria	Spiroindolone								
MMV030734	68	96	Malaria				*PfCDPK1*					
MMV011903	70	74	Malaria	Benzimidazole			CXCR2					
MMV020517	70	100	Malaria	cyclopropyl			histone methyltrans					
MMV026550	71	87	Malaria	2-aminohydantoin			aspartic protease					
MMV023227	73	97	Malaria				PfATP4					
MMV024114	73	99	Malaria	7-azaindole			AMPK					
MMV676350	74	96	Malaria									
MMV019234	74	96	Malaria	Diarylpyrazoline			Pf topoisomerase II					
MMV676358	75	99	Malaria									
MMV084864	75	101	Malaria									
MMV020321	76	104	Malaria									
MMV007471	77	86	Malaria									
MMV024397	78	87	Malaria									
MMV022236	79	95	Malaria	trifluoromethyl oxadiazole			histone deacetylase					
MMV020291	82	103	Malaria	Sulfonamide			PfATP4					
MMV021375	83	102	Malaria									
MMV676270	83	108	Malaria									
MMV085230	83	122	Malaria	Chromane-piperidine			histone deacetylase					
MMV020320	84	101	Malaria									
MMV016838	85	89	Malaria									
MMV021057	85	92	Malaria				Cytochrome bc1					
MMV032995	87	100	Malaria									
MMV676881	87	104	Malaria	Purine			Cysteine protease					

MMV026468	88	95	Malaria	3-Aminopyridine								
MMV020591	88	97	Malaria									DHODH
MMV011765	89	102	Malaria									
MMV1088520	90	115	Malaria									
MMV026313	91	92	Malaria									
MMV019551	91	97	Malaria									
MMV062221	91	102	Malaria									
MMV009135	92	100	Malaria									
MMV019807	92	121	Malaria									
MMV023949	94	99	Malaria									
MMV020388	94	105	Malaria									
MMV019742	94	116	Malaria	Sulfonamide			PfATP4					
MMV1030799	95	101	Malaria	Benzimidazole		CXCR2						
MMV026020	95	102	Malaria									
MMV560185	95	105	Malaria	Quinoline								
MMV1019989	97	99	Malaria									
MMV019087	97	100	Malaria	triazolopyrimidine								
MMV1029203	98	101	Malaria	Thienopyrimidines			*PfPIK4*					
MMV019790	98	101	Malaria									
MMV020289	98	110	Malaria								DHODH	
MMV1037162	99	101	Malaria	Thienopyrimidines			*PfPIK4*					
MMV1028806	101	99	Malaria									
MMV687794	101	103	Malaria									
MMV023370	102	108	Malaria									
MMV011229	103	112	Malaria	imidazopyrimidine							DHODH	
MMV009054	104	108	Malaria									
MMV010764	105	105	Malaria									
MMV007133	107	114	Malaria									
MMV007803	109	118	Malaria									

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Appendix 5(Chapter 5)

This table reports the mBRRoK screening data of 12,514 TCAMS library compounds

TCAMS ID	10µM	2µM	TCAMS ID	10µM	2µM	TCAMS ID	10µM	2µM	TCAMS ID	10µM	2µM	TCAMS ID	10µM	2µM
TCMDC-138172	0	1	TCMDC-142131	42	43	TCMDC-136410	42	66	TCMDC-135230	51	85	TCMDC-138333	72	98
TCMDC-138676	0	1	TCMDC-123745	43	43	TCMDC-134964	42	66	TCMDC-132501	52	85	TCMDC-138078	72	98
TCMDC-136189	1	1	TCMDC-132322	43	43	TCMDC-132331	42	66	TCMDC-125059	52	85	TCMDC-141277	73	98
TCMDC-125200	1	1	TCMDC-138079	2	44	TCMDC-139512	43	66	TCMDC-137122	53	85	TCMDC-135873	75	98
TCMDC-138099	1	1	TCMDC-136000	3	44	TCMDC-138522	43	66	TCMDC-142335	54	85	TCMDC-123659	75	98
TCMDC-124539	1	1	TCMDC-135259	5	44	TCMDC-138796	43	66	TCMDC-139960	54	85	TCMDC-134207	76	98
TCMDC-135382	0	2	TCMDC-138215	5	44	TCMDC-138974	43	66	TCMDC-124249	55	85	TCMDC-125320	77	98
TCMDC-125139	1	2	TCMDC-137944	6	44	TCMDC-132763	43	66	TCMDC-136596	56	85	TCMDC-133698	77	98
TCMDC-124011	1	2	TCMDC-135623	6	44	TCMDC-136547	44	66	TCMDC-138594	57	85	TCMDC-133151	77	98
TCMDC-124791	2	2	TCMDC-139803	6	44	TCMDC-138270	45	66	TCMDC-135431	58	85	TCMDC-137038	77	98
TCMDC-137734	2	2	TCMDC-141592	7	44	TCMDC-132435	46	66	TCMDC-137090	58	85	TCMDC-139457	78	98
TCMDC-138757	1	3	TCMDC-140953	8	44	TCMDC-133767	47	66	TCMDC-124068	60	85	TCMDC-131392	78	98
TCMDC-124570	2	3	TCMDC-139814	9	44	TCMDC-134540	47	66	TCMDC-141620	60	85	TCMDC-137286	80	98
TCMDC-125045	2	3	TCMDC-140622	9	44	TCMDC-134707	48	66	TCMDC-136853	62	85	TCMDC-131419	80	98
TCMDC-138568	3	3	TCMDC-140820	10	44	TCMDC-136763	48	66	TCMDC-134958	62	85	TCMDC-135825	80	98
TCMDC-133480	3	3	TCMDC-142189	10	44	TCMDC-134651	49	66	TCMDC-134753	62	85	TCMDC-137642	80	98
TCMDC-125026	3	3	TCMDC-141084	10	44	TCMDC-125594	49	66	TCMDC-142007	62	85	TCMDC-137692	81	98
TCMDC-124756	3	3	TCMDC-137752	10	44	TCMDC-132182	50	66	TCMDC-137328	62	85	TCMDC-137806	81	98
TCMDC-138648	3	3	TCMDC-133893	10	44	TCMDC-140684	51	66	TCMDC-140981	62	85	TCMDC-131969	81	98
TCMDC-125611	3	3	TCMDC-140987	10	44	TCMDC-132405	52	66	TCMDC-137081	62	85	TCMDC-131944	81	98
TCMDC-125457	3	3	TCMDC-135492	12	44	TCMDC-125236	52	66	TCMDC-133624	63	85	TCMDC-133239	81	98
TCMDC-124139	3	3	TCMDC-140634	13	44	TCMDC-142111	53	66	TCMDC-136315	65	85	TCMDC-140339	81	98
TCMDC-134719	4	3	TCMDC-135651	13	44	TCMDC-124338	55	66	TCMDC-133231	67	85	TCMDC-132119	82	98
TCMDC-141784	4	3	TCMDC-140496	13	44	TCMDC-137740	55	66	TCMDC-124057	67	85	TCMDC-139509	83	98
TCMDC-125114	5	3	TCMDC-141724	13	44	TCMDC-142171	56	66	TCMDC-135245	67	85	TCMDC-123543	84	98
TCMDC-124758	5	3	TCMDC-138900	14	44	TCMDC-138572	57	66	TCMDC-141495	68	85	TCMDC-131615	84	98
TCMDC-132837	1	4	TCMDC-132426	14	44	TCMDC-124830	58	66	TCMDC-137564	69	85	TCMDC-134623	84	98
TCMDC-138677	1	4	TCMDC-132623	14	44	TCMDC-133050	59	66	TCMDC-132971	69	85	TCMDC-140814	85	98
TCMDC-142289	2	4	TCMDC-136374	14	44	TCMDC-138126	59	66	TCMDC-136566	70	85	TCMDC-125601	85	98
TCMDC-125396	2	4	TCMDC-132621	15	44	TCMDC-140093	60	66	TCMDC-132349	71	85	TCMDC-133732	85	98
TCMDC-125016	2	4	TCMDC-138908	15	44	TCMDC-124972	61	66	TCMDC-140076	71	85	TCMDC-134294	86	98
TCMDC-141015	2	4	TCMDC-134072	16	44	TCMDC-137087	61	66	TCMDC-131389	71	85	TCMDC-135072	86	98
TCMDC-135413	2	4	TCMDC-134698	16	44	TCMDC-139306	63	66	TCMDC-125190	71	85	TCMDC-140444	86	98
TCMDC-137529	2	4	TCMDC-135781	16	44	TCMDC-133094	63	66	TCMDC-123475	71	85	TCMDC-124077	86	98
TCMDC-124286	2	4	TCMDC-140482	17	44	TCMDC-138880	63	66	TCMDC-139376	72	85	TCMDC-137819	86	98
TCMDC-125018	3	4	TCMDC-136663	17	44	TCMDC-123553	64	66	TCMDC-137694	72	85	TCMDC-137225	86	98

TCMDC-124494	3	4	TCMDC-133381	18	44	TCMDC-138625	65	66	TCMDC-133256	73	85	TCMDC-134142	86	98
TCMDC-133478	3	4	TCMDC-141088	18	44	TCMDC-123797	65	66	TCMDC-125873	73	85	TCMDC-136851	86	98
TCMDC-133477	3	4	TCMDC-138576	18	44	TCMDC-134187	66	66	TCMDC-133198	73	85	TCMDC-137916	87	98
TCMDC-124789	3	4	TCMDC-139106	19	44	TCMDC-131814	3	67	TCMDC-124049	73	85	TCMDC-125731	88	98
TCMDC-124795	3	4	TCMDC-135857	19	44	TCMDC-139942	4	67	TCMDC-123849	73	85	TCMDC-124305	89	98
TCMDC-138226	3	4	TCMDC-134088	20	44	TCMDC-132815	4	67	TCMDC-139560	74	85	TCMDC-123840	89	98
TCMDC-138718	3	4	TCMDC-142257	20	44	TCMDC-139111	4	67	TCMDC-139461	74	85	TCMDC-137754	89	98
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TCMDC-123994	3	4	TCMDC-125673	20	44	TCMDC-142083	6	67	TCMDC-137049	75	85	TCMDC-132020	89	98
TCMDC-135130	4	4	TCMDC-131417	21	44	TCMDC-138528	11	67	TCMDC-125695	75	85	TCMDC-137380	89	98
TCMDC-123621	4	4	TCMDC-136019	21	44	TCMDC-141465	12	67	TCMDC-134724	75	85	TCMDC-131674	89	98
TCMDC-131825	4	4	TCMDC-132410	21	44	TCMDC-132367	12	67	TCMDC-131873	75	85	TCMDC-125413	90	98
TCMDC-138845	4	4	TCMDC-135803	22	44	TCMDC-132834	13	67	TCMDC-133056	76	85	TCMDC-136387	90	98
TCMDC-139377	4	4	TCMDC-139231	23	44	TCMDC-139200	13	67	TCMDC-123692	77	85	TCMDC-135138	90	98
TCMDC-125289	4	4	TCMDC-141334	23	44	TCMDC-141372	13	67	TCMDC-135422	77	85	TCMDC-131402	90	98
TCMDC-132304	4	4	TCMDC-124443	23	44	TCMDC-139506	13	67	TCMDC-141792	78	85	TCMDC-140513	90	98
TCMDC-134721	4	4	TCMDC-123492	24	44	TCMDC-134324	14	67	TCMDC-134682	78	85	TCMDC-137664	90	98
TCMDC-134717	5	4	TCMDC-132172	24	44	TCMDC-140295	14	67	TCMDC-124222	78	85	TCMDC-140901	90	98
TCMDC-124792	5	4	TCMDC-134559	24	44	TCMDC-131442	14	67	TCMDC-139601	78	85	TCMDC-124787	90	98
TCMDC-124546	5	4	TCMDC-139963	24	44	TCMDC-141584	16	67	TCMDC-142018	79	85	TCMDC-131383	91	98
TCMDC-124760	6	4	TCMDC-133669	25	44	TCMDC-139490	16	67	TCMDC-136850	79	85	TCMDC-137633	92	98
TCMDC-132832	1	5	TCMDC-141095	25	44	TCMDC-139153	17	67	TCMDC-140438	80	85	TCMDC-135816	92	98
TCMDC-139007	1	5	TCMDC-140787	26	44	TCMDC-132127	17	67	TCMDC-123887	80	85	TCMDC-137177	92	98
TCMDC-137750	1	5	TCMDC-132942	26	44	TCMDC-133515	17	67	TCMDC-141499	80	85	TCMDC-137347	92	98
TCMDC-137984	2	5	TCMDC-135862	27	44	TCMDC-142107	19	67	TCMDC-123864	80	85	TCMDC-125613	92	98
TCMDC-136637	2	5	TCMDC-142011	28	44	TCMDC-140213	19	67	TCMDC-136648	80	85	TCMDC-139298	92	98
TCMDC-138645	2	5	TCMDC-139474	30	44	TCMDC-134023	19	67	TCMDC-138809	80	85	TCMDC-138107	92	98
TCMDC-131802	2	5	TCMDC-137881	30	44	TCMDC-139764	21	67	TCMDC-139929	80	85	TCMDC-123866	93	98
TCMDC-123961	3	5	TCMDC-132453	30	44	TCMDC-125690	21	67	TCMDC-123490	80	85	TCMDC-125385	93	98
TCMDC-123544	3	5	TCMDC-123787	32	44	TCMDC-141612	21	67	TCMDC-132800	81	85	TCMDC-125735	93	98
TCMDC-138495	3	5	TCMDC-135854	34	44	TCMDC-132660	21	67	TCMDC-135260	81	85	TCMDC-138970	93	98
TCMDC-125071	3	5	TCMDC-133399	35	44	TCMDC-133812	22	67	TCMDC-137181	81	85	TCMDC-138784	93	98
TCMDC-138716	3	5	TCMDC-134184	37	44	TCMDC-138756	22	67	TCMDC-139025	81	85	TCMDC-139034	93	98
TCMDC-124847	3	5	TCMDC-133199	38	44	TCMDC-139172	22	67	TCMDC-125497	81	85	TCMDC-131603	93	98
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TCMDC-132074	4	5	TCMDC-140774	39	44	TCMDC-139700	23	67	TCMDC-136784	81	85	TCMDC-141127	93	98
TCMDC-124519	4	5	TCMDC-124817	39	44	TCMDC-134650	23	67	TCMDC-125755	82	85	TCMDC-132115	93	98

TCMDC-137869	4	5	TCMDC-125469	40	44	TCMDC-134317	24	67	TCMDC-137822	82	85	TCMDC-138055	93	98
TCMDC-124548	4	5	TCMDC-140102	41	44	TCMDC-134407	24	67	TCMDC-124474	82	85	TCMDC-138927	93	98
TCMDC-124506	4	5	TCMDC-138570	43	44	TCMDC-134073	25	67	TCMDC-123669	83	85	TCMDC-142270	93	98
TCMDC-134208	4	5	TCMDC-139176	43	44	TCMDC-138435	25	67	TCMDC-140331	83	85	TCMDC-139219	93	98
TCMDC-123687	4	5	TCMDC-131861	43	44	TCMDC-134017	25	67	TCMDC-125276	84	85	TCMDC-137756	93	98
TCMDC-137587	4	5	TCMDC-139067	43	44	TCMDC-132770	26	67	TCMDC-138229	84	85	TCMDC-137464	94	98
TCMDC-134715	5	5	TCMDC-123912	43	44	TCMDC-133487	27	67	TCMDC-135308	84	85	TCMDC-131314	94	98
TCMDC-125504	5	5	TCMDC-141722	43	44	TCMDC-134252	27	67	TCMDC-137490	84	85	TCMDC-131586	94	98
TCMDC-141804	5	5	TCMDC-142038	44	44	TCMDC-141382	27	67	TCMDC-137385	84	85	TCMDC-123893	94	98
TCMDC-125133	5	5	TCMDC-133666	44	44	TCMDC-138671	27	67	TCMDC-125612	85	85	TCMDC-124683	94	98
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TCMDC-124793	2	6	TCMDC-123985	44	44	TCMDC-134237	28	67	TCMDC-124067	85	85	TCMDC-136621	94	98
TCMDC-137146	2	6	TCMDC-132757	48	44	TCMDC-134703	28	67	TCMDC-136875	3	86	TCMDC-125767	94	98
TCMDC-125089	3	6	TCMDC-133656	51	44	TCMDC-132752	28	67	TCMDC-125620	6	86	TCMDC-137858	94	98
TCMDC-131250	3	6	TCMDC-131821	1	45	TCMDC-134153	28	67	TCMDC-133233	7	86	TCMDC-125550	94	98
TCMDC-124438	3	6	TCMDC-138922	3	45	TCMDC-141289	28	67	TCMDC-141472	8	86	TCMDC-133201	94	98
TCMDC-123610	3	6	TCMDC-136769	5	45	TCMDC-134050	29	67	TCMDC-133726	12	86	TCMDC-142273	94	98
TCMDC-125123	3	6	TCMDC-132066	5	45	TCMDC-135367	29	67	TCMDC-134617	13	86	TCMDC-123652	94	98
TCMDC-125113	3	6	TCMDC-137832	6	45	TCMDC-136608	29	67	TCMDC-141619	14	86	TCMDC-125304	94	98
TCMDC-125035	3	6	TCMDC-137474	6	45	TCMDC-132661	29	67	TCMDC-141153	14	86	TCMDC-132578	94	98
TCMDC-125130	4	6	TCMDC-140000	6	45	TCMDC-132662	29	67	TCMDC-141580	15	86	TCMDC-123548	95	98
TCMDC-125253	4	6	TCMDC-138776	6	45	TCMDC-140794	30	67	TCMDC-139170	16	86	TCMDC-123567	95	98
TCMDC-138527	4	6	TCMDC-125222	6	45	TCMDC-133068	30	67	TCMDC-138622	20	86	TCMDC-124732	95	98
TCMDC-137813	5	6	TCMDC-134442	7	45	TCMDC-138822	31	67	TCMDC-134356	22	86	TCMDC-138639	95	98
TCMDC-125207	5	6	TCMDC-140579	8	45	TCMDC-138312	31	67	TCMDC-131347	22	86	TCMDC-142321	95	98
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TCMDC-138140	1	7	TCMDC-138555	9	45	TCMDC-141817	34	67	TCMDC-141074	24	86	TCMDC-137270	95	98
TCMDC-124079	2	7	TCMDC-140116	9	45	TCMDC-140645	34	67	TCMDC-134434	26	86	TCMDC-123815	95	98
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TCMDC-125397	2	7	TCMDC-140988	10	45	TCMDC-135261	35	67	TCMDC-136087	28	86	TCMDC-131678	96	98
TCMDC-137977	2	7	TCMDC-141656	11	45	TCMDC-133034	35	67	TCMDC-133270	28	86	TCMDC-124704	96	98
TCMDC-140133	2	7	TCMDC-140590	11	45	TCMDC-134378	36	67	TCMDC-124768	28	86	TCMDC-138251	96	98
TCMDC-141991	3	7	TCMDC-139615	11	45	TCMDC-141674	36	67	TCMDC-134364	29	86	TCMDC-131754	96	98
TCMDC-123556	3	7	TCMDC-141531	11	45	TCMDC-141572	36	67	TCMDC-139529	29	86	TCMDC-135544	96	98
TCMDC-124547	3	7	TCMDC-141526	12	45	TCMDC-138748	36	67	TCMDC-132863	29	86	TCMDC-123903	97	98
TCMDC-138391	3	7	TCMDC-124444	12	45	TCMDC-134500	36	67	TCMDC-136220	29	86	TCMDC-124698	97	98

TCMDC-138400	3	7	TCMDC-134446	12	45	TCMDC-134831	36	67	TCMDC-135161	29	86	TCMDC-124427	97	98
TCMDC-123794	4	7	TCMDC-123476	12	45	TCMDC-134942	37	67	TCMDC-136732	29	86	TCMDC-137698	97	98
TCMDC-125838	5	7	TCMDC-135096	13	45	TCMDC-125679	39	67	TCMDC-136756	30	86	TCMDC-139269	97	98
TCMDC-125835	6	7	TCMDC-141506	13	45	TCMDC-134179	39	67	TCMDC-133365	30	86	TCMDC-140431	97	98
TCMDC-131829	6	7	TCMDC-140580	13	45	TCMDC-141654	39	67	TCMDC-134140	30	86	TCMDC-139147	97	98
TCMDC-124514	7	7	TCMDC-134131	13	45	TCMDC-142066	40	67	TCMDC-134458	31	86	TCMDC-124384	97	98
TCMDC-137976	7	7	TCMDC-125096	13	45	TCMDC-141201	40	67	TCMDC-139086	31	86	TCMDC-123558	97	98
TCMDC-124998	1	8	TCMDC-131274	14	45	TCMDC-140180	40	67	TCMDC-132485	31	86	TCMDC-125470	97	98
TCMDC-137319	1	8	TCMDC-134893	14	45	TCMDC-134539	40	67	TCMDC-133699	32	86	TCMDC-125148	97	98
TCMDC-140136	1	8	TCMDC-133773	15	45	TCMDC-123662	40	67	TCMDC-124155	32	86	TCMDC-136160	97	98
TCMDC-136208	1	8	TCMDC-136224	15	45	TCMDC-140788	41	67	TCMDC-136620	33	86	TCMDC-124315	97	98
TCMDC-137106	2	8	TCMDC-139381	16	45	TCMDC-138733	41	67	TCMDC-141861	34	86	TCMDC-137228	97	98
TCMDC-138155	2	8	TCMDC-135956	16	45	TCMDC-139624	42	67	TCMDC-136116	36	86	TCMDC-131599	97	98
TCMDC-138654	2	8	TCMDC-134070	17	45	TCMDC-133504	42	67	TCMDC-137546	36	86	TCMDC-123819	97	98
TCMDC-124039	2	8	TCMDC-141345	18	45	TCMDC-124747	43	67	TCMDC-137099	37	86	TCMDC-140973	97	98
TCMDC-139068	3	8	TCMDC-134222	18	45	TCMDC-124986	43	67	TCMDC-132806	37	86	TCMDC-125744	97	98
TCMDC-123570	3	8	TCMDC-140407	18	45	TCMDC-141653	43	67	TCMDC-141933	37	86	TCMDC-138960	97	98
TCMDC-137481	3	8	TCMDC-135346	18	45	TCMDC-136988	43	67	TCMDC-135960	38	86	TCMDC-123827	97	98
TCMDC-125361	3	8	TCMDC-123586	19	45	TCMDC-133523	43	67	TCMDC-136861	38	86	TCMDC-125212	97	98
TCMDC-123792	3	8	TCMDC-135333	19	45	TCMDC-136412	43	67	TCMDC-133527	38	86	TCMDC-134836	97	98
TCMDC-141402	3	8	TCMDC-137792	20	45	TCMDC-135503	44	67	TCMDC-140963	38	86	TCMDC-125030	97	98
TCMDC-134720	4	8	TCMDC-134246	20	45	TCMDC-124855	44	67	TCMDC-123986	40	86	TCMDC-131990	97	98
TCMDC-140798	4	8	TCMDC-135530	21	45	TCMDC-135134	44	67	TCMDC-138053	40	86	TCMDC-138253	97	98
TCMDC-142261	4	8	TCMDC-141347	21	45	TCMDC-138352	46	67	TCMDC-140771	40	86	TCMDC-138044	97	98
TCMDC-140737	4	8	TCMDC-141038	21	45	TCMDC-133128	47	67	TCMDC-134016	40	86	TCMDC-131635	97	98
TCMDC-124790	5	8	TCMDC-134701	22	45	TCMDC-124411	48	67	TCMDC-141956	41	86	TCMDC-124560	98	98
TCMDC-125729	5	8	TCMDC-139646	22	45	TCMDC-133130	48	67	TCMDC-141779	41	86	TCMDC-124273	98	98
TCMDC-138015	5	8	TCMDC-138814	22	45	TCMDC-133028	51	67	TCMDC-139679	41	86	TCMDC-135606	98	98
TCMDC-135486	6	8	TCMDC-133369	22	45	TCMDC-138866	53	67	TCMDC-138742	42	86	TCMDC-139421	98	98
TCMDC-125141	6	8	TCMDC-125491	22	45	TCMDC-137074	53	67	TCMDC-135120	42	86	TCMDC-123552	98	98
TCMDC-133929	6	8	TCMDC-132469	23	45	TCMDC-132804	54	67	TCMDC-133979	42	86	TCMDC-124598	98	98
TCMDC-137772	6	8	TCMDC-140670	24	45	TCMDC-124735	56	67	TCMDC-137174	42	86	TCMDC-142051	98	98
TCMDC-138468	7	8	TCMDC-131848	24	45	TCMDC-132947	56	67	TCMDC-131285	42	86	TCMDC-123555	98	98
TCMDC-124876	14	8	TCMDC-132346	25	45	TCMDC-136881	56	67	TCMDC-136267	43	86	TCMDC-135068	98	98
TCMDC-138426	2	9	TCMDC-125394	26	45	TCMDC-124421	57	67	TCMDC-125251	44	86	TCMDC-125293	98	98
TCMDC-133903	2	9	TCMDC-133935	26	45	TCMDC-133079	59	67	TCMDC-132018	44	86	TCMDC-131372	98	98
TCMDC-124794	3	9	TCMDC-139324	27	45	TCMDC-138331	60	67	TCMDC-139121	44	86	TCMDC-131747	98	98

TCMDC-123648	3	9	TCMDC-133225	27	45	TCMDC-134408	61	67	TCMDC-138642	45	86	TCMDC-125524	98	98
TCMDC-139465	3	9	TCMDC-134842	27	45	TCMDC-133890	61	67	TCMDC-132989	45	86	TCMDC-133629	98	98
TCMDC-125424	3	9	TCMDC-133177	28	45	TCMDC-139822	61	67	TCMDC-140197	46	86	TCMDC-133619	98	98
TCMDC-123774	3	9	TCMDC-132937	28	45	TCMDC-123693	62	67	TCMDC-135837	46	86	TCMDC-133458	98	98
TCMDC-137147	3	9	TCMDC-133375	28	45	TCMDC-136460	63	67	TCMDC-138362	47	86	TCMDC-137874	98	98
TCMDC-131551	3	9	TCMDC-141980	28	45	TCMDC-132955	63	67	TCMDC-139541	48	86	TCMDC-125820	98	98
TCMDC-124606	4	9	TCMDC-133546	28	45	TCMDC-137882	63	67	TCMDC-135766	48	86	TCMDC-124864	98	98
TCMDC-124848	4	9	TCMDC-139059	29	45	TCMDC-132131	63	67	TCMDC-135717	48	86	TCMDC-123540	98	98
TCMDC-136607	4	9	TCMDC-142081	30	45	TCMDC-133936	65	67	TCMDC-141684	48	86	TCMDC-123756	98	98
TCMDC-123775	4	9	TCMDC-136214	30	45	TCMDC-141008	65	67	TCMDC-141159	49	86	TCMDC-135504	98	98
TCMDC-125431	4	9	TCMDC-136548	31	45	TCMDC-142055	66	67	TCMDC-136573	49	86	TCMDC-133958	98	98
TCMDC-138909	5	9	TCMDC-139161	32	45	TCMDC-136914	66	67	TCMDC-137585	49	86	TCMDC-137384	98	98
TCMDC-138285	5	9	TCMDC-137022	32	45	TCMDC-137387	66	67	TCMDC-142163	50	86	TCMDC-137423	98	98
TCMDC-125459	6	9	TCMDC-140452	32	45	TCMDC-134336	66	67	TCMDC-131303	51	86	TCMDC-141996	98	98
TCMDC-131247	6	9	TCMDC-135784	32	45	TCMDC-124995	67	67	TCMDC-131845	52	86	TCMDC-135546	98	98
TCMDC-142143	6	9	TCMDC-138912	32	45	TCMDC-141886	67	67	TCMDC-139138	53	86	TCMDC-133164	98	98
TCMDC-124491	7	9	TCMDC-125766	33	45	TCMDC-125312	2	68	TCMDC-136807	53	86	TCMDC-125099	98	98
TCMDC-125849	7	9	TCMDC-124508	33	45	TCMDC-136658	3	68	TCMDC-124083	53	86	TCMDC-135426	98	98
TCMDC-139056	7	9	TCMDC-141631	34	45	TCMDC-141470	6	68	TCMDC-141630	53	86	TCMDC-133176	98	98
TCMDC-135434	9	9	TCMDC-139380	37	45	TCMDC-138732	7	68	TCMDC-136650	53	86	TCMDC-137737	98	98
TCMDC-138321	9	9	TCMDC-138550	37	45	TCMDC-139854	8	68	TCMDC-132557	53	86	TCMDC-133970	98	98
TCMDC-125209	9	9	TCMDC-133407	41	45	TCMDC-136219	8	68	TCMDC-138824	53	86	TCMDC-135017	98	98
TCMDC-137839	1	10	TCMDC-136564	43	45	TCMDC-139621	8	68	TCMDC-137017	54	86	TCMDC-135014	98	98
TCMDC-139074	1	10	TCMDC-141455	44	45	TCMDC-132839	9	68	TCMDC-124422	54	86	TCMDC-138180	98	98
TCMDC-135415	1	10	TCMDC-142161	45	45	TCMDC-134227	9	68	TCMDC-139434	54	86	TCMDC-137828	98	98
TCMDC-137763	2	10	TCMDC-142132	49	45	TCMDC-138808	9	68	TCMDC-134026	54	86	TCMDC-138514	98	98
TCMDC-138703	2	10	TCMDC-139852	1	46	TCMDC-133340	10	68	TCMDC-140679	55	86	TCMDC-138035	99	98
TCMDC-125122	3	10	TCMDC-140137	3	46	TCMDC-141276	12	68	TCMDC-140192	55	86	TCMDC-125234	101	98
TCMDC-123564	3	10	TCMDC-140113	3	46	TCMDC-134150	12	68	TCMDC-134213	56	86	TCMDC-134584	102	98
TCMDC-133889	3	10	TCMDC-138546	4	46	TCMDC-138582	12	68	TCMDC-123942	58	86	TCMDC-133727	7	99
TCMDC-135298	3	10	TCMDC-133442	5	46	TCMDC-133185	12	68	TCMDC-133166	58	86	TCMDC-124924	20	99
TCMDC-137449	4	10	TCMDC-139778	5	46	TCMDC-139909	13	68	TCMDC-133452	60	86	TCMDC-139325	20	99
TCMDC-135270	4	10	TCMDC-136194	6	46	TCMDC-141639	13	68	TCMDC-142249	60	86	TCMDC-141832	29	99
TCMDC-141627	4	10	TCMDC-135564	6	46	TCMDC-139904	13	68	TCMDC-141566	61	86	TCMDC-131591	32	99
TCMDC-137950	4	10	TCMDC-137511	6	46	TCMDC-134553	14	68	TCMDC-134157	61	86	TCMDC-125435	34	99
TCMDC-138120	5	10	TCMDC-140340	7	46	TCMDC-134245	14	68	TCMDC-140793	61	86	TCMDC-138320	35	99
TCMDC-125417	6	10	TCMDC-123865	7	46	TCMDC-136457	14	68	TCMDC-141151	62	86	TCMDC-135884	37	99

TCMDC-138849	6	10	TCMDC-138461	8	46	TCMDC-140205	15	68	TCMDC-138310	62	86	TCMDC-133027	38	99
TCMDC-132308	6	10	TCMDC-141521	9	46	TCMDC-134890	16	68	TCMDC-134979	63	86	TCMDC-134914	39	99
TCMDC-132099	6	10	TCMDC-133714	9	46	TCMDC-138689	16	68	TCMDC-136749	64	86	TCMDC-133035	40	99
TCMDC-125153	7	10	TCMDC-132366	9	46	TCMDC-141161	18	68	TCMDC-134538	64	86	TCMDC-134485	43	99
TCMDC-124917	8	10	TCMDC-139103	9	46	TCMDC-141255	18	68	TCMDC-141946	64	86	TCMDC-136240	43	99
TCMDC-135817	10	10	TCMDC-134892	9	46	TCMDC-140036	18	68	TCMDC-124020	65	86	TCMDC-123851	44	99
TCMDC-142311	10	10	TCMDC-135268	10	46	TCMDC-133336	18	68	TCMDC-137870	65	86	TCMDC-124664	45	99
TCMDC-137838	1	11	TCMDC-133393	10	46	TCMDC-141714	19	68	TCMDC-134502	65	86	TCMDC-123885	45	99
TCMDC-138393	1	11	TCMDC-136553	10	46	TCMDC-139713	19	68	TCMDC-141999	66	86	TCMDC-132186	45	99
TCMDC-140020	2	11	TCMDC-134862	11	46	TCMDC-132537	20	68	TCMDC-133329	66	86	TCMDC-141864	46	99
TCMDC-123638	2	11	TCMDC-134656	11	46	TCMDC-125256	21	68	TCMDC-131850	66	86	TCMDC-131649	46	99
TCMDC-135222	2	11	TCMDC-135391	11	46	TCMDC-135030	21	68	TCMDC-135968	66	86	TCMDC-135709	50	99
TCMDC-139790	2	11	TCMDC-137811	11	46	TCMDC-134116	22	68	TCMDC-142020	67	86	TCMDC-136848	50	99
TCMDC-133476	3	11	TCMDC-132061	11	46	TCMDC-134775	22	68	TCMDC-134955	67	86	TCMDC-142216	52	99
TCMDC-138761	3	11	TCMDC-141321	12	46	TCMDC-138579	22	68	TCMDC-131956	67	86	TCMDC-139320	54	99
TCMDC-138395	3	11	TCMDC-135740	12	46	TCMDC-140817	23	68	TCMDC-123520	69	86	TCMDC-140141	54	99
TCMDC-131560	3	11	TCMDC-136977	12	46	TCMDC-141150	23	68	TCMDC-140759	69	86	TCMDC-141735	55	99
TCMDC-138492	3	11	TCMDC-133564	13	46	TCMDC-132875	23	68	TCMDC-137683	69	86	TCMDC-137233	57	99
TCMDC-125818	3	11	TCMDC-134206	13	46	TCMDC-133314	24	68	TCMDC-141046	70	86	TCMDC-136262	58	99
TCMDC-133863	3	11	TCMDC-132611	13	46	TCMDC-132777	25	68	TCMDC-133048	70	86	TCMDC-136415	61	99
TCMDC-134718	4	11	TCMDC-132291	14	46	TCMDC-133366	25	68	TCMDC-140680	70	86	TCMDC-142022	64	99
TCMDC-134256	4	11	TCMDC-134568	14	46	TCMDC-136472	25	68	TCMDC-125571	70	86	TCMDC-138646	66	99
TCMDC-138538	4	11	TCMDC-140742	14	46	TCMDC-139080	26	68	TCMDC-136856	71	86	TCMDC-133763	67	99
TCMDC-125344	4	11	TCMDC-132551	14	46	TCMDC-133534	26	68	TCMDC-125721	73	86	TCMDC-137725	67	99
TCMDC-140560	4	11	TCMDC-136600	15	46	TCMDC-138848	26	68	TCMDC-135731	74	86	TCMDC-141386	67	99
TCMDC-138416	4	11	TCMDC-137575	15	46	TCMDC-134779	26	68	TCMDC-140428	74	86	TCMDC-124176	67	99
TCMDC-124219	4	11	TCMDC-138075	15	46	TCMDC-133673	26	68	TCMDC-124829	74	86	TCMDC-141252	69	99
TCMDC-135388	5	11	TCMDC-134133	16	46	TCMDC-134799	27	68	TCMDC-124955	75	86	TCMDC-135188	69	99
TCMDC-125628	5	11	TCMDC-141384	17	46	TCMDC-139451	27	68	TCMDC-124899	75	86	TCMDC-133817	69	99
TCMDC-138661	5	11	TCMDC-139373	17	46	TCMDC-136424	27	68	TCMDC-138369	76	86	TCMDC-133357	70	99
TCMDC-136676	6	11	TCMDC-133782	17	46	TCMDC-136334	27	68	TCMDC-139791	76	86	TCMDC-137330	70	99
TCMDC-134045	6	11	TCMDC-141324	18	46	TCMDC-124857	28	68	TCMDC-131949	77	86	TCMDC-131929	72	99
TCMDC-123493	6	11	TCMDC-140873	19	46	TCMDC-139214	28	68	TCMDC-136975	77	86	TCMDC-124322	73	99
TCMDC-124064	6	11	TCMDC-132451	20	46	TCMDC-135330	28	68	TCMDC-141848	78	86	TCMDC-124128	73	99
TCMDC-138449	7	11	TCMDC-138464	20	46	TCMDC-138354	28	68	TCMDC-137367	78	86	TCMDC-139311	74	99
TCMDC-125103	8	11	TCMDC-137981	20	46	TCMDC-133864	29	68	TCMDC-135770	78	86	TCMDC-135618	76	99
TCMDC-141744	8	11	TCMDC-138846	21	46	TCMDC-135806	29	68	TCMDC-139821	79	86	TCMDC-135234	76	99

TCMDC-137323	8	11	TCMDC-133843	21	46	TCMDC-133007	29	68	TCMDC-125125	80	86	TCMDC-139841	77	99
TCMDC-141415	8	11	TCMDC-134550	21	46	TCMDC-141890	29	68	TCMDC-124777	80	86	TCMDC-137689	77	99
TCMDC-125450	8	11	TCMDC-139645	22	46	TCMDC-139348	29	68	TCMDC-123538	80	86	TCMDC-125029	77	99
TCMDC-141737	9	11	TCMDC-139452	22	46	TCMDC-139846	29	68	TCMDC-136846	80	86	TCMDC-137336	77	99
TCMDC-125346	10	11	TCMDC-124611	22	46	TCMDC-138690	30	68	TCMDC-123867	81	86	TCMDC-134854	79	99
TCMDC-138006	10	11	TCMDC-134933	22	46	TCMDC-134757	30	68	TCMDC-137707	81	86	TCMDC-135534	79	99
TCMDC-125199	11	11	TCMDC-140281	22	46	TCMDC-141338	30	68	TCMDC-124727	81	86	TCMDC-138168	79	99
TCMDC-136296	12	11	TCMDC-140672	22	46	TCMDC-138552	30	68	TCMDC-137625	81	86	TCMDC-124466	79	99
TCMDC-125034	12	11	TCMDC-141096	22	46	TCMDC-132694	31	68	TCMDC-137497	82	86	TCMDC-124447	80	99
TCMDC-140818	16	11	TCMDC-138418	22	46	TCMDC-124651	32	68	TCMDC-135791	82	86	TCMDC-137993	80	99
TCMDC-137620	1	12	TCMDC-136084	23	46	TCMDC-135257	33	68	TCMDC-137040	82	86	TCMDC-132135	81	99
TCMDC-140289	2	12	TCMDC-137485	23	46	TCMDC-134198	33	68	TCMDC-138209	83	86	TCMDC-132505	81	99
TCMDC-138838	3	12	TCMDC-140899	23	46	TCMDC-140697	33	68	TCMDC-124803	83	86	TCMDC-135835	81	99
TCMDC-137961	3	12	TCMDC-124312	23	46	TCMDC-132981	33	68	TCMDC-137436	83	86	TCMDC-138238	81	99
TCMDC-140642	3	12	TCMDC-139628	23	46	TCMDC-136523	33	68	TCMDC-123767	84	86	TCMDC-137079	82	99
TCMDC-138493	3	12	TCMDC-141787	24	46	TCMDC-136744	33	68	TCMDC-137124	84	86	TCMDC-135080	82	99
TCMDC-135129	4	12	TCMDC-125136	24	46	TCMDC-131266	33	68	TCMDC-136927	84	86	TCMDC-136494	82	99
TCMDC-138402	4	12	TCMDC-132677	24	46	TCMDC-139908	34	68	TCMDC-139928	84	86	TCMDC-137655	82	99
TCMDC-141753	4	12	TCMDC-141468	25	46	TCMDC-139730	35	68	TCMDC-125749	85	86	TCMDC-125625	82	99
TCMDC-139278	4	12	TCMDC-131947	25	46	TCMDC-139187	35	68	TCMDC-138512	85	86	TCMDC-134304	83	99
TCMDC-125197	5	12	TCMDC-136290	25	46	TCMDC-133046	35	68	TCMDC-125455	85	86	TCMDC-125871	83	99
TCMDC-138491	5	12	TCMDC-132029	25	46	TCMDC-134544	36	68	TCMDC-138072	85	86	TCMDC-124283	84	99
TCMDC-135128	6	12	TCMDC-136055	26	46	TCMDC-135374	36	68	TCMDC-123804	86	86	TCMDC-138507	84	99
TCMDC-124549	6	12	TCMDC-139982	27	46	TCMDC-135302	37	68	TCMDC-132956	86	86	TCMDC-131244	84	99
TCMDC-137503	6	12	TCMDC-139353	28	46	TCMDC-132460	37	68	TCMDC-136588	86	86	TCMDC-133558	84	99
TCMDC-140356	6	12	TCMDC-133192	29	46	TCMDC-136741	37	68	TCMDC-124282	86	86	TCMDC-137346	85	99
TCMDC-125592	7	12	TCMDC-124776	30	46	TCMDC-133191	38	68	TCMDC-139773	92	86	TCMDC-138041	85	99
TCMDC-136088	7	12	TCMDC-133103	30	46	TCMDC-133091	38	68	TCMDC-124138	7	87	TCMDC-125488	85	99
TCMDC-125198	8	12	TCMDC-125069	31	46	TCMDC-131676	38	68	TCMDC-139826	13	87	TCMDC-138019	85	99
TCMDC-134233	9	12	TCMDC-138884	31	46	TCMDC-140495	38	68	TCMDC-134437	16	87	TCMDC-123588	86	99
TCMDC-132231	11	12	TCMDC-132313	31	46	TCMDC-136397	38	68	TCMDC-136723	16	87	TCMDC-123547	86	99
TCMDC-134234	11	12	TCMDC-133611	32	46	TCMDC-137459	38	68	TCMDC-139408	19	87	TCMDC-137660	86	99
TCMDC-131967	0	13	TCMDC-141044	32	46	TCMDC-139497	39	68	TCMDC-134353	20	87	TCMDC-137188	86	99
TCMDC-139828	2	13	TCMDC-133572	32	46	TCMDC-123691	39	68	TCMDC-141582	20	87	TCMDC-131911	86	99
TCMDC-139816	2	13	TCMDC-139058	34	46	TCMDC-136750	40	68	TCMDC-140669	20	87	TCMDC-124729	86	99
TCMDC-138856	3	13	TCMDC-124485	35	46	TCMDC-124308	41	68	TCMDC-139567	20	87	TCMDC-138638	87	99
TCMDC-140752	3	13	TCMDC-142319	35	46	TCMDC-136417	44	68	TCMDC-136473	22	87	TCMDC-134613	87	99

TCMDC-140568	3	13	TCMDC-134205	35	46	TCMDC-140683	44	68	TCMDC-134455	22	87	TCMDC-133928	87	99
TCMDC-133556	4	13	TCMDC-136675	38	46	TCMDC-132672	45	68	TCMDC-139090	22	87	TCMDC-132015	87	99
TCMDC-140546	4	13	TCMDC-138763	39	46	TCMDC-139082	45	68	TCMDC-141540	26	87	TCMDC-125874	88	99
TCMDC-124652	4	13	TCMDC-142092	39	46	TCMDC-123583	46	68	TCMDC-141027	27	87	TCMDC-138325	88	99
TCMDC-125287	4	13	TCMDC-142090	39	46	TCMDC-125129	46	68	TCMDC-133020	28	87	TCMDC-140767	88	99
TCMDC-135561	4	13	TCMDC-133580	39	46	TCMDC-134412	51	68	TCMDC-125832	29	87	TCMDC-123676	89	99
TCMDC-131996	4	13	TCMDC-135821	40	46	TCMDC-133263	51	68	TCMDC-139177	29	87	TCMDC-136563	89	99
TCMDC-139094	4	13	TCMDC-141681	42	46	TCMDC-135959	51	68	TCMDC-137150	29	87	TCMDC-138225	89	99
TCMDC-124823	7	13	TCMDC-138612	42	46	TCMDC-141093	51	68	TCMDC-137864	31	87	TCMDC-125785	89	99
TCMDC-131497	7	13	TCMDC-142039	44	46	TCMDC-133144	53	68	TCMDC-133235	32	87	TCMDC-131866	89	99
TCMDC-124757	9	13	TCMDC-140690	44	46	TCMDC-138306	54	68	TCMDC-125056	32	87	TCMDC-125552	90	99
TCMDC-137778	11	13	TCMDC-138725	44	46	TCMDC-139491	54	68	TCMDC-139531	33	87	TCMDC-139173	90	99
TCMDC-141194	13	13	TCMDC-141182	44	46	TCMDC-142025	56	68	TCMDC-131313	33	87	TCMDC-140951	90	99
TCMDC-138663	13	13	TCMDC-138145	45	46	TCMDC-133648	56	68	TCMDC-133495	34	87	TCMDC-124550	90	99
TCMDC-131902	13	13	TCMDC-125528	46	46	TCMDC-124470	57	68	TCMDC-139528	35	87	TCMDC-133627	90	99
TCMDC-135266	14	13	TCMDC-133015	46	46	TCMDC-132727	57	68	TCMDC-140717	36	87	TCMDC-137663	90	99
TCMDC-136717	1	14	TCMDC-124415	47	46	TCMDC-136376	60	68	TCMDC-139572	37	87	TCMDC-123572	90	99
TCMDC-137543	1	14	TCMDC-140964	4	47	TCMDC-142302	60	68	TCMDC-134496	37	87	TCMDC-125629	90	99
TCMDC-137844	1	14	TCMDC-139800	4	47	TCMDC-124015	61	68	TCMDC-137522	38	87	TCMDC-135574	90	99
TCMDC-139767	2	14	TCMDC-136152	4	47	TCMDC-133238	62	68	TCMDC-137070	38	87	TCMDC-125184	90	99
TCMDC-133898	2	14	TCMDC-132811	6	47	TCMDC-134105	63	68	TCMDC-134114	39	87	TCMDC-131625	92	99
TCMDC-140559	3	14	TCMDC-141120	6	47	TCMDC-140337	64	68	TCMDC-136263	39	87	TCMDC-135579	92	99
TCMDC-137107	3	14	TCMDC-136476	7	47	TCMDC-133031	64	68	TCMDC-139295	40	87	TCMDC-125643	92	99
TCMDC-139613	3	14	TCMDC-136026	7	47	TCMDC-124975	66	68	TCMDC-125802	40	87	TCMDC-136236	92	99
TCMDC-137324	3	14	TCMDC-141511	7	47	TCMDC-140169	66	68	TCMDC-140416	40	87	TCMDC-137967	92	99
TCMDC-139494	3	14	TCMDC-133000	7	47	TCMDC-139389	67	68	TCMDC-132508	40	87	TCMDC-138867	92	99
TCMDC-140553	3	14	TCMDC-140178	8	47	TCMDC-124675	68	68	TCMDC-136771	41	87	TCMDC-134169	92	99
TCMDC-138494	3	14	TCMDC-141368	9	47	TCMDC-138222	68	68	TCMDC-139540	41	87	TCMDC-125499	92	99
TCMDC-136668	3	14	TCMDC-136739	9	47	TCMDC-138227	68	68	TCMDC-125086	42	87	TCMDC-123733	93	99
TCMDC-125799	4	14	TCMDC-134146	10	47	TCMDC-125805	68	68	TCMDC-133951	42	87	TCMDC-125357	93	99
TCMDC-140074	4	14	TCMDC-141305	11	47	TCMDC-124436	69	68	TCMDC-124731	43	87	TCMDC-125848	93	99
TCMDC-135385	4	14	TCMDC-131894	12	47	TCMDC-142299	2	69	TCMDC-136999	43	87	TCMDC-124055	93	99
TCMDC-123874	4	14	TCMDC-136946	12	47	TCMDC-125791	3	69	TCMDC-133257	44	87	TCMDC-125217	93	99
TCMDC-138316	4	14	TCMDC-137221	12	47	TCMDC-139758	9	69	TCMDC-139726	44	87	TCMDC-138592	93	99
TCMDC-131989	4	14	TCMDC-140415	13	47	TCMDC-139579	9	69	TCMDC-141709	44	87	TCMDC-123672	93	99
TCMDC-135773	4	14	TCMDC-135206	14	47	TCMDC-132810	9	69	TCMDC-140104	46	87	TCMDC-123653	93	99
TCMDC-124533	5	14	TCMDC-139341	14	47	TCMDC-139180	9	69	TCMDC-124239	46	87	TCMDC-135084	93	99

TCMDC-133913	5	14	TCMDC-132890	14	47	TCMDC-139707	9	69	TCMDC-141949	46	87	TCMDC-134143	94	99
TCMDC-137355	5	14	TCMDC-141069	14	47	TCMDC-139708	10	69	TCMDC-132542	47	87	TCMDC-138054	94	99
TCMDC-124616	6	14	TCMDC-133847	15	47	TCMDC-141473	10	69	TCMDC-137860	47	87	TCMDC-142293	94	99
TCMDC-132295	6	14	TCMDC-138700	15	47	TCMDC-124661	11	69	TCMDC-124820	48	87	TCMDC-133449	94	99
TCMDC-125196	6	14	TCMDC-141247	16	47	TCMDC-138195	12	69	TCMDC-141477	49	87	TCMDC-137227	94	99
TCMDC-133859	6	14	TCMDC-140464	16	47	TCMDC-138650	12	69	TCMDC-124251	49	87	TCMDC-123967	95	99
TCMDC-124164	6	14	TCMDC-132845	16	47	TCMDC-135778	13	69	TCMDC-141482	49	87	TCMDC-133918	95	99
TCMDC-124602	6	14	TCMDC-134078	17	47	TCMDC-142205	14	69	TCMDC-131359	49	87	TCMDC-135200	95	99
TCMDC-135944	7	14	TCMDC-133856	18	47	TCMDC-139902	14	69	TCMDC-132494	49	87	TCMDC-125132	95	99
TCMDC-123917	7	14	TCMDC-132443	18	47	TCMDC-136201	15	69	TCMDC-134290	49	87	TCMDC-137314	95	99
TCMDC-133933	7	14	TCMDC-138531	18	47	TCMDC-134891	15	69	TCMDC-133473	50	87	TCMDC-137028	95	99
TCMDC-125398	7	14	TCMDC-132008	18	47	TCMDC-134640	15	69	TCMDC-131891	50	87	TCMDC-137729	95	99
TCMDC-132298	8	14	TCMDC-139216	19	47	TCMDC-136601	15	69	TCMDC-132484	51	87	TCMDC-123609	96	99
TCMDC-137556	8	14	TCMDC-140694	19	47	TCMDC-139448	15	69	TCMDC-125340	52	87	TCMDC-131766	96	99
TCMDC-123550	9	14	TCMDC-132455	20	47	TCMDC-139592	16	69	TCMDC-133345	52	87	TCMDC-124328	96	99
TCMDC-135496	9	14	TCMDC-139136	20	47	TCMDC-135156	16	69	TCMDC-124851	52	87	TCMDC-136139	96	99
TCMDC-123535	9	14	TCMDC-140155	20	47	TCMDC-132724	16	69	TCMDC-123600	53	87	TCMDC-123517	96	99
TCMDC-131449	10	14	TCMDC-134086	21	47	TCMDC-135277	16	69	TCMDC-135637	53	87	TCMDC-138999	96	99
TCMDC-137239	11	14	TCMDC-137020	21	47	TCMDC-132388	17	69	TCMDC-132197	53	87	TCMDC-140445	96	99
TCMDC-140996	11	14	TCMDC-132336	21	47	TCMDC-134737	17	69	TCMDC-131846	53	87	TCMDC-131568	96	99
TCMDC-140019	12	14	TCMDC-134525	22	47	TCMDC-134888	17	69	TCMDC-133258	54	87	TCMDC-125761	96	99
TCMDC-137305	12	14	TCMDC-124247	22	47	TCMDC-141700	18	69	TCMDC-142306	54	87	TCMDC-123646	97	99
TCMDC-140990	13	14	TCMDC-140995	23	47	TCMDC-132126	18	69	TCMDC-136989	55	87	TCMDC-124499	97	99
TCMDC-131418	13	14	TCMDC-142119	23	47	TCMDC-133040	18	69	TCMDC-139751	56	87	TCMDC-125362	97	99
TCMDC-138143	14	14	TCMDC-133994	23	47	TCMDC-134101	19	69	TCMDC-139049	56	87	TCMDC-138258	97	99
TCMDC-137598	14	14	TCMDC-140756	23	47	TCMDC-137949	19	69	TCMDC-125353	56	87	TCMDC-141325	97	99
TCMDC-124468	17	14	TCMDC-136428	23	47	TCMDC-140119	19	69	TCMDC-124295	56	87	TCMDC-125542	97	99
TCMDC-132052	1	15	TCMDC-137145	23	47	TCMDC-140782	20	69	TCMDC-138210	57	87	TCMDC-142178	97	99
TCMDC-137966	1	15	TCMDC-140823	24	47	TCMDC-132526	21	69	TCMDC-131369	57	87	TCMDC-131932	97	99
TCMDC-135885	1	15	TCMDC-132952	24	47	TCMDC-132886	21	69	TCMDC-133804	57	87	TCMDC-136582	97	99
TCMDC-137282	2	15	TCMDC-125631	24	47	TCMDC-132612	21	69	TCMDC-133675	58	87	TCMDC-138010	97	99
TCMDC-140615	3	15	TCMDC-141575	25	47	TCMDC-140127	22	69	TCMDC-137528	59	87	TCMDC-124486	97	99
TCMDC-140631	3	15	TCMDC-124852	25	47	TCMDC-139990	22	69	TCMDC-136799	61	87	TCMDC-139489	97	99
TCMDC-124285	3	15	TCMDC-132747	25	47	TCMDC-141399	23	69	TCMDC-123622	61	87	TCMDC-133167	97	99
TCMDC-125151	3	15	TCMDC-138277	26	47	TCMDC-132130	23	69	TCMDC-140768	61	87	TCMDC-131756	97	99
TCMDC-124178	3	15	TCMDC-141086	27	47	TCMDC-134767	23	69	TCMDC-135874	61	87	TCMDC-124123	98	99
TCMDC-131563	4	15	TCMDC-134543	27	47	TCMDC-133387	24	69	TCMDC-132744	63	87	TCMDC-141469	98	99

TCMDC-136673	4	15	TCMDC-132528	28	47	TCMDC-134820	24	69	TCMDC-142210	63	87	TCMDC-137302	98	99
TCMDC-139329	4	15	TCMDC-133401	28	47	TCMDC-138088	24	69	TCMDC-138870	64	87	TCMDC-136729	98	99
TCMDC-133866	4	15	TCMDC-136199	28	47	TCMDC-141685	24	69	TCMDC-123976	65	87	TCMDC-125597	98	99
TCMDC-133865	5	15	TCMDC-124374	29	47	TCMDC-133022	24	69	TCMDC-141462	66	87	TCMDC-125664	98	99
TCMDC-134690	5	15	TCMDC-136411	29	47	TCMDC-134637	24	69	TCMDC-139446	66	87	TCMDC-137706	98	99
TCMDC-133892	5	15	TCMDC-138965	29	47	TCMDC-137001	25	69	TCMDC-131262	66	87	TCMDC-125804	98	99
TCMDC-140543	5	15	TCMDC-134894	29	47	TCMDC-139934	25	69	TCMDC-136779	67	87	TCMDC-123474	98	99
TCMDC-137197	5	15	TCMDC-133072	30	47	TCMDC-125813	26	69	TCMDC-134012	68	87	TCMDC-131769	98	99
TCMDC-132092	6	15	TCMDC-133400	30	47	TCMDC-132202	26	69	TCMDC-136964	68	87	TCMDC-133615	98	99
TCMDC-136481	7	15	TCMDC-132342	30	47	TCMDC-137526	26	69	TCMDC-139344	69	87	TCMDC-137643	98	99
TCMDC-137784	7	15	TCMDC-136664	31	47	TCMDC-135643	26	69	TCMDC-132396	69	87	TCMDC-131584	98	99
TCMDC-132251	7	15	TCMDC-140389	31	47	TCMDC-132857	27	69	TCMDC-134944	69	87	TCMDC-135925	98	99
TCMDC-133539	7	15	TCMDC-139014	32	47	TCMDC-134743	27	69	TCMDC-136905	70	87	TCMDC-135678	98	99
TCMDC-140811	8	15	TCMDC-136186	32	47	TCMDC-135383	27	69	TCMDC-135957	70	87	TCMDC-135789	98	99
TCMDC-123666	8	15	TCMDC-139787	32	47	TCMDC-140693	27	69	TCMDC-140754	70	87	TCMDC-124521	98	99
TCMDC-138157	8	15	TCMDC-138386	34	47	TCMDC-139040	27	69	TCMDC-123707	71	87	TCMDC-132962	98	99
TCMDC-131824	9	15	TCMDC-139181	35	47	TCMDC-135121	28	69	TCMDC-136173	72	87	TCMDC-133300	98	99
TCMDC-142256	9	15	TCMDC-141348	35	47	TCMDC-140212	28	69	TCMDC-135812	72	87	TCMDC-125040	98	99
TCMDC-133195	10	15	TCMDC-135358	35	47	TCMDC-123809	30	69	TCMDC-137841	72	87	TCMDC-123836	98	99
TCMDC-124100	10	15	TCMDC-132348	36	47	TCMDC-139259	30	69	TCMDC-135402	73	87	TCMDC-137361	98	99
TCMDC-135680	11	15	TCMDC-138129	38	47	TCMDC-139112	30	69	TCMDC-123587	74	87	TCMDC-125525	98	99
TCMDC-137458	11	15	TCMDC-134600	39	47	TCMDC-134745	30	69	TCMDC-135409	74	87	TCMDC-137299	98	99
TCMDC-125176	12	15	TCMDC-139563	39	47	TCMDC-124721	30	69	TCMDC-137969	74	87	TCMDC-131863	98	99
TCMDC-134236	13	15	TCMDC-139555	40	47	TCMDC-132430	31	69	TCMDC-134689	75	87	TCMDC-138060	98	99
TCMDC-131460	13	15	TCMDC-133653	40	47	TCMDC-141411	31	69	TCMDC-133468	75	87	TCMDC-137705	98	99
TCMDC-125055	14	15	TCMDC-133141	42	47	TCMDC-141328	31	69	TCMDC-139368	75	87	TCMDC-131405	98	99
TCMDC-141378	14	15	TCMDC-125400	44	47	TCMDC-123801	31	69	TCMDC-124946	76	87	TCMDC-137419	98	99
TCMDC-141889	14	15	TCMDC-124574	44	47	TCMDC-132159	33	69	TCMDC-142027	77	87	TCMDC-125833	98	99
TCMDC-135507	14	15	TCMDC-139095	44	47	TCMDC-124122	33	69	TCMDC-135669	77	87	TCMDC-137182	99	99
TCMDC-138205	14	15	TCMDC-133398	44	47	TCMDC-140923	33	69	TCMDC-125866	77	87	TCMDC-137026	99	99
TCMDC-138976	14	15	TCMDC-136930	44	47	TCMDC-135871	34	69	TCMDC-137071	77	87	TCMDC-123566	99	99
TCMDC-136069	15	15	TCMDC-139338	45	47	TCMDC-142052	34	69	TCMDC-124270	78	87	TCMDC-137536	99	99
TCMDC-138721	15	15	TCMDC-123808	2	48	TCMDC-134783	35	69	TCMDC-135517	78	87	TCMDC-123495	99	99
TCMDC-125170	15	15	TCMDC-138422	3	48	TCMDC-134738	35	69	TCMDC-138173	79	87	TCMDC-136021	99	99
TCMDC-131253	16	15	TCMDC-134828	3	48	TCMDC-134794	35	69	TCMDC-136635	79	87	TCMDC-136782	99	99
TCMDC-125495	17	15	TCMDC-139522	4	48	TCMDC-136453	35	69	TCMDC-123911	80	87	TCMDC-124487	99	99
TCMDC-137965	1	16	TCMDC-139060	4	48	TCMDC-133772	35	69	TCMDC-139273	80	87	TCMDC-131370	99	99

TCMDC-141698	2	16	TCMDC-137618	4	48	TCMDC-123541	36	69	TCMDC-140379	80	87	TCMDC-125534	99	99
TCMDC-142337	2	16	TCMDC-142172	5	48	TCMDC-139244	36	69	TCMDC-124416	80	87	TCMDC-123462	99	99
TCMDC-135858	2	16	TCMDC-136001	5	48	TCMDC-141590	36	69	TCMDC-124473	80	87	TCMDC-131876	99	99
TCMDC-140544	3	16	TCMDC-142218	5	48	TCMDC-125085	37	69	TCMDC-132960	80	87	TCMDC-138063	99	99
TCMDC-136050	4	16	TCMDC-139941	5	48	TCMDC-134526	37	69	TCMDC-124133	80	87	TCMDC-140511	99	99
TCMDC-138388	4	16	TCMDC-136008	5	48	TCMDC-133712	37	69	TCMDC-136868	81	87	TCMDC-124126	99	99
TCMDC-135571	4	16	TCMDC-125803	5	48	TCMDC-132496	38	69	TCMDC-132162	81	87	TCMDC-132118	99	99
TCMDC-140541	5	16	TCMDC-140199	6	48	TCMDC-135506	39	69	TCMDC-133559	81	87	TCMDC-124798	99	99
TCMDC-132838	5	16	TCMDC-132840	6	48	TCMDC-132310	39	69	TCMDC-138787	81	87	TCMDC-135880	99	99
TCMDC-137144	5	16	TCMDC-141054	6	48	TCMDC-141597	40	69	TCMDC-138775	81	87	TCMDC-138875	99	99
TCMDC-134548	6	16	TCMDC-138532	6	48	TCMDC-139668	40	69	TCMDC-123537	82	87	TCMDC-124920	99	99
TCMDC-131999	6	16	TCMDC-123759	6	48	TCMDC-135460	40	69	TCMDC-141009	82	87	TCMDC-125028	99	99
TCMDC-140750	6	16	TCMDC-140483	7	48	TCMDC-140796	40	69	TCMDC-132138	82	87	TCMDC-137537	99	99
TCMDC-137201	6	16	TCMDC-141985	7	48	TCMDC-140090	40	69	TCMDC-132073	82	87	TCMDC-134299	99	99
TCMDC-125241	7	16	TCMDC-136023	7	48	TCMDC-141967	42	69	TCMDC-125282	83	87	TCMDC-135942	8	100
TCMDC-135499	7	16	TCMDC-131828	7	48	TCMDC-123549	42	69	TCMDC-133178	83	87	TCMDC-136804	11	100
TCMDC-132219	8	16	TCMDC-136004	7	48	TCMDC-132924	44	69	TCMDC-135527	83	87	TCMDC-136687	18	100
TCMDC-124061	9	16	TCMDC-137442	8	48	TCMDC-131524	45	69	TCMDC-135906	83	87	TCMDC-140898	19	100
TCMDC-138868	10	16	TCMDC-138108	9	48	TCMDC-136269	46	69	TCMDC-131695	84	87	TCMDC-132823	21	100
TCMDC-133537	10	16	TCMDC-138182	10	48	TCMDC-137031	46	69	TCMDC-142159	84	87	TCMDC-124367	24	100
TCMDC-138113	10	16	TCMDC-134139	10	48	TCMDC-141800	47	69	TCMDC-124044	84	87	TCMDC-140700	24	100
TCMDC-135294	10	16	TCMDC-134647	11	48	TCMDC-136719	47	69	TCMDC-136515	84	87	TCMDC-137158	25	100
TCMDC-131493	10	16	TCMDC-142280	11	48	TCMDC-133455	47	69	TCMDC-133179	84	87	TCMDC-135471	25	100
TCMDC-136063	11	16	TCMDC-138806	11	48	TCMDC-137551	47	69	TCMDC-131725	85	87	TCMDC-133862	25	100
TCMDC-133660	11	16	TCMDC-141078	12	48	TCMDC-140928	48	69	TCMDC-123766	85	87	TCMDC-136674	26	100
TCMDC-137777	11	16	TCMDC-141598	13	48	TCMDC-138699	50	69	TCMDC-123755	85	87	TCMDC-125110	31	100
TCMDC-125172	11	16	TCMDC-138991	13	48	TCMDC-139876	52	69	TCMDC-135636	85	87	TCMDC-133162	33	100
TCMDC-123813	12	16	TCMDC-134099	14	48	TCMDC-133158	53	69	TCMDC-131946	85	87	TCMDC-139723	34	100
TCMDC-141734	13	16	TCMDC-141966	14	48	TCMDC-124613	56	69	TCMDC-142230	86	87	TCMDC-136790	36	100
TCMDC-141216	13	16	TCMDC-134560	14	48	TCMDC-134562	56	69	TCMDC-123636	86	87	TCMDC-141807	38	100
TCMDC-131505	13	16	TCMDC-132922	14	48	TCMDC-124710	60	69	TCMDC-131660	86	87	TCMDC-141948	38	100
TCMDC-124620	14	16	TCMDC-142242	14	48	TCMDC-138829	60	69	TCMDC-138707	86	87	TCMDC-133217	39	100
TCMDC-140815	14	16	TCMDC-132887	14	48	TCMDC-138348	62	69	TCMDC-125605	86	87	TCMDC-139246	39	100
TCMDC-125171	14	16	TCMDC-138668	14	48	TCMDC-138836	63	69	TCMDC-139016	86	87	TCMDC-141869	40	100
TCMDC-140241	14	16	TCMDC-132233	15	48	TCMDC-138339	63	69	TCMDC-125694	86	87	TCMDC-140402	42	100
TCMDC-125175	14	16	TCMDC-140602	15	48	TCMDC-141032	63	69	TCMDC-137998	86	87	TCMDC-138574	42	100
TCMDC-131492	14	16	TCMDC-134427	15	48	TCMDC-124705	64	69	TCMDC-139078	86	87	TCMDC-140744	43	100

TCMDC-142268	15	16	TCMDC-138127	15	48	TCMDC-123969	66	69	TCMDC-125639	86	87	TCMDC-137056	44	100
TCMDC-124672	15	16	TCMDC-135661	15	48	TCMDC-124895	66	69	TCMDC-139554	86	87	TCMDC-141676	45	100
TCMDC-138859	15	16	TCMDC-134087	16	48	TCMDC-142056	67	69	TCMDC-133766	86	87	TCMDC-135838	46	100
TCMDC-125169	15	16	TCMDC-132408	17	48	TCMDC-134110	67	69	TCMDC-137130	86	87	TCMDC-139562	47	100
TCMDC-136043	16	16	TCMDC-139005	17	48	TCMDC-134151	67	69	TCMDC-131301	86	87	TCMDC-136033	48	100
TCMDC-140209	19	16	TCMDC-137143	17	48	TCMDC-141199	68	69	TCMDC-138115	87	87	TCMDC-141323	49	100
TCMDC-137340	2	17	TCMDC-132620	17	48	TCMDC-132958	68	69	TCMDC-124462	87	87	TCMDC-133871	49	100
TCMDC-132474	2	17	TCMDC-132188	18	48	TCMDC-133617	68	69	TCMDC-138204	87	87	TCMDC-134312	50	100
TCMDC-139020	3	17	TCMDC-133710	18	48	TCMDC-132555	68	69	TCMDC-125270	87	87	TCMDC-140790	50	100
TCMDC-135393	4	17	TCMDC-132600	19	48	TCMDC-140030	68	69	TCMDC-124191	88	87	TCMDC-135751	51	100
TCMDC-132243	4	17	TCMDC-137308	19	48	TCMDC-140160	69	69	TCMDC-131648	95	87	TCMDC-135834	51	100
TCMDC-132213	5	17	TCMDC-132450	19	48	TCMDC-125794	69	69	TCMDC-132870	14	88	TCMDC-123922	51	100
TCMDC-141754	5	17	TCMDC-141101	20	48	TCMDC-125309	4	70	TCMDC-133227	15	88	TCMDC-133902	53	100
TCMDC-139652	5	17	TCMDC-133899	20	48	TCMDC-139484	4	70	TCMDC-137560	16	88	TCMDC-139169	53	100
TCMDC-137908	5	17	TCMDC-139361	20	48	TCMDC-133807	4	70	TCMDC-141158	17	88	TCMDC-139310	53	100
TCMDC-140605	5	17	TCMDC-132184	20	48	TCMDC-139641	5	70	TCMDC-134052	18	88	TCMDC-138673	54	100
TCMDC-132746	6	17	TCMDC-137149	20	48	TCMDC-139672	6	70	TCMDC-138817	20	88	TCMDC-134822	55	100
TCMDC-141440	8	17	TCMDC-132203	21	48	TCMDC-142146	8	70	TCMDC-141982	20	88	TCMDC-134462	60	100
TCMDC-125140	9	17	TCMDC-134529	21	48	TCMDC-136475	9	70	TCMDC-136644	21	88	TCMDC-138683	60	100
TCMDC-135497	9	17	TCMDC-140698	21	48	TCMDC-141924	9	70	TCMDC-124115	22	88	TCMDC-137238	62	100
TCMDC-125205	10	17	TCMDC-125406	22	48	TCMDC-139998	9	70	TCMDC-131899	22	88	TCMDC-135704	64	100
TCMDC-136506	10	17	TCMDC-123735	22	48	TCMDC-140227	9	70	TCMDC-136272	24	88	TCMDC-124725	64	100
TCMDC-125173	10	17	TCMDC-133781	22	48	TCMDC-141611	9	70	TCMDC-134389	24	88	TCMDC-139186	65	100
TCMDC-132296	10	17	TCMDC-137046	23	48	TCMDC-138710	9	70	TCMDC-123677	25	88	TCMDC-137695	66	100
TCMDC-132249	11	17	TCMDC-125814	23	48	TCMDC-142063	9	70	TCMDC-136128	26	88	TCMDC-142043	67	100
TCMDC-138151	11	17	TCMDC-133794	24	48	TCMDC-123983	10	70	TCMDC-141073	26	88	TCMDC-140903	67	100
TCMDC-135398	11	17	TCMDC-140932	24	48	TCMDC-139209	10	70	TCMDC-131860	27	88	TCMDC-141687	68	100
TCMDC-141198	12	17	TCMDC-139901	25	48	TCMDC-140190	11	70	TCMDC-133210	28	88	TCMDC-141271	69	100
TCMDC-133384	12	17	TCMDC-125471	25	48	TCMDC-139372	12	70	TCMDC-124771	29	88	TCMDC-141025	69	100
TCMDC-135693	12	17	TCMDC-134714	25	48	TCMDC-137005	13	70	TCMDC-141635	30	88	TCMDC-135910	70	100
TCMDC-135529	12	17	TCMDC-132245	26	48	TCMDC-133709	14	70	TCMDC-133033	30	88	TCMDC-137021	71	100
TCMDC-125778	13	17	TCMDC-136283	26	48	TCMDC-139880	14	70	TCMDC-139198	32	88	TCMDC-131934	71	100
TCMDC-135326	13	17	TCMDC-124673	27	48	TCMDC-139893	15	70	TCMDC-135805	32	88	TCMDC-138659	71	100
TCMDC-131483	14	17	TCMDC-132412	29	48	TCMDC-142078	15	70	TCMDC-133875	33	88	TCMDC-135595	72	100
TCMDC-131429	14	17	TCMDC-137582	29	48	TCMDC-140055	16	70	TCMDC-136111	34	88	TCMDC-133043	74	100
TCMDC-124059	15	17	TCMDC-141622	30	48	TCMDC-141835	17	70	TCMDC-134219	34	88	TCMDC-138563	74	100
TCMDC-140830	15	17	TCMDC-139323	31	48	TCMDC-141529	17	70	TCMDC-136432	34	88	TCMDC-139692	75	100

TCMDC-125726	15	17	TCMDC-139696	31	48	TCMDC-134383	17	70	TCMDC-137667	35	88	TCMDC-131365	75	100
TCMDC-124637	16	17	TCMDC-140708	31	48	TCMDC-132090	17	70	TCMDC-140459	35	88	TCMDC-138810	75	100
TCMDC-135464	16	17	TCMDC-135376	32	48	TCMDC-140232	17	70	TCMDC-141877	35	88	TCMDC-123814	76	100
TCMDC-124074	17	17	TCMDC-132930	32	48	TCMDC-141490	18	70	TCMDC-134564	35	88	TCMDC-136760	76	100
TCMDC-135281	1	18	TCMDC-141451	33	48	TCMDC-141361	18	70	TCMDC-133511	36	88	TCMDC-137563	76	100
TCMDC-141435	2	18	TCMDC-124583	33	48	TCMDC-137213	18	70	TCMDC-139155	36	88	TCMDC-139120	76	100
TCMDC-141443	2	18	TCMDC-139907	35	48	TCMDC-139701	19	70	TCMDC-141740	38	88	TCMDC-140430	77	100
TCMDC-139955	2	18	TCMDC-140080	36	48	TCMDC-139595	19	70	TCMDC-133117	38	88	TCMDC-137118	77	100
TCMDC-134684	3	18	TCMDC-132630	37	48	TCMDC-141896	19	70	TCMDC-132152	38	88	TCMDC-124889	77	100
TCMDC-132258	3	18	TCMDC-133092	37	48	TCMDC-133474	19	70	TCMDC-124292	39	88	TCMDC-133288	78	100
TCMDC-141175	3	18	TCMDC-141087	37	48	TCMDC-136145	19	70	TCMDC-123958	39	88	TCMDC-138109	78	100
TCMDC-140699	3	18	TCMDC-137064	37	48	TCMDC-138968	20	70	TCMDC-125187	39	88	TCMDC-139309	79	100
TCMDC-140198	3	18	TCMDC-125232	38	48	TCMDC-135060	20	70	TCMDC-135562	40	88	TCMDC-125801	79	100
TCMDC-133908	3	18	TCMDC-133406	38	48	TCMDC-139505	21	70	TCMDC-139987	41	88	TCMDC-137211	80	100
TCMDC-135132	4	18	TCMDC-132822	40	48	TCMDC-138181	22	70	TCMDC-136941	41	88	TCMDC-135696	80	100
TCMDC-136349	4	18	TCMDC-136829	40	48	TCMDC-135438	22	70	TCMDC-139552	42	88	TCMDC-142245	80	100
TCMDC-138398	5	18	TCMDC-133663	41	48	TCMDC-135265	22	70	TCMDC-139825	42	88	TCMDC-138771	81	100
TCMDC-125179	5	18	TCMDC-125274	41	48	TCMDC-140890	22	70	TCMDC-136943	43	88	TCMDC-136308	81	100
TCMDC-132257	6	18	TCMDC-133397	44	48	TCMDC-140722	22	70	TCMDC-133885	43	88	TCMDC-137836	81	100
TCMDC-125094	6	18	TCMDC-138282	44	48	TCMDC-124464	23	70	TCMDC-125286	43	88	TCMDC-138214	81	100
TCMDC-140637	6	18	TCMDC-140315	46	48	TCMDC-124987	23	70	TCMDC-124081	43	88	TCMDC-134177	82	100
TCMDC-140288	6	18	TCMDC-138349	46	48	TCMDC-134280	23	70	TCMDC-139483	44	88	TCMDC-124156	82	100
TCMDC-138355	7	18	TCMDC-141467	47	48	TCMDC-132658	23	70	TCMDC-135749	45	88	TCMDC-141270	82	100
TCMDC-140244	7	18	TCMDC-123785	47	48	TCMDC-139830	24	70	TCMDC-135726	45	88	TCMDC-139358	82	100
TCMDC-124488	8	18	TCMDC-133058	47	48	TCMDC-139945	24	70	TCMDC-135893	45	88	TCMDC-131613	83	100
TCMDC-138653	8	18	TCMDC-142034	48	48	TCMDC-141136	24	70	TCMDC-140409	45	88	TCMDC-137375	83	100
TCMDC-132225	8	18	TCMDC-139657	52	48	TCMDC-141066	24	70	TCMDC-133012	45	88	TCMDC-133702	83	100
TCMDC-140305	10	18	TCMDC-141921	2	49	TCMDC-138368	24	70	TCMDC-138681	45	88	TCMDC-124880	84	100
TCMDC-132604	10	18	TCMDC-139337	3	49	TCMDC-141647	24	70	TCMDC-123747	45	88	TCMDC-136996	84	100
TCMDC-134069	10	18	TCMDC-132064	3	49	TCMDC-134486	25	70	TCMDC-133625	46	88	TCMDC-138496	84	100
TCMDC-139796	10	18	TCMDC-140107	4	49	TCMDC-131277	25	70	TCMDC-137138	46	88	TCMDC-137973	84	100
TCMDC-131445	10	18	TCMDC-136205	4	49	TCMDC-134864	25	70	TCMDC-141547	47	88	TCMDC-135986	85	100
TCMDC-134091	11	18	TCMDC-142330	6	49	TCMDC-140168	25	70	TCMDC-134956	47	88	TCMDC-141126	85	100
TCMDC-123795	12	18	TCMDC-131545	6	49	TCMDC-139382	26	70	TCMDC-139379	48	88	TCMDC-125486	85	100
TCMDC-140843	13	18	TCMDC-124633	7	49	TCMDC-136845	26	70	TCMDC-139467	48	88	TCMDC-138023	85	100
TCMDC-136073	13	18	TCMDC-138723	7	49	TCMDC-134845	27	70	TCMDC-142177	48	88	TCMDC-135948	86	100
TCMDC-135912	13	18	TCMDC-125380	8	49	TCMDC-141840	27	70	TCMDC-134710	48	88	TCMDC-137720	86	100

TCMDC-137910	13	18	TCMDC-138290	8	49	TCMDC-132487	27	70	TCMDC-134839	49	88	TCMDC-139972	86	100
TCMDC-140206	14	18	TCMDC-132917	8	49	TCMDC-134782	27	70	TCMDC-133232	49	88	TCMDC-131607	86	100
TCMDC-138738	15	18	TCMDC-135856	8	49	TCMDC-132748	27	70	TCMDC-136775	49	88	TCMDC-134303	87	100
TCMDC-140157	15	18	TCMDC-125615	9	49	TCMDC-139276	28	70	TCMDC-131456	49	88	TCMDC-131712	87	100
TCMDC-142095	15	18	TCMDC-139614	9	49	TCMDC-140739	28	70	TCMDC-139785	50	88	TCMDC-134683	87	100
TCMDC-136520	16	18	TCMDC-136537	9	49	TCMDC-135811	28	70	TCMDC-140449	50	88	TCMDC-123683	88	100
TCMDC-137439	16	18	TCMDC-136695	10	49	TCMDC-140177	29	70	TCMDC-141478	51	88	TCMDC-136558	88	100
TCMDC-132043	16	18	TCMDC-142255	11	49	TCMDC-136391	29	70	TCMDC-135304	51	88	TCMDC-137508	88	100
TCMDC-135820	17	18	TCMDC-134136	11	49	TCMDC-134240	29	70	TCMDC-123598	51	88	TCMDC-131974	88	100
TCMDC-140394	17	18	TCMDC-138837	11	49	TCMDC-140296	29	70	TCMDC-132306	51	88	TCMDC-131918	89	100
TCMDC-125080	18	18	TCMDC-137476	12	49	TCMDC-125442	30	70	TCMDC-140421	51	88	TCMDC-134386	90	100
TCMDC-136018	18	18	TCMDC-139938	12	49	TCMDC-136209	30	70	TCMDC-124923	51	88	TCMDC-134853	90	100
TCMDC-123915	18	18	TCMDC-134807	12	49	TCMDC-135211	31	70	TCMDC-134621	51	88	TCMDC-142100	90	100
TCMDC-136034	18	18	TCMDC-141229	12	49	TCMDC-141541	31	70	TCMDC-138017	53	88	TCMDC-133408	90	100
TCMDC-142310	19	18	TCMDC-134126	12	49	TCMDC-138631	31	70	TCMDC-124969	55	88	TCMDC-136138	90	100
TCMDC-132100	20	18	TCMDC-132866	12	49	TCMDC-140164	32	70	TCMDC-125178	55	88	TCMDC-125809	90	100
TCMDC-138539	1	19	TCMDC-124762	12	49	TCMDC-142180	32	70	TCMDC-135165	56	88	TCMDC-135604	90	100
TCMDC-137617	2	19	TCMDC-142145	14	49	TCMDC-135964	32	70	TCMDC-139534	56	88	TCMDC-141750	90	100
TCMDC-136011	3	19	TCMDC-133811	14	49	TCMDC-134876	32	70	TCMDC-134125	56	88	TCMDC-131397	90	100
TCMDC-124796	3	19	TCMDC-134926	15	49	TCMDC-133483	32	70	TCMDC-135560	56	88	TCMDC-137353	90	100
TCMDC-141553	4	19	TCMDC-136787	15	49	TCMDC-137942	32	70	TCMDC-138844	56	88	TCMDC-133061	91	100
TCMDC-139638	4	19	TCMDC-138430	15	49	TCMDC-139087	33	70	TCMDC-132953	57	88	TCMDC-138380	91	100
TCMDC-139817	4	19	TCMDC-135863	16	49	TCMDC-133328	33	70	TCMDC-134685	58	88	TCMDC-135927	91	100
TCMDC-140596	4	19	TCMDC-132573	17	49	TCMDC-134144	33	70	TCMDC-139404	58	88	TCMDC-137357	91	100
TCMDC-125090	5	19	TCMDC-141782	18	49	TCMDC-132990	33	70	TCMDC-137726	58	88	TCMDC-132107	91	100
TCMDC-135400	5	19	TCMDC-132534	18	49	TCMDC-133581	34	70	TCMDC-137900	58	88	TCMDC-123839	91	100
TCMDC-132229	5	19	TCMDC-135262	18	49	TCMDC-132644	34	70	TCMDC-139877	59	88	TCMDC-125844	91	100
TCMDC-135037	5	19	TCMDC-141154	20	49	TCMDC-134813	34	70	TCMDC-140972	60	88	TCMDC-135088	92	100
TCMDC-132088	5	19	TCMDC-140477	20	49	TCMDC-139514	34	70	TCMDC-141230	61	88	TCMDC-123880	92	100
TCMDC-140291	6	19	TCMDC-141253	20	49	TCMDC-136960	34	70	TCMDC-124111	61	88	TCMDC-123807	92	100
TCMDC-135386	6	19	TCMDC-135489	20	49	TCMDC-139762	35	70	TCMDC-141947	61	88	TCMDC-135528	92	100
TCMDC-132297	7	19	TCMDC-140649	21	49	TCMDC-132386	35	70	TCMDC-141756	61	88	TCMDC-138666	92	100
TCMDC-139654	7	19	TCMDC-140494	22	49	TCMDC-132941	35	70	TCMDC-136443	62	88	TCMDC-124596	92	100
TCMDC-137519	7	19	TCMDC-132830	22	49	TCMDC-134708	35	70	TCMDC-137666	62	88	TCMDC-132384	92	100
TCMDC-125023	8	19	TCMDC-135063	22	49	TCMDC-134819	35	70	TCMDC-140323	63	88	TCMDC-131980	92	100
TCMDC-123816	8	19	TCMDC-140749	22	49	TCMDC-136419	37	70	TCMDC-139315	63	88	TCMDC-133770	93	100
TCMDC-132382	9	19	TCMDC-132669	22	49	TCMDC-131888	37	70	TCMDC-123741	64	88	TCMDC-141422	93	100

TCMDC-131509	11	19	TCMDC-134127	23	49	TCMDC-139500	37	70	TCMDC-132779	64	88	TCMDC-138219	93	100
TCMDC-134556	13	19	TCMDC-140471	23	49	TCMDC-132416	37	70	TCMDC-139137	64	88	TCMDC-138261	93	100
TCMDC-124883	13	19	TCMDC-141900	23	49	TCMDC-125577	37	70	TCMDC-136822	65	88	TCMDC-131353	93	100
TCMDC-131504	13	19	TCMDC-133922	23	49	TCMDC-139073	38	70	TCMDC-135238	65	88	TCMDC-131521	93	100
TCMDC-138452	13	19	TCMDC-133797	23	49	TCMDC-139352	38	70	TCMDC-131872	65	88	TCMDC-133293	94	100
TCMDC-141438	13	19	TCMDC-141259	24	49	TCMDC-139818	38	70	TCMDC-133976	66	88	TCMDC-135554	94	100
TCMDC-137501	13	19	TCMDC-139135	24	49	TCMDC-138685	38	70	TCMDC-135419	66	88	TCMDC-138224	94	100
TCMDC-124887	14	19	TCMDC-140785	24	49	TCMDC-132189	38	70	TCMDC-136965	66	88	TCMDC-131325	94	100
TCMDC-125518	14	19	TCMDC-136524	24	49	TCMDC-141834	40	70	TCMDC-137504	68	88	TCMDC-125666	94	100
TCMDC-131491	14	19	TCMDC-134789	25	49	TCMDC-139994	40	70	TCMDC-131290	68	88	TCMDC-137268	94	100
TCMDC-131552	14	19	TCMDC-135828	25	49	TCMDC-141836	41	70	TCMDC-125447	69	88	TCMDC-123791	95	100
TCMDC-138378	16	19	TCMDC-137306	25	49	TCMDC-124928	41	70	TCMDC-131415	69	88	TCMDC-136141	95	100
TCMDC-137539	16	19	TCMDC-142215	25	49	TCMDC-134833	42	70	TCMDC-139599	70	88	TCMDC-140440	95	100
TCMDC-138298	16	19	TCMDC-139274	25	49	TCMDC-139140	42	70	TCMDC-140087	70	88	TCMDC-133771	95	100
TCMDC-137608	16	19	TCMDC-134514	25	49	TCMDC-139756	43	70	TCMDC-142057	70	88	TCMDC-123488	95	100
TCMDC-136039	16	19	TCMDC-124617	26	49	TCMDC-140403	43	70	TCMDC-138619	70	88	TCMDC-125847	95	100
TCMDC-140304	17	19	TCMDC-138370	26	49	TCMDC-140927	44	70	TCMDC-133086	72	88	TCMDC-124419	95	100
TCMDC-137603	17	19	TCMDC-132758	26	49	TCMDC-141081	46	70	TCMDC-131541	73	88	TCMDC-124325	95	100
TCMDC-125321	18	19	TCMDC-138807	27	49	TCMDC-136928	47	70	TCMDC-137659	74	88	TCMDC-138045	95	100
TCMDC-140806	18	19	TCMDC-138460	27	49	TCMDC-139445	47	70	TCMDC-134509	74	88	TCMDC-124299	96	100
TCMDC-140239	18	19	TCMDC-139254	28	49	TCMDC-132028	47	70	TCMDC-139046	75	88	TCMDC-134165	96	100
TCMDC-140563	18	19	TCMDC-136385	28	49	TCMDC-136421	48	70	TCMDC-124545	75	88	TCMDC-137968	96	100
TCMDC-124635	18	19	TCMDC-133508	28	49	TCMDC-132631	48	70	TCMDC-123883	75	88	TCMDC-137690	96	100
TCMDC-134276	18	19	TCMDC-125410	29	49	TCMDC-133279	48	70	TCMDC-125558	75	88	TCMDC-141220	96	100
TCMDC-137921	18	19	TCMDC-138805	30	49	TCMDC-140920	48	70	TCMDC-124008	76	88	TCMDC-124428	96	100
TCMDC-125414	19	19	TCMDC-138553	30	49	TCMDC-140918	48	70	TCMDC-124943	76	88	TCMDC-134301	96	100
TCMDC-142225	19	19	TCMDC-132199	31	49	TCMDC-134966	49	70	TCMDC-133419	76	88	TCMDC-125658	97	100
TCMDC-141434	19	19	TCMDC-138745	31	49	TCMDC-133074	50	70	TCMDC-123592	77	88	TCMDC-138537	97	100
TCMDC-133993	21	19	TCMDC-135801	31	49	TCMDC-140703	50	70	TCMDC-123824	78	88	TCMDC-123561	97	100
TCMDC-131816	1	20	TCMDC-141041	32	49	TCMDC-139860	52	70	TCMDC-141219	78	88	TCMDC-142262	97	100
TCMDC-124846	2	20	TCMDC-133814	32	49	TCMDC-139871	52	70	TCMDC-132503	78	88	TCMDC-134008	97	100
TCMDC-138476	2	20	TCMDC-141559	33	49	TCMDC-141672	52	70	TCMDC-123878	78	88	TCMDC-138746	97	100
TCMDC-136210	2	20	TCMDC-132098	35	49	TCMDC-123506	53	70	TCMDC-141022	78	88	TCMDC-124786	97	100
TCMDC-141449	2	20	TCMDC-124048	35	49	TCMDC-125663	55	70	TCMDC-135178	78	88	TCMDC-123613	97	100
TCMDC-139805	3	20	TCMDC-138508	36	49	TCMDC-136931	55	70	TCMDC-138670	78	88	TCMDC-137356	97	100
TCMDC-141312	3	20	TCMDC-140657	37	49	TCMDC-133234	56	70	TCMDC-135640	79	88	TCMDC-131694	97	100
TCMDC-141759	3	20	TCMDC-136531	38	49	TCMDC-134100	56	70	TCMDC-142167	79	88	TCMDC-125305	97	100

TCMDC-139786	4	20	TCMDC-125546	39	49	TCMDC-132805	56	70	TCMDC-124503	79	88	TCMDC-124103	97	100
TCMDC-137939	4	20	TCMDC-124544	40	49	TCMDC-138834	57	70	TCMDC-125456	79	88	TCMDC-139438	97	100
TCMDC-136512	4	20	TCMDC-133211	41	49	TCMDC-134830	57	70	TCMDC-134607	80	88	TCMDC-136182	97	100
TCMDC-140629	4	20	TCMDC-125657	41	49	TCMDC-124406	60	70	TCMDC-125514	80	88	TCMDC-124280	97	100
TCMDC-138421	4	20	TCMDC-140026	41	49	TCMDC-137015	60	70	TCMDC-135526	80	88	TCMDC-131376	98	100
TCMDC-140751	4	20	TCMDC-123757	41	49	TCMDC-124014	61	70	TCMDC-124243	80	88	TCMDC-123847	98	100
TCMDC-139750	4	20	TCMDC-138353	43	49	TCMDC-124356	62	70	TCMDC-125147	81	88	TCMDC-134141	98	100
TCMDC-134390	5	20	TCMDC-125102	46	49	TCMDC-133101	62	70	TCMDC-132803	81	88	TCMDC-124372	98	100
TCMDC-134046	5	20	TCMDC-139222	46	49	TCMDC-137379	64	70	TCMDC-124749	82	88	TCMDC-138957	98	100
TCMDC-138614	5	20	TCMDC-132934	48	49	TCMDC-138759	64	70	TCMDC-138526	82	88	TCMDC-125862	98	100
TCMDC-134315	6	20	TCMDC-125389	48	49	TCMDC-134695	65	70	TCMDC-138567	82	88	TCMDC-131345	98	100
TCMDC-124065	7	20	TCMDC-133041	48	49	TCMDC-125584	65	70	TCMDC-137366	82	88	TCMDC-131539	98	100
TCMDC-141725	7	20	TCMDC-132723	49	49	TCMDC-136030	65	70	TCMDC-125780	82	88	TCMDC-131638	98	100
TCMDC-133919	7	20	TCMDC-138477	49	49	TCMDC-138513	65	70	TCMDC-139033	82	88	TCMDC-131646	98	100
TCMDC-124375	8	20	TCMDC-140261	3	50	TCMDC-140451	66	70	TCMDC-123714	82	88	TCMDC-131385	98	100
TCMDC-141761	8	20	TCMDC-132864	4	50	TCMDC-140353	66	70	TCMDC-136866	83	88	TCMDC-131377	98	100
TCMDC-136826	8	20	TCMDC-140604	8	50	TCMDC-133203	66	70	TCMDC-123781	83	88	TCMDC-125868	98	100
TCMDC-137586	9	20	TCMDC-138294	8	50	TCMDC-136627	66	70	TCMDC-123844	83	88	TCMDC-125739	98	100
TCMDC-134847	10	20	TCMDC-140423	8	50	TCMDC-125464	66	70	TCMDC-131300	83	88	TCMDC-123468	98	100
TCMDC-140135	10	20	TCMDC-131803	9	50	TCMDC-137783	66	70	TCMDC-125870	84	88	TCMDC-138090	98	100
TCMDC-137199	10	20	TCMDC-140075	9	50	TCMDC-140344	68	70	TCMDC-124535	84	88	TCMDC-135467	98	100
TCMDC-132821	11	20	TCMDC-141688	10	50	TCMDC-140934	69	70	TCMDC-137161	84	88	TCMDC-136181	98	100
TCMDC-138754	11	20	TCMDC-134445	10	50	TCMDC-133289	69	70	TCMDC-138077	84	88	TCMDC-123838	98	100
TCMDC-125058	12	20	TCMDC-142036	10	50	TCMDC-133190	69	70	TCMDC-137247	85	88	TCMDC-125425	98	100
TCMDC-142227	12	20	TCMDC-141648	10	50	TCMDC-124209	69	70	TCMDC-137371	85	88	TCMDC-124701	98	100
TCMDC-134249	12	20	TCMDC-141466	11	50	TCMDC-140784	70	70	TCMDC-124665	85	88	TCMDC-133956	98	100
TCMDC-141731	12	20	TCMDC-136164	12	50	TCMDC-139573	5	71	TCMDC-138826	85	88	TCMDC-133174	98	100
TCMDC-137164	12	20	TCMDC-134235	12	50	TCMDC-139574	7	71	TCMDC-133161	85	88	TCMDC-135594	98	100
TCMDC-137840	12	20	TCMDC-141303	13	50	TCMDC-133318	7	71	TCMDC-123720	85	88	TCMDC-133286	98	100
TCMDC-125728	13	20	TCMDC-141609	13	50	TCMDC-138186	7	71	TCMDC-141228	86	88	TCMDC-135655	98	100
TCMDC-123661	13	20	TCMDC-125595	14	50	TCMDC-124090	7	71	TCMDC-124720	86	88	TCMDC-137893	98	100
TCMDC-141329	13	20	TCMDC-134292	14	50	TCMDC-124034	10	71	TCMDC-136281	86	88	TCMDC-136712	98	100
TCMDC-141197	13	20	TCMDC-125593	14	50	TCMDC-140326	11	71	TCMDC-124339	86	88	TCMDC-131945	98	100
TCMDC-141439	13	20	TCMDC-134934	14	50	TCMDC-138419	12	71	TCMDC-137372	86	88	TCMDC-133639	98	100
TCMDC-136036	13	20	TCMDC-136869	14	50	TCMDC-132364	13	71	TCMDC-123799	86	88	TCMDC-124237	98	100
TCMDC-138712	14	20	TCMDC-123703	15	50	TCMDC-137196	13	71	TCMDC-125561	86	88	TCMDC-131299	98	100
TCMDC-141367	14	20	TCMDC-140225	15	50	TCMDC-134511	14	71	TCMDC-124492	87	88	TCMDC-124912	99	100

TCMDC-141195	14	20	TCMDC-133800	15	50	TCMDC-124878	15	71	TCMDC-123577	87	88	TCMDC-124380	99	100
TCMDC-140396	14	20	TCMDC-136280	15	50	TCMDC-132222	15	71	TCMDC-123625	87	88	TCMDC-123796	99	100
TCMDC-141039	16	20	TCMDC-136722	15	50	TCMDC-139979	16	71	TCMDC-134058	87	88	TCMDC-133471	99	100
TCMDC-136059	16	20	TCMDC-138744	16	50	TCMDC-125311	16	71	TCMDC-142058	87	88	TCMDC-123734	99	100
TCMDC-141190	16	20	TCMDC-135287	16	50	TCMDC-132624	16	71	TCMDC-125551	87	88	TCMDC-141563	99	100
TCMDC-124252	16	20	TCMDC-134558	17	50	TCMDC-135212	17	71	TCMDC-138042	87	88	TCMDC-125659	99	100
TCMDC-140828	16	20	TCMDC-140478	17	50	TCMDC-132155	18	71	TCMDC-137635	87	88	TCMDC-131630	99	100
TCMDC-140867	17	20	TCMDC-132515	17	50	TCMDC-139597	18	71	TCMDC-131923	87	88	TCMDC-142297	99	100
TCMDC-138658	17	20	TCMDC-136706	17	50	TCMDC-139215	19	71	TCMDC-137294	87	88	TCMDC-131760	99	100
TCMDC-125708	17	20	TCMDC-140285	17	50	TCMDC-138839	19	71	TCMDC-141884	88	88	TCMDC-123752	99	100
TCMDC-131511	17	20	TCMDC-125762	18	50	TCMDC-124569	19	71	TCMDC-125645	88	88	TCMDC-125732	99	100
TCMDC-124579	18	20	TCMDC-139879	18	50	TCMDC-137469	19	71	TCMDC-124263	88	88	TCMDC-125709	99	100
TCMDC-141362	18	20	TCMDC-140040	19	50	TCMDC-136435	19	71	TCMDC-133470	89	88	TCMDC-135283	99	100
TCMDC-136040	18	20	TCMDC-140755	19	50	TCMDC-139988	20	71	TCMDC-136454	4	89	TCMDC-141311	99	100
TCMDC-140734	18	20	TCMDC-136795	20	50	TCMDC-141432	21	71	TCMDC-124426	10	89	TCMDC-123989	99	100
TCMDC-140306	18	20	TCMDC-142193	20	50	TCMDC-132566	21	71	TCMDC-123527	15	89	TCMDC-125219	99	100
TCMDC-134563	18	20	TCMDC-141726	20	50	TCMDC-135353	22	71	TCMDC-139518	18	89	TCMDC-134586	99	100
TCMDC-125699	18	20	TCMDC-137955	21	50	TCMDC-136436	22	71	TCMDC-134741	20	89	TCMDC-138569	99	100
TCMDC-137938	18	20	TCMDC-135804	21	50	TCMDC-132999	22	71	TCMDC-124050	21	89	TCMDC-125745	99	100
TCMDC-123920	18	20	TCMDC-141296	22	50	TCMDC-136020	22	71	TCMDC-137964	26	89	TCMDC-135083	99	100
TCMDC-140895	18	20	TCMDC-137444	22	50	TCMDC-124437	23	71	TCMDC-142212	26	89	TCMDC-131736	99	100
TCMDC-131440	18	20	TCMDC-134573	22	50	TCMDC-141295	23	71	TCMDC-134545	27	89	TCMDC-132026	99	100
TCMDC-141437	19	20	TCMDC-140958	23	50	TCMDC-132892	23	71	TCMDC-139168	27	89	TCMDC-137610	99	100
TCMDC-141188	19	20	TCMDC-137322	23	50	TCMDC-134699	24	71	TCMDC-134739	27	89	TCMDC-125878	99	100
TCMDC-140841	19	20	TCMDC-135782	24	50	TCMDC-139932	26	71	TCMDC-136654	28	89	TCMDC-131870	100	100
TCMDC-125127	19	20	TCMDC-123565	24	50	TCMDC-134021	26	71	TCMDC-136264	29	89	TCMDC-138717	100	100
TCMDC-133142	19	20	TCMDC-132919	24	50	TCMDC-135157	26	71	TCMDC-132311	30	89	TCMDC-131587	100	100
TCMDC-141395	19	20	TCMDC-133998	24	50	TCMDC-140010	26	71	TCMDC-134196	31	89	TCMDC-131666	100	100
TCMDC-137435	19	20	TCMDC-134081	25	50	TCMDC-139513	27	71	TCMDC-133836	31	89	TCMDC-137682	100	100
TCMDC-131543	19	20	TCMDC-137193	25	50	TCMDC-139213	27	71	TCMDC-137453	31	89	TCMDC-124088	100	100
TCMDC-141109	20	20	TCMDC-131843	25	50	TCMDC-140265	27	71	TCMDC-134516	32	89	TCMDC-139462	100	100
TCMDC-135050	21	20	TCMDC-140655	26	50	TCMDC-133067	27	71	TCMDC-136972	32	89	TCMDC-123731	100	100
TCMDC-136602	3	21	TCMDC-140660	26	50	TCMDC-131982	27	71	TCMDC-134481	34	89	TCMDC-124094	100	100
TCMDC-139819	3	21	TCMDC-133145	27	50	TCMDC-140914	28	71	TCMDC-125290	34	89	TCMDC-138057	100	100
TCMDC-139637	3	21	TCMDC-133855	27	50	TCMDC-124200	28	71	TCMDC-133682	34	89	TCMDC-136908	100	100
TCMDC-139867	3	21	TCMDC-138833	27	50	TCMDC-132067	29	71	TCMDC-132144	36	89	TCMDC-125827	8	101
TCMDC-139659	3	21	TCMDC-135189	27	50	TCMDC-134172	29	71	TCMDC-140675	36	89	TCMDC-134547	19	101

TCMDC-132681	3	21	TCMDC-123770	27	50	TCMDC-135166	29	71	TCMDC-138121	37	89	TCMDC-136667	23	101
TCMDC-139768	4	21	TCMDC-132995	27	50	TCMDC-124811	31	71	TCMDC-136768	38	89	TCMDC-137542	27	101
TCMDC-124526	4	21	TCMDC-140682	28	50	TCMDC-135125	31	71	TCMDC-137851	38	89	TCMDC-125073	30	101
TCMDC-138417	4	21	TCMDC-123679	28	50	TCMDC-133873	31	71	TCMDC-139759	39	89	TCMDC-139163	31	101
TCMDC-140530	5	21	TCMDC-140850	28	50	TCMDC-134824	32	71	TCMDC-135711	39	89	TCMDC-139556	37	101
TCMDC-140636	5	21	TCMDC-133614	29	50	TCMDC-138300	32	71	TCMDC-136500	39	89	TCMDC-132464	41	101
TCMDC-137845	5	21	TCMDC-140713	29	50	TCMDC-124399	32	71	TCMDC-134912	39	89	TCMDC-133110	41	101
TCMDC-139487	5	21	TCMDC-132639	29	50	TCMDC-135316	33	71	TCMDC-136187	40	89	TCMDC-137831	41	101
TCMDC-140626	5	21	TCMDC-137224	29	50	TCMDC-135272	33	71	TCMDC-134532	41	89	TCMDC-132146	41	101
TCMDC-141552	6	21	TCMDC-133776	30	50	TCMDC-142093	34	71	TCMDC-136294	41	89	TCMDC-134456	44	101
TCMDC-132230	6	21	TCMDC-140067	30	50	TCMDC-135171	34	71	TCMDC-141968	41	89	TCMDC-131659	45	101
TCMDC-141249	6	21	TCMDC-140388	30	50	TCMDC-133930	34	71	TCMDC-125408	42	89	TCMDC-136297	46	101
TCMDC-141736	7	21	TCMDC-134495	31	50	TCMDC-133942	34	71	TCMDC-136333	42	89	TCMDC-140149	47	101
TCMDC-140691	7	21	TCMDC-141388	32	50	TCMDC-132444	35	71	TCMDC-133685	42	89	TCMDC-135364	47	101
TCMDC-139416	8	21	TCMDC-134773	32	50	TCMDC-136124	35	71	TCMDC-136466	42	89	TCMDC-125119	48	101
TCMDC-140360	8	21	TCMDC-133069	33	50	TCMDC-136917	35	71	TCMDC-140853	42	89	TCMDC-133608	48	101
TCMDC-124120	9	21	TCMDC-133985	34	50	TCMDC-133706	35	71	TCMDC-136031	42	89	TCMDC-135752	49	101
TCMDC-140633	9	21	TCMDC-135379	34	50	TCMDC-139832	35	71	TCMDC-133090	43	89	TCMDC-138632	49	101
TCMDC-137627	10	21	TCMDC-132169	35	50	TCMDC-125876	35	71	TCMDC-132344	43	89	TCMDC-140704	51	101
TCMDC-131530	10	21	TCMDC-125117	35	50	TCMDC-135342	36	71	TCMDC-135684	43	89	TCMDC-136862	52	101
TCMDC-140138	10	21	TCMDC-135322	37	50	TCMDC-139235	37	71	TCMDC-136937	43	89	TCMDC-133646	53	101
TCMDC-132283	10	21	TCMDC-125517	37	50	TCMDC-135401	37	71	TCMDC-137072	44	89	TCMDC-137341	55	101
TCMDC-134066	11	21	TCMDC-138613	38	50	TCMDC-141072	37	71	TCMDC-134432	44	89	TCMDC-135841	55	101
TCMDC-131546	11	21	TCMDC-138377	39	50	TCMDC-138307	38	71	TCMDC-140346	44	89	TCMDC-134229	56	101
TCMDC-134282	11	21	TCMDC-133579	39	50	TCMDC-135485	38	71	TCMDC-133434	44	89	TCMDC-140081	56	101
TCMDC-138665	11	21	TCMDC-134477	41	50	TCMDC-141223	38	71	TCMDC-137789	44	89	TCMDC-131957	56	101
TCMDC-137786	11	21	TCMDC-134940	42	50	TCMDC-133765	39	71	TCMDC-139330	44	89	TCMDC-135905	57	101
TCMDC-132238	11	21	TCMDC-135387	44	50	TCMDC-134020	39	71	TCMDC-132158	45	89	TCMDC-134464	60	101
TCMDC-137200	11	21	TCMDC-131882	44	50	TCMDC-134877	39	71	TCMDC-136274	45	89	TCMDC-132328	61	101
TCMDC-134076	12	21	TCMDC-140644	47	50	TCMDC-139564	39	71	TCMDC-133453	46	89	TCMDC-133764	64	101
TCMDC-136156	12	21	TCMDC-138475	47	50	TCMDC-139378	40	71	TCMDC-137776	46	89	TCMDC-134471	65	101
TCMDC-142248	12	21	TCMDC-141568	48	50	TCMDC-136369	41	71	TCMDC-133240	46	89	TCMDC-136490	65	101
TCMDC-133343	12	21	TCMDC-125322	48	50	TCMDC-132502	41	71	TCMDC-134480	47	89	TCMDC-140120	65	101
TCMDC-131544	12	21	TCMDC-138260	48	50	TCMDC-135203	41	71	TCMDC-137470	47	89	TCMDC-137254	66	101
TCMDC-132307	13	21	TCMDC-140711	49	50	TCMDC-123916	41	71	TCMDC-132318	47	89	TCMDC-137264	66	101
TCMDC-133140	13	21	TCMDC-124121	50	50	TCMDC-142292	42	71	TCMDC-135705	48	89	TCMDC-137468	66	101
TCMDC-124376	13	21	TCMDC-131922	50	50	TCMDC-136541	43	71	TCMDC-135758	48	89	TCMDC-139792	67	101

TCMDC-131451	13	21	TCMDC-137153	50	50	TCMDC-139347	44	71	TCMDC-125541	48	89	TCMDC-139171	67	101
TCMDC-123988	13	21	TCMDC-137281	3	51	TCMDC-140370	44	71	TCMDC-124441	48	89	TCMDC-142199	69	101
TCMDC-140997	13	21	TCMDC-133532	3	51	TCMDC-137996	44	71	TCMDC-136304	48	89	TCMDC-135794	71	101
TCMDC-141283	13	21	TCMDC-137897	3	51	TCMDC-135192	45	71	TCMDC-132652	49	89	TCMDC-140849	72	101
TCMDC-140871	13	21	TCMDC-136501	5	51	TCMDC-132069	45	71	TCMDC-141275	50	89	TCMDC-141231	72	101
TCMDC-132915	13	21	TCMDC-138911	7	51	TCMDC-124854	45	71	TCMDC-138293	51	89	TCMDC-140827	73	101
TCMDC-124168	14	21	TCMDC-135776	7	51	TCMDC-135630	45	71	TCMDC-124446	51	89	TCMDC-141689	73	101
TCMDC-124744	14	21	TCMDC-139553	8	51	TCMDC-141082	46	71	TCMDC-124660	51	89	TCMDC-125448	74	101
TCMDC-136204	14	21	TCMDC-135901	8	51	TCMDC-140345	47	71	TCMDC-137082	51	89	TCMDC-136813	74	101
TCMDC-124062	14	21	TCMDC-141762	8	51	TCMDC-141867	47	71	TCMDC-141667	52	89	TCMDC-136347	75	101
TCMDC-131508	14	21	TCMDC-140009	9	51	TCMDC-141058	48	71	TCMDC-140437	52	89	TCMDC-134015	75	101
TCMDC-124654	15	21	TCMDC-139797	9	51	TCMDC-136966	49	71	TCMDC-124335	52	89	TCMDC-124520	75	101
TCMDC-125249	15	21	TCMDC-132923	9	51	TCMDC-133569	50	71	TCMDC-140325	52	89	TCMDC-135832	76	101
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TCMDC-136227	15	21	TCMDC-135224	11	51	TCMDC-132634	51	71	TCMDC-140336	54	89	TCMDC-133744	77	101
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TCMDC-132876	16	21	TCMDC-134449	12	51	TCMDC-138577	51	71	TCMDC-135706	55	89	TCMDC-123479	81	101
TCMDC-131427	16	21	TCMDC-140531	13	51	TCMDC-131553	52	71	TCMDC-138963	55	89	TCMDC-138524	82	101
TCMDC-125174	16	21	TCMDC-140269	13	51	TCMDC-142016	53	71	TCMDC-137764	55	89	TCMDC-141578	82	101
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TCMDC-132575	17	21	TCMDC-140533	15	51	TCMDC-136060	56	71	TCMDC-131852	58	89	TCMDC-131403	83	101
TCMDC-131444	17	21	TCMDC-131261	15	51	TCMDC-138499	57	71	TCMDC-131779	58	89	TCMDC-141723	83	101
TCMDC-131450	17	21	TCMDC-132005	15	51	TCMDC-137873	57	71	TCMDC-135086	58	89	TCMDC-139820	84	101
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TCMDC-124113	18	21	TCMDC-142183	16	51	TCMDC-139133	60	71	TCMDC-142308	59	89	TCMDC-138230	85	101
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TCMDC-131446	18	21	TCMDC-137311	16	51	TCMDC-135437	61	71	TCMDC-140332	59	89	TCMDC-136693	87	101
TCMDC-141192	18	21	TCMDC-134435	17	51	TCMDC-134962	62	71	TCMDC-134967	60	89	TCMDC-133787	87	101
TCMDC-131503	19	21	TCMDC-141546	17	51	TCMDC-131851	63	71	TCMDC-138986	61	89	TCMDC-141997	88	101
TCMDC-131448	19	21	TCMDC-133053	17	51	TCMDC-132164	63	71	TCMDC-137574	61	89	TCMDC-141815	89	101
TCMDC-139550	20	21	TCMDC-135474	17	51	TCMDC-125826	63	71	TCMDC-132781	61	89	TCMDC-139076	89	101
TCMDC-140159	20	21	TCMDC-134628	17	51	TCMDC-136416	64	71	TCMDC-139984	61	89	TCMDC-124281	89	101
TCMDC-131571	20	21	TCMDC-134746	18	51	TCMDC-124407	64	71	TCMDC-131264	61	89	TCMDC-124502	89	101

TCMDC-123909	20	21	TCMDC-140526	18	51	TCMDC-138590	66	71	TCMDC-131302	61	89	TCMDC-125773	89	101
TCMDC-131995	20	21	TCMDC-141068	18	51	TCMDC-136952	66	71	TCMDC-142153	62	89	TCMDC-132798	90	101
TCMDC-131469	20	21	TCMDC-132610	18	51	TCMDC-123742	66	71	TCMDC-140025	62	89	TCMDC-123526	90	101
TCMDC-136046	21	21	TCMDC-135412	19	51	TCMDC-125648	67	71	TCMDC-123783	62	89	TCMDC-124507	90	101
TCMDC-139359	21	21	TCMDC-135451	19	51	TCMDC-131952	67	71	TCMDC-136203	62	89	TCMDC-137250	90	101
TCMDC-123743	21	21	TCMDC-140866	19	51	TCMDC-136903	69	71	TCMDC-140458	63	89	TCMDC-124605	90	101
TCMDC-140808	21	21	TCMDC-138647	20	51	TCMDC-123582	69	71	TCMDC-131908	64	89	TCMDC-132688	91	101
TCMDC-140858	22	21	TCMDC-140283	21	51	TCMDC-134654	69	71	TCMDC-135133	64	89	TCMDC-124903	91	101
TCMDC-142222	23	21	TCMDC-132438	21	51	TCMDC-133647	69	71	TCMDC-134702	65	89	TCMDC-139301	91	101
TCMDC-135370	1	22	TCMDC-134800	21	51	TCMDC-138935	71	71	TCMDC-133331	67	89	TCMDC-134577	92	101
TCMDC-136190	2	22	TCMDC-133840	21	51	TCMDC-138437	71	71	TCMDC-136830	67	89	TCMDC-141128	92	101
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TCMDC-136007	3	22	TCMDC-132619	22	51	TCMDC-137577	7	72	TCMDC-138556	68	89	TCMDC-142329	92	101
TCMDC-142064	3	22	TCMDC-134660	22	51	TCMDC-139999	7	72	TCMDC-139048	68	89	TCMDC-124517	92	101
TCMDC-138967	3	22	TCMDC-136527	22	51	TCMDC-123674	8	72	TCMDC-138049	68	89	TCMDC-135449	92	101
TCMDC-142186	3	22	TCMDC-141185	22	51	TCMDC-138760	9	72	TCMDC-135089	69	89	TCMDC-135676	92	101
TCMDC-141419	4	22	TCMDC-131335	22	51	TCMDC-139957	9	72	TCMDC-141218	69	89	TCMDC-124527	92	101
TCMDC-140542	4	22	TCMDC-142286	23	51	TCMDC-141610	9	72	TCMDC-125308	70	89	TCMDC-125718	92	101
TCMDC-124323	4	22	TCMDC-140366	23	51	TCMDC-139568	9	72	TCMDC-134963	70	89	TCMDC-124736	92	101
TCMDC-139533	5	22	TCMDC-139754	24	51	TCMDC-134358	10	72	TCMDC-131366	70	89	TCMDC-131334	92	101
TCMDC-136467	5	22	TCMDC-132431	24	51	TCMDC-134329	12	72	TCMDC-124368	70	89	TCMDC-131634	92	101
TCMDC-125789	5	22	TCMDC-141556	24	51	TCMDC-142047	13	72	TCMDC-131941	70	89	TCMDC-124808	93	101
TCMDC-141605	5	22	TCMDC-140658	24	51	TCMDC-124681	14	72	TCMDC-132841	72	89	TCMDC-124010	93	101
TCMDC-141055	5	22	TCMDC-134096	24	51	TCMDC-139578	14	72	TCMDC-134576	73	89	TCMDC-124781	93	101
TCMDC-135971	5	22	TCMDC-124413	25	51	TCMDC-134801	15	72	TCMDC-139442	73	89	TCMDC-137351	93	101
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TCMDC-132253	5	22	TCMDC-131537	26	51	TCMDC-133180	16	72	TCMDC-125215	74	89	TCMDC-131687	93	101
TCMDC-132362	5	22	TCMDC-133507	26	51	TCMDC-131884	16	72	TCMDC-123675	74	89	TCMDC-141704	94	101
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TCMDC-135672	6	22	TCMDC-132125	27	51	TCMDC-141003	18	72	TCMDC-132564	74	89	TCMDC-137430	94	101
TCMDC-132248	6	22	TCMDC-139703	28	51	TCMDC-141591	19	72	TCMDC-139788	75	89	TCMDC-135609	94	101
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TCMDC-140287	6	22	TCMDC-140507	28	51	TCMDC-139617	20	72	TCMDC-136221	76	89	TCMDC-141189	94	101
TCMDC-140292	6	22	TCMDC-139496	29	51	TCMDC-140726	21	72	TCMDC-136702	76	89	TCMDC-124824	95	101
TCMDC-141508	7	22	TCMDC-132992	29	51	TCMDC-133337	21	72	TCMDC-141236	77	89	TCMDC-131693	95	101
TCMDC-132269	7	22	TCMDC-134129	32	51	TCMDC-125092	22	72	TCMDC-124939	77	89	TCMDC-136134	95	101
TCMDC-132237	7	22	TCMDC-135296	32	51	TCMDC-135439	22	72	TCMDC-133713	77	89	TCMDC-125229	95	101

TCMDC-139899	8	22	TCMDC-134837	33	51	TCMDC-140392	22	72	TCMDC-142238	78	89	TCMDC-138863	95	101
TCMDC-138621	8	22	TCMDC-141359	33	51	TCMDC-135958	23	72	TCMDC-125046	78	89	TCMDC-131788	95	101
TCMDC-141442	9	22	TCMDC-141414	35	51	TCMDC-141940	23	72	TCMDC-132163	78	89	TCMDC-124394	95	101
TCMDC-134074	10	22	TCMDC-135378	36	51	TCMDC-137241	23	72	TCMDC-139294	79	89	TCMDC-136306	95	101
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TCMDC-141423	11	22	TCMDC-136535	37	51	TCMDC-139698	24	72	TCMDC-135009	80	89	TCMDC-137888	95	101
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TCMDC-131459	11	22	TCMDC-133916	37	51	TCMDC-135903	24	72	TCMDC-137039	80	89	TCMDC-124431	96	101
TCMDC-135423	11	22	TCMDC-134994	38	51	TCMDC-137684	26	72	TCMDC-134606	81	89	TCMDC-131396	96	101
TCMDC-134121	12	22	TCMDC-133120	38	51	TCMDC-140718	26	72	TCMDC-136375	81	89	TCMDC-131690	96	101
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TCMDC-141051	14	22	TCMDC-125852	42	51	TCMDC-135754	28	72	TCMDC-136309	82	89	TCMDC-141235	97	101
TCMDC-140999	15	22	TCMDC-138557	42	51	TCMDC-140175	29	72	TCMDC-124207	82	89	TCMDC-131384	97	101
TCMDC-131502	15	22	TCMDC-138196	44	51	TCMDC-133333	29	72	TCMDC-131743	83	89	TCMDC-137417	97	101
TCMDC-131252	15	22	TCMDC-125032	45	51	TCMDC-136570	29	72	TCMDC-137852	83	89	TCMDC-133260	97	101
TCMDC-136525	15	22	TCMDC-141202	47	51	TCMDC-134814	30	72	TCMDC-137386	83	89	TCMDC-137266	97	101
TCMDC-141214	16	22	TCMDC-138450	47	51	TCMDC-135123	31	72	TCMDC-124106	84	89	TCMDC-135020	97	101
TCMDC-135118	16	22	TCMDC-136382	47	51	TCMDC-139667	31	72	TCMDC-133560	84	89	TCMDC-137532	97	101
TCMDC-140840	16	22	TCMDC-132031	47	51	TCMDC-123497	32	72	TCMDC-132423	84	89	TCMDC-124956	98	101
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TCMDC-138024	17	22	TCMDC-140654	51	51	TCMDC-133354	33	72	TCMDC-137639	84	89	TCMDC-135070	98	101
TCMDC-131476	17	22	TCMDC-131806	2	52	TCMDC-133503	33	72	TCMDC-125185	85	89	TCMDC-125722	98	101
TCMDC-137890	17	22	TCMDC-140204	3	52	TCMDC-136260	33	72	TCMDC-131234	85	89	TCMDC-131682	98	101
TCMDC-141353	17	22	TCMDC-139812	5	52	TCMDC-136291	34	72	TCMDC-136728	85	89	TCMDC-123881	98	101
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TCMDC-140799	18	22	TCMDC-139266	8	52	TCMDC-134574	37	72	TCMDC-133172	86	89	TCMDC-135779	98	101
TCMDC-142228	18	22	TCMDC-139072	9	52	TCMDC-134790	37	72	TCMDC-124841	86	89	TCMDC-134035	98	101
TCMDC-124006	19	22	TCMDC-125652	9	52	TCMDC-134572	37	72	TCMDC-141650	86	89	TCMDC-124175	98	101
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TCMDC-137165	19	22	TCMDC-140940	9	52	TCMDC-124636	37	72	TCMDC-136841	86	89	TCMDC-124942	99	101

TCMDC-131465	19	22	TCMDC-131561	9	52	TCMDC-138510	37	72	TCMDC-123689	87	89	TCMDC-134565	99	101
TCMDC-131525	19	22	TCMDC-133555	10	52	TCMDC-138340	37	72	TCMDC-124319	87	89	TCMDC-123554	99	101
TCMDC-123998	19	22	TCMDC-125284	11	52	TCMDC-123803	37	72	TCMDC-124835	87	89	TCMDC-124359	99	101
TCMDC-142105	20	22	TCMDC-138573	11	52	TCMDC-139711	38	72	TCMDC-134986	87	89	TCMDC-133461	99	101
TCMDC-141380	20	22	TCMDC-132051	12	52	TCMDC-134283	38	72	TCMDC-124210	87	89	TCMDC-131688	99	101
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TCMDC-131242	20	22	TCMDC-136364	13	52	TCMDC-135131	40	72	TCMDC-132117	88	89	TCMDC-133421	99	101
TCMDC-140836	21	22	TCMDC-139838	13	52	TCMDC-140297	40	72	TCMDC-124700	88	89	TCMDC-131327	99	101
TCMDC-140522	21	22	TCMDC-135347	15	52	TCMDC-136399	41	72	TCMDC-133542	88	89	TCMDC-131609	99	101
TCMDC-137516	21	22	TCMDC-142232	15	52	TCMDC-141865	41	72	TCMDC-135558	88	89	TCMDC-131645	99	101
TCMDC-141193	22	22	TCMDC-139650	15	52	TCMDC-133264	42	72	TCMDC-131286	88	89	TCMDC-131628	99	101
TCMDC-137463	22	22	TCMDC-135394	15	52	TCMDC-135193	42	72	TCMDC-123465	88	89	TCMDC-131777	99	101
TCMDC-132027	22	22	TCMDC-125642	15	52	TCMDC-132576	43	72	TCMDC-123576	89	89	TCMDC-124370	99	101
TCMDC-132574	22	22	TCMDC-132530	16	52	TCMDC-140909	44	72	TCMDC-131608	89	89	TCMDC-134610	99	101
TCMDC-138596	22	22	TCMDC-138879	16	52	TCMDC-139704	45	72	TCMDC-135647	89	89	TCMDC-125828	99	101
TCMDC-124070	22	22	TCMDC-134068	17	52	TCMDC-140971	45	72	TCMDC-134726	89	89	TCMDC-125195	99	101
TCMDC-137853	2	23	TCMDC-132605	17	52	TCMDC-133135	45	72	TCMDC-138973	9	90	TCMDC-138679	99	101
TCMDC-137317	2	23	TCMDC-137983	17	52	TCMDC-133047	45	72	TCMDC-133524	10	90	TCMDC-123480	99	101
TCMDC-139900	2	23	TCMDC-132668	18	52	TCMDC-136147	46	72	TCMDC-123773	10	90	TCMDC-137298	99	101
TCMDC-139642	3	23	TCMDC-134919	18	52	TCMDC-125285	47	72	TCMDC-124036	12	90	TCMDC-123528	100	101
TCMDC-132828	3	23	TCMDC-138384	18	52	TCMDC-138488	47	72	TCMDC-140417	20	90	TCMDC-123560	100	101
TCMDC-141381	3	23	TCMDC-141122	18	52	TCMDC-132160	48	72	TCMDC-132718	21	90	TCMDC-124316	100	101
TCMDC-141098	3	23	TCMDC-141461	18	52	TCMDC-141164	48	72	TCMDC-141428	24	90	TCMDC-123853	100	101
TCMDC-141446	3	23	TCMDC-132513	19	52	TCMDC-140384	48	72	TCMDC-125254	24	90	TCMDC-131655	100	101
TCMDC-125404	3	23	TCMDC-135487	19	52	TCMDC-138174	49	72	TCMDC-136878	24	90	TCMDC-125108	100	101
TCMDC-140628	4	23	TCMDC-134512	19	52	TCMDC-138624	50	72	TCMDC-132147	26	90	TCMDC-123863	100	101
TCMDC-140547	4	23	TCMDC-134747	19	52	TCMDC-134000	50	72	TCMDC-139511	26	90	TCMDC-131912	100	101
TCMDC-136192	4	23	TCMDC-124984	20	52	TCMDC-134152	50	72	TCMDC-135135	26	90	TCMDC-131731	100	101
TCMDC-133941	4	23	TCMDC-138769	20	52	TCMDC-139299	50	72	TCMDC-135747	27	90	TCMDC-131636	100	101
TCMDC-141445	5	23	TCMDC-140957	20	52	TCMDC-138332	51	72	TCMDC-141532	27	90	TCMDC-131768	100	101
TCMDC-140947	5	23	TCMDC-141168	21	52	TCMDC-141895	53	72	TCMDC-135335	28	90	TCMDC-139480	100	101
TCMDC-140290	5	23	TCMDC-141033	21	52	TCMDC-125383	55	72	TCMDC-134472	30	90	TCMDC-133603	100	101
TCMDC-141250	6	23	TCMDC-138562	21	52	TCMDC-125572	56	72	TCMDC-133687	32	90	TCMDC-133248	100	101
TCMDC-132266	6	23	TCMDC-140043	22	52	TCMDC-138470	56	72	TCMDC-135800	34	90	TCMDC-131256	100	101
TCMDC-124542	6	23	TCMDC-133001	22	52	TCMDC-140678	60	72	TCMDC-133589	34	90	TCMDC-124290	100	101
TCMDC-141649	6	23	TCMDC-140813	22	52	TCMDC-138250	61	72	TCMDC-137025	35	90	TCMDC-137425	100	101
TCMDC-138750	6	23	TCMDC-135293	22	52	TCMDC-142162	62	72	TCMDC-135048	35	90	TCMDC-125752	101	101

TCMDC-124354	6	23	TCMDC-137488	23	52	TCMDC-140098	62	72	TCMDC-140216	36	90	TCMDC-124124	101	101
TCMDC-132241	6	23	TCMDC-123627	23	52	TCMDC-140077	62	72	TCMDC-140776	36	90	TCMDC-131595	101	101
TCMDC-133858	7	23	TCMDC-141623	23	52	TCMDC-138674	62	72	TCMDC-139122	37	90	TCMDC-124624	101	101
TCMDC-135389	7	23	TCMDC-134002	23	52	TCMDC-137697	62	72	TCMDC-135697	37	90	TCMDC-125564	101	101
TCMDC-141783	7	23	TCMDC-137936	23	52	TCMDC-133907	63	72	TCMDC-132327	37	90	TCMDC-138252	101	101
TCMDC-138414	8	23	TCMDC-134181	24	52	TCMDC-140446	65	72	TCMDC-139997	37	90	TCMDC-137868	101	101
TCMDC-135036	8	23	TCMDC-132629	24	52	TCMDC-124306	66	72	TCMDC-124739	38	90	TCMDC-125182	101	101
TCMDC-141119	8	23	TCMDC-138893	24	52	TCMDC-124724	66	72	TCMDC-123606	38	90	TCMDC-131348	101	101
TCMDC-134079	8	23	TCMDC-139894	24	52	TCMDC-137148	67	72	TCMDC-135746	39	90	TCMDC-131796	101	101
TCMDC-137738	8	23	TCMDC-134024	24	52	TCMDC-134618	69	72	TCMDC-138587	39	90	TCMDC-123473	101	101
TCMDC-135498	9	23	TCMDC-134599	24	52	TCMDC-138366	70	72	TCMDC-134162	39	90	TCMDC-131706	101	101
TCMDC-124694	9	23	TCMDC-138798	25	52	TCMDC-136858	71	72	TCMDC-131589	39	90	TCMDC-137523	101	101
TCMDC-138865	9	23	TCMDC-135331	25	52	TCMDC-133125	71	72	TCMDC-133228	40	90	TCMDC-138627	101	101
TCMDC-140293	9	23	TCMDC-140223	25	52	TCMDC-133009	72	72	TCMDC-141403	41	90	TCMDC-133801	101	101
TCMDC-140284	9	23	TCMDC-141023	26	52	TCMDC-138308	2	73	TCMDC-125563	41	90	TCMDC-135253	101	101
TCMDC-136242	10	23	TCMDC-138701	26	52	TCMDC-124173	3	73	TCMDC-139403	42	90	TCMDC-140401	101	101
TCMDC-134186	11	23	TCMDC-141907	28	52	TCMDC-125277	5	73	TCMDC-134696	43	90	TCMDC-124921	107	101
TCMDC-137604	11	23	TCMDC-135371	28	52	TCMDC-139910	6	73	TCMDC-133502	43	90	TCMDC-125010	10	102
TCMDC-132264	11	23	TCMDC-139271	28	52	TCMDC-134991	7	73	TCMDC-124640	44	90	TCMDC-135836	16	102
TCMDC-134093	11	23	TCMDC-140758	28	52	TCMDC-141401	8	73	TCMDC-124993	44	90	TCMDC-142101	17	102
TCMDC-140242	11	23	TCMDC-133039	28	52	TCMDC-141936	9	73	TCMDC-133678	44	90	TCMDC-137127	21	102
TCMDC-132335	12	23	TCMDC-141394	29	52	TCMDC-132819	11	73	TCMDC-133284	46	90	TCMDC-125617	22	102
TCMDC-140781	13	23	TCMDC-140094	30	52	TCMDC-139594	12	73	TCMDC-137662	46	90	TCMDC-141819	26	102
TCMDC-125194	13	23	TCMDC-132949	30	52	TCMDC-139591	12	73	TCMDC-137781	46	90	TCMDC-131697	30	102
TCMDC-135329	14	23	TCMDC-134788	31	52	TCMDC-140942	12	73	TCMDC-135951	47	90	TCMDC-123486	30	102
TCMDC-124047	14	23	TCMDC-136828	31	52	TCMDC-138916	13	73	TCMDC-137030	47	90	TCMDC-133846	32	102
TCMDC-140824	14	23	TCMDC-135996	32	52	TCMDC-141827	14	73	TCMDC-139238	47	90	TCMDC-140386	35	102
TCMDC-136793	14	23	TCMDC-141538	32	52	TCMDC-140188	14	73	TCMDC-140309	48	90	TCMDC-134149	37	102
TCMDC-135288	14	23	TCMDC-132187	32	52	TCMDC-140967	15	73	TCMDC-136817	49	90	TCMDC-124743	39	102
TCMDC-124679	14	23	TCMDC-140148	32	52	TCMDC-135897	16	73	TCMDC-141851	49	90	TCMDC-140860	40	102
TCMDC-131482	14	23	TCMDC-141570	33	52	TCMDC-136578	16	73	TCMDC-133245	49	90	TCMDC-141833	41	102
TCMDC-124607	15	23	TCMDC-136949	34	52	TCMDC-140725	18	73	TCMDC-139671	50	90	TCMDC-139108	42	102
TCMDC-131516	15	23	TCMDC-137126	35	52	TCMDC-134768	19	73	TCMDC-134686	50	90	TCMDC-135712	45	102
TCMDC-135470	15	23	TCMDC-136359	35	52	TCMDC-134897	19	73	TCMDC-136870	51	90	TCMDC-141560	46	102
TCMDC-140805	16	23	TCMDC-140912	35	52	TCMDC-132529	20	73	TCMDC-133676	51	90	TCMDC-136451	51	102
TCMDC-135689	16	23	TCMDC-138259	35	52	TCMDC-141694	20	73	TCMDC-141710	51	90	TCMDC-133111	52	102
TCMDC-136166	16	23	TCMDC-134870	35	52	TCMDC-136665	20	73	TCMDC-135026	51	90	TCMDC-132725	52	102

TCMDC-142144	17	23	TCMDC-124966	35	52	TCMDC-133705	20	73	TCMDC-136348	52	90	TCMDC-139423	53	102
TCMDC-136710	17	23	TCMDC-140208	36	52	TCMDC-134411	21	73	TCMDC-139538	53	90	TCMDC-140142	53	102
TCMDC-125636	17	23	TCMDC-141258	37	52	TCMDC-131960	21	73	TCMDC-134951	53	90	TCMDC-141145	54	102
TCMDC-140897	17	23	TCMDC-134267	37	52	TCMDC-141539	21	73	TCMDC-135973	53	90	TCMDC-137083	54	102
TCMDC-141213	18	23	TCMDC-132966	37	52	TCMDC-138589	21	73	TCMDC-136265	53	90	TCMDC-141842	56	102
TCMDC-135475	18	23	TCMDC-133100	38	52	TCMDC-134392	21	73	TCMDC-139390	54	90	TCMDC-124819	57	102
TCMDC-136792	18	23	TCMDC-137830	39	52	TCMDC-139119	22	73	TCMDC-139883	54	90	TCMDC-138203	57	102
TCMDC-132094	19	23	TCMDC-137088	41	52	TCMDC-139583	23	73	TCMDC-136766	56	90	TCMDC-123951	60	102
TCMDC-140845	19	23	TCMDC-142140	42	52	TCMDC-132563	23	73	TCMDC-132177	56	90	TCMDC-136099	60	102
TCMDC-138581	19	23	TCMDC-132899	42	52	TCMDC-141939	23	73	TCMDC-140651	56	90	TCMDC-141845	61	102
TCMDC-141102	19	23	TCMDC-124696	42	52	TCMDC-136009	24	73	TCMDC-138549	57	90	TCMDC-124977	61	102
TCMDC-136633	20	23	TCMDC-123977	42	52	TCMDC-132312	24	73	TCMDC-137767	57	90	TCMDC-136957	61	102
TCMDC-140989	20	23	TCMDC-141071	43	52	TCMDC-135102	24	73	TCMDC-141993	57	90	TCMDC-133280	61	102
TCMDC-123483	20	23	TCMDC-136918	44	52	TCMDC-136256	24	73	TCMDC-123954	58	90	TCMDC-138242	61	102
TCMDC-135972	20	23	TCMDC-141806	44	52	TCMDC-139795	25	73	TCMDC-139396	59	90	TCMDC-139062	61	102
TCMDC-131499	20	23	TCMDC-139114	44	52	TCMDC-132483	25	73	TCMDC-136176	59	90	TCMDC-133574	64	102
TCMDC-138264	20	23	TCMDC-142037	45	52	TCMDC-139919	25	73	TCMDC-141952	59	90	TCMDC-133184	64	102
TCMDC-140073	20	23	TCMDC-140780	45	52	TCMDC-138752	25	73	TCMDC-132738	59	90	TCMDC-140215	64	102
TCMDC-125220	21	23	TCMDC-124868	46	52	TCMDC-132368	25	73	TCMDC-139859	59	90	TCMDC-135869	64	102
TCMDC-140844	21	23	TCMDC-124686	46	52	TCMDC-140974	25	73	TCMDC-136096	60	90	TCMDC-142237	65	102
TCMDC-140153	21	23	TCMDC-134945	46	52	TCMDC-136579	25	73	TCMDC-140760	60	90	TCMDC-136098	66	102
TCMDC-137166	21	23	TCMDC-124716	46	52	TCMDC-124181	25	73	TCMDC-135015	60	90	TCMDC-141494	67	102
TCMDC-140393	21	23	TCMDC-138134	46	52	TCMDC-132570	26	73	TCMDC-138102	61	90	TCMDC-125529	67	102
TCMDC-125075	22	23	TCMDC-135291	47	52	TCMDC-138545	26	73	TCMDC-135933	61	90	TCMDC-135645	70	102
TCMDC-138152	22	23	TCMDC-123876	48	52	TCMDC-141137	27	73	TCMDC-142094	61	90	TCMDC-134272	70	102
TCMDC-125554	22	23	TCMDC-133123	48	52	TCMDC-134879	27	73	TCMDC-140316	62	90	TCMDC-140361	70	102
TCMDC-124888	22	23	TCMDC-133720	49	52	TCMDC-134192	27	73	TCMDC-142110	62	90	TCMDC-140050	70	102
TCMDC-133623	22	23	TCMDC-124634	50	52	TCMDC-142200	28	73	TCMDC-125374	62	90	TCMDC-139995	70	102
TCMDC-136530	23	23	TCMDC-133661	51	52	TCMDC-134311	28	73	TCMDC-131951	62	90	TCMDC-137009	71	102
TCMDC-136062	23	23	TCMDC-133575	51	52	TCMDC-125579	28	73	TCMDC-136235	63	90	TCMDC-140056	71	102
TCMDC-134634	23	23	TCMDC-140078	51	52	TCMDC-138318	28	73	TCMDC-140509	64	90	TCMDC-141464	71	102
TCMDC-131817	1	24	TCMDC-139272	51	52	TCMDC-139608	29	73	TCMDC-133972	64	90	TCMDC-137932	71	102
TCMDC-137816	1	24	TCMDC-140575	52	52	TCMDC-123516	29	73	TCMDC-137441	64	90	TCMDC-136447	72	102
TCMDC-137631	2	24	TCMDC-138735	2	53	TCMDC-139719	29	73	TCMDC-141500	64	90	TCMDC-133246	73	102
TCMDC-142204	2	24	TCMDC-142208	3	53	TCMDC-135204	30	73	TCMDC-135027	65	90	TCMDC-137658	73	102
TCMDC-131564	2	24	TCMDC-139965	4	53	TCMDC-134402	31	73	TCMDC-141816	65	90	TCMDC-133752	75	102
TCMDC-137455	3	24	TCMDC-135472	4	53	TCMDC-133446	31	73	TCMDC-134676	65	90	TCMDC-139733	75	102

TCMDC-140061	3	24	TCMDC-125567	4	53	TCMDC-132993	32	73	TCMDC-140029	65	90	TCMDC-139263	76	102
TCMDC-136070	4	24	TCMDC-139823	5	53	TCMDC-133514	32	73	TCMDC-124405	66	90	TCMDC-137857	76	102
TCMDC-140555	4	24	TCMDC-133513	6	53	TCMDC-139364	32	73	TCMDC-136933	66	90	TCMDC-139418	76	102
TCMDC-140554	4	24	TCMDC-138536	6	53	TCMDC-134254	32	73	TCMDC-132206	67	90	TCMDC-133281	77	102
TCMDC-140545	4	24	TCMDC-132814	8	53	TCMDC-137716	33	73	TCMDC-136594	67	90	TCMDC-124553	77	102
TCMDC-141280	4	24	TCMDC-141513	10	53	TCMDC-132772	33	73	TCMDC-137710	68	90	TCMDC-131367	78	102
TCMDC-137979	4	24	TCMDC-132242	10	53	TCMDC-135870	33	73	TCMDC-139539	69	90	TCMDC-132945	78	102
TCMDC-135416	5	24	TCMDC-132813	10	53	TCMDC-138288	34	73	TCMDC-136798	69	90	TCMDC-137446	78	102
TCMDC-141577	5	24	TCMDC-131423	10	53	TCMDC-138284	34	73	TCMDC-138392	70	90	TCMDC-141433	80	102
TCMDC-125342	5	24	TCMDC-134911	10	53	TCMDC-131986	34	73	TCMDC-139623	70	90	TCMDC-138915	80	102
TCMDC-132325	5	24	TCMDC-138930	10	53	TCMDC-134950	34	73	TCMDC-125336	71	90	TCMDC-124838	81	102
TCMDC-141512	6	24	TCMDC-134176	10	53	TCMDC-135935	34	73	TCMDC-131358	71	90	TCMDC-138924	81	102
TCMDC-132224	6	24	TCMDC-141319	11	53	TCMDC-132750	35	73	TCMDC-135767	71	90	TCMDC-131322	82	102
TCMDC-140627	6	24	TCMDC-133388	11	53	TCMDC-141204	35	73	TCMDC-133250	72	90	TCMDC-137732	83	102
TCMDC-140528	7	24	TCMDC-138765	11	53	TCMDC-135502	36	73	TCMDC-123512	73	90	TCMDC-124159	83	102
TCMDC-124478	7	24	TCMDC-136738	11	53	TCMDC-131898	36	73	TCMDC-135769	74	90	TCMDC-131425	83	102
TCMDC-132227	7	24	TCMDC-142128	12	53	TCMDC-133879	36	73	TCMDC-124609	75	90	TCMDC-135813	83	102
TCMDC-132379	8	24	TCMDC-137985	12	53	TCMDC-135307	36	73	TCMDC-132693	75	90	TCMDC-131751	84	102
TCMDC-137935	8	24	TCMDC-137744	12	53	TCMDC-133070	36	73	TCMDC-136367	75	90	TCMDC-131740	84	102
TCMDC-139896	8	24	TCMDC-132211	14	53	TCMDC-139332	36	73	TCMDC-135889	75	90	TCMDC-137472	85	102
TCMDC-132294	8	24	TCMDC-135620	14	53	TCMDC-132255	36	73	TCMDC-125449	76	90	TCMDC-131356	85	102
TCMDC-124078	9	24	TCMDC-139831	14	53	TCMDC-138861	37	73	TCMDC-131329	76	90	TCMDC-131904	85	102
TCMDC-134095	10	24	TCMDC-135790	14	53	TCMDC-135969	37	73	TCMDC-136857	76	90	TCMDC-134970	86	102
TCMDC-138535	10	24	TCMDC-136469	14	53	TCMDC-141981	38	73	TCMDC-137097	76	90	TCMDC-139030	86	102
TCMDC-133878	10	24	TCMDC-125091	15	53	TCMDC-141673	38	73	TCMDC-133586	77	90	TCMDC-124842	87	102
TCMDC-138322	11	24	TCMDC-134869	15	53	TCMDC-136889	38	73	TCMDC-138036	78	90	TCMDC-136906	87	102
TCMDC-131534	11	24	TCMDC-125409	16	53	TCMDC-142185	38	73	TCMDC-137919	78	90	TCMDC-137943	87	102
TCMDC-134537	11	24	TCMDC-140527	16	53	TCMDC-139468	39	73	TCMDC-125050	78	90	TCMDC-134314	87	102
TCMDC-131567	12	24	TCMDC-134160	17	53	TCMDC-139727	39	73	TCMDC-137327	79	90	TCMDC-139441	88	102
TCMDC-137596	13	24	TCMDC-140986	17	53	TCMDC-124608	40	73	TCMDC-138971	80	90	TCMDC-131360	88	102
TCMDC-140998	13	24	TCMDC-138341	17	53	TCMDC-132635	41	73	TCMDC-134507	80	90	TCMDC-125746	88	102
TCMDC-132278	13	24	TCMDC-135114	17	53	TCMDC-132463	41	73	TCMDC-137743	80	90	TCMDC-123460	88	102
TCMDC-134064	14	24	TCMDC-141090	18	53	TCMDC-140975	41	73	TCMDC-142260	80	90	TCMDC-131606	89	102
TCMDC-131463	14	24	TCMDC-138506	18	53	TCMDC-134848	42	73	TCMDC-131874	80	90	TCMDC-141838	89	102
TCMDC-141196	14	24	TCMDC-141707	18	53	TCMDC-123978	43	73	TCMDC-139410	81	90	TCMDC-137862	89	102
TCMDC-135694	14	24	TCMDC-124511	18	53	TCMDC-132844	43	73	TCMDC-138812	81	90	TCMDC-125367	90	102
TCMDC-125328	14	24	TCMDC-136823	18	53	TCMDC-139633	44	73	TCMDC-123607	82	90	TCMDC-124432	90	102

TCMDC-140539	14	24	TCMDC-133798	19	53	TCMDC-134866	45	73	TCMDC-134384	82	90	TCMDC-124578	90	102
TCMDC-132032	14	24	TCMDC-133320	19	53	TCMDC-125671	46	73	TCMDC-136842	82	90	TCMDC-135054	90	102
TCMDC-124540	15	24	TCMDC-132766	19	53	TCMDC-136550	47	73	TCMDC-133189	83	90	TCMDC-123664	91	102
TCMDC-132212	15	24	TCMDC-138705	19	53	TCMDC-132671	47	73	TCMDC-137505	83	90	TCMDC-124837	91	102
TCMDC-135692	15	24	TCMDC-132735	19	53	TCMDC-135742	47	73	TCMDC-125630	83	90	TCMDC-134972	91	102
TCMDC-123990	16	24	TCMDC-134546	19	53	TCMDC-141430	48	73	TCMDC-137896	83	90	TCMDC-131741	91	102
TCMDC-141043	16	24	TCMDC-132827	19	53	TCMDC-138086	48	73	TCMDC-137212	83	90	TCMDC-137675	91	102
TCMDC-137602	16	24	TCMDC-141945	20	53	TCMDC-124377	49	73	TCMDC-142120	83	90	TCMDC-125562	91	102
TCMDC-125816	17	24	TCMDC-139369	21	53	TCMDC-141104	52	73	TCMDC-138039	84	90	TCMDC-136640	91	102
TCMDC-131461	17	24	TCMDC-139606	22	53	TCMDC-135403	53	73	TCMDC-136747	84	90	TCMDC-124453	92	102
TCMDC-136239	17	24	TCMDC-140156	22	53	TCMDC-141431	53	73	TCMDC-137231	84	90	TCMDC-131892	92	102
TCMDC-140154	17	24	TCMDC-134929	22	53	TCMDC-133481	53	73	TCMDC-133160	85	90	TCMDC-124216	92	102
TCMDC-125377	18	24	TCMDC-135898	23	53	TCMDC-138694	53	73	TCMDC-135847	85	90	TCMDC-125228	92	102
TCMDC-133138	18	24	TCMDC-134776	23	53	TCMDC-135633	53	73	TCMDC-134302	85	90	TCMDC-135589	92	102
TCMDC-124597	19	24	TCMDC-138952	23	53	TCMDC-133905	54	73	TCMDC-123704	86	90	TCMDC-124531	93	102
TCMDC-140822	19	24	TCMDC-139731	24	53	TCMDC-137304	54	73	TCMDC-131593	86	90	TCMDC-123654	93	102
TCMDC-124276	19	24	TCMDC-133347	25	53	TCMDC-137877	56	73	TCMDC-124836	86	90	TCMDC-137889	93	102
TCMDC-124117	20	24	TCMDC-140272	25	53	TCMDC-141476	57	73	TCMDC-136546	86	90	TCMDC-138722	93	102
TCMDC-140862	20	24	TCMDC-133510	25	53	TCMDC-141894	57	73	TCMDC-142290	86	90	TCMDC-125815	94	102
TCMDC-137599	20	24	TCMDC-132429	26	53	TCMDC-135355	57	73	TCMDC-124333	86	90	TCMDC-137748	94	102
TCMDC-141351	21	24	TCMDC-140186	26	53	TCMDC-133921	57	73	TCMDC-142224	87	90	TCMDC-125019	94	102
TCMDC-123484	21	24	TCMDC-136533	26	53	TCMDC-136587	57	73	TCMDC-139065	87	90	TCMDC-133760	94	102
TCMDC-138051	21	24	TCMDC-141227	26	53	TCMDC-137849	58	73	TCMDC-137343	88	90	TCMDC-124530	94	102
TCMDC-140240	21	24	TCMDC-139766	26	53	TCMDC-138799	59	73	TCMDC-136496	88	90	TCMDC-132132	94	102
TCMDC-131468	22	24	TCMDC-134250	26	53	TCMDC-139857	60	73	TCMDC-139023	88	90	TCMDC-137641	94	102
TCMDC-134320	22	24	TCMDC-132568	26	53	TCMDC-135917	62	73	TCMDC-137192	88	90	TCMDC-125797	94	102
TCMDC-135565	22	24	TCMDC-138002	26	53	TCMDC-140143	62	73	TCMDC-123995	88	90	TCMDC-125590	95	102
TCMDC-131473	22	24	TCMDC-141557	27	53	TCMDC-140359	64	73	TCMDC-125224	89	90	TCMDC-134984	95	102
TCMDC-141417	23	24	TCMDC-132625	27	53	TCMDC-142029	64	73	TCMDC-123634	89	90	TCMDC-123644	95	102
TCMDC-131510	23	24	TCMDC-138018	27	53	TCMDC-133423	65	73	TCMDC-131661	89	90	TCMDC-135588	96	102
TCMDC-124114	24	24	TCMDC-140516	28	53	TCMDC-141370	66	73	TCMDC-125445	89	90	TCMDC-138065	96	102
TCMDC-125634	24	24	TCMDC-141974	29	53	TCMDC-136390	66	73	TCMDC-125049	89	90	TCMDC-124211	96	102
TCMDC-132582	24	24	TCMDC-141180	29	53	TCMDC-139339	67	73	TCMDC-140523	89	90	TCMDC-131404	96	102
TCMDC-137452	1	25	TCMDC-132433	30	53	TCMDC-140797	71	73	TCMDC-135429	89	90	TCMDC-124849	96	102
TCMDC-137259	2	25	TCMDC-140681	30	53	TCMDC-124718	71	73	TCMDC-131235	89	90	TCMDC-123931	97	102
TCMDC-140595	2	25	TCMDC-139322	31	53	TCMDC-124960	72	73	TCMDC-142179	89	90	TCMDC-131699	97	102
TCMDC-139851	2	25	TCMDC-141976	31	53	TCMDC-138236	72	73	TCMDC-137121	89	90	TCMDC-124300	97	102

TCMDC-124528	3	25	TCMDC-132881	32	53	TCMDC-138223	72	73	TCMDC-137491	89	90	TCMDC-125775	97	102
TCMDC-136556	3	25	TCMDC-141354	35	53	TCMDC-132185	72	73	TCMDC-134488	90	90	TCMDC-131408	97	102
TCMDC-133842	3	25	TCMDC-141899	35	53	TCMDC-135078	72	73	TCMDC-125211	90	90	TCMDC-131707	97	102
TCMDC-132409	3	25	TCMDC-133412	36	53	TCMDC-134212	73	73	TCMDC-125747	90	90	TCMDC-137495	97	102
TCMDC-139636	4	25	TCMDC-140712	36	53	TCMDC-138786	73	73	TCMDC-139045	90	90	TCMDC-141810	98	102
TCMDC-139866	4	25	TCMDC-139922	37	53	TCMDC-137108	73	73	TCMDC-123513	90	90	TCMDC-135597	98	102
TCMDC-124194	4	25	TCMDC-136532	38	53	TCMDC-132089	2	74	TCMDC-134582	92	90	TCMDC-131624	98	102
TCMDC-137795	5	25	TCMDC-124814	39	53	TCMDC-131600	3	74	TCMDC-133255	96	90	TCMDC-125405	98	102
TCMDC-135495	5	25	TCMDC-136709	39	53	TCMDC-131917	4	74	TCMDC-141594	4	91	TCMDC-135513	98	102
TCMDC-132480	5	25	TCMDC-136986	40	53	TCMDC-124489	4	74	TCMDC-125887	5	91	TCMDC-132329	98	102
TCMDC-140606	5	25	TCMDC-132906	40	53	TCMDC-138641	6	74	TCMDC-137801	5	91	TCMDC-123769	98	102
TCMDC-134829	5	25	TCMDC-139858	41	53	TCMDC-139586	7	74	TCMDC-125258	7	91	TCMDC-124401	98	102
TCMDC-132244	5	25	TCMDC-139141	42	53	TCMDC-124146	7	74	TCMDC-138704	7	91	TCMDC-123837	98	102
TCMDC-141551	6	25	TCMDC-135124	44	53	TCMDC-139515	8	74	TCMDC-125465	8	91	TCMDC-123901	98	102
TCMDC-140497	6	25	TCMDC-138783	47	53	TCMDC-139469	9	74	TCMDC-133382	8	91	TCMDC-138037	98	102
TCMDC-141505	6	25	TCMDC-125098	48	53	TCMDC-139183	10	74	TCMDC-139394	11	91	TCMDC-131691	98	102
TCMDC-138615	7	25	TCMDC-123964	48	53	TCMDC-136659	11	74	TCMDC-139915	14	91	TCMDC-123861	98	102
TCMDC-138762	7	25	TCMDC-138800	48	53	TCMDC-140007	12	74	TCMDC-139127	16	91	TCMDC-132722	98	102
TCMDC-138616	7	25	TCMDC-137129	49	53	TCMDC-139949	12	74	TCMDC-139011	18	91	TCMDC-125213	98	102
TCMDC-134094	8	25	TCMDC-135932	49	53	TCMDC-134049	13	74	TCMDC-140006	19	91	TCMDC-132415	98	102
TCMDC-139071	8	25	TCMDC-138519	50	53	TCMDC-138198	13	74	TCMDC-142291	21	91	TCMDC-134692	98	102
TCMDC-138714	8	25	TCMDC-142149	51	53	TCMDC-132259	13	74	TCMDC-133342	22	91	TCMDC-136495	98	102
TCMDC-141904	8	25	TCMDC-141029	51	53	TCMDC-140187	14	74	TCMDC-132859	23	91	TCMDC-125582	99	102
TCMDC-135034	9	25	TCMDC-139253	51	53	TCMDC-140181	14	74	TCMDC-135671	24	91	TCMDC-131559	99	102
TCMDC-140581	10	25	TCMDC-136195	51	53	TCMDC-139702	14	74	TCMDC-141820	25	91	TCMDC-138200	99	102
TCMDC-136697	10	25	TCMDC-141107	51	53	TCMDC-133371	14	74	TCMDC-124509	26	91	TCMDC-131685	99	102
TCMDC-135999	10	25	TCMDC-124080	52	53	TCMDC-134924	16	74	TCMDC-134742	27	91	TCMDC-131388	99	102
TCMDC-134286	10	25	TCMDC-123596	52	53	TCMDC-135435	17	74	TCMDC-140150	28	91	TCMDC-142014	99	102
TCMDC-131533	10	25	TCMDC-142317	52	53	TCMDC-134648	17	74	TCMDC-136295	28	91	TCMDC-123943	99	102
TCMDC-138795	11	25	TCMDC-133622	53	53	TCMDC-131259	18	74	TCMDC-132579	28	91	TCMDC-131667	99	102
TCMDC-141788	11	25	TCMDC-139855	53	53	TCMDC-135229	18	74	TCMDC-138652	30	91	TCMDC-123481	99	102
TCMDC-125013	12	25	TCMDC-136216	2	54	TCMDC-139517	18	74	TCMDC-139279	30	91	TCMDC-131774	99	102
TCMDC-132226	12	25	TCMDC-136882	2	54	TCMDC-134769	20	74	TCMDC-136703	30	91	TCMDC-124366	99	102
TCMDC-135536	14	25	TCMDC-138657	5	54	TCMDC-139981	20	74	TCMDC-135548	30	91	TCMDC-138376	99	102
TCMDC-136037	14	25	TCMDC-141292	5	54	TCMDC-136452	20	74	TCMDC-135443	30	91	TCMDC-136184	99	102
TCMDC-132007	15	25	TCMDC-137953	7	54	TCMDC-141818	20	74	TCMDC-141683	30	91	TCMDC-134262	100	102
TCMDC-135855	16	25	TCMDC-139804	7	54	TCMDC-133277	20	74	TCMDC-138153	31	91	TCMDC-134594	100	102

TCMDC-131507	16	25	TCMDC-141510	8	54	TCMDC-133721	20	74	TCMDC-141172	31	91	TCMDC-124465	100	102
TCMDC-131513	16	25	TCMDC-132373	9	54	TCMDC-141695	21	74	TCMDC-138167	32	91	TCMDC-124287	100	102
TCMDC-139009	16	25	TCMDC-138241	9	54	TCMDC-134439	21	74	TCMDC-125347	32	91	TCMDC-136561	100	102
TCMDC-137605	17	25	TCMDC-138903	9	54	TCMDC-132640	21	74	TCMDC-123972	32	91	TCMDC-124112	100	102
TCMDC-131490	17	25	TCMDC-141406	9	54	TCMDC-134474	22	74	TCMDC-123711	32	91	TCMDC-131387	100	102
TCMDC-136025	17	25	TCMDC-140126	10	54	TCMDC-133496	22	74	TCMDC-136292	34	91	TCMDC-123981	100	102
TCMDC-140376	17	25	TCMDC-140170	11	54	TCMDC-135149	22	74	TCMDC-140857	34	91	TCMDC-131689	100	102
TCMDC-124253	17	25	TCMDC-135279	11	54	TCMDC-141715	22	74	TCMDC-141489	35	91	TCMDC-131764	100	102
TCMDC-132097	17	25	TCMDC-139251	11	54	TCMDC-139371	23	74	TCMDC-137762	35	91	TCMDC-135815	100	102
TCMDC-131458	18	25	TCMDC-134155	11	54	TCMDC-140875	23	74	TCMDC-139165	35	91	TCMDC-134170	100	102
TCMDC-138128	18	25	TCMDC-131841	11	54	TCMDC-139986	23	74	TCMDC-140089	35	91	TCMDC-139504	100	102
TCMDC-131241	18	25	TCMDC-141327	12	54	TCMDC-140196	24	74	TCMDC-142154	37	91	TCMDC-136325	101	102
TCMDC-124648	18	25	TCMDC-136245	12	54	TCMDC-134898	24	74	TCMDC-132070	37	91	TCMDC-136371	101	102
TCMDC-125632	19	25	TCMDC-137808	12	54	TCMDC-137313	25	74	TCMDC-138515	37	91	TCMDC-135232	101	102
TCMDC-138190	19	25	TCMDC-141459	12	54	TCMDC-132360	25	74	TCMDC-135111	38	91	TCMDC-142152	101	102
TCMDC-142005	19	25	TCMDC-134595	16	54	TCMDC-124961	25	74	TCMDC-136082	39	91	TCMDC-135911	101	102
TCMDC-140397	20	25	TCMDC-132608	16	54	TCMDC-140342	25	74	TCMDC-133734	39	91	TCMDC-136562	101	102
TCMDC-131977	20	25	TCMDC-141488	16	54	TCMDC-133789	25	74	TCMDC-135722	40	91	TCMDC-125736	101	102
TCMDC-131472	20	25	TCMDC-142035	17	54	TCMDC-135998	25	74	TCMDC-132768	40	91	TCMDC-141060	101	102
TCMDC-140837	21	25	TCMDC-142125	17	54	TCMDC-139718	25	74	TCMDC-133437	40	91	TCMDC-131787	101	102
TCMDC-140222	21	25	TCMDC-134916	17	54	TCMDC-140158	26	74	TCMDC-139113	40	91	TCMDC-123843	101	102
TCMDC-124031	21	25	TCMDC-124663	18	54	TCMDC-141917	26	74	TCMDC-134243	43	91	TCMDC-131935	101	102
TCMDC-141717	22	25	TCMDC-140535	18	54	TCMDC-140313	26	74	TCMDC-136940	43	91	TCMDC-124992	102	102
TCMDC-137590	22	25	TCMDC-134863	18	54	TCMDC-139191	26	74	TCMDC-137999	43	91	TCMDC-136625	102	102
TCMDC-132072	22	25	TCMDC-132983	19	54	TCMDC-136006	26	74	TCMDC-136254	43	91	TCMDC-124780	102	102
TCMDC-141416	23	25	TCMDC-136838	20	54	TCMDC-133121	27	74	TCMDC-124825	44	91	TCMDC-124242	102	102
TCMDC-142223	23	25	TCMDC-137261	20	54	TCMDC-134018	28	74	TCMDC-136101	45	91	TCMDC-138375	102	102
TCMDC-140161	23	25	TCMDC-140320	20	54	TCMDC-139710	28	74	TCMDC-137092	45	91	TCMDC-131683	102	102
TCMDC-124003	24	25	TCMDC-123571	20	54	TCMDC-136005	29	74	TCMDC-139255	46	91	TCMDC-137629	102	102
TCMDC-140302	24	25	TCMDC-138940	21	54	TCMDC-141755	29	74	TCMDC-141669	47	91	TCMDC-125697	102	102
TCMDC-136198	24	25	TCMDC-135420	21	54	TCMDC-133736	29	74	TCMDC-135840	47	91	TCMDC-138133	102	102
TCMDC-124009	24	25	TCMDC-135665	22	54	TCMDC-133774	29	74	TCMDC-135859	47	91	TCMDC-125202	102	102
TCMDC-132113	24	25	TCMDC-135309	22	54	TCMDC-134557	30	74	TCMDC-134381	48	91	TCMDC-135466	105	102
TCMDC-134645	24	25	TCMDC-139412	22	54	TCMDC-142234	30	74	TCMDC-132352	48	91	TCMDC-125081	5	103
TCMDC-131515	24	25	TCMDC-132996	23	54	TCMDC-124938	30	74	TCMDC-142322	49	91	TCMDC-124925	9	103
TCMDC-140821	25	25	TCMDC-141616	24	54	TCMDC-132167	31	74	TCMDC-136574	49	91	TCMDC-124927	16	103
TCMDC-136038	25	25	TCMDC-137024	24	54	TCMDC-140411	31	74	TCMDC-135868	50	91	TCMDC-142086	16	103

TCMDC-125247	25	25	TCMDC-140919	24	54	TCMDC-132858	31	74	TCMDC-136215	50	91	TCMDC-140038	25	103
TCMDC-136622	1	26	TCMDC-139921	24	54	TCMDC-136350	32	74	TCMDC-135929	50	91	TCMDC-134289	30	103
TCMDC-139648	2	26	TCMDC-136342	25	54	TCMDC-139083	32	74	TCMDC-133509	51	91	TCMDC-136681	30	103
TCMDC-140609	3	26	TCMDC-141261	25	54	TCMDC-136076	33	74	TCMDC-134946	51	91	TCMDC-134231	33	103
TCMDC-132055	3	26	TCMDC-140789	27	54	TCMDC-135448	33	74	TCMDC-138084	51	91	TCMDC-136365	34	103
TCMDC-136049	5	26	TCMDC-123906	27	54	TCMDC-136107	34	74	TCMDC-134750	51	91	TCMDC-135703	35	103
TCMDC-123748	5	26	TCMDC-133583	27	54	TCMDC-140414	34	74	TCMDC-139188	52	91	TCMDC-131702	35	103
TCMDC-138327	5	26	TCMDC-138523	28	54	TCMDC-136368	34	74	TCMDC-137335	52	91	TCMDC-139789	36	103
TCMDC-132030	5	26	TCMDC-132441	28	54	TCMDC-134759	34	74	TCMDC-135939	52	91	TCMDC-139282	37	103
TCMDC-139898	6	26	TCMDC-137465	28	54	TCMDC-134771	35	74	TCMDC-136114	52	91	TCMDC-133672	37	103
TCMDC-140534	6	26	TCMDC-137043	28	54	TCMDC-123523	35	74	TCMDC-131890	52	91	TCMDC-140254	39	103
TCMDC-135771	7	26	TCMDC-134867	29	54	TCMDC-138949	36	74	TCMDC-136003	52	91	TCMDC-133813	39	103
TCMDC-140677	7	26	TCMDC-131800	29	54	TCMDC-133106	36	74	TCMDC-138484	52	91	TCMDC-134629	43	103
TCMDC-135214	7	26	TCMDC-140487	30	54	TCMDC-135338	37	74	TCMDC-140484	53	91	TCMDC-136967	46	103
TCMDC-125596	8	26	TCMDC-141166	30	54	TCMDC-132561	37	74	TCMDC-135719	53	91	TCMDC-135344	46	103
TCMDC-135572	9	26	TCMDC-125144	30	54	TCMDC-135108	38	74	TCMDC-133291	56	91	TCMDC-133116	46	103
TCMDC-135533	9	26	TCMDC-140224	30	54	TCMDC-133584	38	74	TCMDC-139241	56	91	TCMDC-136679	47	103
TCMDC-140525	9	26	TCMDC-140367	31	54	TCMDC-132741	38	74	TCMDC-140335	56	91	TCMDC-135890	48	103
TCMDC-124594	9	26	TCMDC-133747	32	54	TCMDC-139526	38	74	TCMDC-132049	57	91	TCMDC-135993	50	103
TCMDC-138412	9	26	TCMDC-132646	32	54	TCMDC-135024	39	74	TCMDC-142294	57	91	TCMDC-134274	51	103
TCMDC-141943	9	26	TCMDC-132897	32	54	TCMDC-132538	39	74	TCMDC-124922	57	91	TCMDC-133208	51	103
TCMDC-133535	10	26	TCMDC-133568	33	54	TCMDC-133521	40	74	TCMDC-133132	57	91	TCMDC-134468	53	103
TCMDC-124409	10	26	TCMDC-123979	33	54	TCMDC-137277	41	74	TCMDC-131713	58	91	TCMDC-141824	53	103
TCMDC-138397	10	26	TCMDC-140521	33	54	TCMDC-134735	42	74	TCMDC-136926	58	91	TCMDC-139308	55	103
TCMDC-132254	12	26	TCMDC-138941	34	54	TCMDC-141364	42	74	TCMDC-139747	58	91	TCMDC-134821	57	103
TCMDC-141775	13	26	TCMDC-139444	36	54	TCMDC-136130	42	74	TCMDC-141186	59	91	TCMDC-136942	57	103
TCMDC-131518	14	26	TCMDC-133986	36	54	TCMDC-133424	44	74	TCMDC-142059	59	91	TCMDC-141874	59	103
TCMDC-142246	14	26	TCMDC-137112	37	54	TCMDC-133275	45	74	TCMDC-131263	59	91	TCMDC-141701	59	103
TCMDC-138447	14	26	TCMDC-138403	37	54	TCMDC-140124	46	74	TCMDC-140125	59	91	TCMDC-140249	60	103
TCMDC-137509	15	26	TCMDC-138743	37	54	TCMDC-133052	47	74	TCMDC-140710	60	91	TCMDC-133131	60	103
TCMDC-141995	15	26	TCMDC-133987	38	54	TCMDC-134763	48	74	TCMDC-140013	61	91	TCMDC-132893	60	103
TCMDC-125053	16	26	TCMDC-124968	40	54	TCMDC-135491	49	74	TCMDC-134681	61	91	TCMDC-135626	62	103
TCMDC-140054	16	26	TCMDC-141655	41	54	TCMDC-137051	50	74	TCMDC-135541	61	91	TCMDC-133598	62	103
TCMDC-141165	16	26	TCMDC-140375	42	54	TCMDC-132702	50	74	TCMDC-140921	62	91	TCMDC-132148	62	103
TCMDC-124918	17	26	TCMDC-124979	47	54	TCMDC-124982	50	74	TCMDC-136736	62	91	TCMDC-133834	63	103
TCMDC-135853	17	26	TCMDC-133939	47	54	TCMDC-138361	51	74	TCMDC-133109	63	91	TCMDC-137155	63	103
TCMDC-136200	17	26	TCMDC-133576	47	54	TCMDC-124671	52	74	TCMDC-137210	63	91	TCMDC-139495	64	103

TCMDC-132000	17	26	TCMDC-134293	49	54	TCMDC-141475	53	74	TCMDC-123830	64	91	TCMDC-136191	64	103
TCMDC-133795	17	26	TCMDC-135750	50	54	TCMDC-136393	53	74	TCMDC-131637	64	91	TCMDC-140911	64	103
TCMDC-132079	17	26	TCMDC-135720	51	54	TCMDC-139616	53	74	TCMDC-125395	64	91	TCMDC-136589	65	103
TCMDC-132033	17	26	TCMDC-136740	52	54	TCMDC-140298	54	74	TCMDC-139865	65	91	TCMDC-132178	66	103
TCMDC-141747	18	26	TCMDC-140514	53	54	TCMDC-132691	54	74	TCMDC-137034	65	91	TCMDC-125044	68	103
TCMDC-135690	18	26	TCMDC-131457	54	54	TCMDC-136604	54	74	TCMDC-133265	65	91	TCMDC-125427	68	103
TCMDC-131517	18	26	TCMDC-135052	0	55	TCMDC-136762	55	74	TCMDC-137053	66	91	TCMDC-141322	69	103
TCMDC-141768	18	26	TCMDC-136487	1	55	TCMDC-124576	55	74	TCMDC-141221	66	91	TCMDC-137059	74	103
TCMDC-142196	18	26	TCMDC-139676	2	55	TCMDC-136885	55	74	TCMDC-140848	67	91	TCMDC-132690	74	103
TCMDC-138423	18	26	TCMDC-125079	3	55	TCMDC-132198	56	74	TCMDC-136093	68	91	TCMDC-123850	74	103
TCMDC-136091	19	26	TCMDC-136193	3	55	TCMDC-133029	56	74	TCMDC-135741	68	91	TCMDC-142214	75	103
TCMDC-140926	19	26	TCMDC-139888	3	55	TCMDC-140743	56	74	TCMDC-142165	68	91	TCMDC-138138	75	103
TCMDC-140549	19	26	TCMDC-133479	4	55	TCMDC-131961	57	74	TCMDC-139304	68	91	TCMDC-124599	75	103
TCMDC-139640	19	26	TCMDC-139570	5	55	TCMDC-125109	58	74	TCMDC-133134	68	91	TCMDC-140447	76	103
TCMDC-136812	19	26	TCMDC-134520	5	55	TCMDC-131238	60	74	TCMDC-131412	69	91	TCMDC-139889	77	103
TCMDC-133662	20	26	TCMDC-142284	6	55	TCMDC-141011	60	74	TCMDC-138945	69	91	TCMDC-138953	79	103
TCMDC-141424	20	26	TCMDC-141492	7	55	TCMDC-139092	61	74	TCMDC-141596	70	91	TCMDC-135732	80	103
TCMDC-141330	20	26	TCMDC-138305	7	55	TCMDC-136213	64	74	TCMDC-136094	70	91	TCMDC-139010	80	103
TCMDC-136800	20	26	TCMDC-141245	8	55	TCMDC-132713	65	74	TCMDC-139685	71	91	TCMDC-138898	81	103
TCMDC-124309	20	26	TCMDC-132512	8	55	TCMDC-138295	65	74	TCMDC-140319	71	91	TCMDC-138056	81	103
TCMDC-142315	20	26	TCMDC-133854	8	55	TCMDC-139565	65	74	TCMDC-136991	72	91	TCMDC-139647	81	103
TCMDC-138910	21	26	TCMDC-138304	8	55	TCMDC-137440	65	74	TCMDC-136510	73	91	TCMDC-136778	82	103
TCMDC-139100	22	26	TCMDC-140939	9	55	TCMDC-139252	66	74	TCMDC-133082	74	91	TCMDC-136140	82	103
TCMDC-140207	22	26	TCMDC-131495	9	55	TCMDC-132194	67	74	TCMDC-135432	74	91	TCMDC-123984	83	103
TCMDC-133923	22	26	TCMDC-139333	10	55	TCMDC-124831	67	74	TCMDC-131605	75	91	TCMDC-136379	83	103
TCMDC-132303	22	26	TCMDC-141898	10	55	TCMDC-124901	67	74	TCMDC-136557	76	91	TCMDC-124614	84	103
TCMDC-142135	23	26	TCMDC-139126	10	55	TCMDC-137517	69	74	TCMDC-124455	76	91	TCMDC-139420	84	103
TCMDC-142253	24	26	TCMDC-138708	11	55	TCMDC-138159	69	74	TCMDC-125521	76	91	TCMDC-123708	85	103
TCMDC-136456	24	26	TCMDC-124766	11	55	TCMDC-124450	71	74	TCMDC-131617	76	91	TCMDC-133632	85	103
TCMDC-137934	26	26	TCMDC-137746	11	55	TCMDC-124723	71	74	TCMDC-137078	76	91	TCMDC-141854	86	103
TCMDC-125233	29	26	TCMDC-140977	12	55	TCMDC-124818	72	74	TCMDC-137096	76	91	TCMDC-125057	86	103
TCMDC-135319	1	27	TCMDC-136225	13	55	TCMDC-140099	72	74	TCMDC-142323	77	91	TCMDC-139501	86	103
TCMDC-137972	1	27	TCMDC-140182	13	55	TCMDC-132705	73	74	TCMDC-139622	77	91	TCMDC-124212	86	103
TCMDC-131807	1	27	TCMDC-134909	13	55	TCMDC-139610	73	74	TCMDC-142211	77	91	TCMDC-139748	87	103
TCMDC-137619	2	27	TCMDC-134818	14	55	TCMDC-124832	73	74	TCMDC-133827	77	91	TCMDC-124337	87	103
TCMDC-134209	2	27	TCMDC-133943	14	55	TCMDC-135878	74	74	TCMDC-138988	78	91	TCMDC-140369	87	103
TCMDC-131893	3	27	TCMDC-142079	14	55	TCMDC-142099	74	74	TCMDC-134305	78	91	TCMDC-138956	87	103

TCMDC-140663	3	27	TCMDC-132617	14	55	TCMDC-142190	74	74	TCMDC-124804	79	91	TCMDC-135573	87	103
TCMDC-142195	3	27	TCMDC-136642	15	55	TCMDC-133621	74	74	TCMDC-134855	80	91	TCMDC-124944	89	103
TCMDC-135311	4	27	TCMDC-139799	16	55	TCMDC-140083	74	74	TCMDC-125549	80	91	TCMDC-141748	89	103
TCMDC-137354	6	27	TCMDC-141549	16	55	TCMDC-133222	75	74	TCMDC-137925	80	91	TCMDC-133562	89	103
TCMDC-132282	7	27	TCMDC-138830	16	55	TCMDC-125714	76	74	TCMDC-141268	80	91	TCMDC-141856	90	103
TCMDC-136384	7	27	TCMDC-138667	16	55	TCMDC-125415	78	74	TCMDC-140686	80	91	TCMDC-124134	90	103
TCMDC-124589	7	27	TCMDC-134672	17	55	TCMDC-132701	78	74	TCMDC-135231	81	91	TCMDC-139833	90	103
TCMDC-135494	8	27	TCMDC-140632	17	55	TCMDC-125606	3	75	TCMDC-137290	81	91	TCMDC-125210	90	103
TCMDC-135772	8	27	TCMDC-134134	17	55	TCMDC-139571	3	75	TCMDC-125065	82	91	TCMDC-138560	90	103
TCMDC-137545	8	27	TCMDC-138686	18	55	TCMDC-140349	5	75	TCMDC-136629	82	91	TCMDC-142334	90	103
TCMDC-139229	8	27	TCMDC-134147	18	55	TCMDC-138359	10	75	TCMDC-125371	82	91	TCMDC-134601	91	103
TCMDC-133769	8	27	TCMDC-123929	18	55	TCMDC-141376	12	75	TCMDC-125349	82	91	TCMDC-135363	91	103
TCMDC-131549	8	27	TCMDC-140486	19	55	TCMDC-134925	13	75	TCMDC-125875	82	91	TCMDC-124754	91	103
TCMDC-132250	9	27	TCMDC-135151	19	55	TCMDC-133519	15	75	TCMDC-123762	82	91	TCMDC-137922	91	103
TCMDC-134541	9	27	TCMDC-137044	19	55	TCMDC-125574	15	75	TCMDC-125227	82	91	TCMDC-124626	91	103
TCMDC-137518	9	27	TCMDC-132659	19	55	TCMDC-139157	15	75	TCMDC-134974	83	91	TCMDC-123557	92	103
TCMDC-124893	9	27	TCMDC-136646	20	55	TCMDC-141628	16	75	TCMDC-137636	83	91	TCMDC-125760	92	103
TCMDC-140552	9	27	TCMDC-134901	20	55	TCMDC-136429	16	75	TCMDC-131992	83	91	TCMDC-137562	92	103
TCMDC-132247	9	27	TCMDC-137248	20	55	TCMDC-139152	16	75	TCMDC-137657	83	91	TCMDC-137907	92	103
TCMDC-132272	9	27	TCMDC-133370	20	55	TCMDC-139070	16	75	TCMDC-123539	84	91	TCMDC-123905	92	103
TCMDC-141794	9	27	TCMDC-132932	20	55	TCMDC-137986	17	75	TCMDC-141595	85	91	TCMDC-137376	92	103
TCMDC-141602	11	27	TCMDC-136890	20	55	TCMDC-138302	17	75	TCMDC-123650	85	91	TCMDC-131318	93	103
TCMDC-140017	11	27	TCMDC-139203	21	55	TCMDC-140668	18	75	TCMDC-138149	85	91	TCMDC-131575	93	103
TCMDC-132511	11	27	TCMDC-132547	21	55	TCMDC-124459	20	75	TCMDC-134852	85	91	TCMDC-124691	94	103
TCMDC-134092	11	27	TCMDC-138929	22	55	TCMDC-139042	20	75	TCMDC-140419	85	91	TCMDC-123842	94	103
TCMDC-140532	11	27	TCMDC-133102	23	55	TCMDC-135158	21	75	TCMDC-133294	85	91	TCMDC-123817	94	103
TCMDC-141790	11	27	TCMDC-141163	23	55	TCMDC-136032	21	75	TCMDC-134028	86	91	TCMDC-123643	94	103
TCMDC-132223	11	27	TCMDC-136077	24	55	TCMDC-141643	23	75	TCMDC-137033	86	91	TCMDC-138029	94	103
TCMDC-132603	12	27	TCMDC-133150	25	55	TCMDC-139975	24	75	TCMDC-123702	86	91	TCMDC-131594	94	103
TCMDC-135539	12	27	TCMDC-134003	25	55	TCMDC-125062	24	75	TCMDC-132022	86	91	TCMDC-132314	94	103
TCMDC-132289	12	27	TCMDC-140276	26	55	TCMDC-141097	24	75	TCMDC-135462	86	91	TCMDC-135240	94	103
TCMDC-135883	13	27	TCMDC-141262	26	55	TCMDC-132392	25	75	TCMDC-137688	86	91	TCMDC-124782	95	103
TCMDC-135695	13	27	TCMDC-138436	26	55	TCMDC-136446	25	75	TCMDC-139129	87	91	TCMDC-135576	95	103
TCMDC-139749	13	27	TCMDC-140053	27	55	TCMDC-124719	25	75	TCMDC-135082	87	91	TCMDC-133753	95	103
TCMDC-132476	13	27	TCMDC-140231	27	55	TCMDC-140910	26	75	TCMDC-140762	87	91	TCMDC-132790	95	103
TCMDC-141728	14	27	TCMDC-141138	28	55	TCMDC-123889	27	75	TCMDC-124929	88	91	TCMDC-135578	95	103
TCMDC-137601	14	27	TCMDC-139367	28	55	TCMDC-135186	27	75	TCMDC-123524	88	91	TCMDC-137400	95	103

TCMDC-141764	15	27	TCMDC-138692	28	55	TCMDC-135274	27	75	TCMDC-137230	88	91	TCMDC-136544	95	103
TCMDC-125727	15	27	TCMDC-140041	29	55	TCMDC-136815	28	75	TCMDC-125668	89	91	TCMDC-125052	95	103
TCMDC-131486	15	27	TCMDC-124674	30	55	TCMDC-140735	28	75	TCMDC-139130	89	91	TCMDC-140448	96	103
TCMDC-137773	15	27	TCMDC-133578	30	55	TCMDC-139004	29	75	TCMDC-138905	89	91	TCMDC-140343	96	103
TCMDC-141767	16	27	TCMDC-140268	30	55	TCMDC-134232	29	75	TCMDC-131789	89	91	TCMDC-135994	96	103
TCMDC-125619	16	27	TCMDC-137095	30	55	TCMDC-140383	29	75	TCMDC-123987	89	91	TCMDC-131394	96	103
TCMDC-137170	16	27	TCMDC-140689	30	55	TCMDC-139625	29	75	TCMDC-137006	89	91	TCMDC-125599	96	103
TCMDC-136339	16	27	TCMDC-137035	30	55	TCMDC-135343	30	75	TCMDC-137222	89	91	TCMDC-138112	96	103
TCMDC-131431	16	27	TCMDC-132434	31	55	TCMDC-140271	30	75	TCMDC-138106	89	91	TCMDC-137240	96	103
TCMDC-140398	17	27	TCMDC-138244	31	55	TCMDC-139115	31	75	TCMDC-125585	89	91	TCMDC-125719	96	103
TCMDC-139843	17	27	TCMDC-135411	31	55	TCMDC-135038	31	75	TCMDC-134670	89	91	TCMDC-141565	96	103
TCMDC-141961	18	27	TCMDC-141341	31	55	TCMDC-134163	31	75	TCMDC-124289	89	91	TCMDC-140745	96	103
TCMDC-132337	18	27	TCMDC-133505	32	55	TCMDC-140463	31	75	TCMDC-137373	89	91	TCMDC-132109	96	103
TCMDC-131421	18	27	TCMDC-141501	32	55	TCMDC-137276	31	75	TCMDC-140400	90	91	TCMDC-138100	96	103
TCMDC-124582	19	27	TCMDC-140011	32	55	TCMDC-136761	32	75	TCMDC-124002	90	91	TCMDC-124653	97	103
TCMDC-124631	19	27	TCMDC-138382	32	55	TCMDC-141872	32	75	TCMDC-139024	90	91	TCMDC-131926	97	103
TCMDC-124116	19	27	TCMDC-134111	32	55	TCMDC-133216	33	75	TCMDC-131562	90	91	TCMDC-125015	97	103
TCMDC-131246	19	27	TCMDC-137018	32	55	TCMDC-134868	33	75	TCMDC-131580	90	91	TCMDC-136157	97	103
TCMDC-140650	19	27	TCMDC-133018	32	55	TCMDC-132562	34	75	TCMDC-132905	90	91	TCMDC-123717	97	103
TCMDC-140894	19	27	TCMDC-134992	33	55	TCMDC-141658	35	75	TCMDC-136979	90	91	TCMDC-133618	97	103
TCMDC-133008	20	27	TCMDC-133838	34	55	TCMDC-133026	36	75	TCMDC-131937	90	91	TCMDC-125426	97	103
TCMDC-123502	20	27	TCMDC-139205	34	55	TCMDC-137077	37	75	TCMDC-132481	90	91	TCMDC-132054	97	103
TCMDC-136047	20	27	TCMDC-142266	34	55	TCMDC-138992	38	75	TCMDC-137291	90	91	TCMDC-137363	97	103
TCMDC-124541	21	27	TCMDC-139227	35	55	TCMDC-124396	38	75	TCMDC-125101	91	91	TCMDC-139845	97	103
TCMDC-123908	21	27	TCMDC-132641	35	55	TCMDC-141057	38	75	TCMDC-137899	91	91	TCMDC-141973	98	103
TCMDC-140363	21	27	TCMDC-125235	35	55	TCMDC-123579	38	75	TCMDC-124342	91	91	TCMDC-131656	98	103
TCMDC-141191	22	27	TCMDC-133346	36	55	TCMDC-133693	38	75	TCMDC-137699	91	91	TCMDC-125851	98	103
TCMDC-137484	22	27	TCMDC-132761	36	55	TCMDC-138178	38	75	TCMDC-139433	91	91	TCMDC-124258	98	103
TCMDC-140839	23	27	TCMDC-141024	36	55	TCMDC-133547	38	75	TCMDC-125578	91	91	TCMDC-136328	98	103
TCMDC-137016	23	27	TCMDC-133404	37	55	TCMDC-132586	40	75	TCMDC-140122	91	91	TCMDC-135354	98	103
TCMDC-135965	24	27	TCMDC-139405	37	55	TCMDC-136113	41	75	TCMDC-131633	91	91	TCMDC-135003	98	103
TCMDC-137588	24	27	TCMDC-133014	38	55	TCMDC-141870	41	75	TCMDC-124268	91	91	TCMDC-124947	99	103
TCMDC-136177	24	27	TCMDC-134792	38	55	TCMDC-137884	41	75	TCMDC-125863	91	91	TCMDC-125124	99	103
TCMDC-125717	25	27	TCMDC-133566	40	55	TCMDC-134248	41	75	TCMDC-123509	91	91	TCMDC-137427	99	103
TCMDC-135469	25	27	TCMDC-132543	41	55	TCMDC-136935	42	75	TCMDC-142250	92	91	TCMDC-123716	99	103
TCMDC-132053	25	27	TCMDC-132341	42	55	TCMDC-141862	43	75	TCMDC-125388	9	92	TCMDC-138937	99	103
TCMDC-138276	25	27	TCMDC-138463	44	55	TCMDC-134005	43	75	TCMDC-124254	14	92	TCMDC-131612	99	103

TCMDC-124310	26	27	TCMDC-133252	45	55	TCMDC-138431	43	75	TCMDC-132458	15	92	TCMDC-131585	99	103
TCMDC-124016	26	27	TCMDC-141089	45	55	TCMDC-136983	43	75	TCMDC-133945	15	92	TCMDC-131346	99	103
TCMDC-132081	26	27	TCMDC-132902	46	55	TCMDC-132760	44	75	TCMDC-134835	16	92	TCMDC-125513	99	103
TCMDC-125087	27	27	TCMDC-135949	46	55	TCMDC-135987	44	75	TCMDC-142281	18	92	TCMDC-131627	99	103
TCMDC-138233	27	27	TCMDC-141134	47	55	TCMDC-136859	45	75	TCMDC-142141	19	92	TCMDC-125337	100	103
TCMDC-139725	2	28	TCMDC-139682	51	55	TCMDC-134657	45	75	TCMDC-139293	19	92	TCMDC-140418	100	103
TCMDC-139757	2	28	TCMDC-133065	52	55	TCMDC-125686	45	75	TCMDC-133350	20	92	TCMDC-125390	100	103
TCMDC-139678	3	28	TCMDC-124728	54	55	TCMDC-135628	46	75	TCMDC-133392	20	92	TCMDC-142313	100	103
TCMDC-137796	3	28	TCMDC-141390	55	55	TCMDC-139401	46	75	TCMDC-124564	22	92	TCMDC-136158	100	103
TCMDC-136461	3	28	TCMDC-123962	55	55	TCMDC-135258	48	75	TCMDC-141930	22	92	TCMDC-135271	100	103
TCMDC-140558	4	28	TCMDC-142023	57	55	TCMDC-138011	48	75	TCMDC-137141	22	92	TCMDC-131906	100	103
TCMDC-136289	4	28	TCMDC-139996	0	56	TCMDC-138183	49	75	TCMDC-136764	23	92	TCMDC-131333	100	103
TCMDC-135408	4	28	TCMDC-125653	1	56	TCMDC-133643	50	75	TCMDC-141825	24	92	TCMDC-131311	100	103
TCMDC-140978	4	28	TCMDC-138211	2	56	TCMDC-133861	51	75	TCMDC-138272	27	92	TCMDC-131337	100	103
TCMDC-132267	4	28	TCMDC-123595	4	56	TCMDC-137730	51	75	TCMDC-134239	27	92	TCMDC-125535	100	103
TCMDC-132912	4	28	TCMDC-142084	5	56	TCMDC-132209	52	75	TCMDC-125616	27	92	TCMDC-125845	100	103
TCMDC-135301	5	28	TCMDC-138894	5	56	TCMDC-124615	52	75	TCMDC-124898	27	92	TCMDC-133628	100	103
TCMDC-125711	6	28	TCMDC-140004	6	56	TCMDC-132179	52	75	TCMDC-141829	28	92	TCMDC-125006	100	103
TCMDC-134394	6	28	TCMDC-139017	6	56	TCMDC-138882	54	75	TCMDC-140047	34	92	TCMDC-125064	101	103
TCMDC-133909	6	28	TCMDC-139807	6	56	TCMDC-132716	54	75	TCMDC-135708	35	92	TCMDC-136507	101	103
TCMDC-140109	6	28	TCMDC-139524	7	56	TCMDC-132852	55	75	TCMDC-135710	35	92	TCMDC-134605	101	103
TCMDC-141248	7	28	TCMDC-134441	8	56	TCMDC-132397	57	75	TCMDC-142307	35	92	TCMDC-125294	101	103
TCMDC-140855	7	28	TCMDC-142181	8	56	TCMDC-136257	58	75	TCMDC-133914	35	92	TCMDC-133966	101	103
TCMDC-138852	8	28	TCMDC-141059	8	56	TCMDC-139973	58	75	TCMDC-136108	36	92	TCMDC-124391	101	103
TCMDC-140640	8	28	TCMDC-141720	9	56	TCMDC-135516	59	75	TCMDC-136331	36	92	TCMDC-136661	101	103
TCMDC-133888	8	28	TCMDC-141944	9	56	TCMDC-132252	59	75	TCMDC-136314	37	92	TCMDC-138943	101	103
TCMDC-141053	8	28	TCMDC-138706	9	56	TCMDC-124565	60	75	TCMDC-132807	38	92	TCMDC-135555	101	103
TCMDC-136696	8	28	TCMDC-139327	11	56	TCMDC-125559	61	75	TCMDC-125302	39	92	TCMDC-123948	101	103
TCMDC-132478	9	28	TCMDC-139885	11	56	TCMDC-133925	65	75	TCMDC-134858	40	92	TCMDC-132095	101	103
TCMDC-124073	9	28	TCMDC-141751	11	56	TCMDC-141858	66	75	TCMDC-135177	40	92	TCMDC-135599	101	103
TCMDC-139099	9	28	TCMDC-134425	11	56	TCMDC-137494	66	75	TCMDC-140457	40	92	TCMDC-131742	101	103
TCMDC-139156	9	28	TCMDC-132558	11	56	TCMDC-124408	69	75	TCMDC-134614	40	92	TCMDC-123882	101	103
TCMDC-140948	9	28	TCMDC-139853	11	56	TCMDC-123660	69	75	TCMDC-139105	41	92	TCMDC-132002	101	103
TCMDC-137460	9	28	TCMDC-134043	12	56	TCMDC-140778	70	75	TCMDC-124297	42	92	TCMDC-125669	101	103
TCMDC-137769	10	28	TCMDC-139182	12	56	TCMDC-134060	71	75	TCMDC-125031	44	92	TCMDC-133267	101	103
TCMDC-133850	11	28	TCMDC-136552	12	56	TCMDC-142191	71	75	TCMDC-136745	44	92	TCMDC-138509	101	103
TCMDC-136916	12	28	TCMDC-139199	13	56	TCMDC-124919	72	75	TCMDC-124215	44	92	TCMDC-124386	102	103

TCMDC-141954	12	28	TCMDC-138604	13	56	TCMDC-124891	72	75	TCMDC-140765	45	92	TCMDC-124816	102	103
TCMDC-132615	12	28	TCMDC-134372	13	56	TCMDC-132401	72	75	TCMDC-135984	45	92	TCMDC-125313	102	103
TCMDC-140991	13	28	TCMDC-138672	13	56	TCMDC-133609	72	75	TCMDC-142053	46	92	TCMDC-136162	102	103
TCMDC-135922	13	28	TCMDC-134887	13	56	TCMDC-135181	72	75	TCMDC-137105	46	92	TCMDC-123841	102	103
TCMDC-135923	13	28	TCMDC-125283	14	56	TCMDC-123997	73	75	TCMDC-131889	46	92	TCMDC-137284	102	103
TCMDC-139302	14	28	TCMDC-141251	15	56	TCMDC-123810	75	75	TCMDC-136598	46	92	TCMDC-138792	102	103
TCMDC-142263	14	28	TCMDC-134597	15	56	TCMDC-141007	75	75	TCMDC-132150	48	92	TCMDC-138608	102	103
TCMDC-141758	14	28	TCMDC-138989	15	56	TCMDC-136671	75	75	TCMDC-134823	48	92	TCMDC-140144	102	103
TCMDC-135802	14	28	TCMDC-141013	15	56	TCMDC-139761	4	76	TCMDC-132707	48	92	TCMDC-125724	102	103
TCMDC-141040	15	28	TCMDC-132103	15	56	TCMDC-134164	9	76	TCMDC-136847	48	92	TCMDC-125569	102	103
TCMDC-137321	15	28	TCMDC-139400	16	56	TCMDC-139582	12	76	TCMDC-138273	48	92	TCMDC-138777	102	103
TCMDC-124458	15	28	TCMDC-134906	16	56	TCMDC-142338	12	76	TCMDC-138249	49	92	TCMDC-139148	102	103
TCMDC-139827	15	28	TCMDC-124463	17	56	TCMDC-138636	13	76	TCMDC-133725	49	92	TCMDC-138811	103	103
TCMDC-136810	15	28	TCMDC-140275	17	56	TCMDC-135945	14	76	TCMDC-136491	51	92	TCMDC-138928	103	103
TCMDC-140884	16	28	TCMDC-137139	17	56	TCMDC-141184	15	76	TCMDC-141951	52	92	TCMDC-135798	103	103
TCMDC-138534	16	28	TCMDC-134505	18	56	TCMDC-132174	15	76	TCMDC-137561	52	92	TCMDC-135368	103	103
TCMDC-135184	16	28	TCMDC-138122	18	56	TCMDC-134067	15	76	TCMDC-139195	52	92	TCMDC-133607	103	103
TCMDC-135195	16	28	TCMDC-136352	18	56	TCMDC-138360	15	76	TCMDC-132679	52	92	TCMDC-135658	103	103
TCMDC-140833	17	28	TCMDC-142333	19	56	TCMDC-141006	15	76	TCMDC-139428	53	92	TCMDC-125715	103	103
TCMDC-124165	17	28	TCMDC-135055	19	56	TCMDC-137217	16	76	TCMDC-136284	53	92	TCMDC-137926	103	103
TCMDC-131522	18	28	TCMDC-132024	19	56	TCMDC-139532	17	76	TCMDC-139321	53	92	TCMDC-135603	105	103
TCMDC-125168	18	28	TCMDC-135337	20	56	TCMDC-123521	17	76	TCMDC-138542	53	92	TCMDC-141497	19	104
TCMDC-123628	18	28	TCMDC-132333	20	56	TCMDC-141210	18	76	TCMDC-124195	53	92	TCMDC-141823	25	104
TCMDC-125012	19	28	TCMDC-124958	21	56	TCMDC-139580	18	76	TCMDC-136572	54	92	TCMDC-133188	27	104
TCMDC-138939	19	28	TCMDC-142240	21	56	TCMDC-134860	18	76	TCMDC-123982	55	92	TCMDC-125242	32	104
TCMDC-125635	19	28	TCMDC-139993	21	56	TCMDC-140846	19	76	TCMDC-137191	55	92	TCMDC-131328	34	104
TCMDC-136028	19	28	TCMDC-132818	21	56	TCMDC-134766	20	76	TCMDC-134620	55	92	TCMDC-140500	39	104
TCMDC-138855	19	28	TCMDC-135352	21	56	TCMDC-138311	20	76	TCMDC-133075	56	92	TCMDC-134459	46	104
TCMDC-131462	19	28	TCMDC-135362	21	56	TCMDC-136462	20	76	TCMDC-142069	57	92	TCMDC-135824	47	104
TCMDC-131520	19	28	TCMDC-132050	21	56	TCMDC-136660	20	76	TCMDC-138561	57	92	TCMDC-133439	47	104
TCMDC-131435	19	28	TCMDC-135442	22	56	TCMDC-134426	21	76	TCMDC-140485	58	92	TCMDC-137067	47	104
TCMDC-125547	19	28	TCMDC-132553	22	56	TCMDC-139765	21	76	TCMDC-138770	58	92	TCMDC-132116	48	104
TCMDC-141679	19	28	TCMDC-136641	22	56	TCMDC-134476	21	76	TCMDC-132149	58	92	TCMDC-123902	48	104
TCMDC-137606	20	28	TCMDC-140959	22	56	TCMDC-125640	21	76	TCMDC-135934	59	92	TCMDC-124926	53	104
TCMDC-125479	20	28	TCMDC-132826	23	56	TCMDC-140885	21	76	TCMDC-132129	59	92	TCMDC-133089	55	104
TCMDC-135627	21	28	TCMDC-141493	23	56	TCMDC-139905	21	76	TCMDC-125783	60	92	TCMDC-140425	60	104
TCMDC-131433	21	28	TCMDC-140540	24	56	TCMDC-141902	22	76	TCMDC-139035	60	92	TCMDC-136776	61	104

TCMDC-131484	21	28	TCMDC-138462	24	56	TCMDC-123616	23	76	TCMDC-124873	60	92	TCMDC-123494	61	104
TCMDC-140868	22	28	TCMDC-124163	24	56	TCMDC-136839	23	76	TCMDC-125280	60	92	TCMDC-133999	62	104
TCMDC-140865	22	28	TCMDC-135313	25	56	TCMDC-137512	24	76	TCMDC-135454	60	92	TCMDC-135833	63	104
TCMDC-132175	23	28	TCMDC-134226	25	56	TCMDC-134712	25	76	TCMDC-140218	61	92	TCMDC-124110	64	104
TCMDC-142229	23	28	TCMDC-132991	25	56	TCMDC-136434	25	76	TCMDC-136249	61	92	TCMDC-131710	65	104
TCMDC-136358	23	28	TCMDC-134778	25	56	TCMDC-136354	26	76	TCMDC-137262	62	92	TCMDC-141868	65	104
TCMDC-140870	23	28	TCMDC-133991	25	56	TCMDC-134145	27	76	TCMDC-131938	62	92	TCMDC-135701	66	104
TCMDC-140859	23	28	TCMDC-132729	25	56	TCMDC-140341	27	76	TCMDC-123764	62	92	TCMDC-133170	67	104
TCMDC-124066	23	28	TCMDC-141625	26	56	TCMDC-140185	27	76	TCMDC-136489	62	92	TCMDC-135793	67	104
TCMDC-142254	24	28	TCMDC-141331	26	56	TCMDC-141903	27	76	TCMDC-134959	63	92	TCMDC-135019	68	104
TCMDC-142318	24	28	TCMDC-137252	26	56	TCMDC-134954	27	76	TCMDC-136095	63	92	TCMDC-138043	68	104
TCMDC-124457	25	28	TCMDC-137010	27	56	TCMDC-137829	27	76	TCMDC-133703	64	92	TCMDC-133952	69	104
TCMDC-141335	25	28	TCMDC-138309	27	56	TCMDC-131351	28	76	TCMDC-124556	64	92	TCMDC-141843	71	104
TCMDC-125510	26	28	TCMDC-132643	28	56	TCMDC-133680	28	76	TCMDC-133696	65	92	TCMDC-140140	72	104
TCMDC-123975	26	28	TCMDC-132933	28	56	TCMDC-136241	28	76	TCMDC-140685	65	92	TCMDC-141847	73	104
TCMDC-134189	26	28	TCMDC-124246	28	56	TCMDC-141002	28	76	TCMDC-135006	65	92	TCMDC-141844	73	104
TCMDC-141374	27	28	TCMDC-138170	28	56	TCMDC-138669	29	76	TCMDC-133251	65	92	TCMDC-134705	73	104
TCMDC-139236	27	28	TCMDC-140714	29	56	TCMDC-132200	30	76	TCMDC-131391	66	92	TCMDC-137093	73	104
TCMDC-140303	27	28	TCMDC-136974	29	56	TCMDC-133475	30	76	TCMDC-124069	67	92	TCMDC-137060	74	104
TCMDC-133196	28	28	TCMDC-133512	30	56	TCMDC-141911	30	76	TCMDC-124157	68	92	TCMDC-138547	75	104
TCMDC-133868	2	29	TCMDC-136144	31	56	TCMDC-132500	31	76	TCMDC-132161	68	92	TCMDC-136336	76	104
TCMDC-137791	2	29	TCMDC-133522	32	56	TCMDC-139258	32	76	TCMDC-142269	68	92	TCMDC-125434	76	104
TCMDC-138548	3	29	TCMDC-135064	32	56	TCMDC-132808	32	76	TCMDC-134014	69	92	TCMDC-135831	77	104
TCMDC-125037	4	29	TCMDC-141110	32	56	TCMDC-140724	32	76	TCMDC-134978	69	92	TCMDC-142157	77	104
TCMDC-125882	5	29	TCMDC-136226	33	56	TCMDC-139886	32	76	TCMDC-135297	69	92	TCMDC-123531	79	104
TCMDC-123608	5	29	TCMDC-134080	33	56	TCMDC-134678	32	76	TCMDC-132597	70	92	TCMDC-136505	79	104
TCMDC-139875	6	29	TCMDC-139971	34	56	TCMDC-138993	32	76	TCMDC-136493	70	92	TCMDC-142231	81	104
TCMDC-140611	6	29	TCMDC-132749	34	56	TCMDC-140286	32	76	TCMDC-135310	70	92	TCMDC-140147	81	104
TCMDC-133554	6	29	TCMDC-132642	35	56	TCMDC-140282	33	76	TCMDC-125423	71	92	TCMDC-135608	82	104
TCMDC-135505	6	29	TCMDC-142006	35	56	TCMDC-139365	33	76	TCMDC-132192	71	92	TCMDC-133096	83	104
TCMDC-138944	6	29	TCMDC-132674	36	56	TCMDC-134734	33	76	TCMDC-132165	71	92	TCMDC-132581	83	104
TCMDC-140583	6	29	TCMDC-133541	36	56	TCMDC-140674	33	76	TCMDC-125817	71	92	TCMDC-137219	83	104
TCMDC-131855	6	29	TCMDC-124584	36	56	TCMDC-141927	34	76	TCMDC-139193	71	92	TCMDC-125545	83	104
TCMDC-142252	7	29	TCMDC-139248	36	56	TCMDC-134104	34	76	TCMDC-124423	72	92	TCMDC-132799	83	104
TCMDC-139651	7	29	TCMDC-133525	37	56	TCMDC-134730	35	76	TCMDC-125025	72	92	TCMDC-137918	84	104
TCMDC-132888	8	29	TCMDC-134415	38	56	TCMDC-134740	35	76	TCMDC-133165	72	92	TCMDC-135235	84	104
TCMDC-134375	8	29	TCMDC-139242	38	56	TCMDC-141558	35	76	TCMDC-134975	73	92	TCMDC-141853	85	104

TCMDC-136827	8	29	TCMDC-132347	38	56	TCMDC-135359	35	76	TCMDC-137048	74	92	TCMDC-139243	85	104
TCMDC-135122	9	29	TCMDC-141288	39	56	TCMDC-132357	35	76	TCMDC-131344	74	92	TCMDC-136330	85	104
TCMDC-140489	9	29	TCMDC-139632	40	56	TCMDC-134483	36	76	TCMDC-138726	74	92	TCMDC-125326	86	104
TCMDC-136244	9	29	TCMDC-132343	40	56	TCMDC-141739	36	76	TCMDC-125637	74	92	TCMDC-141857	87	104
TCMDC-123993	9	29	TCMDC-132391	40	56	TCMDC-124643	37	76	TCMDC-131773	75	92	TCMDC-141837	87	104
TCMDC-137061	9	29	TCMDC-140172	41	56	TCMDC-125097	37	76	TCMDC-131772	75	92	TCMDC-123854	87	104
TCMDC-138739	10	29	TCMDC-142137	41	56	TCMDC-133315	37	76	TCMDC-140145	76	92	TCMDC-137029	87	104
TCMDC-135924	11	29	TCMDC-124742	41	56	TCMDC-138469	37	76	TCMDC-138888	77	92	TCMDC-124392	88	104
TCMDC-141257	11	29	TCMDC-132632	41	56	TCMDC-133686	38	76	TCMDC-124213	77	92	TCMDC-123888	88	104
TCMDC-132221	11	29	TCMDC-134733	42	56	TCMDC-134762	39	76	TCMDC-135662	77	92	TCMDC-138026	88	104
TCMDC-135327	12	29	TCMDC-139008	42	56	TCMDC-136079	39	76	TCMDC-140916	77	92	TCMDC-137715	89	104
TCMDC-134374	12	29	TCMDC-142097	44	56	TCMDC-134761	39	76	TCMDC-138995	77	92	TCMDC-138000	90	104
TCMDC-132084	12	29	TCMDC-141103	45	56	TCMDC-138262	39	76	TCMDC-131686	77	92	TCMDC-135607	90	104
TCMDC-132275	12	29	TCMDC-136945	46	56	TCMDC-133671	40	76	TCMDC-136752	78	92	TCMDC-138141	90	104
TCMDC-134075	14	29	TCMDC-138899	49	56	TCMDC-141448	40	76	TCMDC-124937	78	92	TCMDC-125834	91	104
TCMDC-140993	14	29	TCMDC-132577	52	56	TCMDC-133032	40	76	TCMDC-125070	78	92	TCMDC-123655	91	104
TCMDC-125167	14	29	TCMDC-141000	53	56	TCMDC-136146	41	76	TCMDC-124845	80	92	TCMDC-133592	91	104
TCMDC-124765	15	29	TCMDC-125764	53	56	TCMDC-141935	41	76	TCMDC-125418	81	92	TCMDC-124185	91	104
TCMDC-140498	15	29	TCMDC-140031	53	56	TCMDC-133460	41	76	TCMDC-131973	81	92	TCMDC-136757	91	104
TCMDC-137609	15	29	TCMDC-125231	55	56	TCMDC-135314	42	76	TCMDC-141983	81	92	TCMDC-134602	92	104
TCMDC-136206	15	29	TCMDC-133658	55	56	TCMDC-131236	42	76	TCMDC-123604	81	92	TCMDC-135215	92	104
TCMDC-133881	15	29	TCMDC-135660	56	56	TCMDC-137220	42	76	TCMDC-135077	81	92	TCMDC-125560	92	104
TCMDC-124587	16	29	TCMDC-139839	2	57	TCMDC-140354	42	76	TCMDC-136849	81	92	TCMDC-133223	92	104
TCMDC-140381	16	29	TCMDC-140200	3	57	TCMDC-138782	42	76	TCMDC-139290	82	92	TCMDC-138383	92	104
TCMDC-124412	17	29	TCMDC-139936	4	57	TCMDC-131271	42	76	TCMDC-124936	82	92	TCMDC-135239	92	104
TCMDC-141042	17	29	TCMDC-137614	4	57	TCMDC-134258	43	76	TCMDC-136863	82	92	TCMDC-124501	92	104
TCMDC-134119	17	29	TCMDC-139670	5	57	TCMDC-141014	44	76	TCMDC-125461	83	92	TCMDC-135010	92	104
TCMDC-137994	18	29	TCMDC-135414	6	57	TCMDC-138651	45	76	TCMDC-135007	83	92	TCMDC-135591	93	104
TCMDC-123518	19	29	TCMDC-133489	7	57	TCMDC-135143	45	76	TCMDC-123614	84	92	TCMDC-123862	93	104
TCMDC-134536	19	29	TCMDC-132363	7	57	TCMDC-139964	45	76	TCMDC-123788	85	92	TCMDC-125712	93	104
TCMDC-131903	19	29	TCMDC-134285	7	57	TCMDC-135116	46	76	TCMDC-132733	85	92	TCMDC-125134	94	104
TCMDC-124448	20	29	TCMDC-138751	8	57	TCMDC-131955	46	76	TCMDC-137634	85	92	TCMDC-133724	94	104
TCMDC-132085	20	29	TCMDC-141638	8	57	TCMDC-134359	47	76	TCMDC-137521	85	92	TCMDC-124326	94	104
TCMDC-140538	20	29	TCMDC-133389	9	57	TCMDC-125676	48	76	TCMDC-135543	85	92	TCMDC-125453	94	104
TCMDC-140301	21	29	TCMDC-139961	9	57	TCMDC-134731	48	76	TCMDC-140881	85	92	TCMDC-140907	94	104
TCMDC-138885	21	29	TCMDC-131964	9	57	TCMDC-138618	49	76	TCMDC-133273	86	92	TCMDC-133557	94	104
TCMDC-131432	22	29	TCMDC-124610	10	57	TCMDC-132404	50	76	TCMDC-141421	86	92	TCMDC-133242	94	104

TCMDC-140328	22	29	TCMDC-138737	10	57	TCMDC-134534	50	76	TCMDC-139029	86	92	TCMDC-123656	94	104
TCMDC-141035	23	29	TCMDC-137782	10	57	TCMDC-137047	52	76	TCMDC-123618	86	92	TCMDC-136907	94	104
TCMDC-123626	24	29	TCMDC-131478	10	57	TCMDC-141670	53	76	TCMDC-124932	86	92	TCMDC-125526	94	104
TCMDC-125678	24	29	TCMDC-132365	10	57	TCMDC-134339	56	76	TCMDC-133173	86	92	TCMDC-132035	94	104
TCMDC-124203	24	29	TCMDC-138925	11	57	TCMDC-137594	56	76	TCMDC-137696	86	92	TCMDC-124874	95	104
TCMDC-138586	24	29	TCMDC-137611	11	57	TCMDC-139260	57	76	TCMDC-134508	86	92	TCMDC-123890	95	104
TCMDC-140243	24	29	TCMDC-139634	11	57	TCMDC-134988	59	76	TCMDC-138110	87	92	TCMDC-123926	95	104
TCMDC-140869	24	29	TCMDC-134902	13	57	TCMDC-135455	59	76	TCMDC-124301	87	92	TCMDC-124346	95	104
TCMDC-134098	25	29	TCMDC-139328	13	57	TCMDC-135004	61	76	TCMDC-140924	87	92	TCMDC-141238	95	104
TCMDC-125638	25	29	TCMDC-134269	15	57	TCMDC-131883	62	76	TCMDC-137249	87	92	TCMDC-137128	95	104
TCMDC-137595	25	29	TCMDC-138052	15	57	TCMDC-124853	63	76	TCMDC-133271	87	92	TCMDC-137293	95	104
TCMDC-134266	27	29	TCMDC-124058	15	57	TCMDC-131921	64	76	TCMDC-125750	87	92	TCMDC-136319	96	104
TCMDC-138027	27	29	TCMDC-125116	16	57	TCMDC-140032	64	76	TCMDC-137702	87	92	TCMDC-124496	96	104
TCMDC-131998	28	29	TCMDC-139066	16	57	TCMDC-133299	65	76	TCMDC-137866	87	92	TCMDC-133692	96	104
TCMDC-133425	28	29	TCMDC-134725	16	57	TCMDC-142336	66	76	TCMDC-124662	88	92	TCMDC-124518	96	104
TCMDC-135282	3	30	TCMDC-141117	16	57	TCMDC-142028	68	76	TCMDC-125811	88	92	TCMDC-123946	96	104
TCMDC-136711	3	30	TCMDC-141265	17	57	TCMDC-134025	68	76	TCMDC-124435	89	92	TCMDC-133595	96	104
TCMDC-137827	3	30	TCMDC-141436	17	57	TCMDC-139498	69	76	TCMDC-137050	89	92	TCMDC-125674	96	104
TCMDC-139653	3	30	TCMDC-124639	17	57	TCMDC-135097	69	76	TCMDC-131652	89	92	TCMDC-125433	96	104
TCMDC-137825	3	30	TCMDC-137592	17	57	TCMDC-124959	71	76	TCMDC-125324	89	92	TCMDC-124865	96	104
TCMDC-133229	4	30	TCMDC-140880	17	57	TCMDC-123744	73	76	TCMDC-133187	89	92	TCMDC-125121	96	104
TCMDC-138626	4	30	TCMDC-132417	17	57	TCMDC-135476	74	76	TCMDC-124244	89	92	TCMDC-125149	97	104
TCMDC-137975	4	30	TCMDC-139985	18	57	TCMDC-133927	74	76	TCMDC-136867	89	92	TCMDC-123601	97	104
TCMDC-137731	5	30	TCMDC-132959	18	57	TCMDC-140443	75	76	TCMDC-137041	89	92	TCMDC-139039	97	104
TCMDC-124344	5	30	TCMDC-135029	18	57	TCMDC-140426	75	76	TCMDC-138640	90	92	TCMDC-133802	97	104
TCMDC-141047	5	30	TCMDC-141179	18	57	TCMDC-132903	75	76	TCMDC-125181	90	92	TCMDC-131577	97	104
TCMDC-133718	5	30	TCMDC-132622	18	57	TCMDC-140318	75	76	TCMDC-141970	90	92	TCMDC-137332	97	104
TCMDC-141339	5	30	TCMDC-125063	19	57	TCMDC-136840	76	76	TCMDC-137003	90	92	TCMDC-137408	97	104
TCMDC-141450	5	30	TCMDC-139234	19	57	TCMDC-138897	76	76	TCMDC-123603	90	92	TCMDC-124996	97	104
TCMDC-141703	5	30	TCMDC-132776	19	57	TCMDC-139882	76	76	TCMDC-124345	90	92	TCMDC-131732	98	104
TCMDC-140585	6	30	TCMDC-140352	19	57	TCMDC-132904	76	76	TCMDC-125737	90	92	TCMDC-138877	98	104
TCMDC-136072	6	30	TCMDC-132518	19	57	TCMDC-134203	76	76	TCMDC-123563	90	92	TCMDC-131785	98	104
TCMDC-139635	6	30	TCMDC-132527	20	57	TCMDC-133076	76	76	TCMDC-138169	90	92	TCMDC-131677	98	104
TCMDC-140612	6	30	TCMDC-134124	20	57	TCMDC-137184	76	76	TCMDC-135484	91	92	TCMDC-131745	98	104
TCMDC-138603	6	30	TCMDC-139355	21	57	TCMDC-135056	5	77	TCMDC-124298	91	92	TCMDC-123945	98	104
TCMDC-141050	6	30	TCMDC-141360	22	57	TCMDC-140707	5	77	TCMDC-135418	91	92	TCMDC-131680	98	104
TCMDC-131822	6	30	TCMDC-125271	22	57	TCMDC-134377	9	77	TCMDC-124398	91	92	TCMDC-137531	98	104

TCMDC-137833	6	30	TCMDC-132280	23	57	TCMDC-123772	9	77	TCMDC-135081	91	92	TCMDC-124365	98	104
TCMDC-133443	6	30	TCMDC-141618	23	57	TCMDC-139917	10	77	TCMDC-132393	91	92	TCMDC-125808	98	104
TCMDC-141984	7	30	TCMDC-134806	23	57	TCMDC-132383	11	77	TCMDC-131576	91	92	TCMDC-135254	98	104
TCMDC-139204	7	30	TCMDC-136549	23	57	TCMDC-136896	12	77	TCMDC-124086	91	92	TCMDC-134057	98	104
TCMDC-141554	7	30	TCMDC-138278	25	57	TCMDC-133520	12	77	TCMDC-133465	91	92	TCMDC-134996	98	104
TCMDC-140625	7	30	TCMDC-134625	25	57	TCMDC-138132	14	77	TCMDC-135852	91	92	TCMDC-135005	98	104
TCMDC-132292	7	30	TCMDC-139162	26	57	TCMDC-139714	15	77	TCMDC-137711	91	92	TCMDC-125003	98	104
TCMDC-141357	7	30	TCMDC-135765	26	57	TCMDC-141441	15	77	TCMDC-137974	91	92	TCMDC-125723	98	104
TCMDC-138847	7	30	TCMDC-124340	27	57	TCMDC-139530	16	77	TCMDC-131709	91	92	TCMDC-131761	98	104
TCMDC-134322	7	30	TCMDC-140770	27	57	TCMDC-125078	16	77	TCMDC-137538	91	92	TCMDC-135087	99	104
TCMDC-140638	8	30	TCMDC-132638	28	57	TCMDC-136477	16	77	TCMDC-140422	92	92	TCMDC-123724	99	104
TCMDC-134387	8	30	TCMDC-140263	28	57	TCMDC-142282	17	77	TCMDC-133149	92	92	TCMDC-131307	99	104
TCMDC-137915	8	30	TCMDC-124119	28	57	TCMDC-139576	17	77	TCMDC-132791	92	92	TCMDC-131668	99	104
TCMDC-140676	8	30	TCMDC-140878	29	57	TCMDC-136947	18	77	TCMDC-132788	92	92	TCMDC-137498	99	104
TCMDC-135649	8	30	TCMDC-133413	29	57	TCMDC-140838	19	77	TCMDC-137076	92	92	TCMDC-125460	99	104
TCMDC-134688	9	30	TCMDC-141232	29	57	TCMDC-139712	19	77	TCMDC-131640	92	92	TCMDC-141404	99	104
TCMDC-134376	9	30	TCMDC-133405	29	57	TCMDC-139705	20	77	TCMDC-124953	92	92	TCMDC-140429	100	104
TCMDC-132217	9	30	TCMDC-141200	30	57	TCMDC-134423	20	77	TCMDC-136381	92	92	TCMDC-134985	100	104
TCMDC-140956	10	30	TCMDC-140183	30	57	TCMDC-133312	20	77	TCMDC-138779	92	92	TCMDC-124403	100	104
TCMDC-135866	11	30	TCMDC-132911	31	57	TCMDC-141809	22	77	TCMDC-141447	92	92	TCMDC-135926	100	104
TCMDC-140091	11	30	TCMDC-135315	31	57	TCMDC-125689	22	77	TCMDC-124809	92	92	TCMDC-138994	100	104
TCMDC-132407	11	30	TCMDC-133013	31	57	TCMDC-139388	23	77	TCMDC-124935	92	92	TCMDC-131618	100	104
TCMDC-140476	11	30	TCMDC-138283	32	57	TCMDC-141115	23	77	TCMDC-124296	92	92	TCMDC-123470	100	104
TCMDC-138828	12	30	TCMDC-141083	32	57	TCMDC-141486	24	77	TCMDC-138071	92	92	TCMDC-142342	100	104
TCMDC-137515	13	30	TCMDC-134706	32	57	TCMDC-132754	24	77	TCMDC-125824	92	92	TCMDC-131598	100	104
TCMDC-124767	13	30	TCMDC-133105	33	57	TCMDC-139208	24	77	TCMDC-125839	92	92	TCMDC-135256	101	104
TCMDC-141785	13	30	TCMDC-141471	33	57	TCMDC-133518	24	77	TCMDC-125155	93	92	TCMDC-132139	101	104
TCMDC-132276	14	30	TCMDC-131826	33	57	TCMDC-138465	24	77	TCMDC-140764	6	93	TCMDC-133049	101	104
TCMDC-138455	15	30	TCMDC-140151	34	57	TCMDC-140893	24	77	TCMDC-141491	13	93	TCMDC-138016	101	104
TCMDC-123499	15	30	TCMDC-140930	34	57	TCMDC-139596	25	77	TCMDC-139520	13	93	TCMDC-123546	101	104
TCMDC-138873	16	30	TCMDC-134795	35	57	TCMDC-138163	26	77	TCMDC-134616	13	93	TCMDC-125523	101	104
TCMDC-132584	16	30	TCMDC-141299	36	57	TCMDC-139399	26	77	TCMDC-131895	14	93	TCMDC-131597	101	104
TCMDC-124746	16	30	TCMDC-136581	36	57	TCMDC-140008	27	77	TCMDC-136317	21	93	TCMDC-131791	101	104
TCMDC-136230	16	30	TCMDC-135127	36	57	TCMDC-139856	27	77	TCMDC-140800	21	93	TCMDC-138025	101	104
TCMDC-141772	16	30	TCMDC-133107	37	57	TCMDC-139675	27	77	TCMDC-141522	26	93	TCMDC-133833	101	104
TCMDC-125095	17	30	TCMDC-141001	38	57	TCMDC-134195	28	77	TCMDC-125831	27	93	TCMDC-137557	102	104
TCMDC-131350	18	30	TCMDC-133748	38	57	TCMDC-133805	29	77	TCMDC-124543	30	93	TCMDC-125378	102	104

TCMDC-125082	19	30	TCMDC-124826	39	57	TCMDC-125885	30	77	TCMDC-138996	30	93	TCMDC-125138	102	104
TCMDC-138001	19	30	TCMDC-141263	39	57	TCMDC-138137	32	77	TCMDC-124807	34	93	TCMDC-133359	102	104
TCMDC-131400	19	30	TCMDC-131237	39	57	TCMDC-123722	33	77	TCMDC-139354	35	93	TCMDC-137971	102	104
TCMDC-131438	19	30	TCMDC-132628	40	57	TCMDC-138655	33	77	TCMDC-133978	36	93	TCMDC-125218	102	104
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TCMDC-141170	19	30	TCMDC-136463	40	57	TCMDC-141972	34	77	TCMDC-134084	37	93	TCMDC-135065	103	104
TCMDC-140917	20	30	TCMDC-140652	41	57	TCMDC-141958	35	77	TCMDC-131254	39	93	TCMDC-125325	103	104
TCMDC-134107	20	30	TCMDC-141885	41	57	TCMDC-141212	35	77	TCMDC-125598	39	93	TCMDC-137374	103	104
TCMDC-141036	20	30	TCMDC-133129	43	57	TCMDC-142046	36	77	TCMDC-135700	40	93	TCMDC-125077	103	104
TCMDC-138564	23	30	TCMDC-139093	43	57	TCMDC-138747	36	77	TCMDC-135053	41	93	TCMDC-141237	103	104
TCMDC-136238	23	30	TCMDC-124971	44	57	TCMDC-135375	37	77	TCMDC-135668	41	93	TCMDC-140033	103	104
TCMDC-125607	25	30	TCMDC-138662	45	57	TCMDC-137800	37	77	TCMDC-136894	41	93	TCMDC-131954	103	104
TCMDC-136276	25	30	TCMDC-142174	47	57	TCMDC-137856	38	77	TCMDC-137739	42	93	TCMDC-138046	103	104
TCMDC-136035	25	30	TCMDC-136580	47	57	TCMDC-136117	38	77	TCMDC-125043	43	93	TCMDC-138599	103	104
TCMDC-135182	26	30	TCMDC-125602	48	57	TCMDC-124863	38	77	TCMDC-133791	44	93	TCMDC-137416	103	104
TCMDC-125667	26	30	TCMDC-142127	53	57	TCMDC-134083	38	77	TCMDC-134215	44	93	TCMDC-125748	104	104
TCMDC-125503	27	30	TCMDC-138207	55	57	TCMDC-133104	38	77	TCMDC-132488	45	93	TCMDC-124498	104	104
TCMDC-138942	28	30	TCMDC-136631	55	57	TCMDC-140264	38	77	TCMDC-136814	45	93	TCMDC-131583	104	104
TCMDC-138275	28	30	TCMDC-132704	56	57	TCMDC-138850	39	77	TCMDC-135453	45	93	TCMDC-131616	104	104
TCMDC-140879	28	30	TCMDC-140028	56	57	TCMDC-134202	39	77	TCMDC-136127	47	93	TCMDC-123941	104	104
TCMDC-138768	29	30	TCMDC-124500	57	57	TCMDC-136110	40	77	TCMDC-133644	47	93	TCMDC-137303	104	104
TCMDC-142264	30	30	TCMDC-135321	57	57	TCMDC-140933	41	77	TCMDC-136567	47	93	TCMDC-133601	104	104
TCMDC-141581	2	31	TCMDC-137733	57	57	TCMDC-137584	41	77	TCMDC-139989	48	93	TCMDC-135190	104	104
TCMDC-137952	3	31	TCMDC-132743	57	57	TCMDC-134758	42	77	TCMDC-138978	48	93	TCMDC-125751	104	104
TCMDC-132047	4	31	TCMDC-125208	57	57	TCMDC-137928	42	77	TCMDC-137638	49	93	TCMDC-139598	104	104
TCMDC-139844	4	31	TCMDC-125407	63	57	TCMDC-135490	42	77	TCMDC-133645	49	93	TCMDC-136770	104	104
TCMDC-137837	4	31	TCMDC-132816	2	58	TCMDC-125691	43	77	TCMDC-133356	49	93	TCMDC-134039	106	104
TCMDC-136502	5	31	TCMDC-140984	5	58	TCMDC-132655	43	77	TCMDC-136950	49	93	TCMDC-131298	108	104
TCMDC-140573	5	31	TCMDC-133197	7	58	TCMDC-141205	43	77	TCMDC-135046	49	93	TCMDC-136513	7	105
TCMDC-142048	5	31	TCMDC-137513	7	58	TCMDC-134664	44	77	TCMDC-137510	50	93	TCMDC-125411	30	105
TCMDC-140220	5	31	TCMDC-139593	7	58	TCMDC-135468	44	77	TCMDC-134042	51	93	TCMDC-140023	41	105
TCMDC-136730	5	31	TCMDC-139575	7	58	TCMDC-139557	44	77	TCMDC-136400	51	93	TCMDC-133119	43	105
TCMDC-136479	6	31	TCMDC-139836	7	58	TCMDC-135895	44	77	TCMDC-134241	51	93	TCMDC-134343	48	105
TCMDC-135919	6	31	TCMDC-138914	8	58	TCMDC-131269	44	77	TCMDC-142123	51	93	TCMDC-141841	50	105
TCMDC-138969	6	31	TCMDC-136178	8	58	TCMDC-139117	46	77	TCMDC-125788	52	93	TCMDC-141777	55	105
TCMDC-135168	7	31	TCMDC-139760	9	58	TCMDC-138797	47	77	TCMDC-139326	53	93	TCMDC-139913	55	105
TCMDC-135797	7	31	TCMDC-132522	9	58	TCMDC-123522	47	77	TCMDC-141274	53	93	TCMDC-134652	55	105

TCMDC-134371	7	31	TCMDC-134803	9	58	TCMDC-134732	48	77	TCMDC-133995	54	93	TCMDC-140252	56	105
TCMDC-123957	8	31	TCMDC-132916	9	58	TCMDC-133597	48	77	TCMDC-125443	54	93	TCMDC-135734	57	105
TCMDC-141614	8	31	TCMDC-132056	9	58	TCMDC-141839	49	77	TCMDC-140027	54	93	TCMDC-125440	57	105
TCMDC-140557	8	31	TCMDC-139677	10	58	TCMDC-123580	49	77	TCMDC-141398	54	93	TCMDC-141135	57	105
TCMDC-135025	8	31	TCMDC-135473	11	58	TCMDC-136370	50	77	TCMDC-125877	55	93	TCMDC-139312	58	105
TCMDC-134840	8	31	TCMDC-137576	12	58	TCMDC-142301	50	77	TCMDC-136217	55	93	TCMDC-133845	59	105
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TCMDC-140944	8	31	TCMDC-141458	12	58	TCMDC-131965	52	77	TCMDC-134971	56	93	TCMDC-137057	63	105
TCMDC-142339	8	31	TCMDC-141332	13	58	TCMDC-141922	52	77	TCMDC-142103	56	93	TCMDC-135714	64	105
TCMDC-134506	9	31	TCMDC-139212	13	58	TCMDC-135366	53	77	TCMDC-125370	58	93	TCMDC-133081	66	105
TCMDC-125093	10	31	TCMDC-136639	14	58	TCMDC-141875	55	77	TCMDC-135154	58	93	TCMDC-133088	67	105
TCMDC-135625	10	31	TCMDC-136151	15	58	TCMDC-135974	57	77	TCMDC-139291	60	93	TCMDC-124231	69	105
TCMDC-136478	10	31	TCMDC-140404	15	58	TCMDC-133254	58	77	TCMDC-132685	61	93	TCMDC-140965	69	105
TCMDC-132510	11	31	TCMDC-137799	15	58	TCMDC-142021	58	77	TCMDC-139316	61	93	TCMDC-138114	70	105
TCMDC-134687	11	31	TCMDC-141389	15	58	TCMDC-139673	58	77	TCMDC-134585	62	93	TCMDC-125740	71	105
TCMDC-136053	11	31	TCMDC-124655	16	58	TCMDC-140203	59	77	TCMDC-140454	62	93	TCMDC-141846	72	105
TCMDC-132214	11	31	TCMDC-142332	17	58	TCMDC-136086	60	77	TCMDC-137283	62	93	TCMDC-136837	72	105
TCMDC-134416	12	31	TCMDC-136058	17	58	TCMDC-136834	60	77	TCMDC-138497	62	93	TCMDC-124951	72	105
TCMDC-134063	12	31	TCMDC-138289	17	58	TCMDC-136759	61	77	TCMDC-139478	62	93	TCMDC-125348	73	105
TCMDC-140613	12	31	TCMDC-139481	17	58	TCMDC-133295	61	77	TCMDC-133484	63	93	TCMDC-139479	75	105
TCMDC-132240	13	31	TCMDC-134889	17	58	TCMDC-140057	61	77	TCMDC-133588	64	93	TCMDC-137066	77	105
TCMDC-133891	14	31	TCMDC-134393	18	58	TCMDC-125262	65	77	TCMDC-132908	64	93	TCMDC-142114	78	105
TCMDC-142239	14	31	TCMDC-133944	18	58	TCMDC-135012	67	77	TCMDC-139655	64	93	TCMDC-135141	79	105
TCMDC-138904	14	31	TCMDC-132637	18	58	TCMDC-125017	68	77	TCMDC-134527	64	93	TCMDC-137032	80	105
TCMDC-124621	14	31	TCMDC-134904	18	58	TCMDC-140072	68	77	TCMDC-142221	64	93	TCMDC-136402	80	105
TCMDC-136521	15	31	TCMDC-134881	18	58	TCMDC-139476	68	77	TCMDC-134457	65	93	TCMDC-133762	81	105
TCMDC-140892	15	31	TCMDC-134197	18	58	TCMDC-125402	68	77	TCMDC-132759	65	93	TCMDC-134880	81	105
TCMDC-139250	15	31	TCMDC-135104	19	58	TCMDC-135983	69	77	TCMDC-125422	65	93	TCMDC-124275	81	105
TCMDC-123699	15	31	TCMDC-137085	19	58	TCMDC-135848	70	77	TCMDC-139477	65	93	TCMDC-141852	82	105
TCMDC-138448	16	31	TCMDC-138702	19	58	TCMDC-124711	72	77	TCMDC-135739	65	93	TCMDC-135823	84	105
TCMDC-136312	16	31	TCMDC-138087	19	58	TCMDC-133650	72	77	TCMDC-138146	66	93	TCMDC-131704	84	105
TCMDC-140961	16	31	TCMDC-139237	20	58	TCMDC-132565	72	77	TCMDC-138623	66	93	TCMDC-134319	85	105
TCMDC-138142	16	31	TCMDC-134760	20	58	TCMDC-132954	74	77	TCMDC-138064	66	93	TCMDC-137970	85	105
TCMDC-137167	16	31	TCMDC-135091	20	58	TCMDC-136832	74	77	TCMDC-136969	66	93	TCMDC-135242	86	105
TCMDC-140816	17	31	TCMDC-140048	21	58	TCMDC-138554	74	77	TCMDC-131718	68	93	TCMDC-137393	86	105
TCMDC-123952	17	31	TCMDC-137151	21	58	TCMDC-125843	75	77	TCMDC-133570	69	93	TCMDC-136958	86	105
TCMDC-132234	17	31	TCMDC-132449	22	58	TCMDC-123884	75	77	TCMDC-132176	70	93	TCMDC-138862	87	105

TCMDC-125753	19	31	TCMDC-134009	22	58	TCMDC-134106	76	77	TCMDC-133969	71	93	TCMDC-135427	88	105
TCMDC-131447	19	31	TCMDC-134135	22	58	TCMDC-136669	77	77	TCMDC-138034	72	93	TCMDC-137628	88	105
TCMDC-140661	19	31	TCMDC-132572	23	58	TCMDC-133183	77	77	TCMDC-142121	72	93	TCMDC-138890	89	105
TCMDC-135440	20	31	TCMDC-132550	23	58	TCMDC-137027	77	77	TCMDC-134754	73	93	TCMDC-124604	89	105
TCMDC-131437	21	31	TCMDC-133323	23	58	TCMDC-124125	77	77	TCMDC-136175	73	93	TCMDC-139139	89	105
TCMDC-140049	21	31	TCMDC-138371	23	58	TCMDC-133593	77	77	TCMDC-134309	73	93	TCMDC-133285	90	105
TCMDC-133143	22	31	TCMDC-132891	24	58	TCMDC-134957	77	77	TCMDC-134277	74	93	TCMDC-125769	90	105
TCMDC-124167	22	31	TCMDC-139069	25	58	TCMDC-125792	78	77	TCMDC-136971	75	93	TCMDC-125468	91	105
TCMDC-131443	22	31	TCMDC-131424	25	58	TCMDC-137648	1	78	TCMDC-137647	75	93	TCMDC-124933	91	105
TCMDC-132334	22	31	TCMDC-140748	25	58	TCMDC-139207	9	78	TCMDC-140382	75	93	TCMDC-124642	91	105
TCMDC-140812	22	31	TCMDC-134900	25	58	TCMDC-124042	12	78	TCMDC-139837	76	93	TCMDC-139091	91	105
TCMDC-140163	23	31	TCMDC-124445	26	58	TCMDC-136024	13	78	TCMDC-133602	77	93	TCMDC-125515	91	105
TCMDC-141355	23	31	TCMDC-124410	26	58	TCMDC-125641	13	78	TCMDC-125516	78	93	TCMDC-135947	92	105
TCMDC-133351	24	31	TCMDC-132820	27	58	TCMDC-132369	16	78	TCMDC-137080	79	93	TCMDC-136854	92	105
TCMDC-132350	24	31	TCMDC-132731	27	58	TCMDC-138934	16	78	TCMDC-135850	80	93	TCMDC-140059	92	105
TCMDC-140405	24	31	TCMDC-136066	27	58	TCMDC-139753	17	78	TCMDC-134517	80	93	TCMDC-124452	92	105
TCMDC-141990	24	31	TCMDC-132323	27	58	TCMDC-141147	17	78	TCMDC-139463	81	93	TCMDC-125458	93	105
TCMDC-134668	26	31	TCMDC-132437	28	58	TCMDC-123590	20	78	TCMDC-131942	81	93	TCMDC-135585	93	105
TCMDC-131479	26	31	TCMDC-134777	28	58	TCMDC-124510	20	78	TCMDC-135918	81	93	TCMDC-125368	94	105
TCMDC-124193	26	31	TCMDC-141769	28	58	TCMDC-123934	21	78	TCMDC-139385	81	93	TCMDC-124644	94	105
TCMDC-141805	27	31	TCMDC-135887	28	58	TCMDC-134910	21	78	TCMDC-131776	81	93	TCMDC-132039	94	105
TCMDC-137607	29	31	TCMDC-135150	29	58	TCMDC-133490	22	78	TCMDC-141269	82	93	TCMDC-133155	94	105
TCMDC-141171	3	32	TCMDC-133377	29	58	TCMDC-140312	22	78	TCMDC-125484	82	93	TCMDC-125660	94	105
TCMDC-138730	3	32	TCMDC-136056	31	58	TCMDC-133946	22	78	TCMDC-124052	82	93	TCMDC-131643	94	105
TCMDC-140618	3	32	TCMDC-134117	31	58	TCMDC-142188	23	78	TCMDC-124748	83	93	TCMDC-124037	94	105
TCMDC-136307	3	32	TCMDC-137216	32	58	TCMDC-135827	23	78	TCMDC-139660	83	93	TCMDC-131557	95	105
TCMDC-132459	4	32	TCMDC-139482	33	58	TCMDC-141548	24	78	TCMDC-138709	83	93	TCMDC-137653	95	105
TCMDC-137940	5	32	TCMDC-135458	33	58	TCMDC-136125	24	78	TCMDC-142139	84	93	TCMDC-138785	95	105
TCMDC-140937	5	32	TCMDC-137753	33	58	TCMDC-140179	25	78	TCMDC-124828	84	93	TCMDC-124105	96	105
TCMDC-140621	6	32	TCMDC-141260	33	58	TCMDC-137780	25	78	TCMDC-137297	84	93	TCMDC-135656	96	105
TCMDC-124910	6	32	TCMDC-137058	33	58	TCMDC-134612	26	78	TCMDC-136142	84	93	TCMDC-138595	96	105
TCMDC-123800	6	32	TCMDC-133895	34	58	TCMDC-139375	26	78	TCMDC-141429	84	93	TCMDC-138032	96	105
TCMDC-138474	6	32	TCMDC-132514	34	58	TCMDC-136061	26	78	TCMDC-138841	84	93	TCMDC-125436	96	105
TCMDC-136480	7	32	TCMDC-124226	34	58	TCMDC-140938	26	78	TCMDC-125359	84	93	TCMDC-140250	97	105
TCMDC-132256	7	32	TCMDC-136888	34	58	TCMDC-134335	27	78	TCMDC-138946	84	93	TCMDC-125041	97	105
TCMDC-140597	7	32	TCMDC-137880	35	58	TCMDC-135023	27	78	TCMDC-123534	85	93	TCMDC-123649	97	105
TCMDC-140488	8	32	TCMDC-133506	37	58	TCMDC-140014	28	78	TCMDC-131243	85	93	TCMDC-124089	97	105

TCMDC-132377	8	32	TCMDC-132847	37	58	TCMDC-135556	28	78	TCMDC-133695	85	93	TCMDC-136197	97	105
TCMDC-125700	8	32	TCMDC-136575	37	58	TCMDC-138139	28	78	TCMDC-124467	86	93	TCMDC-124420	97	105
TCMDC-132281	8	32	TCMDC-140702	38	58	TCMDC-133493	29	78	TCMDC-125644	86	93	TCMDC-142040	97	105
TCMDC-140610	9	32	TCMDC-138889	38	58	TCMDC-141621	30	78	TCMDC-124806	86	93	TCMDC-125135	97	105
TCMDC-136482	9	32	TCMDC-141176	39	58	TCMDC-132546	30	78	TCMDC-131880	87	93	TCMDC-124364	97	105
TCMDC-139895	9	32	TCMDC-132302	39	58	TCMDC-134413	30	78	TCMDC-133543	87	93	TCMDC-137348	97	105
TCMDC-133436	9	32	TCMDC-132670	39	58	TCMDC-132136	31	78	TCMDC-125581	87	93	TCMDC-133605	97	105
TCMDC-139197	9	32	TCMDC-140519	40	58	TCMDC-134815	31	78	TCMDC-125060	87	93	TCMDC-125481	97	105
TCMDC-139275	10	32	TCMDC-125557	40	58	TCMDC-133674	32	78	TCMDC-124007	88	93	TCMDC-134728	97	105
TCMDC-141615	10	32	TCMDC-132721	40	58	TCMDC-136647	32	78	TCMDC-131454	88	93	TCMDC-123895	98	105
TCMDC-132613	10	32	TCMDC-139012	41	58	TCMDC-139285	32	78	TCMDC-133761	88	93	TCMDC-124523	98	105
TCMDC-132228	10	32	TCMDC-136743	42	58	TCMDC-135829	32	78	TCMDC-135681	88	93	TCMDC-123739	98	105
TCMDC-135480	11	32	TCMDC-125201	43	58	TCMDC-132112	32	78	TCMDC-125183	88	93	TCMDC-125120	98	105
TCMDC-124095	12	32	TCMDC-133896	44	58	TCMDC-140442	33	78	TCMDC-136899	88	93	TCMDC-137891	98	105
TCMDC-140472	12	32	TCMDC-124206	45	58	TCMDC-138184	33	78	TCMDC-131604	88	93	TCMDC-131644	98	105
TCMDC-140274	12	32	TCMDC-135365	47	58	TCMDC-140667	33	78	TCMDC-135810	88	93	TCMDC-137691	98	105
TCMDC-138451	12	32	TCMDC-137140	48	58	TCMDC-124680	33	78	TCMDC-125189	89	93	TCMDC-124601	98	105
TCMDC-141721	12	32	TCMDC-139267	48	58	TCMDC-133997	34	78	TCMDC-138950	89	93	TCMDC-124770	98	105
TCMDC-132274	12	32	TCMDC-124708	50	58	TCMDC-131868	34	78	TCMDC-125575	89	93	TCMDC-134260	98	105
TCMDC-140962	13	32	TCMDC-123949	52	58	TCMDC-134330	34	78	TCMDC-135524	89	93	TCMDC-125226	98	105
TCMDC-132411	13	32	TCMDC-124600	53	58	TCMDC-124632	34	78	TCMDC-141855	90	93	TCMDC-135008	98	105
TCMDC-138401	13	32	TCMDC-133911	53	58	TCMDC-137902	34	78	TCMDC-131927	90	93	TCMDC-134056	98	105
TCMDC-134523	13	32	TCMDC-138936	53	58	TCMDC-141733	34	78	TCMDC-136737	90	93	TCMDC-123829	99	105
TCMDC-139351	13	32	TCMDC-141741	54	58	TCMDC-139370	34	78	TCMDC-132504	90	93	TCMDC-125741	99	105
TCMDC-141344	13	32	TCMDC-133055	54	58	TCMDC-123904	35	78	TCMDC-131914	90	93	TCMDC-133636	99	105
TCMDC-132210	13	32	TCMDC-133335	54	58	TCMDC-136774	35	78	TCMDC-125698	90	93	TCMDC-132004	99	105
TCMDC-131547	13	32	TCMDC-139689	55	58	TCMDC-135728	36	78	TCMDC-125675	90	93	TCMDC-131393	99	105
TCMDC-124882	14	32	TCMDC-133062	56	58	TCMDC-134983	36	78	TCMDC-142168	90	93	TCMDC-142341	99	105
TCMDC-132273	15	32	TCMDC-123641	58	58	TCMDC-137255	36	78	TCMDC-137471	90	93	TCMDC-131708	99	105
TCMDC-139809	16	32	TCMDC-137113	58	58	TCMDC-134810	36	78	TCMDC-124667	91	93	TCMDC-137679	99	105
TCMDC-125387	16	32	TCMDC-131910	58	58	TCMDC-136431	36	78	TCMDC-134257	91	93	TCMDC-141918	100	105
TCMDC-141310	16	32	TCMDC-132567	58	58	TCMDC-137073	37	78	TCMDC-132686	91	93	TCMDC-124045	100	105
TCMDC-135488	16	32	TCMDC-125310	1	59	TCMDC-133815	37	78	TCMDC-141964	91	93	TCMDC-133961	100	105
TCMDC-140068	17	32	TCMDC-132871	3	59	TCMDC-140913	40	78	TCMDC-132021	91	93	TCMDC-123821	100	105
TCMDC-142009	18	32	TCMDC-124590	3	59	TCMDC-135373	41	78	TCMDC-123871	92	93	TCMDC-131757	100	105
TCMDC-124525	19	32	TCMDC-134323	5	59	TCMDC-132545	42	78	TCMDC-141942	92	93	TCMDC-135654	100	105
TCMDC-137487	20	32	TCMDC-136163	5	59	TCMDC-137548	43	78	TCMDC-133244	92	93	TCMDC-142104	101	105

TCMDC-131475	20	32	TCMDC-137751	5	59	TCMDC-141876	44	78	TCMDC-123760	92	93	TCMDC-125154	101	105
TCMDC-133409	20	32	TCMDC-135384	7	59	TCMDC-135736	45	78	TCMDC-140034	92	93	TCMDC-125881	101	105
TCMDC-135907	21	32	TCMDC-124641	7	59	TCMDC-135509	45	78	TCMDC-138372	92	93	TCMDC-125687	101	105
TCMDC-131434	23	32	TCMDC-141509	9	59	TCMDC-131924	46	78	TCMDC-140908	92	93	TCMDC-136329	102	105
TCMDC-138566	23	32	TCMDC-133319	9	59	TCMDC-140058	46	78	TCMDC-136538	92	93	TCMDC-123897	102	105
TCMDC-141130	24	32	TCMDC-141076	9	59	TCMDC-132023	46	78	TCMDC-124188	92	93	TCMDC-135444	102	105
TCMDC-141333	24	32	TCMDC-141266	9	59	TCMDC-132633	47	78	TCMDC-123511	92	93	TCMDC-125033	102	105
TCMDC-140256	24	32	TCMDC-131963	9	59	TCMDC-135849	48	78	TCMDC-131675	92	93	TCMDC-136300	102	105
TCMDC-137550	24	32	TCMDC-138583	11	59	TCMDC-134531	48	78	TCMDC-124186	92	93	TCMDC-123575	102	105
TCMDC-140847	25	32	TCMDC-138734	12	59	TCMDC-140747	48	78	TCMDC-132783	93	93	TCMDC-124293	102	105
TCMDC-133654	25	32	TCMDC-132171	12	59	TCMDC-139303	48	78	TCMDC-123637	93	93	TCMDC-133304	102	105
TCMDC-140390	27	32	TCMDC-140088	13	59	TCMDC-136065	49	78	TCMDC-125830	93	93	TCMDC-124788	102	105
TCMDC-141217	28	32	TCMDC-137007	13	59	TCMDC-132493	49	78	TCMDC-133307	93	93	TCMDC-139146	103	105
TCMDC-135634	28	32	TCMDC-142217	13	59	TCMDC-139061	50	78	TCMDC-140766	93	93	TCMDC-135071	103	105
TCMDC-134247	29	32	TCMDC-139946	14	59	TCMDC-133716	51	78	TCMDC-137226	93	93	TCMDC-131658	104	105
TCMDC-142160	29	32	TCMDC-138871	15	59	TCMDC-139914	52	78	TCMDC-135970	93	93	TCMDC-134583	104	105
TCMDC-133137	29	32	TCMDC-140992	15	59	TCMDC-139870	52	78	TCMDC-136183	93	93	TCMDC-125267	104	105
TCMDC-132170	30	32	TCMDC-136514	15	59	TCMDC-141564	53	78	TCMDC-140139	93	93	TCMDC-125278	104	105
TCMDC-137911	31	32	TCMDC-139887	16	59	TCMDC-136920	53	78	TCMDC-141065	93	93	TCMDC-136303	104	105
TCMDC-131839	31	32	TCMDC-141542	16	59	TCMDC-136925	53	78	TCMDC-125583	93	93	TCMDC-135787	104	105
TCMDC-142275	32	32	TCMDC-140565	16	59	TCMDC-139661	54	78	TCMDC-136643	93	93	TCMDC-123529	104	105
TCMDC-139270	1	33	TCMDC-133540	16	59	TCMDC-140706	55	78	TCMDC-137709	93	93	TCMDC-135657	104	105
TCMDC-141573	2	33	TCMDC-134284	16	59	TCMDC-136824	55	78	TCMDC-133616	93	93	TCMDC-124271	104	105
TCMDC-138177	2	33	TCMDC-141211	16	59	TCMDC-135768	56	78	TCMDC-131380	93	93	TCMDC-138271	104	105
TCMDC-138664	2	33	TCMDC-132548	17	59	TCMDC-135090	56	78	TCMDC-124551	14	94	TCMDC-124896	105	105
TCMDC-141444	3	33	TCMDC-140219	17	59	TCMDC-131878	56	78	TCMDC-134138	14	94	TCMDC-142015	105	105
TCMDC-132301	3	33	TCMDC-134861	17	59	TCMDC-133870	57	78	TCMDC-141586	17	94	TCMDC-123845	105	105
TCMDC-125600	3	33	TCMDC-137133	17	59	TCMDC-135098	57	78	TCMDC-141400	20	94	TCMDC-123657	105	105
TCMDC-132829	3	33	TCMDC-142129	18	59	TCMDC-135950	57	78	TCMDC-125186	21	94	TCMDC-139277	105	105
TCMDC-140572	3	33	TCMDC-124745	18	59	TCMDC-131939	57	78	TCMDC-139043	24	94	TCMDC-131361	105	105
TCMDC-125118	4	33	TCMDC-141608	18	59	TCMDC-132316	58	78	TCMDC-124023	24	94	TCMDC-139144	108	105
TCMDC-141284	5	33	TCMDC-132627	19	59	TCMDC-125360	58	78	TCMDC-123728	27	94	TCMDC-133362	25	106
TCMDC-140601	5	33	TCMDC-134797	19	59	TCMDC-125158	59	78	TCMDC-135569	29	94	TCMDC-135707	31	106
TCMDC-140561	5	33	TCMDC-140809	19	59	TCMDC-125570	59	78	TCMDC-133023	31	94	TCMDC-140259	38	106
TCMDC-141905	6	33	TCMDC-136619	20	59	TCMDC-137132	59	78	TCMDC-135761	33	94	TCMDC-136923	40	106
TCMDC-140949	6	33	TCMDC-139211	20	59	TCMDC-135417	63	78	TCMDC-138790	33	94	TCMDC-137110	42	106
TCMDC-141141	6	33	TCMDC-123939	20	59	TCMDC-136944	64	78	TCMDC-134453	34	94	TCMDC-132867	43	106

TCMDC-142080	7	33	TCMDC-135147	21	59	TCMDC-139777	64	78	TCMDC-134431	35	94	TCMDC-132470	44	106
TCMDC-132262	7	33	TCMDC-140746	21	59	TCMDC-138164	65	78	TCMDC-135757	36	94	TCMDC-141352	52	106
TCMDC-133376	7	33	TCMDC-133193	22	59	TCMDC-139158	66	78	TCMDC-134519	36	94	TCMDC-140037	52	106
TCMDC-141743	8	33	TCMDC-137098	22	59	TCMDC-133118	66	78	TCMDC-135843	36	94	TCMDC-135339	56	106
TCMDC-137103	8	33	TCMDC-140262	22	59	TCMDC-133253	67	78	TCMDC-125317	37	94	TCMDC-134492	57	106
TCMDC-135652	8	33	TCMDC-132626	22	59	TCMDC-131382	67	78	TCMDC-140329	38	94	TCMDC-139218	62	106
TCMDC-133538	8	33	TCMDC-139079	23	59	TCMDC-125588	68	78	TCMDC-137749	38	94	TCMDC-132354	62	106
TCMDC-132456	9	33	TCMDC-139962	23	59	TCMDC-136610	68	78	TCMDC-136119	38	94	TCMDC-132461	63	106
TCMDC-138773	9	33	TCMDC-141169	23	59	TCMDC-137179	70	78	TCMDC-139969	39	94	TCMDC-142147	65	106
TCMDC-141160	9	33	TCMDC-139190	24	59	TCMDC-137135	72	78	TCMDC-135226	40	94	TCMDC-124018	66	106
TCMDC-131979	9	33	TCMDC-141814	24	59	TCMDC-138232	72	78	TCMDC-134497	42	94	TCMDC-138131	66	106
TCMDC-125710	9	33	TCMDC-141959	24	59	TCMDC-138192	72	78	TCMDC-124712	42	94	TCMDC-140060	70	106
TCMDC-141702	9	33	TCMDC-139688	24	59	TCMDC-133133	73	78	TCMDC-135937	42	94	TCMDC-135735	72	106
TCMDC-137758	9	33	TCMDC-125507	24	59	TCMDC-138520	74	78	TCMDC-133730	43	94	TCMDC-140462	72	106
TCMDC-135152	10	33	TCMDC-123974	25	59	TCMDC-124272	74	78	TCMDC-137929	43	94	TCMDC-134428	73	106
TCMDC-134727	10	33	TCMDC-136984	25	59	TCMDC-123651	74	78	TCMDC-137948	44	94	TCMDC-141410	75	106
TCMDC-135865	11	33	TCMDC-139618	25	59	TCMDC-133153	74	78	TCMDC-134846	44	94	TCMDC-139435	76	106
TCMDC-135624	11	33	TCMDC-124227	25	59	TCMDC-132695	74	78	TCMDC-140012	45	94	TCMDC-132591	77	106
TCMDC-141908	12	33	TCMDC-134673	25	59	TCMDC-123630	76	78	TCMDC-141233	45	94	TCMDC-132128	77	106
TCMDC-133912	13	33	TCMDC-141392	25	59	TCMDC-124472	76	78	TCMDC-123834	45	94	TCMDC-135699	78	106
TCMDC-137612	13	33	TCMDC-141925	26	59	TCMDC-135066	77	78	TCMDC-135675	45	94	TCMDC-140517	78	106
TCMDC-142072	13	33	TCMDC-138373	26	59	TCMDC-136271	77	78	TCMDC-134478	47	94	TCMDC-123750	79	106
TCMDC-141342	14	33	TCMDC-132825	27	59	TCMDC-136628	78	78	TCMDC-132599	47	94	TCMDC-133363	80	106
TCMDC-132525	14	33	TCMDC-138281	27	59	TCMDC-136185	78	78	TCMDC-140966	47	94	TCMDC-136398	81	106
TCMDC-140408	15	33	TCMDC-135685	27	59	TCMDC-136773	6	79	TCMDC-141849	48	94	TCMDC-141691	81	106
TCMDC-136232	15	33	TCMDC-132413	27	59	TCMDC-139447	6	79	TCMDC-135755	48	94	TCMDC-134976	81	106
TCMDC-133851	15	33	TCMDC-134793	28	59	TCMDC-139055	7	79	TCMDC-135762	48	94	TCMDC-123504	81	106
TCMDC-124063	16	33	TCMDC-141105	29	59	TCMDC-132872	9	79	TCMDC-134466	48	94	TCMDC-139488	81	106
TCMDC-137045	16	33	TCMDC-139630	29	59	TCMDC-141004	9	79	TCMDC-137094	48	94	TCMDC-131783	82	106
TCMDC-140481	16	33	TCMDC-124985	29	59	TCMDC-132017	9	79	TCMDC-133777	49	94	TCMDC-133755	83	106
TCMDC-131488	17	33	TCMDC-124668	29	59	TCMDC-140420	12	79	TCMDC-140234	49	94	TCMDC-142272	84	106
TCMDC-141774	17	33	TCMDC-134851	29	59	TCMDC-134366	14	79	TCMDC-139970	50	94	TCMDC-136612	85	106
TCMDC-135639	17	33	TCMDC-140226	30	59	TCMDC-133717	15	79	TCMDC-125393	51	94	TCMDC-139536	86	106
TCMDC-125556	17	33	TCMDC-134952	30	59	TCMDC-134827	17	79	TCMDC-132843	54	94	TCMDC-131320	86	106
TCMDC-134190	18	33	TCMDC-133317	31	59	TCMDC-141828	19	79	TCMDC-139967	54	94	TCMDC-124060	86	106
TCMDC-138396	18	33	TCMDC-138344	31	59	TCMDC-139084	20	79	TCMDC-140410	54	94	TCMDC-137368	86	106
TCMDC-136536	19	33	TCMDC-132680	31	59	TCMDC-137119	21	79	TCMDC-133641	54	94	TCMDC-124217	88	106

TCMDC-141978	19	33	TCMDC-132181	31	59	TCMDC-137101	22	79	TCMDC-139740	54	94	TCMDC-124877	89	106
TCMDC-141132	19	33	TCMDC-141391	32	59	TCMDC-139916	22	79	TCMDC-138955	54	94	TCMDC-131896	89	106
TCMDC-125485	19	33	TCMDC-134404	32	59	TCMDC-140888	22	79	TCMDC-135457	55	94	TCMDC-123726	91	106
TCMDC-140279	19	33	TCMDC-135205	33	59	TCMDC-137997	23	79	TCMDC-137898	55	94	TCMDC-134007	91	106
TCMDC-135493	19	33	TCMDC-139639	35	59	TCMDC-135328	25	79	TCMDC-134306	55	94	TCMDC-125376	91	106
TCMDC-125633	20	33	TCMDC-137180	36	59	TCMDC-139116	25	79	TCMDC-136097	55	94	TCMDC-141576	92	106
TCMDC-140593	20	33	TCMDC-139317	36	59	TCMDC-140720	25	79	TCMDC-132394	56	94	TCMDC-138907	92	106
TCMDC-132104	20	33	TCMDC-140071	38	59	TCMDC-138980	26	79	TCMDC-138335	56	94	TCMDC-135303	92	106
TCMDC-140395	21	33	TCMDC-140548	39	59	TCMDC-135395	26	79	TCMDC-138048	57	94	TCMDC-123848	92	106
TCMDC-135691	21	33	TCMDC-133548	39	59	TCMDC-134318	27	79	TCMDC-137757	57	94	TCMDC-131797	92	106
TCMDC-142003	22	33	TCMDC-135963	39	59	TCMDC-141387	27	79	TCMDC-131681	57	94	TCMDC-125859	92	106
TCMDC-132263	22	33	TCMDC-141092	40	59	TCMDC-139287	28	79	TCMDC-136929	58	94	TCMDC-137359	92	106
TCMDC-124056	22	33	TCMDC-124656	41	59	TCMDC-134639	28	79	TCMDC-139808	58	94	TCMDC-136508	93	106
TCMDC-131838	22	33	TCMDC-142117	41	59	TCMDC-132678	29	79	TCMDC-139687	58	94	TCMDC-134570	93	106
TCMDC-123718	23	33	TCMDC-141651	42	59	TCMDC-137104	30	79	TCMDC-141309	58	94	TCMDC-138076	93	106
TCMDC-131837	23	33	TCMDC-132687	43	59	TCMDC-139305	30	79	TCMDC-133756	59	94	TCMDC-139050	93	106
TCMDC-138886	24	33	TCMDC-136332	46	59	TCMDC-134173	30	79	TCMDC-141950	59	94	TCMDC-124595	93	106
TCMDC-124091	26	33	TCMDC-138257	46	59	TCMDC-125068	31	79	TCMDC-136437	60	94	TCMDC-141502	94	106
TCMDC-124021	26	33	TCMDC-141738	47	59	TCMDC-136879	31	79	TCMDC-131915	60	94	TCMDC-124522	94	106
TCMDC-134185	26	33	TCMDC-140128	47	59	TCMDC-141910	32	79	TCMDC-139745	60	94	TCMDC-140891	95	106
TCMDC-132345	26	33	TCMDC-141094	48	59	TCMDC-141913	32	79	TCMDC-131555	61	94	TCMDC-124230	95	106
TCMDC-140118	27	33	TCMDC-133897	50	59	TCMDC-139391	32	79	TCMDC-138067	61	94	TCMDC-137766	95	106
TCMDC-124886	30	33	TCMDC-134288	53	59	TCMDC-133368	33	79	TCMDC-142106	62	94	TCMDC-131867	95	106
TCMDC-124071	31	33	TCMDC-137012	54	59	TCMDC-138740	33	79	TCMDC-139742	63	94	TCMDC-125650	95	106
TCMDC-136085	31	33	TCMDC-138780	55	59	TCMDC-141287	33	79	TCMDC-139739	63	94	TCMDC-132787	95	106
TCMDC-124170	31	33	TCMDC-136078	56	59	TCMDC-136149	33	79	TCMDC-123665	64	94	TCMDC-137280	95	106
TCMDC-142226	33	33	TCMDC-134624	57	59	TCMDC-136751	34	79	TCMDC-133867	64	94	TCMDC-136321	96	106
TCMDC-133872	2	34	TCMDC-133466	57	59	TCMDC-132260	34	79	TCMDC-140228	65	94	TCMDC-124362	96	106
TCMDC-136883	2	34	TCMDC-123966	57	59	TCMDC-135290	34	79	TCMDC-141771	65	94	TCMDC-135796	96	106
TCMDC-137703	3	34	TCMDC-141030	57	59	TCMDC-133973	34	79	TCMDC-136363	65	94	TCMDC-125519	96	106
TCMDC-132824	3	34	TCMDC-140646	57	59	TCMDC-136590	34	79	TCMDC-140217	65	94	TCMDC-139249	96	106
TCMDC-125163	4	34	TCMDC-135243	57	59	TCMDC-136115	35	79	TCMDC-142325	66	94	TCMDC-124240	96	106
TCMDC-138682	4	34	TCMDC-139665	58	59	TCMDC-135264	35	79	TCMDC-139620	66	94	TCMDC-123670	97	106
TCMDC-137885	4	34	TCMDC-133448	58	59	TCMDC-140229	35	79	TCMDC-136418	67	94	TCMDC-133414	97	106
TCMDC-140943	4	34	TCMDC-133577	59	59	TCMDC-134510	35	79	TCMDC-136405	69	94	TCMDC-124085	97	106
TCMDC-140779	5	34	TCMDC-132898	59	59	TCMDC-136100	36	79	TCMDC-133112	69	94	TCMDC-124361	97	106
TCMDC-140925	5	34	TCMDC-123729	2	60	TCMDC-139605	36	79	TCMDC-123457	69	94	TCMDC-135433	97	106

TCMDC-140589	6	34	TCMDC-123971	5	60	TCMDC-133684	36	79	TCMDC-138240	70	94	TCMDC-125126	97	106
TCMDC-140983	6	34	TCMDC-139924	5	60	TCMDC-134569	37	79	TCMDC-137693	70	94	TCMDC-131759	98	106
TCMDC-134948	7	34	TCMDC-131554	5	60	TCMDC-132751	38	79	TCMDC-132305	70	94	TCMDC-131762	98	106
TCMDC-139794	7	34	TCMDC-135267	5	60	TCMDC-125111	38	79	TCMDC-123780	70	94	TCMDC-138981	98	106
TCMDC-140584	8	34	TCMDC-139589	6	60	TCMDC-136754	38	79	TCMDC-140427	71	94	TCMDC-123723	98	106
TCMDC-142089	8	34	TCMDC-138541	6	60	TCMDC-136121	39	79	TCMDC-125487	72	94	TCMDC-135605	98	106
TCMDC-140492	9	34	TCMDC-136509	6	60	TCMDC-142017	39	79	TCMDC-124267	72	94	TCMDC-125477	99	106
TCMDC-140639	9	34	TCMDC-132036	7	60	TCMDC-137069	39	79	TCMDC-125007	73	94	TCMDC-131711	99	106
TCMDC-134128	9	34	TCMDC-132994	7	60	TCMDC-141020	40	79	TCMDC-136755	73	94	TCMDC-137433	99	106
TCMDC-132796	10	34	TCMDC-136471	7	60	TCMDC-132645	40	79	TCMDC-142002	73	94	TCMDC-140753	99	106
TCMDC-139644	10	34	TCMDC-141888	8	60	TCMDC-138069	40	79	TCMDC-133202	73	94	TCMDC-138103	99	106
TCMDC-141812	10	34	TCMDC-132862	8	60	TCMDC-136273	41	79	TCMDC-134693	74	94	TCMDC-135518	100	106
TCMDC-123754	10	34	TCMDC-141085	8	60	TCMDC-141662	42	79	TCMDC-138038	75	94	TCMDC-131953	100	106
TCMDC-140569	11	34	TCMDC-135035	9	60	TCMDC-136844	42	79	TCMDC-124256	75	94	TCMDC-135683	100	106
TCMDC-140586	12	34	TCMDC-141063	9	60	TCMDC-135396	43	79	TCMDC-139864	75	94	TCMDC-131726	100	106
TCMDC-132520	12	34	TCMDC-133839	10	60	TCMDC-137567	43	79	TCMDC-132385	75	94	TCMDC-123900	100	106
TCMDC-132290	12	34	TCMDC-134443	11	60	TCMDC-125530	44	79	TCMDC-131958	76	94	TCMDC-124318	101	106
TCMDC-141379	12	34	TCMDC-138815	12	60	TCMDC-135112	44	79	TCMDC-136919	76	94	TCMDC-123725	101	106
TCMDC-138982	13	34	TCMDC-134921	12	60	TCMDC-138977	44	79	TCMDC-133230	77	94	TCMDC-136351	101	106
TCMDC-132216	13	34	TCMDC-132019	12	60	TCMDC-140121	44	79	TCMDC-132663	77	94	TCMDC-131930	101	106
TCMDC-125419	13	34	TCMDC-141663	13	60	TCMDC-132753	45	79	TCMDC-131390	77	94	TCMDC-123868	101	106
TCMDC-125352	14	34	TCMDC-133030	13	60	TCMDC-141887	45	79	TCMDC-139387	77	94	TCMDC-131578	101	106
TCMDC-141786	14	34	TCMDC-140889	13	60	TCMDC-137257	45	79	TCMDC-134461	78	94	TCMDC-125865	101	106
TCMDC-140046	14	34	TCMDC-140237	16	60	TCMDC-139471	46	79	TCMDC-134658	78	94	TCMDC-124909	102	106
TCMDC-138585	16	34	TCMDC-132585	16	60	TCMDC-140039	46	79	TCMDC-131292	78	94	TCMDC-123568	102	106
TCMDC-142194	16	34	TCMDC-135039	16	60	TCMDC-136777	47	79	TCMDC-124329	79	94	TCMDC-140399	102	106
TCMDC-141100	16	34	TCMDC-140201	17	60	TCMDC-133326	47	79	TCMDC-124262	79	94	TCMDC-124902	102	106
TCMDC-139890	17	34	TCMDC-138365	17	60	TCMDC-124471	49	79	TCMDC-135515	80	94	TCMDC-124336	102	106
TCMDC-125856	17	34	TCMDC-132532	18	60	TCMDC-132402	49	79	TCMDC-138125	80	94	TCMDC-135461	102	106
TCMDC-141742	18	34	TCMDC-137237	18	60	TCMDC-125661	49	79	TCMDC-133157	81	94	TCMDC-135586	102	106
TCMDC-138789	18	34	TCMDC-134552	18	60	TCMDC-141116	49	79	TCMDC-132794	81	94	TCMDC-131920	102	106
TCMDC-124677	18	34	TCMDC-139991	19	60	TCMDC-132715	49	79	TCMDC-125823	82	94	TCMDC-139431	102	106
TCMDC-124038	18	34	TCMDC-141544	20	60	TCMDC-141555	49	79	TCMDC-141408	82	94	TCMDC-125462	103	106
TCMDC-142076	19	34	TCMDC-134796	21	60	TCMDC-139604	50	79	TCMDC-124229	82	94	TCMDC-125670	103	106
TCMDC-125238	19	34	TCMDC-135390	21	60	TCMDC-137014	50	79	TCMDC-142098	83	94	TCMDC-139000	103	106
TCMDC-125696	20	34	TCMDC-139940	21	60	TCMDC-135570	50	79	TCMDC-135614	83	94	TCMDC-125014	103	106
TCMDC-125609	20	34	TCMDC-140861	21	60	TCMDC-132398	51	79	TCMDC-140450	83	94	TCMDC-132300	103	106

TCMDC-132271	21	34	TCMDC-136518	21	60	TCMDC-136742	51	79	TCMDC-137747	83	94	TCMDC-137175	103	106
TCMDC-123790	21	34	TCMDC-133025	21	60	TCMDC-133820	53	79	TCMDC-124844	83	94	TCMDC-125482	103	106
TCMDC-140832	22	34	TCMDC-134918	22	60	TCMDC-136516	55	79	TCMDC-135085	84	94	TCMDC-124999	104	106
TCMDC-125297	22	34	TCMDC-141928	22	60	TCMDC-138012	55	79	TCMDC-139443	84	94	TCMDC-125266	104	106
TCMDC-135324	22	34	TCMDC-134251	23	60	TCMDC-139666	56	79	TCMDC-123892	84	94	TCMDC-124657	104	106
TCMDC-141254	22	34	TCMDC-141765	23	60	TCMDC-140236	56	79	TCMDC-124833	84	94	TCMDC-132969	104	106
TCMDC-141133	22	34	TCMDC-137480	23	60	TCMDC-135557	56	79	TCMDC-133017	85	94	TCMDC-124482	104	106
TCMDC-133268	23	34	TCMDC-135045	24	60	TCMDC-139289	58	79	TCMDC-138758	85	94	TCMDC-123806	104	106
TCMDC-136155	23	34	TCMDC-134871	24	60	TCMDC-124970	59	79	TCMDC-133186	86	94	TCMDC-138998	104	106
TCMDC-138693	24	34	TCMDC-124646	24	60	TCMDC-137136	60	79	TCMDC-137876	86	94	TCMDC-136624	105	106
TCMDC-133739	24	34	TCMDC-139077	24	60	TCMDC-136067	62	79	TCMDC-135269	86	94	TCMDC-132792	105	106
TCMDC-136154	24	34	TCMDC-141343	25	60	TCMDC-133697	62	79	TCMDC-138297	86	94	TCMDC-125036	105	106
TCMDC-136170	24	34	TCMDC-134780	25	60	TCMDC-132963	62	79	TCMDC-124591	86	94	TCMDC-136169	105	106
TCMDC-131251	24	34	TCMDC-125188	25	60	TCMDC-132059	63	79	TCMDC-139128	86	94	TCMDC-137719	105	106
TCMDC-131428	26	34	TCMDC-139217	25	60	TCMDC-132846	64	79	TCMDC-135175	86	94	TCMDC-142296	105	106
TCMDC-124989	27	34	TCMDC-138237	26	60	TCMDC-124973	65	79	TCMDC-136912	86	94	TCMDC-139774	106	106
TCMDC-138644	27	34	TCMDC-137823	26	60	TCMDC-131413	65	79	TCMDC-135013	86	94	TCMDC-134271	106	106
TCMDC-133664	27	34	TCMDC-124442	27	60	TCMDC-138821	66	79	TCMDC-133084	87	94	TCMDC-134592	106	106
TCMDC-140874	28	34	TCMDC-135107	27	60	TCMDC-131750	67	79	TCMDC-137245	87	94	TCMDC-124904	106	106
TCMDC-133374	29	34	TCMDC-137805	27	60	TCMDC-142019	67	79	TCMDC-139440	87	94	TCMDC-124740	106	106
TCMDC-125074	30	34	TCMDC-124666	28	60	TCMDC-138248	67	79	TCMDC-142271	87	94	TCMDC-136161	106	106
TCMDC-140854	30	34	TCMDC-142288	28	60	TCMDC-136833	68	79	TCMDC-124885	88	94	TCMDC-124393	107	106
TCMDC-137131	30	34	TCMDC-137555	28	60	TCMDC-123713	70	79	TCMDC-123584	88	94	TCMDC-123545	112	106
TCMDC-138022	31	34	TCMDC-139356	28	60	TCMDC-124475	71	79	TCMDC-131352	88	94	TCMDC-136649	114	106
TCMDC-141483	31	34	TCMDC-133949	29	60	TCMDC-138345	71	79	TCMDC-123953	88	94	TCMDC-124461	115	106
TCMDC-141957	32	34	TCMDC-133809	29	60	TCMDC-139075	74	79	TCMDC-123768	88	94	TCMDC-139430	6	107
TCMDC-124884	33	34	TCMDC-132439	29	60	TCMDC-133361	75	79	TCMDC-124451	89	94	TCMDC-132465	23	107
TCMDC-125496	33	34	TCMDC-140804	29	60	TCMDC-136953	75	79	TCMDC-137646	89	94	TCMDC-139690	42	107
TCMDC-124145	33	34	TCMDC-124349	30	60	TCMDC-124360	76	79	TCMDC-137438	89	94	TCMDC-135115	42	107
TCMDC-140129	34	34	TCMDC-139585	30	60	TCMDC-123536	76	79	TCMDC-137686	89	94	TCMDC-141479	45	107
TCMDC-134115	2	35	TCMDC-134785	30	60	TCMDC-124714	76	79	TCMDC-123715	89	94	TCMDC-136897	46	107
TCMDC-137802	2	35	TCMDC-136465	30	60	TCMDC-139318	76	79	TCMDC-138083	90	94	TCMDC-135047	46	107
TCMDC-138649	3	35	TCMDC-139345	31	60	TCMDC-134395	76	79	TCMDC-125758	90	94	TCMDC-139027	47	107
TCMDC-138324	4	35	TCMDC-139349	31	60	TCMDC-131905	77	79	TCMDC-131673	90	94	TCMDC-138715	53	107
TCMDC-137842	4	35	TCMDC-134571	31	60	TCMDC-132692	77	79	TCMDC-137656	90	94	TCMDC-139426	54	107
TCMDC-134044	4	35	TCMDC-136211	31	60	TCMDC-136638	77	79	TCMDC-137242	90	94	TCMDC-137055	64	107
TCMDC-136731	4	35	TCMDC-124981	31	60	TCMDC-133124	77	79	TCMDC-137670	90	94	TCMDC-125327	66	107

TCMDC-132324	6	35	TCMDC-133450	32	60	TCMDC-137358	77	79	TCMDC-124750	91	94	TCMDC-138781	68	107
TCMDC-141281	7	35	TCMDC-135861	32	60	TCMDC-132598	78	79	TCMDC-123612	91	94	TCMDC-133947	70	107
TCMDC-135318	7	35	TCMDC-135674	33	60	TCMDC-125273	78	79	TCMDC-124504	91	94	TCMDC-135992	72	107
TCMDC-141524	7	35	TCMDC-133759	33	60	TCMDC-134085	6	80	TCMDC-141892	91	94	TCMDC-140251	72	107
TCMDC-135452	7	35	TCMDC-139878	33	60	TCMDC-134171	7	80	TCMDC-123875	91	94	TCMDC-134980	72	107
TCMDC-133784	7	35	TCMDC-137579	33	60	TCMDC-132075	8	80	TCMDC-137859	91	94	TCMDC-135985	74	107
TCMDC-133444	7	35	TCMDC-140092	34	60	TCMDC-124151	8	80	TCMDC-124101	91	94	TCMDC-133948	76	107
TCMDC-136718	7	35	TCMDC-133051	34	60	TCMDC-139581	13	80	TCMDC-137947	91	94	TCMDC-133968	80	107
TCMDC-140603	8	35	TCMDC-141938	36	60	TCMDC-142071	15	80	TCMDC-125573	91	94	TCMDC-137301	80	107
TCMDC-137810	8	35	TCMDC-141123	36	60	TCMDC-136540	16	80	TCMDC-142274	92	94	TCMDC-123611	81	107
TCMDC-123812	8	35	TCMDC-133544	37	60	TCMDC-137218	16	80	TCMDC-133221	92	94	TCMDC-135872	81	107
TCMDC-141301	9	35	TCMDC-132414	37	60	TCMDC-139449	17	80	TCMDC-132421	92	94	TCMDC-124593	82	107
TCMDC-141358	9	35	TCMDC-135299	38	60	TCMDC-139721	18	80	TCMDC-125363	92	94	TCMDC-141239	82	107
TCMDC-141601	10	35	TCMDC-124687	38	60	TCMDC-134581	19	80	TCMDC-125112	92	94	TCMDC-123737	82	107
TCMDC-133783	10	35	TCMDC-139732	38	60	TCMDC-139947	19	80	TCMDC-136196	92	94	TCMDC-140466	83	107
TCMDC-133785	10	35	TCMDC-133516	39	60	TCMDC-139167	21	80	TCMDC-138033	92	94	TCMDC-142304	83	107
TCMDC-133883	10	35	TCMDC-141657	39	60	TCMDC-135621	22	80	TCMDC-133163	92	94	TCMDC-131794	83	107
TCMDC-138938	10	35	TCMDC-141801	40	60	TCMDC-141525	22	80	TCMDC-125177	92	94	TCMDC-132801	83	107
TCMDC-141641	11	35	TCMDC-124965	41	60	TCMDC-124075	22	80	TCMDC-131349	92	94	TCMDC-135738	85	107
TCMDC-140635	11	35	TCMDC-124980	41	60	TCMDC-133037	22	80	TCMDC-124784	93	94	TCMDC-131804	85	107
TCMDC-132517	12	35	TCMDC-142314	42	60	TCMDC-141520	23	80	TCMDC-123602	93	94	TCMDC-136229	86	107
TCMDC-132277	12	35	TCMDC-134022	42	60	TCMDC-133983	24	80	TCMDC-142309	93	94	TCMDC-132972	87	107
TCMDC-134071	12	35	TCMDC-124603	43	60	TCMDC-138827	24	80	TCMDC-134680	93	94	TCMDC-137846	87	107
TCMDC-124135	12	35	TCMDC-135997	43	60	TCMDC-137903	25	80	TCMDC-132789	93	94	TCMDC-135514	88	107
TCMDC-140479	13	35	TCMDC-123730	44	60	TCMDC-134332	26	80	TCMDC-124274	93	94	TCMDC-133950	88	107
TCMDC-140469	13	35	TCMDC-125339	45	60	TCMDC-141503	26	80	TCMDC-135846	93	94	TCMDC-123835	88	107
TCMDC-132782	13	35	TCMDC-139663	45	60	TCMDC-136123	26	80	TCMDC-137717	93	94	TCMDC-131341	89	107
TCMDC-131862	13	35	TCMDC-138287	45	60	TCMDC-135275	27	80	TCMDC-140308	93	94	TCMDC-140255	90	107
TCMDC-136343	13	35	TCMDC-134193	46	60	TCMDC-142244	28	80	TCMDC-124198	93	94	TCMDC-141989	91	107
TCMDC-135059	13	35	TCMDC-142173	47	60	TCMDC-134228	28	80	TCMDC-133298	93	94	TCMDC-137632	91	107
TCMDC-123973	13	35	TCMDC-134120	47	60	TCMDC-134691	29	80	TCMDC-141019	93	94	TCMDC-124136	91	107
TCMDC-132376	14	35	TCMDC-124628	47	60	TCMDC-135619	29	80	TCMDC-131775	93	94	TCMDC-123820	91	107
TCMDC-138724	15	35	TCMDC-141285	47	60	TCMDC-132774	30	80	TCMDC-131381	93	94	TCMDC-123501	92	107
TCMDC-138951	15	35	TCMDC-134225	48	60	TCMDC-133701	30	80	TCMDC-135428	94	94	TCMDC-133464	92	107
TCMDC-140052	15	35	TCMDC-133087	48	60	TCMDC-141863	31	80	TCMDC-131871	94	94	TCMDC-124279	92	107
TCMDC-136313	16	35	TCMDC-138424	51	60	TCMDC-134713	31	80	TCMDC-123597	94	94	TCMDC-131801	92	107
TCMDC-124581	17	35	TCMDC-135447	52	60	TCMDC-132636	31	80	TCMDC-123503	94	94	TCMDC-124418	92	107

TCMDC-140757	17	35	TCMDC-141881	53	60	TCMDC-138533	31	80	TCMDC-131654	94	94	TCMDC-131291	92	107
TCMDC-139360	18	35	TCMDC-124715	55	60	TCMDC-132651	31	80	TCMDC-123828	94	94	TCMDC-133745	93	107
TCMDC-134224	18	35	TCMDC-125587	56	60	TCMDC-139123	31	80	TCMDC-137125	94	94	TCMDC-135601	93	107
TCMDC-141571	18	35	TCMDC-137114	57	60	TCMDC-133728	31	80	TCMDC-137924	94	94	TCMDC-131734	93	107
TCMDC-138005	18	35	TCMDC-133821	59	60	TCMDC-136122	32	80	TCMDC-124221	94	94	TCMDC-125837	94	107
TCMDC-132479	18	35	TCMDC-133934	59	60	TCMDC-139145	33	80	TCMDC-142155	96	94	TCMDC-131582	94	107
TCMDC-138755	19	35	TCMDC-142166	59	60	TCMDC-141242	33	80	TCMDC-134479	3	95	TCMDC-124355	94	107
TCMDC-131994	19	35	TCMDC-139691	59	60	TCMDC-136499	33	80	TCMDC-137803	7	95	TCMDC-131981	94	107
TCMDC-138442	20	35	TCMDC-125300	60	60	TCMDC-134764	34	80	TCMDC-136805	10	95	TCMDC-125855	94	107
TCMDC-141798	21	35	TCMDC-135244	60	60	TCMDC-134223	34	80	TCMDC-135879	12	95	TCMDC-124307	95	107
TCMDC-131422	21	35	TCMDC-124225	60	60	TCMDC-136982	34	80	TCMDC-141994	19	95	TCMDC-125654	95	107
TCMDC-141298	22	35	TCMDC-141932	1	61	TCMDC-141527	35	80	TCMDC-137583	19	95	TCMDC-133147	96	107
TCMDC-133529	22	35	TCMDC-139003	4	61	TCMDC-133360	35	80	TCMDC-140801	21	95	TCMDC-137279	96	107
TCMDC-123485	22	35	TCMDC-138363	5	61	TCMDC-134102	35	80	TCMDC-141793	22	95	TCMDC-131784	96	107
TCMDC-141155	23	35	TCMDC-139824	5	61	TCMDC-124906	36	80	TCMDC-135721	27	95	TCMDC-137886	96	107
TCMDC-136954	25	35	TCMDC-138255	5	61	TCMDC-135351	37	80	TCMDC-133792	29	95	TCMDC-138575	96	107
TCMDC-125166	25	35	TCMDC-142091	6	61	TCMDC-138948	37	80	TCMDC-140887	29	95	TCMDC-138117	96	107
TCMDC-132339	25	35	TCMDC-139715	6	61	TCMDC-139978	38	80	TCMDC-133364	30	95	TCMDC-124764	96	107
TCMDC-139223	27	35	TCMDC-133433	8	61	TCMDC-137310	38	80	TCMDC-141686	31	95	TCMDC-138014	96	107
TCMDC-132077	27	35	TCMDC-139930	8	61	TCMDC-123530	39	80	TCMDC-134391	31	95	TCMDC-139429	96	107
TCMDC-125454	27	35	TCMDC-123673	9	61	TCMDC-141206	39	80	TCMDC-136261	31	95	TCMDC-123891	97	107
TCMDC-131844	28	35	TCMDC-137580	9	61	TCMDC-138429	39	80	TCMDC-131570	34	95	TCMDC-123738	97	107
TCMDC-125707	28	35	TCMDC-136179	9	61	TCMDC-133690	39	80	TCMDC-141385	34	95	TCMDC-131879	97	107
TCMDC-125104	29	35	TCMDC-140003	10	61	TCMDC-124019	40	80	TCMDC-132559	34	95	TCMDC-132506	98	107
TCMDC-140131	29	35	TCMDC-138405	10	61	TCMDC-134221	40	80	TCMDC-141934	35	95	TCMDC-134937	98	107
TCMDC-124425	31	35	TCMDC-132985	10	61	TCMDC-142192	40	80	TCMDC-124773	35	95	TCMDC-133786	98	107
TCMDC-132330	31	35	TCMDC-138206	11	61	TCMDC-137995	40	80	TCMDC-133931	35	95	TCMDC-124385	98	107
TCMDC-125467	32	35	TCMDC-125157	12	61	TCMDC-132080	40	80	TCMDC-124076	37	95	TCMDC-123999	98	107
TCMDC-135682	33	35	TCMDC-138269	12	61	TCMDC-134403	41	80	TCMDC-136781	37	95	TCMDC-137451	98	107
TCMDC-135191	33	35	TCMDC-137520	13	61	TCMDC-132657	41	80	TCMDC-123802	39	95	TCMDC-137159	99	107
TCMDC-142265	33	35	TCMDC-132683	13	61	TCMDC-133715	41	80	TCMDC-133894	40	95	TCMDC-142305	99	107
TCMDC-132110	34	35	TCMDC-138719	14	61	TCMDC-133550	41	80	TCMDC-125204	40	95	TCMDC-124220	99	107
TCMDC-135062	34	35	TCMDC-138286	14	61	TCMDC-137019	41	80	TCMDC-140436	41	95	TCMDC-123937	100	107
TCMDC-133139	34	35	TCMDC-133853	14	61	TCMDC-139873	43	80	TCMDC-133002	43	95	TCMDC-135523	100	107
TCMDC-133010	34	35	TCMDC-136708	15	61	TCMDC-138135	43	80	TCMDC-135748	43	95	TCMDC-136136	100	107
TCMDC-142042	34	35	TCMDC-139063	15	61	TCMDC-124567	44	80	TCMDC-136401	43	95	TCMDC-131727	100	107
TCMDC-134204	35	35	TCMDC-142065	15	61	TCMDC-139422	44	80	TCMDC-135915	44	95	TCMDC-123950	100	107

TCMDC-139470	3	36	TCMDC-141645	15	61	TCMDC-134238	44	80	TCMDC-133276	44	95	TCMDC-141396	101	107
TCMDC-140063	3	36	TCMDC-141567	16	61	TCMDC-135538	46	80	TCMDC-132706	44	95	TCMDC-123758	101	107
TCMDC-137848	4	36	TCMDC-140171	16	61	TCMDC-136148	47	80	TCMDC-139780	46	95	TCMDC-123463	101	107
TCMDC-136378	4	36	TCMDC-132588	16	61	TCMDC-135044	47	80	TCMDC-142122	46	95	TCMDC-132951	101	107
TCMDC-132121	4	36	TCMDC-141588	16	61	TCMDC-135176	47	80	TCMDC-139245	46	95	TCMDC-137988	102	107
TCMDC-142201	5	36	TCMDC-132913	16	61	TCMDC-124379	48	80	TCMDC-134220	46	95	TCMDC-123870	102	107
TCMDC-135106	5	36	TCMDC-140524	17	61	TCMDC-134255	49	80	TCMDC-139850	47	95	TCMDC-139436	102	107
TCMDC-138851	5	36	TCMDC-136551	17	61	TCMDC-132927	50	80	TCMDC-134484	48	95	TCMDC-124350	102	107
TCMDC-133390	5	36	TCMDC-136444	18	61	TCMDC-133704	50	80	TCMDC-125544	48	95	TCMDC-131452	102	107
TCMDC-139834	6	36	TCMDC-141589	18	61	TCMDC-138199	51	80	TCMDC-136413	48	95	TCMDC-123925	103	107
TCMDC-142124	6	36	TCMDC-139906	19	61	TCMDC-139510	51	80	TCMDC-134755	48	95	TCMDC-123682	103	107
TCMDC-141463	6	36	TCMDC-137507	19	61	TCMDC-131375	52	80	TCMDC-139602	48	95	TCMDC-133953	103	107
TCMDC-141316	6	36	TCMDC-139716	19	61	TCMDC-125796	54	80	TCMDC-135718	49	95	TCMDC-134033	104	107
TCMDC-137843	6	36	TCMDC-124566	20	61	TCMDC-132040	54	80	TCMDC-125244	49	95	TCMDC-125784	104	107
TCMDC-141148	7	36	TCMDC-141629	20	61	TCMDC-140413	54	80	TCMDC-133688	49	95	TCMDC-125250	105	107
TCMDC-141048	7	36	TCMDC-131780	21	61	TCMDC-132878	55	80	TCMDC-125000	50	95	TCMDC-136670	105	107
TCMDC-135312	8	36	TCMDC-134749	21	61	TCMDC-124051	58	80	TCMDC-136258	50	95	TCMDC-136188	105	107
TCMDC-139891	8	36	TCMDC-141659	22	61	TCMDC-132387	58	80	TCMDC-134027	52	95	TCMDC-137265	105	107
TCMDC-132860	8	36	TCMDC-140529	22	61	TCMDC-132583	58	80	TCMDC-125790	53	95	TCMDC-125473	105	107
TCMDC-141300	8	36	TCMDC-132535	22	61	TCMDC-124311	59	80	TCMDC-135961	54	95	TCMDC-136135	105	107
TCMDC-132235	8	36	TCMDC-124685	22	61	TCMDC-132166	60	80	TCMDC-124976	54	95	TCMDC-131581	105	107
TCMDC-124141	8	36	TCMDC-132509	23	61	TCMDC-124954	60	80	TCMDC-139458	55	95	TCMDC-136735	105	107
TCMDC-136474	9	36	TCMDC-134065	23	61	TCMDC-138171	60	80	TCMDC-133852	55	95	TCMDC-135407	105	107
TCMDC-132288	9	36	TCMDC-141515	23	61	TCMDC-132499	61	80	TCMDC-139743	55	95	TCMDC-124778	106	107
TCMDC-133303	9	36	TCMDC-123681	23	61	TCMDC-141914	62	80	TCMDC-136251	55	95	TCMDC-135667	106	107
TCMDC-140473	10	36	TCMDC-141340	23	61	TCMDC-142073	62	80	TCMDC-135931	56	95	TCMDC-124866	106	107
TCMDC-140608	10	36	TCMDC-133545	23	61	TCMDC-142133	62	80	TCMDC-136734	56	95	TCMDC-134041	106	107
TCMDC-125269	10	36	TCMDC-141297	23	61	TCMDC-139664	63	80	TCMDC-133241	56	95	TCMDC-124707	106	107
TCMDC-141363	10	36	TCMDC-132208	24	61	TCMDC-136721	63	80	TCMDC-136255	58	95	TCMDC-125022	106	107
TCMDC-136808	10	36	TCMDC-136282	24	61	TCMDC-142158	65	80	TCMDC-137154	58	95	TCMDC-136022	106	107
TCMDC-124255	10	36	TCMDC-132309	24	61	TCMDC-124834	66	80	TCMDC-139966	58	95	TCMDC-125061	107	107
TCMDC-140364	10	36	TCMDC-139109	25	61	TCMDC-125693	66	80	TCMDC-140317	60	95	TCMDC-125020	107	107
TCMDC-137913	10	36	TCMDC-138158	25	61	TCMDC-136748	67	80	TCMDC-136132	60	95	TCMDC-125621	107	107
TCMDC-140599	11	36	TCMDC-139233	25	61	TCMDC-123667	69	80	TCMDC-139527	61	95	TCMDC-124733	107	107
TCMDC-140600	11	36	TCMDC-124046	25	61	TCMDC-137360	69	80	TCMDC-140872	62	95	TCMDC-133990	107	107
TCMDC-142203	11	36	TCMDC-141909	26	61	TCMDC-132195	70	80	TCMDC-136816	62	95	TCMDC-125051	107	107
TCMDC-132516	11	36	TCMDC-134405	26	61	TCMDC-124469	70	80	TCMDC-136174	62	95	TCMDC-125649	107	107

TCMDC-140955	11	36	TCMDC-132765	28	61	TCMDC-124559	71	80	TCMDC-124516	63	95	TCMDC-124104	108	107
TCMDC-137958	11	36	TCMDC-136080	28	61	TCMDC-132137	71	80	TCMDC-139425	64	95	TCMDC-136843	25	108
TCMDC-140480	12	36	TCMDC-133044	28	61	TCMDC-136698	72	80	TCMDC-137466	64	95	TCMDC-124575	25	108
TCMDC-132215	12	36	TCMDC-142082	29	61	TCMDC-139683	74	80	TCMDC-139164	64	95	TCMDC-136688	28	108
TCMDC-140467	13	36	TCMDC-134786	29	61	TCMDC-138235	74	80	TCMDC-125786	65	95	TCMDC-137872	43	108
TCMDC-140692	13	36	TCMDC-141677	29	61	TCMDC-132571	75	80	TCMDC-137454	65	95	TCMDC-134533	44	108
TCMDC-125626	14	36	TCMDC-138895	29	61	TCMDC-132957	75	80	TCMDC-140097	65	95	TCMDC-124678	50	108
TCMDC-133793	14	36	TCMDC-132428	29	61	TCMDC-135392	75	80	TCMDC-138600	66	95	TCMDC-140314	52	108
TCMDC-135553	14	36	TCMDC-132979	29	61	TCMDC-137251	75	80	TCMDC-139923	68	95	TCMDC-142004	54	108
TCMDC-135216	14	36	TCMDC-132452	30	61	TCMDC-135099	75	80	TCMDC-138987	68	95	TCMDC-133876	56	108
TCMDC-141636	14	36	TCMDC-141831	31	61	TCMDC-136852	76	80	TCMDC-140424	68	95	TCMDC-124388	64	108
TCMDC-140214	14	36	TCMDC-136528	31	61	TCMDC-138118	77	80	TCMDC-140350	69	95	TCMDC-133742	78	108
TCMDC-141246	15	36	TCMDC-136234	31	61	TCMDC-132970	78	80	TCMDC-125107	69	95	TCMDC-133459	79	108
TCMDC-132279	15	36	TCMDC-136275	31	61	TCMDC-142045	79	80	TCMDC-133757	69	95	TCMDC-123930	81	108
TCMDC-135228	16	36	TCMDC-137307	32	61	TCMDC-124099	79	80	TCMDC-137178	69	95	TCMDC-123694	81	108
TCMDC-138530	16	36	TCMDC-123959	32	61	TCMDC-125145	80	80	TCMDC-138212	71	95	TCMDC-135551	82	108
TCMDC-134097	17	36	TCMDC-132854	32	61	TCMDC-132973	80	80	TCMDC-136970	71	95	TCMDC-137654	82	108
TCMDC-131538	17	36	TCMDC-132180	32	61	TCMDC-125299	84	80	TCMDC-134973	71	95	TCMDC-125164	82	108
TCMDC-140851	17	36	TCMDC-132964	32	61	TCMDC-134264	4	81	TCMDC-139313	72	95	TCMDC-131620	83	108
TCMDC-132338	18	36	TCMDC-134253	33	61	TCMDC-123956	5	81	TCMDC-137499	72	95	TCMDC-135677	85	108
TCMDC-132879	18	36	TCMDC-134878	34	61	TCMDC-141017	5	81	TCMDC-132943	73	95	TCMDC-133098	86	108
TCMDC-134518	18	36	TCMDC-135809	34	61	TCMDC-134915	6	81	TCMDC-136503	73	95	TCMDC-124223	86	108
TCMDC-132246	19	36	TCMDC-141291	34	61	TCMDC-140005	11	81	TCMDC-134977	73	95	TCMDC-125452	86	108
TCMDC-124147	19	36	TCMDC-134619	35	61	TCMDC-132873	11	81	TCMDC-132156	73	95	TCMDC-124424	87	108
TCMDC-141369	20	36	TCMDC-138753	36	61	TCMDC-139939	12	81	TCMDC-139240	74	95	TCMDC-131289	87	108
TCMDC-124650	20	36	TCMDC-132569	37	61	TCMDC-134671	12	81	TCMDC-125356	75	95	TCMDC-134995	87	108
TCMDC-131526	20	36	TCMDC-140688	37	61	TCMDC-139752	12	81	TCMDC-137721	75	95	TCMDC-137673	87	108
TCMDC-141413	20	36	TCMDC-134872	37	61	TCMDC-141624	13	81	TCMDC-134631	75	95	TCMDC-136701	87	108
TCMDC-133981	21	36	TCMDC-139897	39	61	TCMDC-142233	14	81	TCMDC-131985	76	95	TCMDC-134632	89	108
TCMDC-131470	21	36	TCMDC-134004	40	61	TCMDC-136801	14	81	TCMDC-123615	76	95	TCMDC-124908	89	108
TCMDC-131519	21	36	TCMDC-141923	40	61	TCMDC-140825	15	81	TCMDC-140070	76	95	TCMDC-125819	89	108
TCMDC-139041	22	36	TCMDC-140732	40	61	TCMDC-136597	16	81	TCMDC-125364	77	95	TCMDC-136362	89	108
TCMDC-136534	22	36	TCMDC-134214	41	61	TCMDC-141523	19	81	TCMDC-141273	77	95	TCMDC-123811	90	108
TCMDC-131494	22	36	TCMDC-132190	42	61	TCMDC-139154	19	81	TCMDC-132689	77	95	TCMDC-133825	90	108
TCMDC-140257	22	36	TCMDC-140246	44	61	TCMDC-124430	20	81	TCMDC-134704	77	95	TCMDC-135213	91	108
TCMDC-131480	23	36	TCMDC-140380	44	61	TCMDC-139189	20	81	TCMDC-136997	78	95	TCMDC-138471	91	108
TCMDC-123551	24	36	TCMDC-133984	45	61	TCMDC-123690	21	81	TCMDC-123777	78	95	TCMDC-138175	91	108

TCMDC-141031	24	36	TCMDC-133373	46	61	TCMDC-139911	22	81	TCMDC-132372	78	95	TCMDC-137678	91	108
TCMDC-138778	26	36	TCMDC-132157	47	61	TCMDC-141550	23	81	TCMDC-135522	79	95	TCMDC-138194	91	108
TCMDC-136811	26	36	TCMDC-134736	47	61	TCMDC-125421	23	81	TCMDC-125263	79	95	TCMDC-138601	92	108
TCMDC-131496	26	36	TCMDC-142187	48	61	TCMDC-134433	23	81	TCMDC-140115	79	95	TCMDC-139537	92	108
TCMDC-140829	27	36	TCMDC-133874	49	61	TCMDC-134566	23	81	TCMDC-124941	80	95	TCMDC-136425	92	108
TCMDC-138637	27	36	TCMDC-124684	50	61	TCMDC-133915	24	81	TCMDC-131317	80	95	TCMDC-125624	92	108
TCMDC-134183	29	36	TCMDC-140929	50	61	TCMDC-132205	24	81	TCMDC-137904	80	95	TCMDC-125338	92	108
TCMDC-125683	29	36	TCMDC-141883	51	61	TCMDC-137062	25	81	TCMDC-142024	81	95	TCMDC-133633	92	108
TCMDC-133262	30	36	TCMDC-138343	51	61	TCMDC-123910	26	81	TCMDC-125589	82	95	TCMDC-125354	93	108
TCMDC-131835	30	36	TCMDC-124717	52	61	TCMDC-141696	26	81	TCMDC-124997	82	95	TCMDC-141791	93	108
TCMDC-141893	31	36	TCMDC-125042	57	61	TCMDC-134178	26	81	TCMDC-139627	83	95	TCMDC-131739	93	108
TCMDC-140299	32	36	TCMDC-136987	57	61	TCMDC-133552	27	81	TCMDC-138525	84	95	TCMDC-131626	93	108
TCMDC-133402	33	36	TCMDC-138350	59	61	TCMDC-124948	27	81	TCMDC-137978	84	95	TCMDC-124327	93	108
TCMDC-132168	34	36	TCMDC-132191	59	61	TCMDC-133700	27	81	TCMDC-131897	84	95	TCMDC-125836	93	108
TCMDC-138872	34	36	TCMDC-124568	59	61	TCMDC-136222	28	81	TCMDC-131430	85	95	TCMDC-133243	93	108
TCMDC-124813	34	36	TCMDC-138518	60	61	TCMDC-136758	28	81	TCMDC-125375	85	95	TCMDC-135590	93	108
TCMDC-125506	35	36	TCMDC-132420	60	61	TCMDC-138923	29	81	TCMDC-123869	85	95	TCMDC-125333	94	108
TCMDC-137779	35	36	TCMDC-124964	60	61	TCMDC-133282	31	81	TCMDC-140432	85	95	TCMDC-135596	94	108
TCMDC-138062	1	37	TCMDC-134123	60	61	TCMDC-141955	31	81	TCMDC-133630	85	95	TCMDC-139927	95	108
TCMDC-133707	3	37	TCMDC-142279	61	61	TCMDC-133313	31	81	TCMDC-135276	85	95	TCMDC-131368	95	108
TCMDC-141183	3	37	TCMDC-133064	65	61	TCMDC-141498	31	81	TCMDC-124480	86	95	TCMDC-125330	95	108
TCMDC-134047	5	37	TCMDC-139280	4	62	TCMDC-141969	32	81	TCMDC-137285	86	95	TCMDC-123765	95	108
TCMDC-141157	5	37	TCMDC-135777	5	62	TCMDC-140001	33	81	TCMDC-137668	86	95	TCMDC-134838	95	108
TCMDC-140112	5	37	TCMDC-138347	5	62	TCMDC-139542	33	81	TCMDC-137790	86	95	TCMDC-124945	96	108
TCMDC-140065	5	37	TCMDC-125315	5	62	TCMDC-131853	33	81	TCMDC-131401	86	95	TCMDC-124860	96	108
TCMDC-139362	6	37	TCMDC-138578	6	62	TCMDC-132101	33	81	TCMDC-124821	86	95	TCMDC-135067	96	108
TCMDC-141407	7	37	TCMDC-139584	6	62	TCMDC-138156	34	81	TCMDC-125743	87	95	TCMDC-135617	96	108
TCMDC-140617	7	37	TCMDC-141693	7	62	TCMDC-139196	34	81	TCMDC-136143	87	95	TCMDC-125705	96	108
TCMDC-125115	7	37	TCMDC-132831	8	62	TCMDC-135568	34	81	TCMDC-123471	87	95	TCMDC-137189	96	108
TCMDC-142075	8	37	TCMDC-140465	9	62	TCMDC-136715	34	81	TCMDC-135946	87	95	TCMDC-135975	96	108
TCMDC-132700	8	37	TCMDC-138432	10	62	TCMDC-123935	35	81	TCMDC-137296	87	95	TCMDC-124433	96	108
TCMDC-138351	8	37	TCMDC-140117	11	62	TCMDC-124658	35	81	TCMDC-131703	87	95	TCMDC-125332	96	108
TCMDC-135537	8	37	TCMDC-139918	11	62	TCMDC-140324	36	81	TCMDC-136716	88	95	TCMDC-124751	97	108
TCMDC-140173	8	37	TCMDC-137797	11	62	TCMDC-142243	36	81	TCMDC-135978	88	95	TCMDC-133352	97	108
TCMDC-132265	9	37	TCMDC-124957	11	62	TCMDC-135450	37	81	TCMDC-131778	88	95	TCMDC-142102	97	108
TCMDC-134108	10	37	TCMDC-139102	11	62	TCMDC-123599	38	81	TCMDC-124028	88	95	TCMDC-123629	97	108
TCMDC-135334	10	37	TCMDC-133491	12	62	TCMDC-133327	38	81	TCMDC-124840	88	95	TCMDC-131663	97	108

TCMDC-139232	10	37	TCMDC-134132	13	62	TCMDC-140723	38	81	TCMDC-135011	88	95	TCMDC-137804	97	108
TCMDC-123833	10	37	TCMDC-134805	13	62	TCMDC-136027	38	81	TCMDC-124109	89	95	TCMDC-137674	97	108
TCMDC-138009	10	37	TCMDC-135225	14	62	TCMDC-136592	39	81	TCMDC-123928	89	95	TCMDC-134729	97	108
TCMDC-136543	11	37	TCMDC-134430	15	62	TCMDC-140842	39	81	TCMDC-139398	89	95	TCMDC-124429	97	108
TCMDC-137163	11	37	TCMDC-134896	15	62	TCMDC-125444	40	81	TCMDC-124900	89	95	TCMDC-133819	98	108
TCMDC-139262	11	37	TCMDC-140877	15	62	TCMDC-123525	40	81	TCMDC-131386	89	95	TCMDC-131556	98	108
TCMDC-133063	12	37	TCMDC-135201	16	62	TCMDC-134655	41	81	TCMDC-123907	89	95	TCMDC-125329	98	108
TCMDC-142067	12	37	TCMDC-134675	16	62	TCMDC-142136	41	81	TCMDC-124839	89	95	TCMDC-137927	98	108
TCMDC-138854	12	37	TCMDC-134414	16	62	TCMDC-140715	41	81	TCMDC-135142	90	95	TCMDC-135587	98	108
TCMDC-132236	12	37	TCMDC-137527	17	62	TCMDC-139374	41	81	TCMDC-135164	90	95	TCMDC-138593	98	108
TCMDC-135886	12	37	TCMDC-139959	17	62	TCMDC-136293	42	81	TCMDC-137959	90	95	TCMDC-136327	99	108
TCMDC-132440	13	37	TCMDC-141634	17	62	TCMDC-139439	43	81	TCMDC-133626	90	95	TCMDC-131701	99	108
TCMDC-140018	13	37	TCMDC-141797	17	62	TCMDC-135223	43	81	TCMDC-133261	91	95	TCMDC-133209	99	108
TCMDC-134200	13	37	TCMDC-133445	18	62	TCMDC-136388	43	81	TCMDC-125221	91	95	TCMDC-125548	99	108
TCMDC-141705	13	37	TCMDC-140412	18	62	TCMDC-124897	44	81	TCMDC-138697	92	95	TCMDC-124916	100	108
TCMDC-141225	13	37	TCMDC-132533	18	62	TCMDC-139741	44	81	TCMDC-125260	92	95	TCMDC-125466	100	108
TCMDC-142085	13	37	TCMDC-141487	18	62	TCMDC-135980	45	81	TCMDC-123605	92	95	TCMDC-131398	100	108
TCMDC-137253	13	37	TCMDC-138317	18	62	TCMDC-136455	45	81	TCMDC-138984	92	95	TCMDC-131795	100	108
TCMDC-139892	14	37	TCMDC-139466	19	62	TCMDC-135095	46	81	TCMDC-124334	92	95	TCMDC-124783	101	108
TCMDC-125392	14	37	TCMDC-134580	20	62	TCMDC-131833	46	81	TCMDC-125730	92	95	TCMDC-124801	101	108
TCMDC-135280	15	37	TCMDC-134920	20	62	TCMDC-136753	48	81	TCMDC-133635	92	95	TCMDC-124861	101	108
TCMDC-140968	15	37	TCMDC-136623	20	62	TCMDC-133637	48	81	TCMDC-137540	93	95	TCMDC-124822	102	108
TCMDC-137168	15	37	TCMDC-139952	20	62	TCMDC-135792	48	81	TCMDC-125651	93	95	TCMDC-133182	102	108
TCMDC-137572	15	37	TCMDC-131284	20	62	TCMDC-137798	49	81	TCMDC-136324	93	95	TCMDC-125316	102	108
TCMDC-132436	16	37	TCMDC-135540	21	62	TCMDC-123749	49	81	TCMDC-135074	93	95	TCMDC-134420	103	108
TCMDC-124381	16	37	TCMDC-136277	21	62	TCMDC-124208	51	81	TCMDC-138802	93	95	TCMDC-123940	103	108
TCMDC-134567	16	37	TCMDC-142031	21	62	TCMDC-135760	53	81	TCMDC-135187	93	95	TCMDC-136323	103	108
TCMDC-134844	17	37	TCMDC-136526	21	62	TCMDC-140152	54	81	TCMDC-133057	93	95	TCMDC-125230	103	108
TCMDC-132122	17	37	TCMDC-140803	21	62	TCMDC-124726	54	81	TCMDC-124622	93	95	TCMDC-124395	103	108
TCMDC-135381	17	37	TCMDC-139521	21	62	TCMDC-123719	54	81	TCMDC-125248	93	95	TCMDC-138243	103	108
TCMDC-136231	17	37	TCMDC-136318	22	62	TCMDC-132592	55	81	TCMDC-124907	93	95	TCMDC-125498	103	108
TCMDC-141037	19	37	TCMDC-135197	22	62	TCMDC-124371	55	81	TCMDC-141919	94	95	TCMDC-138021	103	108
TCMDC-125480	19	37	TCMDC-133321	23	62	TCMDC-135989	56	81	TCMDC-123706	94	95	TCMDC-137534	103	108
TCMDC-131489	19	37	TCMDC-138990	23	62	TCMDC-125372	57	81	TCMDC-123635	94	95	TCMDC-124867	104	108
TCMDC-124638	20	37	TCMDC-141315	23	62	TCMDC-131808	58	81	TCMDC-135217	94	95	TCMDC-135584	104	108
TCMDC-140035	20	37	TCMDC-139607	23	62	TCMDC-125105	59	81	TCMDC-132948	94	95	TCMDC-133740	104	108
TCMDC-133886	20	37	TCMDC-134931	23	62	TCMDC-139612	60	81	TCMDC-134661	94	95	TCMDC-134038	104	108

TCMDC-141745	21	37	TCMDC-132521	23	62	TCMDC-125307	60	81	TCMDC-141986	94	95	TCMDC-136386	104	108
TCMDC-137467	21	37	TCMDC-134774	24	62	TCMDC-124871	62	81	TCMDC-131746	94	95	TCMDC-137042	105	108
TCMDC-140368	21	37	TCMDC-133837	24	62	TCMDC-136788	63	81	TCMDC-137878	94	95	TCMDC-124577	105	108
TCMDC-136357	22	37	TCMDC-134244	24	62	TCMDC-136994	63	81	TCMDC-132133	94	95	TCMDC-132974	105	108
TCMDC-133006	22	37	TCMDC-138920	24	62	TCMDC-134965	64	81	TCMDC-133818	94	95	TCMDC-133959	105	108
TCMDC-140819	22	37	TCMDC-131282	24	62	TCMDC-138804	64	81	TCMDC-123705	94	95	TCMDC-124702	105	108
TCMDC-134522	22	37	TCMDC-141067	24	62	TCMDC-133848	65	81	TCMDC-137920	94	95	TCMDC-135688	105	108
TCMDC-141730	22	37	TCMDC-133844	25	62	TCMDC-137102	65	81	TCMDC-125742	94	95	TCMDC-131579	105	108
TCMDC-132340	22	37	TCMDC-139473	25	62	TCMDC-138843	65	81	TCMDC-138315	94	95	TCMDC-136699	105	108
TCMDC-141727	23	37	TCMDC-134700	25	62	TCMDC-131832	65	81	TCMDC-133266	94	95	TCMDC-125474	106	108
TCMDC-132091	23	37	TCMDC-136707	25	62	TCMDC-134175	67	81	TCMDC-131295	94	95	TCMDC-136320	106	108
TCMDC-136809	23	37	TCMDC-125656	26	62	TCMDC-135913	68	81	TCMDC-137232	94	95	TCMDC-125255	106	108
TCMDC-137724	24	37	TCMDC-138874	26	62	TCMDC-131374	68	81	TCMDC-133642	94	95	TCMDC-125314	106	108
TCMDC-131471	24	37	TCMDC-140238	27	62	TCMDC-140852	68	81	TCMDC-137676	95	95	TCMDC-123721	106	108
TCMDC-137589	24	37	TCMDC-134791	27	62	TCMDC-139968	70	81	TCMDC-133719	95	95	TCMDC-133778	106	108
TCMDC-137875	24	37	TCMDC-134082	27	62	TCMDC-133567	70	81	TCMDC-134291	95	95	TCMDC-125264	106	108
TCMDC-140310	24	37	TCMDC-135799	27	62	TCMDC-135285	70	81	TCMDC-125807	95	95	TCMDC-138030	106	108
TCMDC-133670	25	37	TCMDC-132648	27	62	TCMDC-137665	70	81	TCMDC-136051	95	95	TCMDC-125323	106	108
TCMDC-141294	26	37	TCMDC-125137	28	62	TCMDC-133274	72	81	TCMDC-138374	95	95	TCMDC-132041	106	108
TCMDC-124481	26	37	TCMDC-136980	28	62	TCMDC-141272	72	81	TCMDC-125853	95	95	TCMDC-139288	107	108
TCMDC-136064	27	37	TCMDC-137123	28	62	TCMDC-132371	72	81	TCMDC-131315	95	95	TCMDC-133236	107	108
TCMDC-125880	27	37	TCMDC-132432	29	62	TCMDC-133585	72	81	TCMDC-125555	95	95	TCMDC-124629	107	108
TCMDC-141626	27	37	TCMDC-136423	29	62	TCMDC-125301	73	81	TCMDC-139363	95	95	TCMDC-133955	107	108
TCMDC-136483	28	37	TCMDC-136591	29	62	TCMDC-138529	73	81	TCMDC-125821	95	95	TCMDC-125161	107	108
TCMDC-136876	29	37	TCMDC-138660	29	62	TCMDC-140783	73	81	TCMDC-137879	95	95	TCMDC-124905	107	108
TCMDC-141536	31	37	TCMDC-134953	29	62	TCMDC-137713	73	81	TCMDC-135550	95	95	TCMDC-135593	107	108
TCMDC-138346	32	37	TCMDC-141209	30	62	TCMDC-135727	74	81	TCMDC-131540	95	95	TCMDC-135227	107	108
TCMDC-135441	32	37	TCMDC-124978	30	62	TCMDC-133790	74	81	TCMDC-137533	95	95	TCMDC-141234	107	108
TCMDC-135421	34	37	TCMDC-125685	30	62	TCMDC-125580	75	81	TCMDC-131925	95	95	TCMDC-139220	107	108
TCMDC-132764	35	37	TCMDC-134784	30	62	TCMDC-123632	75	81	TCMDC-137420	95	95	TCMDC-136322	108	108
TCMDC-133651	35	37	TCMDC-124627	30	62	TCMDC-136632	76	81	TCMDC-131339	95	95	TCMDC-124730	108	108
TCMDC-135679	35	37	TCMDC-137462	30	62	TCMDC-133003	76	81	TCMDC-136488	95	95	TCMDC-124875	108	108
TCMDC-142060	35	37	TCMDC-140582	31	62	TCMDC-125476	76	81	TCMDC-123846	95	95	TCMDC-125159	108	108
TCMDC-124911	37	37	TCMDC-142033	31	62	TCMDC-124414	76	81	TCMDC-137342	95	95	TCMDC-133219	108	108
TCMDC-132894	37	37	TCMDC-137142	31	62	TCMDC-136913	77	81	TCMDC-137318	96	95	TCMDC-136286	108	108
TCMDC-138221	37	37	TCMDC-136498	31	62	TCMDC-134158	77	81	TCMDC-125391	96	95	TCMDC-124800	24	109
TCMDC-131820	0	38	TCMDC-137500	32	62	TCMDC-137712	77	81	TCMDC-125088	100	95	TCMDC-125412	30	109

TCMDC-137502	3	38	TCMDC-139674	32	62	TCMDC-140248	78	81	TCMDC-133906	12	96	TCMDC-133237	31	109
TCMDC-123642	3	38	TCMDC-137554	32	62	TCMDC-134055	79	81	TCMDC-136288	20	96	TCMDC-133737	37	109
TCMDC-140114	4	38	TCMDC-139340	32	62	TCMDC-136921	79	81	TCMDC-134159	22	96	TCMDC-141926	40	109
TCMDC-139057	4	38	TCMDC-136057	32	62	TCMDC-140086	79	81	TCMDC-133536	23	96	TCMDC-136223	41	109
TCMDC-140355	4	38	TCMDC-141760	32	62	TCMDC-138504	79	81	TCMDC-133349	24	96	TCMDC-140648	49	109
TCMDC-132016	4	38	TCMDC-132650	33	62	TCMDC-125084	81	81	TCMDC-124277	26	96	TCMDC-136865	54	109
TCMDC-124013	5	38	TCMDC-133711	34	62	TCMDC-139475	81	81	TCMDC-142219	27	96	TCMDC-123938	56	109
TCMDC-142287	5	38	TCMDC-140374	34	62	TCMDC-139840	81	81	TCMDC-141243	29	96	TCMDC-135888	59	109
TCMDC-140979	6	38	TCMDC-140266	34	62	TCMDC-138975	5	82	TCMDC-139697	29	96	TCMDC-134961	64	109
TCMDC-141264	7	38	TCMDC-133367	34	62	TCMDC-136873	6	82	TCMDC-135756	31	96	TCMDC-136372	64	109
TCMDC-132068	8	38	TCMDC-135101	34	62	TCMDC-132261	8	82	TCMDC-136247	31	96	TCMDC-123589	67	109
TCMDC-140044	9	38	TCMDC-134001	35	62	TCMDC-137479	10	82	TCMDC-134913	34	96	TCMDC-134398	67	109
TCMDC-140501	9	38	TCMDC-133533	35	62	TCMDC-137573	10	82	TCMDC-136120	34	96	TCMDC-140307	68	109
TCMDC-123678	9	38	TCMDC-134981	35	62	TCMDC-131267	10	82	TCMDC-131859	35	96	TCMDC-134062	71	109
TCMDC-137569	9	38	TCMDC-141383	35	62	TCMDC-135875	11	82	TCMDC-141778	36	96	TCMDC-136821	72	109
TCMDC-137613	9	38	TCMDC-134360	36	62	TCMDC-142108	12	82	TCMDC-135744	37	96	TCMDC-134385	73	109
TCMDC-140592	10	38	TCMDC-141652	36	62	TCMDC-141929	12	82	TCMDC-132486	39	96	TCMDC-135612	74	109
TCMDC-134180	10	38	TCMDC-132998	36	62	TCMDC-132218	12	82	TCMDC-138247	40	96	TCMDC-141409	75	109
TCMDC-139225	11	38	TCMDC-139545	36	62	TCMDC-137640	13	82	TCMDC-124497	42	96	TCMDC-132802	76	109
TCMDC-138857	11	38	TCMDC-138598	37	62	TCMDC-134444	17	82	TCMDC-142328	44	96	TCMDC-125191	76	109
TCMDC-132929	11	38	TCMDC-140786	37	62	TCMDC-123746	18	82	TCMDC-137205	44	96	TCMDC-133438	78	109
TCMDC-132270	12	38	TCMDC-140045	37	62	TCMDC-139933	19	82	TCMDC-132142	44	96	TCMDC-140132	79	109
TCMDC-135673	12	38	TCMDC-125072	38	62	TCMDC-137820	19	82	TCMDC-141971	44	96	TCMDC-137957	82	109
TCMDC-140616	13	38	TCMDC-136985	38	62	TCMDC-136316	19	82	TCMDC-132684	45	96	TCMDC-124257	84	109
TCMDC-135774	13	38	TCMDC-133451	39	62	TCMDC-135349	20	82	TCMDC-139406	45	96	TCMDC-136345	85	109
TCMDC-132606	14	38	TCMDC-132507	39	62	TCMDC-136886	20	82	TCMDC-135759	46	96	TCMDC-134167	86	109
TCMDC-140567	14	38	TCMDC-138328	39	62	TCMDC-132554	21	82	TCMDC-134499	48	96	TCMDC-124449	88	109
TCMDC-125680	14	38	TCMDC-136887	40	62	TCMDC-141821	22	82	TCMDC-136680	48	96	TCMDC-136380	89	109
TCMDC-140896	15	38	TCMDC-135170	40	62	TCMDC-135162	22	82	TCMDC-134649	48	96	TCMDC-124317	89	109
TCMDC-132667	15	38	TCMDC-124994	41	62	TCMDC-135350	24	82	TCMDC-140834	48	96	TCMDC-136855	89	109
TCMDC-136090	15	38	TCMDC-138188	41	62	TCMDC-134677	25	82	TCMDC-132877	50	96	TCMDC-135076	90	109
TCMDC-125841	16	38	TCMDC-134265	42	62	TCMDC-140338	25	82	TCMDC-133729	50	96	TCMDC-140900	90	109
TCMDC-140470	16	38	TCMDC-138818	42	62	TCMDC-139492	26	82	TCMDC-133677	50	96	TCMDC-134609	91	109
TCMDC-140591	16	38	TCMDC-139600	42	62	TCMDC-140831	26	82	TCMDC-135745	51	96	TCMDC-131336	91	109
TCMDC-133887	16	38	TCMDC-132390	44	62	TCMDC-141304	26	82	TCMDC-123898	52	96	TCMDC-123823	91	109
TCMDC-132889	17	38	TCMDC-135501	45	62	TCMDC-141543	27	82	TCMDC-133206	52	96	TCMDC-125343	91	109
TCMDC-124137	18	38	TCMDC-134421	45	62	TCMDC-137946	27	82	TCMDC-136366	52	96	TCMDC-132048	91	109

TCMDC-132447	18	38	TCMDC-141585	46	62	TCMDC-134218	27	82	TCMDC-140084	52	96	TCMDC-136129	92	109
TCMDC-140273	18	38	TCMDC-136835	47	62	TCMDC-134615	27	82	TCMDC-131331	53	96	TCMDC-133591	92	109
TCMDC-136662	19	38	TCMDC-135483	47	62	TCMDC-134627	28	82	TCMDC-139736	53	96	TCMDC-123896	93	109
TCMDC-139658	19	38	TCMDC-139535	49	62	TCMDC-141177	29	82	TCMDC-138629	54	96	TCMDC-137917	93	109
TCMDC-139097	20	38	TCMDC-140505	49	62	TCMDC-136656	29	82	TCMDC-132355	55	96	TCMDC-133751	94	109
TCMDC-132378	20	38	TCMDC-138932	52	62	TCMDC-132711	29	82	TCMDC-141062	55	96	TCMDC-135577	95	109
TCMDC-131535	20	38	TCMDC-124054	52	62	TCMDC-141079	29	82	TCMDC-139424	56	96	TCMDC-124738	95	109
TCMDC-139549	21	38	TCMDC-124869	53	62	TCMDC-141149	30	82	TCMDC-134467	56	96	TCMDC-131936	96	109
TCMDC-134048	21	38	TCMDC-132699	53	62	TCMDC-124189	31	82	TCMDC-133467	56	96	TCMDC-137378	96	109
TCMDC-133563	22	38	TCMDC-140079	53	62	TCMDC-136207	33	82	TCMDC-135940	56	96	TCMDC-133816	97	109
TCMDC-141034	22	38	TCMDC-138505	54	62	TCMDC-135332	33	82	TCMDC-141880	57	96	TCMDC-137735	97	109
TCMDC-124404	22	38	TCMDC-142170	54	62	TCMDC-135938	33	82	TCMDC-141732	58	96	TCMDC-123858	97	109
TCMDC-133530	22	38	TCMDC-142176	58	62	TCMDC-135109	34	82	TCMDC-135715	59	96	TCMDC-125437	97	109
TCMDC-138265	22	38	TCMDC-125539	58	62	TCMDC-135785	34	82	TCMDC-133571	59	96	TCMDC-133992	98	109
TCMDC-139178	23	38	TCMDC-138749	58	62	TCMDC-134051	35	82	TCMDC-141140	59	96	TCMDC-141241	98	109
TCMDC-124797	23	38	TCMDC-132997	59	62	TCMDC-133488	35	82	TCMDC-139455	60	96	TCMDC-131622	98	109
TCMDC-132375	24	38	TCMDC-124353	60	62	TCMDC-133974	35	82	TCMDC-124187	60	96	TCMDC-131672	98	109
TCMDC-133403	24	38	TCMDC-138584	60	62	TCMDC-136468	35	82	TCMDC-124261	60	96	TCMDC-131790	98	109
TCMDC-141770	24	38	TCMDC-139544	60	62	TCMDC-142150	36	82	TCMDC-135348	61	96	TCMDC-131823	98	109
TCMDC-135103	24	38	TCMDC-138197	61	62	TCMDC-139350	36	82	TCMDC-140562	61	96	TCMDC-134999	98	109
TCMDC-137581	24	38	TCMDC-138620	61	62	TCMDC-133152	36	82	TCMDC-134463	62	96	TCMDC-124439	99	109
TCMDC-124040	24	38	TCMDC-132975	62	62	TCMDC-133679	36	82	TCMDC-139464	62	96	TCMDC-124699	99	109
TCMDC-142258	25	38	TCMDC-131811	2	63	TCMDC-141665	37	82	TCMDC-137741	62	96	TCMDC-124358	99	109
TCMDC-131420	25	38	TCMDC-140946	7	63	TCMDC-135753	37	82	TCMDC-141485	63	96	TCMDC-135610	99	109
TCMDC-124580	26	38	TCMDC-124805	8	63	TCMDC-132473	37	82	TCMDC-140624	63	96	TCMDC-131306	99	109
TCMDC-137312	26	38	TCMDC-139717	8	63	TCMDC-136978	37	82	TCMDC-135247	64	96	TCMDC-131737	99	109
TCMDC-136074	26	38	TCMDC-135822	9	63	TCMDC-132773	38	82	TCMDC-141336	64	96	TCMDC-131767	99	109
TCMDC-137065	26	38	TCMDC-133810	10	63	TCMDC-136836	39	82	TCMDC-133573	65	96	TCMDC-135463	99	109
TCMDC-135908	27	38	TCMDC-133722	10	63	TCMDC-134549	39	82	TCMDC-139863	65	96	TCMDC-135289	99	109
TCMDC-141599	27	38	TCMDC-132370	10	63	TCMDC-131281	39	82	TCMDC-132495	65	96	TCMDC-135002	99	109
TCMDC-133667	27	38	TCMDC-132918	10	63	TCMDC-138892	39	82	TCMDC-136909	65	96	TCMDC-125438	100	109
TCMDC-141716	28	38	TCMDC-139493	11	63	TCMDC-136118	40	82	TCMDC-139006	66	96	TCMDC-135646	100	109
TCMDC-136825	29	38	TCMDC-139629	12	63	TCMDC-135730	40	82	TCMDC-140772	66	96	TCMDC-135547	100	109
TCMDC-132096	29	38	TCMDC-136464	12	63	TCMDC-133292	40	82	TCMDC-135410	66	96	TCMDC-142303	100	109
TCMDC-135642	30	38	TCMDC-139835	12	63	TCMDC-135842	40	82	TCMDC-125725	67	96	TCMDC-124390	101	109
TCMDC-123913	30	38	TCMDC-139720	12	63	TCMDC-141660	41	82	TCMDC-140333	67	96	TCMDC-124775	101	109
TCMDC-138551	30	38	TCMDC-139201	13	63	TCMDC-125268	42	82	TCMDC-138059	68	96	TCMDC-140253	101	109

TCMDC-124248	31	38	TCMDC-133316	15	63	TCMDC-133996	42	82	TCMDC-136993	68	96	TCMDC-131343	101	109
TCMDC-139257	31	38	TCMDC-140167	16	63	TCMDC-124043	42	82	TCMDC-138558	68	96	TCMDC-125532	101	109
TCMDC-139044	31	38	TCMDC-136253	17	63	TCMDC-133599	42	82	TCMDC-141240	68	96	TCMDC-137117	101	109
TCMDC-136559	32	38	TCMDC-139159	17	63	TCMDC-132353	42	82	TCMDC-142044	68	96	TCMDC-135581	102	109
TCMDC-133665	33	38	TCMDC-135317	17	63	TCMDC-134781	43	82	TCMDC-133462	69	96	TCMDC-134297	102	109
TCMDC-139085	33	38	TCMDC-138983	17	63	TCMDC-136555	43	82	TCMDC-132697	69	96	TCMDC-133957	102	109
TCMDC-136092	33	38	TCMDC-132836	18	63	TCMDC-136126	44	82	TCMDC-136818	70	96	TCMDC-138675	102	109
TCMDC-125765	36	38	TCMDC-135436	18	63	TCMDC-138148	44	82	TCMDC-139427	70	96	TCMDC-133723	103	109
TCMDC-125206	37	38	TCMDC-134941	18	63	TCMDC-136102	44	82	TCMDC-138050	70	96	TCMDC-133960	103	109
TCMDC-134542	38	38	TCMDC-137814	19	63	TCMDC-135882	45	82	TCMDC-131364	70	96	TCMDC-138835	103	109
TCMDC-141418	38	38	TCMDC-134802	21	63	TCMDC-133016	45	82	TCMDC-140792	70	96	TCMDC-124772	104	109
TCMDC-138933	2	39	TCMDC-133565	21	63	TCMDC-139089	47	82	TCMDC-125734	70	96	TCMDC-125540	104	109
TCMDC-140950	4	39	TCMDC-125420	21	63	TCMDC-141425	48	82	TCMDC-135139	71	96	TCMDC-124703	104	109
TCMDC-139096	4	39	TCMDC-132102	21	63	TCMDC-124991	49	82	TCMDC-142109	71	96	TCMDC-125243	104	109
TCMDC-141456	5	39	TCMDC-132780	21	63	TCMDC-131357	49	82	TCMDC-133754	71	96	TCMDC-138185	104	109
TCMDC-141518	5	39	TCMDC-141668	22	63	TCMDC-124172	49	82	TCMDC-134400	71	96	TCMDC-124479	105	109
TCMDC-140587	5	39	TCMDC-134873	22	63	TCMDC-132778	50	82	TCMDC-138319	71	96	TCMDC-125446	105	109
TCMDC-124815	5	39	TCMDC-134804	22	63	TCMDC-137075	50	82	TCMDC-139503	72	96	TCMDC-125292	105	109
TCMDC-141519	6	39	TCMDC-138189	23	63	TCMDC-139734	51	82	TCMDC-138791	72	96	TCMDC-137704	105	109
TCMDC-141977	6	39	TCMDC-137063	23	63	TCMDC-125566	52	82	TCMDC-136584	73	96	TCMDC-134528	106	109
TCMDC-141803	7	39	TCMDC-132883	24	63	TCMDC-134968	53	82	TCMDC-134295	73	96	TCMDC-123697	106	109
TCMDC-133391	7	39	TCMDC-140883	24	63	TCMDC-125812	53	82	TCMDC-139724	74	96	TCMDC-125156	106	109
TCMDC-137084	8	39	TCMDC-136270	24	63	TCMDC-140095	54	82	TCMDC-134388	75	96	TCMDC-124619	106	109
TCMDC-134103	8	39	TCMDC-124962	25	63	TCMDC-142151	55	82	TCMDC-133207	76	96	TCMDC-125245	106	109
TCMDC-141337	9	39	TCMDC-135531	25	63	TCMDC-137687	55	82	TCMDC-140826	76	96	TCMDC-136337	106	109
TCMDC-137736	9	39	TCMDC-124097	25	63	TCMDC-136955	56	82	TCMDC-137701	76	96	TCMDC-131596	106	109
TCMDC-140110	9	39	TCMDC-140146	26	63	TCMDC-132491	56	82	TCMDC-136326	77	96	TCMDC-125027	107	109
TCMDC-139813	9	39	TCMDC-132448	28	63	TCMDC-134211	57	82	TCMDC-133290	78	96	TCMDC-133358	107	109
TCMDC-140922	9	39	TCMDC-141879	28	63	TCMDC-137669	57	82	TCMDC-124331	79	96	TCMDC-133965	107	109
TCMDC-131988	10	39	TCMDC-125005	29	63	TCMDC-137912	59	82	TCMDC-133278	79	96	TCMDC-132785	107	109
TCMDC-140980	10	39	TCMDC-132664	30	63	TCMDC-141859	61	82	TCMDC-138047	79	96	TCMDC-125162	107	109
TCMDC-132239	10	39	TCMDC-133528	30	63	TCMDC-133097	61	82	TCMDC-123569	80	96	TCMDC-125160	107	109
TCMDC-141302	10	39	TCMDC-135094	30	63	TCMDC-132698	61	82	TCMDC-135140	81	96	TCMDC-125365	107	109
TCMDC-132220	11	39	TCMDC-132445	31	63	TCMDC-132853	64	82	TCMDC-137742	81	96	TCMDC-133758	107	109
TCMDC-137774	12	39	TCMDC-140656	31	63	TCMDC-142054	66	82	TCMDC-124092	81	96	TCMDC-141118	107	109
TCMDC-141603	12	39	TCMDC-125692	31	63	TCMDC-131641	66	82	TCMDC-137223	81	96	TCMDC-125024	108	109
TCMDC-134424	12	39	TCMDC-140733	32	63	TCMDC-124974	68	82	TCMDC-139686	82	96	TCMDC-125543	108	109

TCMDC-135648	13	39	TCMDC-135169	33	63	TCMDC-141866	69	82	TCMDC-133631	82	96	TCMDC-138813	108	109
TCMDC-134666	14	39	TCMDC-141666	33	63	TCMDC-124238	71	82	TCMDC-140439	83	96	TCMDC-131623	108	109
TCMDC-140327	14	39	TCMDC-132446	34	63	TCMDC-136785	71	82	TCMDC-123894	83	96	TCMDC-138119	108	109
TCMDC-140614	15	39	TCMDC-135345	34	63	TCMDC-124027	72	82	TCMDC-125192	83	96	TCMDC-131705	108	109
TCMDC-139793	15	39	TCMDC-142088	34	63	TCMDC-132123	72	82	TCMDC-125432	84	96	TCMDC-125416	109	109
TCMDC-135500	16	39	TCMDC-134816	34	63	TCMDC-133159	73	82	TCMDC-136484	84	96	TCMDC-134006	109	109
TCMDC-141897	16	39	TCMDC-124552	35	63	TCMDC-140347	74	82	TCMDC-142312	85	96	TCMDC-137570	24	110
TCMDC-137945	16	39	TCMDC-135218	35	63	TCMDC-138842	74	82	TCMDC-135137	85	96	TCMDC-132835	40	110
TCMDC-132063	16	39	TCMDC-140936	35	63	TCMDC-140574	75	82	TCMDC-124802	85	96	TCMDC-136939	49	110
TCMDC-140994	16	39	TCMDC-132399	36	63	TCMDC-133472	76	82	TCMDC-125793	86	96	TCMDC-124558	50	110
TCMDC-131531	16	39	TCMDC-132940	36	63	TCMDC-132714	76	82	TCMDC-131631	86	96	TCMDC-124706	51	110
TCMDC-134089	17	39	TCMDC-140351	37	63	TCMDC-136959	76	82	TCMDC-123688	86	96	TCMDC-139264	54	110
TCMDC-133808	17	39	TCMDC-139937	38	63	TCMDC-136626	77	82	TCMDC-134261	87	96	TCMDC-141307	54	110
TCMDC-141412	18	39	TCMDC-133344	38	63	TCMDC-131592	78	82	TCMDC-133620	87	96	TCMDC-139386	62	110
TCMDC-140474	18	39	TCMDC-133884	38	63	TCMDC-136611	78	82	TCMDC-137930	87	96	TCMDC-125106	63	110
TCMDC-140876	18	39	TCMDC-139265	38	63	TCMDC-125083	78	82	TCMDC-125054	87	96	TCMDC-125373	64	110
TCMDC-134122	19	39	TCMDC-139543	39	63	TCMDC-133042	79	82	TCMDC-139558	87	96	TCMDC-135981	65	110
TCMDC-125021	20	39	TCMDC-140882	39	63	TCMDC-137865	80	82	TCMDC-123594	88	96	TCMDC-136414	69	110
TCMDC-139342	20	39	TCMDC-135532	40	63	TCMDC-138387	80	82	TCMDC-138245	88	96	TCMDC-141562	81	110
TCMDC-142277	20	39	TCMDC-135900	40	63	TCMDC-124330	81	82	TCMDC-136725	88	96	TCMDC-135663	81	110
TCMDC-135909	21	39	TCMDC-134826	40	63	TCMDC-136915	81	82	TCMDC-139551	88	96	TCMDC-131371	86	110
TCMDC-140330	21	39	TCMDC-133380	41	63	TCMDC-139283	2	83	TCMDC-139395	88	96	TCMDC-125610	87	110
TCMDC-141114	22	39	TCMDC-140664	41	63	TCMDC-138741	5	83	TCMDC-139485	88	96	TCMDC-135580	87	110
TCMDC-139224	22	39	TCMDC-124988	41	63	TCMDC-138788	5	83	TCMDC-137344	89	96	TCMDC-142298	87	110
TCMDC-140985	23	39	TCMDC-133038	42	63	TCMDC-140233	8	83	TCMDC-137331	89	96	TCMDC-136015	87	110
TCMDC-138246	23	39	TCMDC-132665	42	63	TCMDC-133226	11	83	TCMDC-137651	89	96	TCMDC-139784	88	110
TCMDC-136302	24	39	TCMDC-142126	43	63	TCMDC-139392	13	83	TCMDC-133561	89	96	TCMDC-135644	88	110
TCMDC-140123	24	39	TCMDC-133301	44	63	TCMDC-140377	15	83	TCMDC-133287	90	96	TCMDC-124625	89	110
TCMDC-132232	25	39	TCMDC-140294	44	63	TCMDC-124158	16	83	TCMDC-131715	90	96	TCMDC-133746	90	110
TCMDC-140184	25	39	TCMDC-136797	45	63	TCMDC-136010	17	83	TCMDC-142331	90	96	TCMDC-124585	91	110
TCMDC-142182	25	39	TCMDC-138467	45	63	TCMDC-142184	18	83	TCMDC-124460	90	96	TCMDC-131913	91	110
TCMDC-141349	25	39	TCMDC-123466	45	63	TCMDC-136653	18	83	TCMDC-123456	90	96	TCMDC-138220	91	110
TCMDC-138767	26	39	TCMDC-139738	45	63	TCMDC-141822	20	83	TCMDC-125869	90	96	TCMDC-125341	92	110
TCMDC-136645	26	39	TCMDC-141962	47	63	TCMDC-138543	20	83	TCMDC-123658	90	96	TCMDC-131650	93	110
TCMDC-133099	26	39	TCMDC-140960	47	63	TCMDC-134436	21	83	TCMDC-125787	90	96	TCMDC-133463	93	110
TCMDC-138453	27	39	TCMDC-135479	49	63	TCMDC-124512	21	83	TCMDC-140461	91	96	TCMDC-135430	93	110
TCMDC-133668	27	39	TCMDC-132965	49	63	TCMDC-133738	21	83	TCMDC-135069	91	96	TCMDC-132457	94	110

TCMDC-131836	28	39	TCMDC-142324	50	63	TCMDC-139958	21	83	TCMDC-136796	91	96	TCMDC-135159	96	110
TCMDC-124373	29	39	TCMDC-133655	50	63	TCMDC-124534	21	83	TCMDC-132196	91	96	TCMDC-134118	96	110
TCMDC-134188	30	39	TCMDC-138695	50	63	TCMDC-140864	22	83	TCMDC-138089	91	96	TCMDC-133832	96	110
TCMDC-138482	30	39	TCMDC-125295	52	63	TCMDC-137134	22	83	TCMDC-131294	91	96	TCMDC-134399	96	110
TCMDC-135369	32	39	TCMDC-139384	52	63	TCMDC-141830	23	83	TCMDC-137004	91	96	TCMDC-138591	97	110
TCMDC-131840	32	39	TCMDC-138217	53	63	TCMDC-132058	23	83	TCMDC-124859	91	96	TCMDC-124769	97	110
TCMDC-135928	32	39	TCMDC-135207	53	63	TCMDC-136655	24	83	TCMDC-131257	91	96	TCMDC-136016	97	110
TCMDC-140211	33	39	TCMDC-133587	54	63	TCMDC-139662	24	83	TCMDC-125259	92	96	TCMDC-124204	97	110
TCMDC-141162	34	39	TCMDC-142142	55	63	TCMDC-139098	24	83	TCMDC-125076	92	96	TCMDC-123732	98	110
TCMDC-125608	34	39	TCMDC-132742	55	63	TCMDC-138565	24	83	TCMDC-137923	92	96	TCMDC-124618	98	110
TCMDC-138379	34	39	TCMDC-141121	56	63	TCMDC-141941	25	83	TCMDC-139547	92	96	TCMDC-135582	98	110
TCMDC-136165	34	39	TCMDC-133799	56	63	TCMDC-124513	25	83	TCMDC-137052	92	96	TCMDC-135042	98	110
TCMDC-135051	36	39	TCMDC-138961	58	63	TCMDC-139525	25	83	TCMDC-123761	92	96	TCMDC-135016	98	110
TCMDC-123633	36	39	TCMDC-136029	58	63	TCMDC-139284	25	83	TCMDC-125798	92	96	TCMDC-124810	99	110
TCMDC-136539	37	39	TCMDC-133073	59	63	TCMDC-137457	25	83	TCMDC-125706	93	96	TCMDC-124913	99	110
TCMDC-137672	37	39	TCMDC-138330	59	63	TCMDC-133501	26	83	TCMDC-137002	93	96	TCMDC-137760	99	110
TCMDC-133649	38	39	TCMDC-134113	61	63	TCMDC-139507	26	83	TCMDC-124352	93	96	TCMDC-124536	100	110
TCMDC-133596	38	39	TCMDC-135320	62	63	TCMDC-123617	27	83	TCMDC-132946	93	96	TCMDC-135613	100	110
TCMDC-135183	38	39	TCMDC-139036	62	63	TCMDC-135356	27	83	TCMDC-135666	93	96	TCMDC-123771	100	110
TCMDC-141375	39	39	TCMDC-123686	63	63	TCMDC-140176	27	83	TCMDC-139021	93	96	TCMDC-131610	100	110
TCMDC-135481	39	39	TCMDC-138082	3	64	TCMDC-133877	27	83	TCMDC-134998	93	96	TCMDC-131735	100	110
TCMDC-135482	44	39	TCMDC-139956	5	64	TCMDC-141706	27	83	TCMDC-136864	93	96	TCMDC-131323	100	110
TCMDC-141931	2	40	TCMDC-141516	6	64	TCMDC-124524	27	83	TCMDC-139502	94	96	TCMDC-124588	101	110
TCMDC-131819	2	40	TCMDC-133338	6	64	TCMDC-124555	28	83	TCMDC-134259	94	96	TCMDC-132950	101	110
TCMDC-139951	3	40	TCMDC-134475	8	64	TCMDC-141713	28	83	TCMDC-132010	94	96	TCMDC-123684	102	110
TCMDC-140387	3	40	TCMDC-138544	8	64	TCMDC-135567	28	83	TCMDC-124347	94	96	TCMDC-140763	102	110
TCMDC-137992	3	40	TCMDC-138926	8	64	TCMDC-136356	29	83	TCMDC-124759	94	96	TCMDC-124098	103	110
TCMDC-138794	4	40	TCMDC-139577	9	64	TCMDC-132536	29	83	TCMDC-137173	94	96	TCMDC-124456	103	110
TCMDC-139798	4	40	TCMDC-139706	10	64	TCMDC-135723	30	83	TCMDC-139281	94	96	TCMDC-133963	104	110
TCMDC-142206	4	40	TCMDC-139869	10	64	TCMDC-136109	30	83	TCMDC-137887	94	96	TCMDC-125646	105	110
TCMDC-139811	4	40	TCMDC-141313	10	64	TCMDC-124265	30	83	TCMDC-123753	94	96	TCMDC-123620	106	110
TCMDC-141018	6	40	TCMDC-137493	10	64	TCMDC-136874	30	83	TCMDC-137863	94	96	TCMDC-133988	106	110
TCMDC-137850	6	40	TCMDC-141156	11	64	TCMDC-139815	31	83	TCMDC-123624	95	96	TCMDC-123578	106	110
TCMDC-136048	7	40	TCMDC-132921	11	64	TCMDC-136353	31	83	TCMDC-141474	95	96	TCMDC-133743	107	110
TCMDC-141061	7	40	TCMDC-140174	11	64	TCMDC-139125	31	83	TCMDC-123542	95	96	TCMDC-134166	108	110
TCMDC-139286	7	40	TCMDC-139247	12	64	TCMDC-140740	33	83	TCMDC-124387	95	96	TCMDC-140433	108	110
TCMDC-132556	8	40	TCMDC-141583	13	64	TCMDC-134450	33	83	TCMDC-131647	95	96	TCMDC-132784	108	110

TCMDC-135446	8	40	TCMDC-134191	13	64	TCMDC-133780	33	83	TCMDC-133691	95	96	TCMDC-133741	108	110
TCMDC-140969	8	40	TCMDC-139944	14	64	TCMDC-139256	34	83	TCMDC-137630	95	96	TCMDC-123574	109	110
TCMDC-138517	9	40	TCMDC-138727	14	64	TCMDC-124799	34	83	TCMDC-131799	95	96	TCMDC-125672	109	110
TCMDC-140623	9	40	TCMDC-139519	14	64	TCMDC-141963	34	83	TCMDC-131310	95	96	TCMDC-125475	110	110
TCMDC-140952	9	40	TCMDC-134447	15	64	TCMDC-140709	34	83	TCMDC-131642	95	96	TCMDC-134997	110	110
TCMDC-141178	9	40	TCMDC-123727	15	64	TCMDC-136794	35	83	TCMDC-134397	95	96	TCMDC-124879	110	110
TCMDC-141226	10	40	TCMDC-134938	16	64	TCMDC-134825	35	83	TCMDC-124303	95	96	TCMDC-133749	110	110
TCMDC-135783	10	40	TCMDC-140719	16	64	TCMDC-140931	35	83	TCMDC-141010	95	96	TCMDC-134263	113	110
TCMDC-132285	11	40	TCMDC-134917	16	64	TCMDC-135117	36	83	TCMDC-125738	95	96	TCMDC-132462	29	111
TCMDC-137514	11	40	TCMDC-139669	16	64	TCMDC-133071	36	83	TCMDC-140738	95	96	TCMDC-132153	35	111
TCMDC-140536	11	40	TCMDC-136083	17	64	TCMDC-139228	36	83	TCMDC-139052	96	96	TCMDC-132730	43	111
TCMDC-140491	11	40	TCMDC-135199	18	64	TCMDC-139124	36	83	TCMDC-137429	96	96	TCMDC-133469	47	111
TCMDC-135512	11	40	TCMDC-134748	18	64	TCMDC-135058	37	83	TCMDC-138876	96	96	TCMDC-133681	47	111
TCMDC-141457	11	40	TCMDC-141796	18	64	TCMDC-138680	37	83	TCMDC-135795	96	96	TCMDC-131536	47	111
TCMDC-135033	12	40	TCMDC-142197	19	64	TCMDC-134811	38	83	TCMDC-125591	96	96	TCMDC-132850	59	111
TCMDC-141600	13	40	TCMDC-134765	19	64	TCMDC-132490	38	83	TCMDC-137755	96	96	TCMDC-135733	70	111
TCMDC-140802	13	40	TCMDC-133485	19	64	TCMDC-123519	38	83	TCMDC-123886	96	96	TCMDC-124304	70	111
TCMDC-132616	14	40	TCMDC-140195	20	64	TCMDC-134373	38	83	TCMDC-140731	96	96	TCMDC-123685	84	111
TCMDC-138410	14	40	TCMDC-135278	20	64	TCMDC-135725	39	83	TCMDC-134310	96	96	TCMDC-137288	85	111
TCMDC-133386	15	40	TCMDC-125810	20	64	TCMDC-125463	39	83	TCMDC-123996	96	96	TCMDC-134554	86	111
TCMDC-135465	15	40	TCMDC-133982	21	64	TCMDC-142115	39	83	TCMDC-134030	96	96	TCMDC-136389	88	111
TCMDC-140620	16	40	TCMDC-139912	21	64	TCMDC-133694	39	83	TCMDC-124179	96	96	TCMDC-125622	88	111
TCMDC-141746	16	40	TCMDC-133394	21	64	TCMDC-124260	39	83	TCMDC-134454	1	97	TCMDC-134752	89	111
TCMDC-139118	16	40	TCMDC-131881	21	64	TCMDC-139160	39	83	TCMDC-124341	10	97	TCMDC-125703	89	111
TCMDC-132531	17	40	TCMDC-135145	22	64	TCMDC-123855	40	83	TCMDC-136803	14	97	TCMDC-124029	90	111
TCMDC-142283	17	40	TCMDC-136605	22	64	TCMDC-125319	40	83	TCMDC-138902	18	97	TCMDC-125165	91	111
TCMDC-141028	18	40	TCMDC-139132	23	64	TCMDC-134665	40	83	TCMDC-138266	22	97	TCMDC-140391	91	111
TCMDC-136599	18	40	TCMDC-139609	24	64	TCMDC-139104	40	83	TCMDC-136228	23	97	TCMDC-125623	92	111
TCMDC-140042	18	40	TCMDC-135631	25	64	TCMDC-139881	40	83	TCMDC-141882	30	97	TCMDC-136403	92	111
TCMDC-139134	18	40	TCMDC-133900	25	64	TCMDC-133806	41	83	TCMDC-137547	30	97	TCMDC-135545	93	111
TCMDC-133775	19	40	TCMDC-139709	26	64	TCMDC-142113	42	83	TCMDC-125401	31	97	TCMDC-131943	93	111
TCMDC-125237	19	40	TCMDC-142236	26	64	TCMDC-136568	42	83	TCMDC-135445	31	97	TCMDC-133156	95	111
TCMDC-125351	19	40	TCMDC-138280	26	64	TCMDC-137622	45	83	TCMDC-137883	31	97	TCMDC-124314	95	111
TCMDC-135196	19	40	TCMDC-136233	26	64	TCMDC-134469	46	83	TCMDC-134460	32	97	TCMDC-137815	95	111
TCMDC-141766	19	40	TCMDC-133204	26	64	TCMDC-132204	46	83	TCMDC-132675	34	97	TCMDC-133971	96	111
TCMDC-140863	19	40	TCMDC-132541	26	64	TCMDC-134369	46	83	TCMDC-133372	35	97	TCMDC-125246	96	111
TCMDC-139776	20	40	TCMDC-140695	27	64	TCMDC-142148	46	83	TCMDC-139684	36	97	TCMDC-136634	96	111

TCMDC-135105	22	40	TCMDC-134883	27	64	TCMDC-139681	48	83	TCMDC-123631	37	97	TCMDC-138136	96	111
TCMDC-139611	22	40	TCMDC-134905	27	64	TCMDC-134960	48	83	TCMDC-139414	37	97	TCMDC-138678	96	111
TCMDC-124321	22	40	TCMDC-132427	28	64	TCMDC-139407	48	83	TCMDC-139561	37	97	TCMDC-141356	96	111
TCMDC-140571	22	40	TCMDC-141222	28	64	TCMDC-135198	49	83	TCMDC-141530	37	97	TCMDC-141719	97	111
TCMDC-132607	22	40	TCMDC-132539	28	64	TCMDC-140769	49	83	TCMDC-138696	38	97	TCMDC-131532	98	111
TCMDC-136511	22	40	TCMDC-132710	29	64	TCMDC-133200	49	83	TCMDC-134494	38	97	TCMDC-123822	99	111
TCMDC-131464	22	40	TCMDC-134410	29	64	TCMDC-139292	50	83	TCMDC-140856	40	97	TCMDC-124934	99	111
TCMDC-135325	24	40	TCMDC-142010	29	64	TCMDC-139746	51	83	TCMDC-124592	41	97	TCMDC-125335	99	111
TCMDC-135340	24	40	TCMDC-142326	29	64	TCMDC-135286	51	83	TCMDC-136765	41	97	TCMDC-132124	99	111
TCMDC-141988	24	40	TCMDC-139110	30	64	TCMDC-131590	52	83	TCMDC-125428	41	97	TCMDC-138516	99	111
TCMDC-136212	24	40	TCMDC-132737	30	64	TCMDC-142041	54	83	TCMDC-133640	41	97	TCMDC-137204	99	111
TCMDC-124692	25	40	TCMDC-142134	31	64	TCMDC-135921	54	83	TCMDC-133860	42	97	TCMDC-134029	99	111
TCMDC-134201	25	40	TCMDC-140270	32	64	TCMDC-140515	54	83	TCMDC-136268	42	97	TCMDC-135967	100	111
TCMDC-136893	25	40	TCMDC-138958	32	64	TCMDC-137847	54	83	TCMDC-136872	42	97	TCMDC-125039	100	111
TCMDC-141405	26	40	TCMDC-139319	33	64	TCMDC-123487	55	83	TCMDC-133638	43	97	TCMDC-131324	100	111
TCMDC-138720	27	40	TCMDC-124950	33	64	TCMDC-131265	55	83	TCMDC-133272	44	97	TCMDC-123879	101	111
TCMDC-131487	27	40	TCMDC-135899	34	64	TCMDC-142070	55	83	TCMDC-136571	44	97	TCMDC-136705	101	111
TCMDC-141992	27	40	TCMDC-137054	34	64	TCMDC-138985	55	83	TCMDC-124649	45	97	TCMDC-124915	102	111
TCMDC-133652	28	40	TCMDC-132183	34	64	TCMDC-140935	55	83	TCMDC-138208	45	97	TCMDC-131798	102	111
TCMDC-133659	29	40	TCMDC-132925	36	64	TCMDC-137137	56	83	TCMDC-135194	47	97	TCMDC-136880	102	111
TCMDC-140687	29	40	TCMDC-134667	37	64	TCMDC-137901	56	83	TCMDC-133977	47	97	TCMDC-131733	103	111
TCMDC-135174	29	40	TCMDC-132762	38	64	TCMDC-132134	57	83	TCMDC-141279	49	97	TCMDC-136613	104	111
TCMDC-140210	31	40	TCMDC-137671	38	64	TCMDC-135941	57	83	TCMDC-134470	50	97	TCMDC-125002	105	111
TCMDC-124201	31	40	TCMDC-141781	39	64	TCMDC-141607	57	83	TCMDC-133066	51	97	TCMDC-131297	105	111
TCMDC-139184	31	40	TCMDC-136934	40	64	TCMDC-136992	57	83	TCMDC-140795	52	97	TCMDC-124930	106	111
TCMDC-123932	32	40	TCMDC-133454	41	64	TCMDC-131792	57	83	TCMDC-135729	53	97	TCMDC-125240	107	111
TCMDC-136355	33	40	TCMDC-139300	41	64	TCMDC-135966	57	83	TCMDC-125795	53	97	TCMDC-136159	108	111
TCMDC-142175	34	40	TCMDC-135136	41	64	TCMDC-133247	58	83	TCMDC-124722	53	97	TCMDC-131875	108	111
TCMDC-140162	34	40	TCMDC-136075	43	64	TCMDC-136651	60	83	TCMDC-132319	54	97	TCMDC-137229	108	111
TCMDC-138329	37	40	TCMDC-138070	44	64	TCMDC-138081	60	83	TCMDC-135399	56	97	TCMDC-124753	109	111
TCMDC-134182	37	40	TCMDC-139649	45	64	TCMDC-125565	61	83	TCMDC-139925	56	97	TCMDC-124669	109	111
TCMDC-123921	38	40	TCMDC-135635	45	64	TCMDC-142327	61	83	TCMDC-133122	56	97	TCMDC-132967	109	111
TCMDC-140665	39	40	TCMDC-134772	46	64	TCMDC-136248	61	83	TCMDC-134465	57	97	TCMDC-138997	109	111
TCMDC-138691	39	40	TCMDC-132317	46	64	TCMDC-139643	63	83	TCMDC-142241	57	97	TCMDC-142213	109	111
TCMDC-132968	39	40	TCMDC-134857	48	64	TCMDC-138068	63	83	TCMDC-133456	58	97	TCMDC-132593	41	112
TCMDC-142259	40	40	TCMDC-133136	49	64	TCMDC-139499	64	83	TCMDC-140082	58	97	TCMDC-133901	44	112
TCMDC-125403	4	41	TCMDC-133045	49	64	TCMDC-136406	65	83	TCMDC-136895	58	97	TCMDC-133826	50	112

TCMDC-124093	4	41	TCMDC-141664	51	64	TCMDC-132141	66	83	TCMDC-139735	58	97	TCMDC-136900	51	112
TCMDC-141318	5	41	TCMDC-124983	52	64	TCMDC-124218	66	83	TCMDC-134313	59	97	TCMDC-133297	52	112
TCMDC-138609	5	41	TCMDC-135775	53	64	TCMDC-136998	67	83	TCMDC-135167	60	97	TCMDC-124931	68	112
TCMDC-141697	6	41	TCMDC-138228	54	64	TCMDC-133249	68	83	TCMDC-133938	60	97	TCMDC-136404	69	112
TCMDC-132361	6	41	TCMDC-131827	55	64	TCMDC-133310	68	83	TCMDC-135153	60	97	TCMDC-139771	71	112
TCMDC-140630	7	41	TCMDC-136922	56	64	TCMDC-135892	68	83	TCMDC-133613	61	97	TCMDC-137980	72	112
TCMDC-132082	7	41	TCMDC-136831	57	64	TCMDC-140576	69	83	TCMDC-139194	61	97	TCMDC-139779	72	112
TCMDC-132268	8	41	TCMDC-139051	58	64	TCMDC-123899	70	83	TCMDC-131721	61	97	TCMDC-140460	72	112
TCMDC-139230	8	41	TCMDC-136902	59	64	TCMDC-139829	70	83	TCMDC-125451	62	97	TCMDC-135600	77	112
TCMDC-135764	8	41	TCMDC-123593	59	64	TCMDC-131950	70	83	TCMDC-136250	62	97	TCMDC-131692	84	112
TCMDC-139992	8	41	TCMDC-137152	59	64	TCMDC-141045	71	83	TCMDC-125756	63	97	TCMDC-136724	86	112
TCMDC-141012	8	41	TCMDC-123784	60	64	TCMDC-124779	72	83	TCMDC-136172	64	97	TCMDC-125366	90	112
TCMDC-133395	8	41	TCMDC-124278	60	64	TCMDC-136911	72	83	TCMDC-140666	64	97	TCMDC-125288	91	112
TCMDC-141711	8	41	TCMDC-142032	61	64	TCMDC-125662	73	83	TCMDC-124963	65	97	TCMDC-138483	91	112
TCMDC-124284	10	41	TCMDC-131258	61	64	TCMDC-134694	73	83	TCMDC-140441	67	97	TCMDC-125382	93	112
TCMDC-140280	10	41	TCMDC-136565	63	64	TCMDC-124102	74	83	TCMDC-135716	68	97	TCMDC-133308	94	112
TCMDC-140741	10	41	TCMDC-135377	63	64	TCMDC-133175	74	83	TCMDC-132976	68	97	TCMDC-136780	94	112
TCMDC-132154	10	41	TCMDC-136963	63	64	TCMDC-138540	74	83	TCMDC-125782	69	97	TCMDC-137011	95	112
TCMDC-140373	10	41	TCMDC-136630	64	64	TCMDC-133060	74	83	TCMDC-136603	69	97	TCMDC-135583	96	112
TCMDC-140490	11	41	TCMDC-138503	65	64	TCMDC-133803	75	83	TCMDC-131887	69	97	TCMDC-135977	96	112
TCMDC-134418	12	41	TCMDC-123877	2	65	TCMDC-123515	76	83	TCMDC-134148	70	97	TCMDC-124940	97	112
TCMDC-131966	12	41	TCMDC-138630	4	65	TCMDC-136783	76	83	TCMDC-137960	71	97	TCMDC-133962	97	112
TCMDC-137700	12	41	TCMDC-138105	4	65	TCMDC-133418	76	83	TCMDC-135021	72	97	TCMDC-123709	97	112
TCMDC-141282	13	41	TCMDC-140066	6	65	TCMDC-133011	77	83	TCMDC-134947	72	97	TCMDC-131416	97	112
TCMDC-141346	13	41	TCMDC-136618	7	65	TCMDC-138858	77	83	TCMDC-135914	72	97	TCMDC-124324	97	112
TCMDC-142087	13	41	TCMDC-135622	7	65	TCMDC-123585	80	83	TCMDC-137091	73	97	TCMDC-131651	98	112
TCMDC-142074	13	41	TCMDC-140945	7	65	TCMDC-124695	80	83	TCMDC-132403	73	97	TCMDC-125379	98	112
TCMDC-124001	14	41	TCMDC-137723	7	65	TCMDC-139874	80	83	TCMDC-133171	74	97	TCMDC-142320	98	112
TCMDC-140267	14	41	TCMDC-124030	9	65	TCMDC-138611	80	83	TCMDC-124264	74	97	TCMDC-135819	99	112
TCMDC-137477	14	41	TCMDC-135284	9	65	TCMDC-124682	81	83	TCMDC-131354	74	97	TCMDC-123805	99	112
TCMDC-141901	14	41	TCMDC-140777	10	65	TCMDC-135018	81	83	TCMDC-141099	74	97	TCMDC-133831	99	112
TCMDC-140468	14	41	TCMDC-140362	10	65	TCMDC-124483	82	83	TCMDC-132120	76	97	TCMDC-124320	99	112
TCMDC-133975	15	41	TCMDC-134808	11	65	TCMDC-125128	82	83	TCMDC-137954	76	97	TCMDC-123573	101	112
TCMDC-141108	15	41	TCMDC-141317	12	65	TCMDC-125281	82	83	TCMDC-134296	76	97	TCMDC-124812	101	112
TCMDC-136789	15	41	TCMDC-132587	12	65	TCMDC-141579	82	83	TCMDC-137364	77	97	TCMDC-125203	101	112
TCMDC-131548	15	41	TCMDC-134626	12	65	TCMDC-134530	82	83	TCMDC-139872	77	97	TCMDC-123712	101	112
TCMDC-137566	16	41	TCMDC-138326	12	65	TCMDC-136586	82	83	TCMDC-132896	77	97	TCMDC-136968	102	112

TCMDC-132454	16	41	TCMDC-125306	13	65	TCMDC-135255	83	83	TCMDC-132356	77	97	TCMDC-135043	102	112
TCMDC-132736	16	41	TCMDC-139239	13	65	TCMDC-136583	83	83	TCMDC-131679	77	97	TCMDC-124505	103	112
TCMDC-138323	16	41	TCMDC-135180	14	65	TCMDC-141953	83	83	TCMDC-136395	78	97	TCMDC-135185	103	112
TCMDC-138764	17	41	TCMDC-133441	14	65	TCMDC-125441	84	83	TCMDC-132422	78	97	TCMDC-137339	103	112
TCMDC-141080	17	41	TCMDC-139261	14	65	TCMDC-139335	2	84	TCMDC-137295	78	97	TCMDC-132400	104	112
TCMDC-134535	17	41	TCMDC-133194	15	65	TCMDC-123671	6	84	TCMDC-131830	79	97	TCMDC-135525	104	112
TCMDC-141021	18	41	TCMDC-141026	15	65	TCMDC-124162	7	84	TCMDC-142316	79	97	TCMDC-125275	105	112
TCMDC-125399	18	41	TCMDC-132682	15	65	TCMDC-132472	8	84	TCMDC-124118	81	97	TCMDC-123736	105	112
TCMDC-132381	19	41	TCMDC-141481	16	65	TCMDC-125298	8	84	TCMDC-137333	82	97	TCMDC-124850	105	112
TCMDC-141979	19	41	TCMDC-139903	16	65	TCMDC-124561	14	84	TCMDC-124024	82	97	TCMDC-137535	105	112
TCMDC-141350	19	41	TCMDC-131602	17	65	TCMDC-139626	15	84	TCMDC-137645	83	97	TCMDC-133283	105	112
TCMDC-134077	19	41	TCMDC-134875	17	65	TCMDC-141142	17	84	TCMDC-137677	83	97	TCMDC-132786	107	112
TCMDC-141174	19	41	TCMDC-125614	17	65	TCMDC-140221	17	84	TCMDC-140904	83	97	TCMDC-135653	107	112
TCMDC-141998	20	41	TCMDC-141187	18	65	TCMDC-132549	18	84	TCMDC-137650	83	97	TCMDC-123960	109	112
TCMDC-136609	20	41	TCMDC-132734	18	65	TCMDC-140727	20	84	TCMDC-136606	83	97	TCMDC-125318	109	112
TCMDC-140551	20	41	TCMDC-133494	18	65	TCMDC-134340	21	84	TCMDC-132471	84	97	TCMDC-136301	109	112
TCMDC-141256	20	41	TCMDC-132618	18	65	TCMDC-135061	22	84	TCMDC-135079	84	97	TCMDC-137861	38	113
TCMDC-138878	20	41	TCMDC-135638	19	65	TCMDC-133440	22	84	TCMDC-137649	84	97	TCMDC-132861	40	113
TCMDC-135032	22	41	TCMDC-142062	19	65	TCMDC-134013	23	84	TCMDC-140730	84	97	TCMDC-131611	56	113
TCMDC-132524	22	41	TCMDC-135424	21	65	TCMDC-135818	23	84	TCMDC-132795	84	97	TCMDC-135075	61	113
TCMDC-140659	22	41	TCMDC-132865	21	65	TCMDC-123700	24	84	TCMDC-138147	85	97	TCMDC-139460	63	113
TCMDC-133657	22	41	TCMDC-139053	21	65	TCMDC-136542	24	84	TCMDC-135521	86	97	TCMDC-140130	66	113
TCMDC-141975	22	41	TCMDC-132467	21	65	TCMDC-124032	25	84	TCMDC-131877	86	97	TCMDC-132025	66	113
TCMDC-133880	24	41	TCMDC-139415	22	65	TCMDC-141480	26	84	TCMDC-125704	86	97	TCMDC-135236	71	113
TCMDC-141152	24	41	TCMDC-124761	23	65	TCMDC-137456	26	84	TCMDC-125774	86	97	TCMDC-136956	80	113
TCMDC-135659	24	41	TCMDC-123532	23	65	TCMDC-135110	27	84	TCMDC-125511	86	97	TCMDC-136346	85	113
TCMDC-124676	26	41	TCMDC-137770	24	65	TCMDC-139417	27	84	TCMDC-137160	87	97	TCMDC-132961	85	113
TCMDC-132173	27	41	TCMDC-132315	24	65	TCMDC-135336	28	84	TCMDC-136202	87	97	TCMDC-133215	86	113
TCMDC-140736	28	41	TCMDC-136278	25	65	TCMDC-141306	28	84	TCMDC-132424	87	97	TCMDC-125150	89	113
TCMDC-133582	29	41	TCMDC-140372	25	65	TCMDC-124670	29	84	TCMDC-131296	87	97	TCMDC-137263	89	113
TCMDC-136052	30	41	TCMDC-140662	25	65	TCMDC-124348	29	84	TCMDC-137089	87	97	TCMDC-125048	91	113
TCMDC-124734	30	41	TCMDC-132673	26	65	TCMDC-136441	30	84	TCMDC-136492	88	97	TCMDC-133549	91	113
TCMDC-141207	31	41	TCMDC-141173	27	65	TCMDC-139516	30	84	TCMDC-137530	88	97	TCMDC-125331	93	113
TCMDC-132207	31	41	TCMDC-133517	27	65	TCMDC-141534	30	84	TCMDC-133610	88	97	TCMDC-138511	93	113
TCMDC-125568	34	41	TCMDC-139064	27	65	TCMDC-132769	30	84	TCMDC-136137	89	97	TCMDC-138906	94	113
TCMDC-141752	37	41	TCMDC-135031	27	65	TCMDC-132596	31	84	TCMDC-125490	89	97	TCMDC-136394	96	113
TCMDC-124563	38	41	TCMDC-132656	27	65	TCMDC-133492	32	84	TCMDC-142220	89	97	TCMDC-137431	96	113

TCMDC-138336	41	41	TCMDC-133339	28	65	TCMDC-141808	33	84	TCMDC-137708	89	97	TCMDC-124166	96	113
TCMDC-137937	41	41	TCMDC-125261	28	65	TCMDC-135360	33	84	TCMDC-131639	89	97	TCMDC-139775	97	113
TCMDC-132708	41	41	TCMDC-139868	28	65	TCMDC-141528	34	84	TCMDC-139001	89	97	TCMDC-137382	97	113
TCMDC-138803	44	41	TCMDC-139953	28	65	TCMDC-139950	35	84	TCMDC-137162	89	97	TCMDC-131308	97	113
TCMDC-136720	1	42	TCMDC-141144	28	65	TCMDC-141427	35	84	TCMDC-138124	89	97	TCMDC-131662	99	113
TCMDC-123786	1	42	TCMDC-132984	28	65	TCMDC-135022	35	84	TCMDC-124269	89	97	TCMDC-123763	100	113
TCMDC-124557	3	42	TCMDC-134674	29	65	TCMDC-135629	35	84	TCMDC-134555	89	97	TCMDC-136017	100	113
TCMDC-125702	4	42	TCMDC-133334	29	65	TCMDC-135113	36	84	TCMDC-125800	89	97	TCMDC-131321	101	113
TCMDC-133882	4	42	TCMDC-138881	29	65	TCMDC-139150	36	84	TCMDC-125100	89	97	TCMDC-123857	101	113
TCMDC-125754	4	42	TCMDC-136976	29	65	TCMDC-133324	36	84	TCMDC-140434	90	97	TCMDC-138154	102	113
TCMDC-139769	5	42	TCMDC-124529	29	65	TCMDC-135713	37	84	TCMDC-139849	90	97	TCMDC-139031	102	113
TCMDC-134642	5	42	TCMDC-141077	29	65	TCMDC-141871	37	84	TCMDC-137597	90	97	TCMDC-125252	104	113
TCMDC-134551	5	42	TCMDC-132920	29	65	TCMDC-136105	37	84	TCMDC-131907	90	97	TCMDC-124440	104	113
TCMDC-142077	5	42	TCMDC-139202	29	65	TCMDC-134338	38	84	TCMDC-123514	90	97	TCMDC-135073	105	113
TCMDC-131523	5	42	TCMDC-139174	29	65	TCMDC-142235	39	84	TCMDC-141484	90	97	TCMDC-133824	105	113
TCMDC-125214	6	42	TCMDC-132594	30	65	TCMDC-139974	39	84	TCMDC-134268	90	97	TCMDC-139297	106	113
TCMDC-138607	7	42	TCMDC-137260	30	65	TCMDC-138766	41	84	TCMDC-125493	90	97	TCMDC-124737	107	113
TCMDC-132065	7	42	TCMDC-134409	30	65	TCMDC-135988	42	84	TCMDC-137352	91	97	TCMDC-135615	107	113
TCMDC-141049	8	42	TCMDC-136652	30	65	TCMDC-141671	42	84	TCMDC-139307	91	97	TCMDC-132703	108	113
TCMDC-141937	9	42	TCMDC-132666	31	65	TCMDC-136497	42	84	TCMDC-123559	91	97	TCMDC-137406	108	113
TCMDC-123914	9	42	TCMDC-134850	31	65	TCMDC-132560	42	84	TCMDC-131928	91	97	TCMDC-137788	109	113
TCMDC-140598	9	42	TCMDC-138931	31	65	TCMDC-137023	43	84	TCMDC-139383	91	97	TCMDC-125713	111	113
TCMDC-134422	9	42	TCMDC-134596	32	65	TCMDC-141124	43	84	TCMDC-125677	91	97	TCMDC-131919	113	113
TCMDC-138713	9	42	TCMDC-135172	32	65	TCMDC-140886	43	84	TCMDC-123947	91	97	TCMDC-136112	38	114
TCMDC-137824	9	42	TCMDC-141286	32	65	TCMDC-134711	43	84	TCMDC-135552	91	97	TCMDC-123639	40	114
TCMDC-140641	10	42	TCMDC-133422	32	65	TCMDC-139013	44	84	TCMDC-138061	92	97	TCMDC-132540	60	114
TCMDC-140941	10	42	TCMDC-140696	32	65	TCMDC-134588	45	84	TCMDC-124383	92	97	TCMDC-136396	75	114
TCMDC-136459	12	42	TCMDC-134884	32	65	TCMDC-124990	45	84	TCMDC-136002	92	97	TCMDC-136408	76	114
TCMDC-124053	12	42	TCMDC-132712	33	65	TCMDC-133108	45	84	TCMDC-132003	92	97	TCMDC-140537	77	114
TCMDC-134217	12	42	TCMDC-137111	33	65	TCMDC-125429	45	84	TCMDC-123778	92	97	TCMDC-140902	77	114
TCMDC-137771	12	42	TCMDC-140166	35	65	TCMDC-137068	45	84	TCMDC-124291	92	97	TCMDC-136426	84	114
TCMDC-135650	13	42	TCMDC-136392	35	65	TCMDC-138972	45	84	TCMDC-125501	92	97	TCMDC-139450	84	114
TCMDC-140588	13	42	TCMDC-136990	35	65	TCMDC-135845	46	84	TCMDC-131669	92	97	TCMDC-125009	87	114
TCMDC-140475	13	42	TCMDC-137821	35	65	TCMDC-135361	47	84	TCMDC-132114	92	97	TCMDC-134987	87	114
TCMDC-140235	13	42	TCMDC-139729	36	65	TCMDC-140106	47	84	TCMDC-141314	93	97	TCMDC-137194	89	114
TCMDC-136767	13	42	TCMDC-139002	36	65	TCMDC-125763	47	84	TCMDC-135160	93	97	TCMDC-125603	91	114
TCMDC-132287	13	42	TCMDC-134756	36	65	TCMDC-138832	47	84	TCMDC-131869	93	97	TCMDC-135575	92	114

TCMDC-131886	13	42	TCMDC-132042	36	65	TCMDC-123591	48	84	TCMDC-139142	93	97	TCMDC-133115	92	114
TCMDC-132931	14	42	TCMDC-125180	37	65	TCMDC-134216	48	84	TCMDC-131558	93	97	TCMDC-136924	92	114
TCMDC-134090	15	42	TCMDC-139175	37	65	TCMDC-140096	48	84	TCMDC-135780	93	97	TCMDC-136962	93	114
TCMDC-140619	15	42	TCMDC-132419	38	65	TCMDC-131268	48	84	TCMDC-123944	93	97	TCMDC-131696	93	114
TCMDC-133917	16	42	TCMDC-135664	39	65	TCMDC-132497	49	84	TCMDC-124082	93	97	TCMDC-137424	93	114
TCMDC-133383	16	42	TCMDC-135632	39	65	TCMDC-132755	50	84	TCMDC-139022	93	97	TCMDC-137013	94	114
TCMDC-135763	17	42	TCMDC-136973	39	65	TCMDC-133779	50	84	TCMDC-123798	93	97	TCMDC-135826	94	114
TCMDC-124689	17	42	TCMDC-133212	40	65	TCMDC-134490	50	84	TCMDC-123668	93	97	TCMDC-139546	97	114
TCMDC-125854	17	42	TCMDC-134130	40	65	TCMDC-142164	50	84	TCMDC-123826	93	97	TCMDC-139763	97	114
TCMDC-132654	17	42	TCMDC-139728	41	65	TCMDC-135100	51	84	TCMDC-125665	93	97	TCMDC-131319	98	114
TCMDC-137309	17	42	TCMDC-137623	41	65	TCMDC-134939	52	84	TCMDC-136692	93	97	TCMDC-124862	100	114
TCMDC-136338	18	42	TCMDC-142130	44	65	TCMDC-137745	53	84	TCMDC-124084	94	97	TCMDC-131409	100	114
TCMDC-133708	18	42	TCMDC-140716	44	65	TCMDC-124389	54	84	TCMDC-124012	94	97	TCMDC-123647	102	114
TCMDC-138917	18	42	TCMDC-137036	44	65	TCMDC-136938	55	84	TCMDC-140322	94	97	TCMDC-135220	102	114
TCMDC-140311	18	42	TCMDC-138831	44	65	TCMDC-139028	56	84	TCMDC-136287	94	97	TCMDC-123924	103	114
TCMDC-135263	19	42	TCMDC-139976	44	65	TCMDC-139744	57	84	TCMDC-137867	94	97	TCMDC-132793	103	114
TCMDC-125152	19	42	TCMDC-134010	47	65	TCMDC-138823	58	84	TCMDC-141420	94	97	TCMDC-133954	103	114
TCMDC-124713	20	42	TCMDC-125684	47	65	TCMDC-140385	59	84	TCMDC-124108	94	97	TCMDC-137399	104	114
TCMDC-141113	20	42	TCMDC-133019	47	65	TCMDC-132145	61	84	TCMDC-124872	94	97	TCMDC-135976	106	114
TCMDC-132601	20	42	TCMDC-140165	48	65	TCMDC-137334	63	84	TCMDC-132001	94	97	TCMDC-123825	107	114
TCMDC-140111	20	42	TCMDC-132938	50	65	TCMDC-138301	63	84	TCMDC-137661	95	97	TCMDC-125861	107	114
TCMDC-124313	21	42	TCMDC-125193	51	65	TCMDC-140512	64	84	TCMDC-132797	95	97	TCMDC-124493	113	114
TCMDC-132728	21	42	TCMDC-133224	52	65	TCMDC-136819	64	84	TCMDC-125533	95	97	TCMDC-140455	52	115
TCMDC-135273	22	42	TCMDC-133430	52	65	TCMDC-136877	64	84	TCMDC-123936	95	97	TCMDC-133828	53	115
TCMDC-132358	22	42	TCMDC-138385	53	65	TCMDC-124892	64	84	TCMDC-131453	95	97	TCMDC-132696	57	115
TCMDC-140101	23	42	TCMDC-133004	54	65	TCMDC-141290	64	84	TCMDC-132140	95	97	TCMDC-140453	77	115
TCMDC-139453	23	42	TCMDC-141460	56	65	TCMDC-138698	65	84	TCMDC-124343	95	97	TCMDC-123782	78	115
TCMDC-135867	23	42	TCMDC-138292	56	65	TCMDC-132720	66	84	TCMDC-133683	96	97	TCMDC-141070	82	115
TCMDC-136168	24	42	TCMDC-125004	57	65	TCMDC-124490	68	84	TCMDC-137714	96	97	TCMDC-137370	92	115
TCMDC-139296	24	42	TCMDC-124709	61	65	TCMDC-137906	68	84	TCMDC-137329	96	97	TCMDC-137398	93	115
TCMDC-141776	24	42	TCMDC-133594	61	65	TCMDC-134679	69	84	TCMDC-132425	96	97	TCMDC-136285	94	115
TCMDC-141203	25	42	TCMDC-138820	61	65	TCMDC-136344	69	84	TCMDC-138711	96	97	TCMDC-124571	96	115
TCMDC-135144	25	42	TCMDC-142013	61	65	TCMDC-137377	69	84	TCMDC-125768	96	97	TCMDC-125216	96	115
TCMDC-137761	25	42	TCMDC-138216	62	65	TCMDC-137115	70	84	TCMDC-131573	96	97	TCMDC-137437	96	115
TCMDC-139983	26	42	TCMDC-132732	62	65	TCMDC-140671	71	84	TCMDC-131378	96	97	TCMDC-139149	97	115
TCMDC-139019	26	42	TCMDC-124369	63	65	TCMDC-139848	71	84	TCMDC-131729	96	97	TCMDC-135891	97	115
TCMDC-139026	26	42	TCMDC-133551	63	65	TCMDC-132709	74	84	TCMDC-131406	96	97	TCMDC-124697	97	115

TCMDC-134156	27	42	TCMDC-132332	63	65	TCMDC-124096	74	84	TCMDC-124774	96	97	TCMDC-137421	99	115
TCMDC-133095	27	42	TCMDC-140260	64	65	TCMDC-135179	75	84	TCMDC-134230	96	97	TCMDC-123478	100	115
TCMDC-132756	27	42	TCMDC-134659	64	65	TCMDC-134722	76	84	TCMDC-136576	96	97	TCMDC-131723	100	115
TCMDC-137552	28	42	TCMDC-133059	65	65	TCMDC-125345	77	84	TCMDC-125886	96	97	TCMDC-133447	102	115
TCMDC-124476	28	42	TCMDC-139548	65	65	TCMDC-124378	78	84	TCMDC-133154	96	97	TCMDC-124160	102	115
TCMDC-124858	29	42	TCMDC-134199	65	65	TCMDC-123491	78	84	TCMDC-135737	96	97	TCMDC-124417	103	115
TCMDC-142008	29	42	TCMDC-124107	66	65	TCMDC-139411	78	84	TCMDC-136012	96	97	TCMDC-124914	103	115
TCMDC-142169	30	42	TCMDC-140258	66	65	TCMDC-125066	79	84	TCMDC-131948	96	97	TCMDC-133148	104	115
TCMDC-124127	30	42	TCMDC-139459	1	66	TCMDC-135877	80	84	TCMDC-123496	96	97	TCMDC-123696	105	115
TCMDC-125850	32	42	TCMDC-139336	2	66	TCMDC-123965	80	84	TCMDC-131305	96	97	TCMDC-133306	105	115
TCMDC-132498	32	42	TCMDC-123955	3	66	TCMDC-140100	80	84	TCMDC-125505	96	97	TCMDC-124434	105	115
TCMDC-136133	32	42	TCMDC-124130	4	66	TCMDC-138058	81	84	TCMDC-137681	97	97	TCMDC-134513	105	115
TCMDC-140245	32	42	TCMDC-139559	6	66	TCMDC-123581	81	84	TCMDC-123623	97	97	TCMDC-132193	106	115
TCMDC-132013	34	42	TCMDC-125647	6	66	TCMDC-138840	81	84	TCMDC-125604	97	97	TCMDC-137244	106	115
TCMDC-136310	34	42	TCMDC-125142	6	66	TCMDC-138559	81	84	TCMDC-133146	97	97	TCMDC-139772	107	115
TCMDC-137871	35	42	TCMDC-123779	7	66	TCMDC-137895	81	84	TCMDC-123695	97	97	TCMDC-124741	107	115
TCMDC-142116	36	42	TCMDC-139590	8	66	TCMDC-132418	82	84	TCMDC-125537	97	97	TCMDC-137325	108	115
TCMDC-142026	38	42	TCMDC-125296	8	66	TCMDC-134396	82	84	TCMDC-131414	97	97	TCMDC-137768	109	115
TCMDC-132359	40	42	TCMDC-140002	9	66	TCMDC-135830	82	84	TCMDC-123508	97	97	TCMDC-133829	35	116
TCMDC-142061	40	42	TCMDC-139722	9	66	TCMDC-137894	83	84	TCMDC-134298	97	97	TCMDC-132740	49	116
TCMDC-133499	41	42	TCMDC-133526	10	66	TCMDC-136305	83	84	TCMDC-138571	97	97	TCMDC-137320	64	116
TCMDC-132977	42	42	TCMDC-139566	11	66	TCMDC-135549	84	84	TCMDC-131971	97	97	TCMDC-124532	75	116
TCMDC-131812	1	43	TCMDC-135456	11	66	TCMDC-133332	84	84	TCMDC-125733	97	97	TCMDC-135592	75	116
TCMDC-137963	1	43	TCMDC-134834	13	66	TCMDC-124143	84	84	TCMDC-139508	97	97	TCMDC-132590	76	116
TCMDC-141699	3	43	TCMDC-140202	13	66	TCMDC-139432	4	85	TCMDC-136517	97	97	TCMDC-134843	92	116
TCMDC-140357	4	43	TCMDC-139179	14	66	TCMDC-139569	5	85	TCMDC-137413	97	97	TCMDC-131755	92	116
TCMDC-132580	5	43	TCMDC-139523	14	66	TCMDC-138729	9	85	TCMDC-137933	97	97	TCMDC-136616	95	116
TCMDC-124630	6	43	TCMDC-141056	14	66	TCMDC-135459	10	85	TCMDC-134630	98	97	TCMDC-141293	97	116
TCMDC-140791	6	43	TCMDC-141517	14	66	TCMDC-134137	11	85	TCMDC-134608	98	97	TCMDC-133989	100	116
TCMDC-139931	6	43	TCMDC-139587	15	66	TCMDC-136218	11	85	TCMDC-125781	98	97	TCMDC-135687	101	116
TCMDC-131270	7	43	TCMDC-138602	15	66	TCMDC-142198	14	85	TCMDC-134321	100	97	TCMDC-137172	102	116
TCMDC-133500	8	43	TCMDC-138864	15	66	TCMDC-141987	14	85	TCMDC-139770	102	97	TCMDC-133964	103	116
TCMDC-138166	8	43	TCMDC-137086	16	66	TCMDC-138254	15	85	TCMDC-136806	11	98	TCMDC-136615	103	116
TCMDC-125439	9	43	TCMDC-132389	16	66	TCMDC-124894	16	85	TCMDC-125776	12	98	TCMDC-134059	104	116
TCMDC-137544	9	43	TCMDC-141545	18	66	TCMDC-134438	17	85	TCMDC-134589	18	98	TCMDC-133169	105	116
TCMDC-135510	10	43	TCMDC-141960	19	66	TCMDC-142049	17	85	TCMDC-141920	21	98	TCMDC-134969	106	116
TCMDC-134841	10	43	TCMDC-141537	19	66	TCMDC-142030	17	85	TCMDC-136298	23	98	TCMDC-137402	106	116

TCMDC-134561	10	43	TCMDC-141613	19	66	TCMDC-139694	18	85	TCMDC-136103	29	98	TCMDC-138901	106	116
TCMDC-132519	11	43	TCMDC-135542	19	66	TCMDC-124332	19	85	TCMDC-139107	30	98	TCMDC-133788	109	116
TCMDC-142050	11	43	TCMDC-137987	19	66	TCMDC-132726	23	85	TCMDC-140835	31	98	TCMDC-137428	109	116
TCMDC-141507	12	43	TCMDC-124659	20	66	TCMDC-133910	23	85	TCMDC-141692	34	98	TCMDC-123963	110	116
TCMDC-125716	12	43	TCMDC-141504	21	66	TCMDC-139842	23	85	TCMDC-138688	35	98	TCMDC-135814	110	116
TCMDC-136246	12	43	TCMDC-138357	21	66	TCMDC-141533	25	85	TCMDC-140954	35	98	TCMDC-135982	112	116
TCMDC-141574	13	43	TCMDC-140193	22	66	TCMDC-134859	25	85	TCMDC-133926	36	98	TCMDC-141129	113	116
TCMDC-139018	13	43	TCMDC-132552	22	66	TCMDC-141826	26	85	TCMDC-125131	38	98	TCMDC-133093	113	116
TCMDC-132982	13	43	TCMDC-135221	22	66	TCMDC-133220	26	85	TCMDC-140435	40	98	TCMDC-137616	15	117
TCMDC-140321	13	43	TCMDC-140807	22	66	TCMDC-134011	26	85	TCMDC-132869	40	98	TCMDC-132492	49	117
TCMDC-125553	14	43	TCMDC-138150	22	66	TCMDC-134370	27	85	TCMDC-141780	40	98	TCMDC-135881	84	117
TCMDC-135786	14	43	TCMDC-139603	23	66	TCMDC-136259	27	85	TCMDC-139656	41	98	TCMDC-131338	90	117
TCMDC-138921	14	43	TCMDC-132589	23	66	TCMDC-133348	28	85	TCMDC-133835	42	98	TCMDC-135520	91	117
TCMDC-137578	14	43	TCMDC-136104	24	66	TCMDC-132320	28	85	TCMDC-133869	43	98	TCMDC-131373	92	117
TCMDC-142096	15	43	TCMDC-141916	24	66	TCMDC-132595	29	85	TCMDC-136106	44	98	TCMDC-123469	93	117
TCMDC-134440	15	43	TCMDC-125688	25	66	TCMDC-136341	29	85	TCMDC-133689	45	98	TCMDC-125384	95	117
TCMDC-135535	15	43	TCMDC-133849	26	66	TCMDC-141139	31	85	TCMDC-136383	45	98	TCMDC-138502	95	117
TCMDC-132719	16	43	TCMDC-135209	26	66	TCMDC-136279	31	85	TCMDC-135930	45	98	TCMDC-131698	96	117
TCMDC-141224	16	43	TCMDC-140191	27	66	TCMDC-140705	31	85	TCMDC-136585	47	98	TCMDC-125334	97	117
TCMDC-134281	16	43	TCMDC-139588	27	66	TCMDC-134382	32	85	TCMDC-135477	48	98	TCMDC-124890	98	117
TCMDC-133980	16	43	TCMDC-139699	27	66	TCMDC-124693	32	85	TCMDC-135295	50	98	TCMDC-131758	99	117
TCMDC-141593	16	43	TCMDC-138486	27	66	TCMDC-124495	33	85	TCMDC-133457	52	98	TCMDC-134275	100	117
TCMDC-135210	16	43	TCMDC-135904	27	66	TCMDC-134273	34	85	TCMDC-138633	52	98	TCMDC-124214	100	117
TCMDC-134270	17	43	TCMDC-132321	27	66	TCMDC-123933	34	85	TCMDC-133296	53	98	TCMDC-131632	101	117
TCMDC-134521	17	43	TCMDC-133213	28	66	TCMDC-134593	35	85	TCMDC-124397	53	98	TCMDC-131670	101	117
TCMDC-138415	17	43	TCMDC-134895	28	66	TCMDC-139206	35	85	TCMDC-136733	53	98	TCMDC-137383	104	117
TCMDC-125777	18	43	TCMDC-137109	28	66	TCMDC-133113	36	85	TCMDC-140085	54	98	TCMDC-138772	104	117
TCMDC-141181	18	43	TCMDC-134406	29	66	TCMDC-133796	36	85	TCMDC-131245	54	98	TCMDC-125759	104	117
TCMDC-138869	18	43	TCMDC-132833	30	66	TCMDC-139847	36	85	TCMDC-141661	55	98	TCMDC-133750	106	117
TCMDC-135864	18	43	TCMDC-141426	30	66	TCMDC-135357	36	85	TCMDC-132201	56	98	TCMDC-131738	106	117
TCMDC-124870	19	43	TCMDC-134787	31	66	TCMDC-134501	37	85	TCMDC-123640	56	98	TCMDC-124033	110	117
TCMDC-125272	19	43	TCMDC-134429	31	66	TCMDC-133325	38	85	TCMDC-138267	56	98	TCMDC-125047	115	117
TCMDC-140278	19	43	TCMDC-136420	32	66	TCMDC-136266	38	85	TCMDC-123980	57	98	TCMDC-134575	116	117
TCMDC-136442	20	43	TCMDC-141644	32	66	TCMDC-141131	38	85	TCMDC-139737	58	98	TCMDC-134949	117	117
TCMDC-134524	20	43	TCMDC-133330	32	66	TCMDC-132326	39	85	TCMDC-124087	58	98	TCMDC-141535	27	118
TCMDC-141773	21	43	TCMDC-142247	32	66	TCMDC-139884	40	85	TCMDC-135936	59	98	TCMDC-135057	55	118
TCMDC-138234	21	43	TCMDC-138687	33	66	TCMDC-132771	40	85	TCMDC-133731	60	98	TCMDC-136407	57	118

TCMDC-124690	21	43	TCMDC-135559	33	66	TCMDC-136422	41	85	TCMDC-136700	61	98	TCMDC-137403	89	118
TCMDC-135241	23	43	TCMDC-141632	33	66	TCMDC-135566	42	85	TCMDC-134493	61	98	TCMDC-137407	97	118
TCMDC-141111	24	43	TCMDC-138364	34	66	TCMDC-135119	43	85	TCMDC-132676	62	98	TCMDC-124538	107	118
TCMDC-140021	25	43	TCMDC-134812	34	66	TCMDC-138521	43	85	TCMDC-123991	63	98	TCMDC-125265	107	118
TCMDC-133904	25	43	TCMDC-133553	35	66	TCMDC-141873	44	85	TCMDC-125350	63	98	TCMDC-134669	82	119
TCMDC-124477	25	43	TCMDC-135851	35	66	TCMDC-132060	44	85	TCMDC-123619	63	98	TCMDC-138498	82	119
TCMDC-131481	26	43	TCMDC-124688	36	66	TCMDC-138213	44	85	TCMDC-133435	63	98	TCMDC-134061	83	119
TCMDC-141106	27	43	TCMDC-134598	36	66	TCMDC-141393	44	85	TCMDC-138896	64	98	TCMDC-136450	88	119
TCMDC-125279	27	43	TCMDC-132649	36	66	TCMDC-135686	44	85	TCMDC-138597	64	98	TCMDC-125884	99	119
TCMDC-133205	29	43	TCMDC-142202	36	66	TCMDC-137345	45	85	TCMDC-123710	64	98	TCMDC-131722	101	119
TCMDC-139038	29	43	TCMDC-135233	36	66	TCMDC-134809	45	85	TCMDC-132111	65	98	TCMDC-133085	103	119
TCMDC-140729	29	43	TCMDC-132647	36	66	TCMDC-131849	45	85	TCMDC-136901	66	98	TCMDC-139192	105	119
TCMDC-139185	29	43	TCMDC-134603	36	66	TCMDC-134368	46	85	TCMDC-135962	66	98	TCMDC-132944	110	119
TCMDC-139357	29	43	TCMDC-134242	37	66	TCMDC-134168	46	85	TCMDC-135724	67	98	TCMDC-132143	113	119
TCMDC-134362	30	43	TCMDC-141208	37	66	TCMDC-135001	46	85	TCMDC-135250	67	98	TCMDC-135219	102	120
TCMDC-141167	31	43	TCMDC-141678	37	66	TCMDC-140728	47	85	TCMDC-133077	67	98	TCMDC-124949	116	120
TCMDC-140647	31	43	TCMDC-132442	39	66	TCMDC-133322	47	85	TCMDC-137365	67	98	TCMDC-137818	101	121
TCMDC-137571	32	43	TCMDC-134361	40	66	TCMDC-132151	47	85	TCMDC-133410	67	98	TCMDC-135602	103	121
TCMDC-140653	33	43	TCMDC-141675	40	66	TCMDC-136995	48	85	TCMDC-124382	68	98	TCMDC-141680	104	121
TCMDC-139454	34	43	TCMDC-141802	41	66	TCMDC-141878	49	85	TCMDC-137243	69	98	TCMDC-136014	106	121
TCMDC-125381	35	43	TCMDC-132717	41	66	TCMDC-134697	49	85	TCMDC-131730	69	98	TCMDC-123533	115	123
TCMDC-141718	38	43	TCMDC-125067	41	66	TCMDC-140504	49	85	TCMDC-141850	69	98	TCMDC-124402	101	125
TCMDC-137120	39	43	TCMDC-136981	41	66	TCMDC-140701	50	85	TCMDC-135702	70	98	TCMDC-124612	72	126
TCMDC-125682	40	43	TCMDC-138580	41	66	TCMDC-135000	50	85	TCMDC-125772	70	98	TCMDC-137855	103	126
TCMDC-123968	41	43	TCMDC-123663	41	66	TCMDC-133005	51	85	TCMDC-136252	71	98			

Appendix 6: Chapter 5

This table reports the predicted antimalarial mode of action for 195 compounds of TCAMS library

TCAMS ID	MMVID	10µM	2µM	Ullah et al (1)	Dennis et al (2)	Allman et al (3)	Raphemot et al (4)	Gomez-Lorenzo et al (5)
TCMDC-125399	MMV665890	18	41	PfATP4				
TCMDC-125450	MMV665803	8	11	PfATP4				
TCMDC-125424	MMV665826	3	9	PfATP4				
TCMDC-124168	MMV009063	14	21	PfATP4				
TCMDC-123535	MMV019017	9	14	PfATP4				
TCMDC-125401	MMV020660	31	97	PfATP4				
TCMDC-123742	MMV665796	66	71	PfATP4				
TCMDC-124545	MMV666124	75	88	PfATP4				
TCMDC-124652	MMV001059	4	13		PfATP4			
TCMDC-125457	MMV020710	3	3		PfATP4			
TCMDC-124847	MMV020136	3	5		PfATP4			
TCMDC-125133	MMV665878	5	5	PfATP4				
TCMDC-124792	MMV020081	5	4		PfATP4			
TCMDC-124874		95	104				Folate Biosynthesis	
TCMDC-124305	MMV665906	89	98	Folate Biosynthesis				
TCMDC-125185	MMV665883	85	89	Folate Biosynthesis				
TCMDC-124422	MMV019758	54	86	Folate Biosynthesis				
TCMDC-123598	MMV019074	51	88	Folate Biosynthesis				
TCMDC-125390	MMV020651	100	103	Folate Biosynthesis				
TCMDC-123889	MMV019313	27	75	Folate Biosynthesis				
TCMDC-125597	MMV665798	98	99	Folate Biosynthesis				
TCMDC-124658	MMV666067	35	81	Folate Biosynthesis				
TCMDC-137930		87	96				Folate Biosynthesis	
TCMDC-124964		60	61				Folate Biosynthesis	
TCMDC-123658	MMV019124	90	96	Folate Biosynthesis				
TCMDC-124644	MMV666070	94	105	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-125446	MMV020700	105	109	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-123825	MMV665876	107	114	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-123478	MMV018984	100	115	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-125583	MMV086103	93	93	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-124350	MMV019700	102	107	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-123824	MMV019258	78	88	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-124577	MMV666693	105	108	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-124653	MMV666072	97	103	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-125164	MMV020439	82	108	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-123826	MMV011256	93	97	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-124919	MMV665874	72	75	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-124396	MMV019738	38	75	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-125426	MMV666103	97	103	DHODH		mtETC/ Pyrimidine Synthesis		
TCMDC-124062	MMV000248	14	21	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-124458	MMV011795	15	28	Hemoglobin Catabolism		Hemoglobin Catabolism		

TCMDC-124635	MMV666061	18	19	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-123502	MMV665928	20	27	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-124620	MMV666116	14	16	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-125708	MMV006455	17	20	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-125394	MMV020654	26	45	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-124573	MMV011944	51	71	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-123835	MMV019266	88	107	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-123585	MMV019064	80	83	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-125853	MMV666057	95	95	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-125233	MMV020500	29	26	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-125282	MMV020549	83	87	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-123739	MMV665799	98	105	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-124555	MMV019871	28	83	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-125281	MMV020548	82	83	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-124488	MMV008956	8	18	Hemoglobin Catabolism		Hemoglobin Catabolism		
TCMDC-123870	MMV006309	102	107	ETC bc1				
TCMDC-124156	MMV665827	82	100	ETC bc1				
TCMDC-123496	MMV645672	96	97	ETC bc1				
TCMDC-124486	MMV666691	97	99	ETC bc1				
TCMDC-135461		102	106				ETC bc1	ETC bc1
TCMDC-135546		98	98				ETC bc1	ETC bc1
TCMDC-135678		98	99				ETC bc1	ETC bc1
TCMDC-135795		96	96				ETC bc1	ETC bc1
TCMDC-137384		98	98				ETC bc1	ETC bc1
TCMDC-137403		89	118				ETC bc1	ETC bc1
TCMDC-135796		96	106				ETC bc1	ETC bc1
TCMDC-136185		78	78				ETC bc1	ETC bc1
TCMDC-136286		108	108				ETC bc1	ETC bc1
TCMDC-136303		104	105				ETC bc1	ETC bc1
TCMDC-135289		99	109				ETC bc1	ETC bc1
TCMDC-136157		97	103				ETC bc1	ETC bc1
TCMDC-137377		69	84				ETC bc1	ETC bc1
TCMDC-138010		97	99				ETC bc1	ETC bc1
TCMDC-123667		69	80				ETC bc1	
TCMDC-124103		97	100				ETC bc1	
TCMDC-135787		104	105				ETC bc1	
TCMDC-137383		104	117				ETC bc1	
TCMDC-136300		102	105				ETC bc1	
TCMDC-138214		81	100				ETC bc1	
TCMDC-138141		90	104				ETC bc1	
TCMDC-124258		98	103				ETC bc1	
TCMDC-139660		83	93				ETC bc1	

TCMDC-123515		76	83				ETC bc1	
TCMDC-138901		106	116					ETC bc1
TCMDC-136197		97	105					ETC bc1
TCMDC-138928		103	103					ETC bc1
TCMDC-137416		103	104					ETC bc1
TCMDC-137421		99	115					ETC bc1
TCMDC-135655		98	100					ETC bc1
TCMDC-135444		102	105					ETC bc1
TCMDC-135462		86	91					ETC bc1
TCMDC-135555		101	103					ETC bc1
TCMDC-135654		100	105					ETC bc1
TCMDC-136196		92	94					ETC bc1
TCMDC-134692		98	102					ETC bc1
TCMDC-136060		56	71					ETC bc1
TCMDC-135303		92	106					ETC bc1
TCMDC-134729		97	108					ETC bc1
TCMDC-135253		101	101					ETC bc1
TCMDC-136134		95	101					ETC bc1
TCMDC-134726		89	89					ETC bc1
TCMDC-134728		97	105					ETC bc1
TCMDC-135256		101	104					ETC bc1
TCMDC-138826		85	88					ETC bc1
TCMDC-138136		96	111					ETC bc1
TCMDC-137266		97	101					ETC bc1
TCMDC-137265		105	107					ETC bc1
TCMDC-137419		98	99					ETC bc1
TCMDC-137407		97	118					ETC bc1
TCMDC-137387		66	67					ETC bc1
TCMDC-137325		108	115					ETC bc1
TCMDC-137420		95	95					ETC bc1
TCMDC-133308		94	112					ETC bc1
TCMDC-132415		98	102					ETC bc1
TCMDC-132123		72	82					ETC bc1
TCMDC-135042		98	110					ETC bc1
TCMDC-135554		94	100					ETC bc1
TCMDC-135779		98	101					ETC bc1
TCMDC-135220		102	114					ETC bc1
TCMDC-132416		37	70					ETC bc1
TCMDC-136051		95	95					ETC bc1
TCMDC-135683		100	106					ETC bc1
TCMDC-135676		92	101					ETC bc1
TCMDC-135656		96	105					ETC bc1

TCMDC-136014		106	121					ETC bc1
TCMDC-135677		85	108					ETC bc1
TCMDC-135687		101	116					ETC bc1
TCMDC-136015		87	110					ETC bc1
TCMDC-135881		84	117					ETC bc1
TCMDC-135814		110	116					ETC bc1
TCMDC-135911		101	102					ETC bc1
TCMDC-135815		100	102					ETC bc1
TCMDC-135816		92	98					ETC bc1
TCMDC-135254		98	104					ETC bc1
TCMDC-136013		99	101					ETC bc1
TCMDC-136301		109	112					ETC bc1
TCMDC-135271		100	103					ETC bc1
TCMDC-137431		96	113					ETC bc1
TCMDC-137538		91	92					ETC bc1
TCMDC-137423		98	98					ETC bc1
TCMDC-141680		104	121					ETC bc1
TCMDC-124160		102	115					ETC bc1
TCMDC-136129		92	109					ETC bc1
TCMDC-137042		105	108					ETC bc1
TCMDC-138812		81	90					ETC bc1
TCMDC-125226		98	105					ETC bc1
TCMDC-138813		108	109					ETC bc1
TCMDC-137425		100	101					ETC bc1
TCMDC-137268		94	100					ETC bc1
TCMDC-137173		94	96					ETC bc1
TCMDC-124085		97	106					ETC bc1
TCMDC-123947		91	97					ETC bc1
TCMDC-124347		94	96					ETC bc1
TCMDC-135219		102	120					ETC bc1
TCMDC-132026		99	100					ETC bc1
TCMDC-134575		116	117					ETC bc1
TCMDC-124874		95	104					ETC bc1
TCMDC-124699		99	109					ETC bc1
TCMDC-124698		97	98					ETC bc1
TCMDC-124701		98	100					ETC bc1
TCMDC-125243		104	109					ETC bc1
TCMDC-125868		98	100					ETC bc1
TCMDC-123758		101	107					ETC bc1
TCMDC-123479		81	101					ETC bc1
TCMDC-125709		99	100					ETC bc1
TCMDC-123689		87	89					ETC bc1

TCMDC-125391		96	95					ETC bc1
TCMDC-125470		97	98					ETC bc1
TCMDC-124428		96	100					ETC bc1
TCMDC-133955		107	108					ETC bc1
TCMDC-133757		69	95					ETC bc1
TCMDC-133970		98	98					ETC bc1
TCMDC-125325		103	104					ETC bc1
TCMDC-124479		105	109					ETC bc1
TCMDC-137172		102	116					ETC bc1
TCMDC-125039		100	111					ETC bc1
TCMDC-124578		90	102					ETC bc1
TCMDC-138029		94	103					ETC bc1
TCMDC-124577		105	108					ETC bc1
TCMDC-125024		108	109					ETC bc1
TCMDC-134937		98	107					ETC bc1
TCMDC-136021		99	99					ETC bc1
TCMDC-136022		106	107					ETC bc1
TCMDC-131540		95	95					ETC bc1
TCMDC-125724		102	103					ETC bc1
TCMDC-134513		105	115					ETC bc1
TCMDC-137675		91	102					ETC bc1
TCMDC-133459		79	108					ETC bc1
TCMDC-139030		86	102					ETC bc1
TCMDC-140069		59	89					ETC bc1
TCMDC-140513		90	98					ETC bc1
TCMDC-139889		77	103					ETC bc1
TCMDC-123969		66	69					ETC bc1
TCMDC-133253		67	78					ETC bc1

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Appendix 7: Chapter 6

Table A reports the EC_{50} and PC1 values of selected TCAMS library compounds against the $Dd2^{luc}$ and $NF54^{luc}$, while table B reports the EC_{50} and PC1 values of selected MMV Pathogen Box compounds against $Dd2^{luc}$.

(A)			
Compound name	EC_{50} (nM)	(PC1) $Dd2^{luc}$	(PC1) $NF54^{luc}$
TCMDC-125071	912.2	-105.5	-105.5
TCMDC-123773	818.7	17.3	7.5
TCMDC-140154	967.2	-85.3	-47.4
TCMDC-136189	650.9	-121.2	-116.5
TCMDC-124113	712.2	-50.6	-87.0
TCMDC-124047	115.4	7.9	-32.2
TCMDC-125254	972.0	-26.8	-6.1
TCMDC-139900	387.2	-31.5	15.5
TCMDC-135423	125.1	-14.9	-13.5
TCMDC-138614	295.8	18.2	25.1
TCMDC-137603	497.0	-87.4	-90.3
TCMDC-124491	874.4	-81.4	-67.9
TCMDC-142036	698.4	-8.0	-4.6
TCMDC-138358	628.5	-49.8	-52.1
TCMDC-133478	360.3	-103.8	-91.8
TCMDC-123564	843.6	-76.9	-55.6
TCMDC-125253	899.0	-95.5	-78.4
TCMDC-131242	1176.8	-83.4	-82.2
TCMDC-140040	776.9	-0.6	38.1
TCMDC-125016	970.7	-105.1	-92.5
TCMDC-136607	776.7	-95.8	-88.7
TCMDC-136239	445.6	-2.6	-19.9
TCMDC-125397	747.0	-63.5	-51.4
TCMDC-135135	1434.8	-5.3	25.8
TCMDC-124168	991.0	-69.8	-89.8
TCMDC-133687	1110.4	31.7	18.5
TCMDC-125139	701.2	-95.2	-112.3
TCMDC-136088	763.3	-106.6	-121.4
TCMDC-135773	80.6	4.4	49.0
TCMDC-140871	550.1	-54.1	-93.2
TCMDC-125321	689.0	-10.3	-65.4
TCMDC-124887	521.4	-57.4	-96.1
TCMDC-124579	279.4	48.4	-27.5
TCMDC-141043	247.7	-7.2	-14.8
TCMDC-125424	878.2	-105.3	-119.8
TCMDC-125361	843.1	-92.8	-110.2
TCMDC-131436	804.3	-83.6	-108.7

TCMDC-140815	836.0	-41.4	-105.1
TCMDC-124252	892.8	-72.1	-104.7
TCMDC-140157	559.4	-53.8	-70.8
TCMDC-136792	872.6	-67.6	-92.5
TCMDC-125055	831.4	-18.4	-54.1
TCMDC-138973	993.0	9.5	-91.1
TCMDC-124036	530.3	-21.8	-19.8
TCMDC-132515	757.9	4.8	16.0
TCMDC-142268	26.3	-38.7	-83.1
TCMDC-140755	969.2	-2.9	-23.6
TCMDC-140417	975.5	10.7	5.1
TCMDC-136878	182.1	47.8	49.0
TCMDC-135804	37.6	45.9	46.2
TCMDC-135800	810.0	23.3	33.2
TCMDC-137323	59.1	3.2	-6.5
TCMDC-135335	1038.8	-17.6	-20.9
TCMDC-135747	772.6	8.1	13.1
TCMDC-136795	122.0	39.3	-16.7
TCMDC-124760	46.4	-121.0	-115.8
TCMDC-142193	676.2	19.3	-41.2
TCMDC-136043	570.9	24.4	-36.8

(B)

Compound name	EC_{50} (nM)	(PC1) $Dd2^{luc}$
MMV020391	833.7	-64.3
MMV000858	511.3	-59.5
MMV020136	711.7	-42.1
MMV022029	622.5	-56.3
MMV020081	48.3	-40.7
MMV001059	672.3	-76.4
MMV006239	569.3	-66.2
MMV023183	620.9	-18.8
MMV637229	561.2	-8.6
MMV634140	184.0	-79.1
MMV021057	19.9	16.7
MMV659004	321.8	39.5
MMV020537	1980.0	51.8
MMV024397	843.5	52.1