SYNTHESIS OF NOVEL QUININE DERIVATIVES VIA THE HECK REACTION

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# TABLE OF CONTENTS

ABSTRACT ........................................................................................................................................ iii

LIST OF TABLES ........................................................................................................................... iv

LIST OF FIGURES ........................................................................................................................ v

INTRODUCTION .......................................................................................................................... 1

RESULTS AND DISCUSSION ..................................................................................................... 9

Optimization of Reaction ........................................................................................................ 9

Substrate Scope ......................................................................................................................... 14

Unsuccessful Substrates .......................................................................................................... 16

Biological Data ........................................................................................................................ 18

EXPERIMENTAL .................................................................................................................... 21

REFERENCES ........................................................................................................................ 32

APPENDIX .................................................................................................................................. 34
ABSTRACT

Malaria continues to burden a large number of the world’s population, and is projected to affect more people in the future. The parasitic genus *Plasmodium* is the cause of this demoralizing disease. Parasitic resistance has proliferated to various drugs used for the treatment of malaria. A commonly used, cheap drug for treatment of malaria is a derivative of quinine called chloroquine. It has been shown that chloroquine is only approximately 50% effective because of the resistance *Plasmodium* strains have exhibited against this drug. Situations where chloroquine is ineffective, quinine, a natural product derived from the cinchona tree and the first malaria treatment, will be administered. Problems exist with the use of quinine, including harsh side effects. Since quinine has shown great resistance to Plasmodium for over 350 years, a synthesis has been designed for new anti-malarial remedies using quinine as the core. A rapid one-step synthesis using the Heck reaction has been developed for the addition of aryl bromides to the olefin group of quinine. Purification of desired products was challenging, but 15 novel compounds have been isolated pure in good yield. Biological screening of the synthesized compounds using a SYBR Green growth inhibition assay was run against a quinine sensitive and quinine resistance parasite. Compounds 10 and 13 showed positive activity during the assay. Consequently, IC$_{50}$ data was obtained for compounds 10 and 13 along with quinine and chloroquine. Although compounds 10 and 13 exhibited less potency than quinine and chloroquine; 10 and 13 appear to have bypassed the resistance mechanism quinine and chloroquine encounter.
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Optimization of reaction conditions</td>
<td>9</td>
</tr>
<tr>
<td>2. Reaction yields after flash column chromatography using optimized conditions</td>
<td>15</td>
</tr>
<tr>
<td>3. Substrates unable to be isolated</td>
<td>17</td>
</tr>
<tr>
<td>4. IC&lt;sub&gt;50&lt;/sub&gt; data against HB3 and Dd2 parasite strains for compound 10, 13, quinine and chloroquine</td>
<td>19</td>
</tr>
</tbody>
</table>
**LIST OF FIGURES**

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anti-malarial drugs (1) quinine, (2) chloroquine, (3) mefloquine, and (4) artemisinin.</td>
<td>2</td>
</tr>
<tr>
<td>2. Key intermediates of the Jacobsen asymmetric catalytic synthesis of quinine.</td>
<td>3</td>
</tr>
<tr>
<td>3. Structure of tryptanthrin, used to design a pharmacophore model for examining anti-malarial activity in an assortment of compounds.</td>
<td>5</td>
</tr>
<tr>
<td>4. Illustration of important binding functional groups within quinine determined by tryptanthrin pharmacophore.</td>
<td>5</td>
</tr>
<tr>
<td>5. Representation of the proposed five-membered ring formation when quinine binds to heme.</td>
<td>6</td>
</tr>
<tr>
<td>6. Proposed mechanism for the Heck reaction.</td>
<td>7</td>
</tr>
<tr>
<td>7. Heck reaction conditions used on a cinchonidine derivative.</td>
<td>8</td>
</tr>
<tr>
<td>8. Optimizing reaction conditions for synthesis of novel quinine derivatives.</td>
<td>9</td>
</tr>
<tr>
<td>9. Example of $^1$H-NMR internal standard analysis for crude reaction contents.</td>
<td>11</td>
</tr>
<tr>
<td>10. Alkene region of the synthesized product 11-(phenyl)-quinine illustrating \textit{trans} stereochemistry.</td>
<td>14</td>
</tr>
</tbody>
</table>
INTRODUCTION

Malaria is one of the most common infectious diseases and continues to devastate specific areas of the world. In tropical areas of the earth, along with the continent of Africa south of the Sahara desert, malaria poses the greatest threat to humans. Approximately 41% of the world’s population lives in areas with malaria.\(^1\) It is estimated that there are about 515 million new cases of malaria each year causing almost one million deaths, mainly people of Africa.\(^2\) Transmission of malaria is facilitated by an Anopheles female mosquito. The mosquitoes are not infected themselves, but the malaria parasite, species *Plasmodium*, is exchanged by the mosquito between people resulting in its spread. A vaccine for malaria currently does not exist, but there are preventative measures that can be utilized to reduce the chance of infection. Mosquito nets, insect repellent, long sleeves and pants, and preventative drugs are all used to try and combat malarial contraction. The problem with all the preventative measures is that many of the people living in endemic areas, especially Africa, are very poor and cannot afford to practice any of the defensive actions, specifically the use of drugs to thwart or fight the disease. Therefore, there is a dire need to produce more effective malaria drugs at an economical cost to increase world-wide treatment.

The first treatment of malaria can be traced all the way back to the inhabitants of Peru who used to chew on the bark of the Cinchona tree to control the disease’s feverish effects.\(^3\) Cinchona trees, native to South America, contain a mixture of alkaloids in its bark appropriately called Cinchona alkaloids. These natural products are responsible for the tree’s anti-malarial activity. In 1820, French scientists Pelletier and Caventou were able to purify the major alkaloid, quinine (I), from the Cinchona tree bark (Figure1).\(^3\)
Quinine was used exclusively until the early 1900’s when chloroquine was synthesized for treatment of malaria. Chloroquine was the drug of choice because of its low cost and quinine’s side-effects, which can be quite harsh in some instances. Quinine side-effects include cardiotoxicity, visual disturbance/blindness, deafness, convulsions, and hypoglycemia. A particular side-effect observed from an overdose of quinine is cinchonism, named after the Cinchona tree. Cinchonism can be expressed through various symptoms including rashes, headache, confusion, and vomiting.

Figure 1: Anti-malarial drugs (1) quinine, (2) chloroquine, (3) mefloquine, and (4) artemisinin.

Chloroquine surpassed quinine for malaria treatment because it was also made at a cost effective price. According to a 2002 study, prices for tablet treatments of antimalarial drugs are as follows: $0.09 chloroquine, $2.73 quinine, $5.04 mefloquine, and $5.34 artemisinin. In Figure 1, quinine (1) and chloroquine (2) are shown, along with mefloquine (3) and artemisinin (4). It can be seen how the natural product of quinine influenced the design of the chloroquine and mefloquine. Both of these synthetic anti-malarial drugs contain the quinoline core along with amine groups, just like quinine. Artemisinin is a natural product that is extracted from the plant *Artemisia annua* and currently is a sought after compound for its anti-malarial properties.
The wide use of chloroquine has resulted in high levels of drug resistance for the malaria parasite *Plasmodium*, particularly the most prevalent type *Plasmodium falciparum*. It is now thought that greater than 50% of this parasite infecting people is resistant to the treatment with chloroquine.\(^6\) People infected with chloroquine resistant malaria strains, and other drugs that are becoming ineffective, use quinine treatment, which has much less parasitic resistance around the world. However, quinine resistant strains of *P. falciparum* also exist. New artemisinin combination therapies (ACTs) have become a preferred treatment in many countries; although, resistance has begun to surface in some locations.\(^7,8\)

Quinine is a complex natural product that is capable of being made synthetically in numerous steps. Initially, quinine was reported to have been synthesized in a publication in the year 1944 by Woodward and Doering.\(^9\) It has been since disputed if the synthesis of quinine was valid or not. In 2001, the first stereo-controlled synthesis of all 4 stereocenters of quinine was reported by Stork *et al.*\(^10\) in 20 steps with a 7% overall yield. Research has continued on finding a more efficient, stereoselective synthesis of quinine with a recent attempt using an asymmetric catalytic method to produce synthetic quinine in 16 steps, the shortest synthesis of quinine, with a 5% overall yield\(^11\) (Figure 2).

![Figure 2. Key intermediates of the Jacobsen asymmetric catalytic synthesis of quinine.\(^11\)](image-url)
A major objective of our research project is to keep cost to a bare minimum. When considering the length of quinine syntheses, it would be impractical to produce new derivatives containing the core in a cost efficient manner.

Since anti-malarial drugs are becoming less successful because of enhanced resistance by the parasitic malarial species, new drugs must be synthesized to combat the growing resistance of this disease. Synthetic production of anti-malarial drugs, such as chloroquine and mefloquine, is the classic approach to developing new malaria treatments. The development of simplified endoperoxides related to artemisinin is underway in several laboratories. Current efforts are also progressing in the identification of unique chemical architectures that possess anti-malarial activity. The synthesis of quinine derivatives has recently received much less attention, in part, because it is an arduous task to produce this natural product. Instead of synthesizing the quinine core, functional group manipulation will be considered.

Quinine contains various functional groups, and a proper analysis of the molecule’s interactions must be done in order to locate an ideal place for the one-step synthesis. A recent publication created a pharmacophore model using a program called CATALYST\textsuperscript{12} to examine anti-malarial activity of various compounds. The pharmacophore model is based on an alkaloid from a Taiwanese medicinal plant called tryptanthrin (indolo[2,1-b]quinazoline-6,12-dione)\textsuperscript{13} seen in Figure 3. Various anti-
malarial drugs, including quinine, were placed into the same pharmacophore model and showed excellent correlation. The model based on tryptanthrin suggests that quinine exhibits the two necessary hydrogen bonding requirements with the molecule’s alcohol and tertiary amine groups. The remaining two functional groups of interest, the alkene and quinoline, take part in the two required aromatic hydrophobic interactions. Compared to all other potential anti-malarial agents, quinine received the highest “Best-Fit Score” for the model. Figure 4 reveals the binding of quinine according to the model with the appropriate hydrogen bond and hydrophobic aromatic interactions. It is seen within the quinine molecule that the alkene is more accessible and cost-effective to modify, so it has been chosen as the functional group to participate in the synthesis.

Figure 3: Structure of tryptanthrin, used to design a pharmacophore model for examining anti-malarial activity in an assortment of compounds.

Figure 4: Illustration of important binding functional groups within quinine determined by tryptanthrin pharmacophore.
A complete understanding of how quinine effectively counters the malaria parasite is still unidentified. There is strong evidence that quinoline containing anti-malarials act on the digestive vacuole of the parasite.\textsuperscript{14,15} \textit{P. falciparum} has shown to form hemozin by polymerizing ferriprotoporphyrin IX heme units, while breaking down hemoglobin in human red blood cells.\textsuperscript{16} Pertinent research shows that quinine binds to heme, interfering with hemozoin formation, thus leaving toxic ferriprotoporphyrin IX heme to thwart the parasite.\textsuperscript{17,18} Roepe and coworkers recently disclosed a binding studying of quinine to heme that proposes the formation of an intramolecular hydrogen bond by quinine (Figure 5).\textsuperscript{19} This model is consistent with the pharmacophore model previously described (Figure 4). These studies seem to support alteration of quinine at

![Figure 5: Representation of the proposed five-membered ring formation when quinine binds to heme.\textsuperscript{19}](image)

the vinyl group for potential pharmacological improvement.

An excellent method for modifying alkenes is a well known catalytic reaction called the Heck reaction (Figure 6). In the early 1970s, Heck and Mizoroki
developed a reaction using a palladium catalyst to form substituted olefins.\textsuperscript{20,21} Wide use of the Heck reaction has been observed in organic chemistry since its discovery because of reaction’s ability to form carbon-carbon bonds, resulting in Heck sharing the 2010 Nobel Prize in Chemistry.\textsuperscript{22} Initiation of the Heck reaction begins when a Pd(II) species becomes reduced to Pd(0), \textit{in situ} (1, Figure 6). Oxidative addition of the aryl bromide (2) to palladium generates an aryl palladium (II) complex (3). The olefin (4) is coordinated by the Pd(II) intermediate (5) and is followed by insertion of the alkene between the carbon-Pd(II) bond, which favors syn-addition to produce 6. After the syn-addition of the alkene and aryl group, a $\beta$-hydride elimination occurs to generate the \textit{trans}-alkene (8). If the substrate contains an alternate $\beta$-hydrogen it can be improperly eliminated giving an undesired product (7). Reductive elimination of HBr from 9, with help from a base, completes the catalytic cycle regenerating 1, the Pd(0) species.

Products of the Heck reaction predominately show \textit{trans} stereochemistry because the alkene addition and $\beta$-hydride elimination steps occur in a \textit{syn} fashion.

\textbf{Figure 6:} Proposed mechanism for the Heck reaction.
Quinine is an ideal candidate to use for the Heck reaction for a variety of reasons: 1) quinine contains a mono-substituted olefin, 2) quinine has a variety of functional groups tolerated by the Heck reaction, and 3) a variety of cheap, aryl bromides are commercially available enabling an assortment of compounds to be synthesized. Variables including palladium catalysts, bases, and solvents of the Heck reaction are to be determined in this study for optimal catalytic conditions. It should be noted that a recent paper by Castle et al.\textsuperscript{23} successfully used the Heck reaction to add aryl compounds to the olefin group of a cinchona alkaloid (1, Figure 7), cinchonidine, during an intermediate step of their overall synthesis (Figure 7).

\begin{align*}
\text{(1)} & \xrightarrow{\text{Ar-}I, \text{Et}_3\text{N}} \text{PdCl}_2 (8 \text{ mol } \% ) \\
& \text{DMF, 100}^\circ\text{C} \\
& 63\% \text{ for } a \\
& 51\% \text{ for } b \\
\text{(2)}
\end{align*}

\textbf{Figure 7: } Heck reaction conditions used on a cinchonidine derivative.\textsuperscript{23}
RESULTS AND DISCUSSION

Optimizing Conditions

The initial project goal was to achieve an optimized, one-step synthesis of a quinine derivative by using the Heck reaction between quinine (1) and bromobenzene (2, Figure 8). Numerous synthetic conditions have been developed for the Heck reaction.24

![Figure 8: Optimizing reaction conditions for synthesis of novel quinine derivatives.](image)

Much work was spent fine tuning the following catalytic variables: solvent, base, catalyst, ligand, time, and temperature. An assortment of reactions had already been performed by an undergraduate researcher (Ms. Amanda Roberts) and are incorporated into the optimization of reactions conditions (entries 1-6, Table 1).

Table 1: Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>#</th>
<th>Halide</th>
<th>Catalyst</th>
<th>Temperature (°C)</th>
<th>Base</th>
<th>Solvent</th>
<th>NMRYield(%)&lt;sup&gt;c&lt;/sup&gt; of #</th>
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<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Br</td>
<td>Pd&lt;sub&gt;3&lt;/sub&gt;(DBA)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>120</td>
<td>K&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>DMA</td>
<td>64</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Br</td>
<td>Pd&lt;sub&gt;3&lt;/sub&gt;(DBA)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>120</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>DMA</td>
<td>66</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Br</td>
<td>Pd&lt;sub&gt;3&lt;/sub&gt;(DBA)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>120</td>
<td>(NH&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>DMA</td>
<td>55</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Br</td>
<td>Pd&lt;sub&gt;3&lt;/sub&gt;(DBA)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>120</td>
<td>DBU</td>
<td>DMA</td>
<td>54</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Br</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>120</td>
<td>TEA</td>
<td>DMA</td>
<td>59</td>
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<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>I</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>TEA</td>
<td>DMA</td>
<td>58</td>
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<tr>
<td>7</td>
<td>Br</td>
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<td>Bu&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>DMA</td>
<td>20</td>
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<td>PhMe</td>
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<tr>
<td>13</td>
<td>Br</td>
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<td>110</td>
<td>TEA</td>
<td>PhMe</td>
<td>52</td>
</tr>
<tr>
<td>14</td>
<td>Br</td>
<td>Pd(OAc)₂ / (Ph)₃P</td>
<td>110</td>
<td>TEA</td>
<td>PhMe</td>
<td>74³, ⁴, ⁵</td>
</tr>
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</table>

*General reaction conditions: 0.3 mmol of quinine was heated with 2 equivalents of halide, 3 equivalents of base, and 0.05 equivalents of catalyst in the indicated solvent. Reactions were heated to the indicated temperature for 24 hours. For entry 14, 0.05 equivalents Pd(OAc)₂ and 0.1 equivalents of (Ph)₃P.

³Reactions run previously
⁴NMR yield determined by addition of 1-chloro-2,4-dinitrobenzene as an internal standard
⁵Yields determined after column
⁶Optimized reaction conditions

* DBA = dibenzylideneacetone, DMA = dimethylacetamide, TEA = triethylamine

Thin layer chromatography (TLC) was used to determine product formation after a reaction was completed. A quinine standard was spotted simultaneously with reaction contents during TLC to aid in product identification. Detection of reaction products was possible with ultra-violet (UV) light. If product was deemed present, an ¹H-NMR yield was determined. An internal standard was used initially to calculate ¹H-NMR reaction yields before any product purification was attempted. The internal standard used was 1-chloro-2,4-dinitrobenzene because of the compound’s unique ¹H-NMR signals. Quinine exhibits characteristic alkene peaks that disappear and are replaced by trans alkene protons of product when a successful Heck reaction occurs on the molecule as seen below in Figure 9. Integration of the methoxy singlet peak, shifted the same in quinine and the product, was used to account for the percent of starting material after reactions were conducted. Ratios of ¹H-NMR integrated signals were calculated for the internal standard peaks to both the starting material and product peaks. Formulas used for calculating yields can be seen in equations 1, 2, 3, and 4. Figure 9 illustrates an example of a full internal standard analysis.
My research began by repeating the reaction involving an inorganic base $K_3PO_4$ and the polar aprotic solvent dimethyl acetamide (DMA), which gave a high NMR yield of 78% (entry 8, Table 1). Organic bases in DMA were much less successful (entries 7,
In general, Ms. Roberts observed the same trend with inorganic bases and DMA as a solvent giving the highest yields. However, she never attempted product isolation. Difficulties employing an aqueous work-up led us to consider other reaction conditions. There were two reactions performed in earlier research using Pd(PPh$_3$)$_4$ as a catalyst and an organic base, triethyl amine (TEA), that gave yields of 59 and 58% (entries 5–6). A synthesis involving TEA and toluene (PhMe) as a solvent was proposed and gave a very similar NMR yield at 52%. Further adjustment of the catalyst to Pd(OAc)$_2$, combined with only two equivalents of the ligand triphenyl phosphine ((Ph)$_3$P) per palladium equivalent, gave a yield of 74% along with a considerably easier work-up than with inorganic bases and DMA as a solvent. Both Pd(OAc)$_2$ and (Ph)$_3$P are readily weighed out on the bench top along with all the other reaction contents. No extraction is required before purification. A simple filtration of reaction contents through a cotton plug, and removal of solvent via roto-evaporator are the only steps required before purification by flash column chromatography (FCC). Entry 14 is considered the optimized conditions for the one-step synthesis involving quinine and bromobenzene (Table 1).

Purification of quinine derivatives by FCC proved to be an extensively meticulous endeavor. After catalytic conditions were established, obtaining viable column chromatography systems was more challenging than anticipated. Along with any lingering quinine, side products from the reactions added another dimensional of difficulty during FCC. Side products were observed during TLC, and had very similar retention factors ($R_f$) to desired products. These side products, although not formed in significant yields, were probable isomers of the $trans$-derivatives, thus exhibited very similar $R_f$ values. Various FCC solvent systems were tested in order to maximize purity.
and yields. Two different solvent systems were effectively instituted for isolating products. A combination of ethyl acetate (EtOAc), methanol (MeOH), and triethyl amine (TEA) was the preferred system. Only a small percent of TEA was used (between 0.25-0.50%) for the solvent system. TEA is commonly added for purification of amine-containing compounds since silica gel is acidic and can partially protonate and retain organic amines. It was interesting that without the use of TEA, virtually no product would elute. The second solvent system used was dichloromethane (DCM) and MeOH. This system did not display similar separation as the former, but was needed to isolate some products. Unfortunately, product was often discarded using both solvent systems because undesired products were almost always present in some of the same fractions; ultimately leading to lower isolated yields.

Alkene stereochemistry of the dominate product was determined through the use of $^1$H-NMR coupling constants. All the major products synthesized during the research contained alkene proton coupling constants concurrent with trans stereochemistry literature values. A common trans coupling constant value is 16 Hertz (Hz), and can range from approximately 11-18 Hz. If products were to exhibit cis stereochemistry the coupling constants would have ranged from 6-15 Hz, with normally a value around 8 Hz. Coupling constants of all synthesized, major products ranged from 15.2-16 Hz. An example of an $^1$H-NMR alkene region for an isolated trans product is shown in Figure 10 for 11-(phenyl)-quinine (entry 1, Table 2).
Figure 10. Alkene region of the synthesized product 11-(phenyl)-quinine illustrating \textit{trans} stereochemistry.

Substrate Scope

Employing the optimized reaction conditions, 15 novel quinine derivatives were synthesized and purified by FCC. Reaction substrates with the corresponding product structures are listed in Table 2. Product yields obtained were moderate to excellent ranging from 51-84%. Structures of all successfully isolated products were verified by $^1$H-NMR, $^{13}$C-NMR and HR-MS. $^1$H-NMR and $^{13}$C-NMR spectra can be seen in the Appendix. Rarely did reaction conditions deviate except for a few minor adjustments. One such adjustment was the increase in equivalents of the two bromo-fluoro substituted substrates (entries 7 and 15, Table 2). Both the para and ortho substituted bromo-fluoro
substrates required four equivalents for the reaction to reach completion. Two equivalents of all other substrates were sufficient for product formation in all other reactions. Reaction times varied, but all were completed between 20-27 hours.

Table 2: Reaction yields after flash column chromatography using optimized conditions.

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>(\text{Br}^-)</td>
<td>![Product Image]</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>7</td>
<td>(\text{Br}^-)</td>
<td>![Product Image]</td>
<td>52</td>
</tr>
</tbody>
</table>
Unsuccessful Substrates

Nine other substrates were explored using the research’s optimized Heck reaction conditions (Table 3). The para-substituted nitro substrate reacted very well under optimized conditions. Issues purifying the nitro compound via FCC arose, leading to no isolated compound. It appears the nitro product may have been decomposing.
**Table 3.** Substrates unable to be isolated

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
</table>
| 4-bromo-nitrobenzene          | ![Structure](image)
| 1-bromo-2-methoxynaphthalene  | ![Structure](image) |
| 2-bromoanisole                | ![Structure](image) |
| 4-bromoacetanilide            | ![Structure](image) |
| 3-bromopyradine               | ![Structure](image) |
| 2-bromothiazole               | ![Structure](image) |
| 4-bromo-N,N-dimethylanaline   | ![Structure](image) |
| 2-bromobenzotrifluoride       | ![Structure](image) |
| 2-bromofluorobenzene          | ![Structure](image) |

All other substrates in Table 3 displayed varying degrees of success during reactions, but none reacted to completion. An interesting observation is that most ortho-substituted aryl bromides were poor reaction substrates. The most likely explanation is possible steric hindrance associated with ortho-functional groups during oxidative addition of the
reaction mechanism; consequently these reactions did not reach completion. Reactions short of completion showed residual quinine by $^1$H-NMR. A major difficulty within the research was separating quinine from product using FCC. Quinine would streak excessively off the column during isolation attempts, rendering any product isolation futile. Many of these substrates could be utilized if alternate purification methods, such as reverse phase chromatography or medium pressure chromatography, could be further developed.

**Biological Data**

A growth inhibitory assay was employed to screen for anti-malarial activity shown by the novel quinine compounds. The biological testing was completed by Alex Gorka through a collaboration with the Roepe lab from Georgetown University using the SYBR Green I-based plate method. This specific assay is run with a quinine sensitive *P. Falciparum* strain (QNS), HB3, and a quinine resistant (QNR), Dd2 *P. Falciparum* strain. Initial screening experiments used three compound concentrations, 75, 500, and 1500 nM, to evaluate efficacy against both parasitic strains. After this initial screening, it was found that two compounds exhibited strong enough growth inhibition to run full half maximal inhibitory concentration (IC$_{50}$) binding curves. IC$_{50}$ curves are commonly sought during drug development because they express the amount of a compound necessary to inhibit a biological system by half. The two compounds selected for IC$_{50}$ examination were compound 10 and 13 (Table 2). Along with compounds 13 and 10, quinine and chloroquine IC$_{50}$ values were obtained. A collection of the IC$_{50}$ data is compiled in Table 4.
Table 4. *IC*$_{50}$ data against HB3 and Dd2 parasite strains for compound 10, 13, quinine and chloroquine.

<table>
<thead>
<tr>
<th>Compound</th>
<th>HB3 (QNS) <em>IC</em>$_{50}$ (nM)</th>
<th>Dd2 (QNR) <em>IC</em>$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>476.0</td>
<td>479.7</td>
</tr>
<tr>
<td>13</td>
<td>341.2</td>
<td>428.1</td>
</tr>
<tr>
<td>Quinine</td>
<td>309.9</td>
<td>736.5</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>49.1</td>
<td>327.8</td>
</tr>
</tbody>
</table>

Analysis of the data shows that compounds 10 and 13 are not as potent against the QNS compared to quinine and chloroquine. However, the QNR data shows a significant increase in concentration of quinine, almost a 2.5 fold increase, and chloroquine, about a 6.5 fold increase, to inhibit the Dd2 (QNR) parasite strain. This is not observed with compounds 10 and 13. Compound 10 hardly exhibited an increase in concentration from 476.0 to 479.7 nM, while compound 13 needed less than a 0.5 fold increase. Based on the *IC*$_{50}$ data, it appears that compound 10 and 13 may have bypassed the parasitic resistance mechanism that quinine and chloroquine encounter.

It is of interest that both potent novel compounds 10 and 13 contain a para-substituted, electron withdrawing substituent group. Compound 10 contains a strongly withdrawing trifluoromethyl group, while compound 13 has a temperately withdrawing ethyl ester. There is no clear reason why these two functionality requirements would bypass resistance, because there were other para-substituted electron withdrawing substituents tested, i.e. para-chloro and para-fluoro. It remains possible compound 10 and 13 act on the parasite through a secondary mechanism rather than the hemozoin inhibition.

Supplementary biological examination is necessary to decipher the reasoning behind compound’s 10 and 13 apparent activity. A β-hematin inhibitory assay will show
if the compounds are indeed exhibiting heme binding. Future experiments involving
synthesis of additional novel quinine derivatives with electron withdrawing, para-
substituted functional groups are planned. Alternatively, other cinchona alkaloids will be
used in place of quinine executing the optimized Heck reaction conditions for potential
anti-malarial compounds. Subsequent biological data of further novel quinine and
cinchona alkaloid compounds will be integral for understanding this research data, and
potentially the resistance against quinine and other quinoline derived anti-malarial
compounds.
EXPERIMENTAL

**General.** $^1$H NMR spectra were recorded on Bruker DRX (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl$_3$: 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}$C NMR spectra were recorded on a Bruker DRX 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl$_3$: 77.0 ppm). HRMS data was acquired with a DART-TOF at Duke University.

Liquid chromatography was performed using forced flow (flash chromatography) on EMD Chemicals Geduran® 60 silica gel (SiO$_2$, 40 to 63µm) purchased from VWR International. Thin layer chromatography (TLC) was performed on EMD Chemicals 0.25 mm silica gel 60 plates. Visualization was achieved with UV light at 254 nm.

All reactions were conducted in oven and flame dried glassware under an inert atmosphere of argon. All solvents were EMD Chemicals anhydrous solvents sold by VWR International. Each solvent was purged with Argon for a minimum of 15 minutes and stored over activated 3Å molecular sieves in sure-seal bottles. Bromobenzene, 4-bromo-o-xylene, 3-bromoanisole, 4-bromobenzotrifluoride, 3-bromobenzotrifluoride, ethyl-4-bromobenzoate, 4-bromo-1,2-(methyleneoxy)benzene, and 3-bromofluorobenzene were purchased from Alfa Aesar. p-Bromotoluene, o-bromotoluene, and p-bromoanisole were purchased from Eastman Kodak. p-Bromochlorobenzene was purchased from Aldrich Chemical Company. 1-Bromonaphthalene, 2-bromonaphthalene, and p-bromofluorobenzene were purchased
from TCI International. Triethyl amine was purchased from Acros Chemical Company. Triphenyl phosphine and palladium(II)acetate were purchased from Strem Chemical Company.

**Synthetic Method.** Quinine (81.1 mg, 0.25 mmol), palladium(II)acetate (2.8 mg, 0.0125 mmol), and triphenyl phosphine (6.6 mg, 0.025 mmol) were all weighed out on the bench top and placed into a reaction vial. The indicated aryl bromide and dry toluene (1mL, 9.4M) were added to the reaction vial by syringes. TEA (69.7 µL, 0.50 mmol) was added last, drop-wise, into the reaction vial via syringe. The reaction was placed under argon and stirred at 110°C for 20-27 hours. Contents were allowed to cool to room temperature, followed by filtration through a cotton plug. The solid was washed 2 times with 0.5 mL of toluene. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography using one of the three following solvent systems: 1)EtOAc, MeOH, and TEA 2)DCM and MeOH or 3)DCM, MeOH, and TEA. Fractions containing product were combined and concentrated under reduced pressure to give a slightly yellow/clear oil. An azeotrope of DCM and benzene was used to transfer combined fractions, which were then concentrated under reduced pressure to give a slightly brown solid for yield between 51-84%.

**11- pheyl-quinine (entry 1, Table 2).** Bromobenzene (53.0 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 20 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 90.5% EtOAc, 9.5% MeOH, and 0.5% TEA to yield 0.066g (66%). HRMS: Calculated for C_{26}H_{28}N_{2}O_{2}: 401.2229 (M+H^+), found 401.2220 (M+H^+). $^1$H-NMR (CDCl₃): δ 8.63
ppm (1H, d, J = 4 Hz), 7.95 (1H, d, J = 9.2), 7.54 (1H, d, J = 4.4), 7.29 (1H, dd, J = 2.0, 9.2), 7.24 (5H, m), 7.18 (1H, m), 6.36 (1H, d, J = 16.0), 6.10 (1H, dd, J = 8.0, 16.0), 5.76 (1H, s), 3.88 (3H, s), 3.65 (1H, m), 3.26 (2H, m), 2.78 (2H, m), 2.54 (1H, m), 1.95 (1H, m), 1.88 (2H, m), 1.62 (2H, m). $^{13}$C-NMR (CDCl$_3$): δ 157.87 ppm, 147.47, 147.25, 143.83, 136.96, 132.49, 131.19, 130.60, 128.51, 127.30, 126.39, 126.04, 121.63, 118.61, 101.21, 70.41, 60.20, 57.18, 56.10, 43.34, 39.09, 28.13, 26.89, 20.96.

11- (4-methylphenyl)-quinine (entry 2, Table 2). p-Bromotoluene (61.5 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 20 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 90.5% EtOAc, 9.5% MeOH, and 0.5% TEA to yield 0.087g (84%). HRMS: Calculated for C$_{27}$H$_{30}$N$_2$O$_2$: 415.2386 (M+H$^+$), found 415.2383 (M+H$^+$). $^1$H-NMR (CDCl$_3$): δ 8.67 ppm (1H, d, J = 4 Hz), 7.94 (1H, d, J = 9.2), 7.57 (1H, d, J = 4.4), 7.28 (1H, d, J = 9.2), 7.21 (1H, d, J = 2.4), 7.14 (2H, d, J = 8.4), 7.05 (2H, d, J = 8.0), 6.33 (1H, d, 15.6), 6.02 (1H, dd, J = 8.0, 15.6), 5.86 (1H, s), 3.86 (3H, s), 3.74 (1H, m), 3.30 (2H, m), 2.82 (2H, m), 2.56 (1H, m), 2.3 (3H, s), 1.93 (3H, m), 1.63 (2H, m). $^{13}$C-NMR (CDCl$_3$): δ 158.01 ppm, 147.14, 146.77, 143.74, 137.28, 133.88, 131.14, 130.99, 130.35, 129.21, 128.34, 126.17, 125.97, 121.83, 118.75, 100.99, 69.20, 60.24, 56.83, 56.51, 43.53, 38.51, 28.00, 26.22, 21.13, 20.30.

11-(2-naphthyl)-quinine (entry 3, Table 2). 2-Bromonaphthalene (103.5 mg, 0.50 mmol) was used with all other general synthesis conditions and reacted for 24 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 90.5% EtOAc, 9.5% MeOH, and 0.5% TEA to yield 0.087g (84%). HRMS: Calculated for C$_{27}$H$_{30}$N$_2$O$_2$: 415.2386 (M+H$^+$), found 415.2383 (M+H$^+$). $^1$H-NMR (CDCl$_3$): δ 8.67 ppm (1H, d, J = 4 Hz), 7.94 (1H, d, J = 9.2), 7.57 (1H, d, J = 4.4), 7.28 (1H, d, J = 9.2), 7.21 (1H, d, J = 2.4), 7.14 (2H, d, J = 8.4), 7.05 (2H, d, J = 8.0), 6.33 (1H, d, 15.6), 6.02 (1H, dd, J = 8.0, 15.6), 5.86 (1H, s), 3.86 (3H, s), 3.74 (1H, m), 3.30 (2H, m), 2.82 (2H, m), 2.56 (1H, m), 2.3 (3H, s), 1.93 (3H, m), 1.63 (2H, m). $^{13}$C-NMR (CDCl$_3$): δ 158.01 ppm, 147.14, 146.77, 143.74, 137.28, 133.88, 131.14, 130.99, 130.35, 129.21, 128.34, 126.17, 125.97, 121.83, 118.75, 100.99, 69.20, 60.24, 56.83, 56.51, 43.53, 38.51, 28.00, 26.22, 21.13, 20.30.
system of 91% EtOAc, 8.75% MeOH, and 0.25% TEA to yield 0.060g (53%).

Calculated for C$_{30}$H$_{30}$N$_2$O$_2$: 451.2386 (M+H$^+$), found 451.2383 (M+H$^+$). $^1$H-NMR (CDCl$_3$): $\delta$ 8.54 ppm (1H, d, J = 4.0 Hz), 7.90 (1H, d, J = 9.2), 7.75 (2H, m), 7.69 (1H, d, J = 8.4), 7.60 (1H, s), 7.56 (1H, d, J = 4.8), 7.42 (2H, m), 7.25 (3H, m), 6.51 (1H, d, J = 15.6), 6.20 (1H, dd, J = 8.0, 15.6), 5.85 (1H, s), 3.88 (3H, s), 3.77 (1H, m), 3.30 (2H, m), 2.84 (2H, m), 2.60 (1H, m), 1.94 (3H, m), 1.63 2H, m). $^{13}$C-NMR (CDCl$_3$): $\delta$ 157.93 ppm, 147.26, 143.82, 134.34, 133.53, 132.80, 132.59, 131.21, 130.89, 128.36, 128.15, 127.85, 127.62, 126.36, 126.26, 126.06, 125.81, 125.76, 123.36, 121.71, 118.68, 101.20, 70.09, 60.26, 57.08, 56.25, 43.42, 39.10, 28.13, 26.72, 20.84.

11-(4-chlorophenyl)-quinine (entry 4, Table 2). p-Bromochlorobenzene (95.7 mg, 0.50 mmol) was used with all other general synthesis conditions and reacted for 27 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 92% DCM, and 8% MeOH to yield 0.057g (53%). HRMS:

Calculated for C$_{26}$H$_{27}$ClN$_2$O$_2$: 435.1839 (M+H$^+$), found 435.1836 (M+H$^+$). $^1$H-NMR (CDCl$_3$): $\delta$ 8.69 ppm (1H, d, J = 4.0 Hz), 7.98 (1H, dd, J = 1.6, 9.2), 7.56 (1H, d, J = 4.4), 7.32 (1H, d, J = 9.2), 7.19 (5H, m), 6.31 (1H, d, J = 16.0), 6.08 (1H, dd, J = 8.0, 15.8), 5.72 (1H, s), 3.86 (3H, s), 3.64 (1H, m), 3.25 (2H, m), 2.76 (2H, m), 2.51 (1H, m), 1.94 (1H, m), 1.87 (2H, m), 1.59 (2H, m). $^{13}$C-NMR (CDCl$_3$): $\delta$ 179.34 ppm, 157.78, 147.64, 147.28, 143.84, 135.51, 133.39, 132.78, 131.23, 129.32, 128.60, 127.91, 127.24, 126.37, 121.49, 118.53, 101.16, 70.48, 60.16, 57.07, 55.77, 43.17, 39.21, 28.13, 26.95, 20.93.
11-(2-methylphenyl)-quinine (entry 5, Table 2). 2-Bromotoluene (60.1 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 20 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 90.5% EtOAc, 9.5% MeOH, and 0.5% TEA to yield 0.072g (70%). HRMS: Calculated for C_{27}H_{30}N_{2}O_{2}: 415.2386 (M+H\(^{+}\)), found 415.2388 (M+H\(^{+}\)). \(^{1}\)H-NMR (CDCl\(_{3}\)): δ 8.64 ppm (1H, d, J = 3.6 Hz), 7.93 (1H, d, J = 9.2), 7.55 (1H, d, J = 4.4), 7.26 (2H, m), 7.21 (1H, d, J = 2.4), 7.07 (3H, m). 6.55 (1H, d, J = 15.6), 5.94 (1H, dd, J = 8.0, 15.6), 5.83 (1H, s), 3.86 (3H, s), 3.75 (1H, m), 3.29 (2H, m), 2.83 (2H, m), 2.59 (1H, m), 2.18 (3H, s), 1.93 (3H, m), 1.62 (2H, m). \(^{13}\)C-NMR (CDCl\(_{3}\)): δ 157.94 ppm, 147.21, 143.83, 136.09, 134.99, 133.72, 131.21, 130.17, 128.50, 127.27, 126.30, 126.02, 125.46, 121.69, 118.62, 101.14, 70.14, 60.18, 57.01, 56.20, 43.42, 39.09, 28.23, 26.72, 20.78, 19.62.

11-(3,4-dimethylphenyl)-quinine (entry 6, Table 2). 4-Bromo-o-xylene (67.5 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 24 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 91% EtOAc, 8.75% MeOH, and 0.25% TEA to yield 0.079g (74%). HRMS: Calculated for C_{28}H_{32}N_{2}O_{2}: 429.2542 (M+H\(^{+}\)), found 429.2550 (M+H\(^{+}\)). \(^{1}\)H-NMR (CDCl\(_{3}\)): δ 8.49 ppm (1H, d, J = 4.8 Hz), 7.87 (1H, d, J = 9.2), 7.54 (1H, d, J = 4.8), 7.25 (3H, m), 6.99 (2H, m), 6.28 (1H, d, J = 15.6), 5.99 (1H, dd, J = 8.0, 16.0), 5.81 (1H, s), 3.86 (3H, s), 3.75 (1H, m), 3.22 (2H, m), 2.75 (2H, m), 2.50 (1H, m), 2.21 (6H, m), 1.89 (3H, m), 1.56 (2H, m). \(^{13}\)C-NMR (CDCl\(_{3}\)): δ 157.60 ppm, 147.29,
11-(4-fluorophenyl)-quinine (entry 7, Table 2). p-Bromofluorobenzene (109.8 µL, 1.0 mmol) was used with all other general synthesis conditions and reacted for 21 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 92% DCM, and 8% MeOH to yield 0.054g (52%). HRMS: Calculated for C_{26}H_{27}FN_{2}O_{2}: 419.2135 (M+H^+), found 419.2128 (M+H^+). ^1H-NMR (CDCl_3): δ 8.67 ppm (1H, d, J = 3.6 Hz), 7.97 (1H, dd, J = 3.2, 9.2), 7.55 (1H, d, J = 4.4), 7.32 (1H, dd, J = 2.8, 9.2), 7.21 (3H, m), 6.93 (2H, t, J = 8.6), 6.31 (1H, d, J = 15.6), 6.02 (1H, dd, J = 7.8, 15.8), 5.68 (1H, s), 3.87 (3H, s), 3.59 (1H, m), 3.23 (2H, m), 2.74 (2H, m), 2.49 (1H, m), 1.92 (1H, m), 1.85 (2H, m), 1.60 (2H, m). ^13C-NMR (CDCl_3): δ 160.82 ppm, 157.77, 147.70, 147.31, 143.86, 133.19, 132.53, 131.24, 129.26, 127.52, 127.44, 126.39, 121.48, 118.52, 115.46, 115.25, 101.16, 70.63, 60.15, 57.20, 55.74, 43.17, 39.21, 28.18, 27.03, 20.97.

11-(4-methoxyphenyl)-quinine (entry 8, Table 2). p-Bromoanisole (62.8 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 27 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 91% EtOAc, 8.75% MeOH, and 0.25% TEA to yield 0.064g (59%). HRMS: Calculated for C_{27}H_{30}N_{2}O_{3}: 431.2335 (M+H^+), found 431.2330 (M+H^+). ^1H-NMR (CDCl_3): δ 8.61 ppm (1H, d, J = 4.8 Hz), 7.88 (1H, d, J =
9.2), 7.60 (1H, d, J = 4.4), 7.19 (5H, m), 6.76 (2H, d, J = 8.8), 6.29 (1H, d, J = 15.6), 5.94 (1H, s), 5.88 (1H, dd, J = 8.2, 15.8), 3.82 (3H, s), 3.75 (3H, s), 3.29 (2H, m), 2.83 (2H, m), 2.58 (1H, m), 1.95 (3H, m), 1.67 (1H, m), 1.57 (1H, m). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}): \( \delta \) 158.95 ppm, 157.87, 147.21, 143.79, 131.15, 130.11, 130.04, 129.72, 128.34, 127.63, 127.17, 126.34, 121.66, 118.62, 113.90, 113.74, 101.17, 70.19, 60.19, 57.25, 56.16, 55.27, 43.36, 38.97, 28.16, 26.79, 20.79.

\textbf{11-(3-methoxyphenyl)-quinine (entry 9, Table 2).} \ 3-Bromoanisole \((63.2 \mu\text{L}, 0.50 \text{mmol})\) was used with all other general synthesis conditions and reacted for 24 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 91% EtOAc, 8.75% MeOH, and 0.25% TEA to yield 0.065g (60%). HRMS: Calculated for C\(_{27}\)H\(_{30}\)N\(_2\)O\(_3\): 431.2335 (M+H\(^+\)), found 431.2323 (M+H\(^+\)). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): \( \delta \) 8.54 ppm (1H, d, \( J = 4.8 \) Hz), 7.89 (1H, d, \( J = 5.6 \)), 7.54 (1H, d, \( J = 4.4 \)), 7.25 (2H, m), 7.15 (1H, t, \( J = 7.8 \)), 6.83 (1H, d, \( J = 7.6 \)), 6.74 (2H, m), 6.32 (1H, d, \( J = 15.6 \)), 6.05 (1H, dd, \( J = 8.0, 16.0 \)), 5.81 (1H, s), 3.86 (3H, s), 3.74 (3H, s), 3.26 (2H, m), 2.79 (2H, m), 2.54 (1H, m), 1.91 (3H, m), 1.57 (2H, m). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}): \( \delta \) 159.71 ppm, 157.98, 147.18, 143.76, 138.15, 138.15, 131.85, 131.20, 130.98, 129.52, 128.52, 126.15, 126.07, 121.80, 118.71, 113.01, 111.46, 100.95, 69.39, 60.22, 56.78, 56.44, 55.20, 43.52, 38.56, 27.96, 26.20, 20.30.

\textbf{11-(4-(trifluoromethyl)-phenyl)-quinine (entry 10, Table 2).} \ 4-Bromobenzotrifluoride \((70.0 \mu\text{L}, 0.50 \text{mmol})\) was used with all other general synthesis conditions and reacted for 24 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column.
chromatography with the solvent system of 92% DCM, and 8% MeOH to yield 0.066g (56%). HRMS: Calculated for C_{27}H_{27}F_{3}N_{2}O_{2}: 469.2103 (M+H^+), found 469.2103 (M+H^+). ^1H-NMR (CDCl₃): δ 8.49 ppm (1H, d, J = 4 Hz), 7.84 (2H, d, J = 9.2), 7.52 (1H, d, J = 4.4), 7.47 (2H, d, J = 8.0), 7.32 (2H, d, J = 8.4), 7.25 (2H, m), 6.37 (1H, d, J = 16), 6.17 (1H, dd, J = 8.2, 15.8), 5.73 (1H, s), 3.86 (3H, s), 3.68 (1H, m), 3.23 (2H, m), 2.74 (2H, m), 2.53 (1H, m), 1.91 (3H, m), 1.54 (2H, m). ^13C-NMR (CDCl₃): δ 157.84 ppm, 147.62, 147.24, 143.81, 140.47, 135.41, 131.17, 129.35, 129.17, 128.85, 126.39, 126.18, 125.44, 125.41, 122.80, 121.53, 118.56, 101.24, 70.47, 60.23, 56.98, 55.95, 43.25, 39.25, 28.08, 26.90, 20.99.

11-(3-(trifluoromethyl)-phenyl)-quinine (entry 11, Table 2). 3-Bromobenzotri fluoride (70.0 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 24 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 92% DCM, and 8% MeOH to yield 0.071g (60%). Calculated for C_{27}H_{27}F_{3}N_{2}O_{2}: 469.2103 (M+H^+), found 469.2099. ^1H-NMR (CDCl₃): δ 8.46 ppm (1H, d, J = 4.8 Hz), 7.87 (1H, d, J = 10), 7.51 (1H, d, J = 4.4), 7.47 (1H, s), 7.38 (3H, m), 7.25 (2H, m), 6.35 (1H, d, J = 15.6), 6.16 (1H, dd, J = 7.8, 15.8), 5.67 (1H, s), 3.86 (3H, s), 3.63 (1H, m), 3.20 (2H, m), 2.72 (2H, m), 2.49 (1H, m), 1.89 (3H, m), 1.56 (2H, m). ^13C-NMR (CDCl₃): δ 157.78, 147.79, 147.26, 143.82, 137.84, 134.84, 131.18, 131.01, 130.69, 129.37, 129.13, 128.92, 126.44, 123.71, 122.69, 121.47, 118.55, 101.31, 70.77, 60.21, 57.03, 55.81, 43.18, 39.31, 28.11, 27.07, 21.16.
**11-(1-naphthyl)-quinine (entry 12, Table 2).** 1-Bromonaphthalene (69.5 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 20 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 90.5% EtOAc, 9.5% MeOH, and 0.5% TEA to yield 0.066g (58%). Calculated for C₃₀H₃₀N₂O₂: 451.2386 (M+H⁺), found 451.2382 (M+H⁺). ¹H-NMR (CDCl₃): δ 8.66 ppm (1H, d, J = 4.0 Hz), 7.90 (2H, m), 7.80 (1H, dd, J = 2.6, 7.2), 7.71 (1H, d, J = 8), 7.59 (1H, d, J = 4.4), 7.45 (2H, m), 7.34 (2H, m), 7.20 (2H, m), 7.11 (1H, d, J = 15.6), 6.06 (1H, dd, J = 8.0, 15.2), 5.99 (1H, s), 3.93 (1H, s), 3.82 (3H, s), 3.39 (2H, m), 2.94 (2H, m), 2.77 (1H, m), 2.00 (3H, m), 1.75 (1H, m), 1.62 (1H, m). ¹³C-NMR (CDCl₃): δ 158.03 ppm, 147.20, 146.55, 143.80, 134.88, 134.47, 133.49, 131.23, 130.90, 128.53, 128.43, 128.36, 127.88, 126.14, 126.04, 125.78, 125.52, 123.77, 123.48, 121.87, 118.73, 100.89, 69.32, 60.26, 56.81, 56.49, 43.59, 38.86, 28.15, 26.24, 20.43.

**11-(4-(ethylcarboxy)phenyl)-quinine (entry 13, Table 2).** Ethyl-4-bromobenzoate (80.1 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 24 hours. The contents were concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 95% DCM and 5% MeOH to yield 0.073g, (62%). Calculated for C₂₉H₃₂N₂O₄: 473.2440 (M+H⁺), found 473.2438 (M+H⁺). ¹H-NMR (CDCl₃): δ 8.65 ppm (1H, d, J = 4.4 Hz), 7.83 (2H, d, J = 8.4), 7.71 (1H, d, J = 9.2), 7.67 (1H, d, J = 4.0), 7.19 (2H, d, J = 8.4), 7.01 (2H, m), 6.44
(1H, s), 6.40 (1H, d, J = 16.0), 5.99 (1H, dd, J = 7.8, 15.8), 4.47 (1H, m), 4.28 (2H, q, J = 7.2), 3.66 (3H, s), 3.57 (1H, t, J = 11.2), 3.41 (1H, t, J = 8.8), 3.15 (1H, m), 3.02 (1H, m), 2.89 (1H, s), 2.20 (3H, m), 1.90 (1H, m), 1.40 (1H, m), 1.34 (3H, t, 7.2). $^{13}$C-NMR (CDCl$_3$): $\delta$ 166.19 ppm, 158.33, 146.92, 144.32, 143.53, 140.15, 131.86, 131.17, 129.81, 129.63, 125.46, 122.35, 119.01, 100.15, 66.22, 60.99, 60.37, 57.52, 55.54, 44.23, 37.17, 27.51, 24.43, 18.68, 14.27.

11-((3,4-methylenedioxy)phenyl)-quinine (entry 14, Table 2). 4-Bromo-1,2-(methylenedioxy) benzene (60.5 µL, 0.50 mmol) was used with all other general synthesis conditions and reacted for 27 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with the solvent system of 94% DCM, 5.75% MeOH, and 0.25% TEA to yield 0.066g (58%). Calculated for C$_{27}$H$_{28}$N$_2$O$_4$: 445.2127 (M+H$^+$), found 445.2129 (M+H$^+$). $^1$H-NMR (CDCl$_3$): $\delta$ 8.53 ppm (1H, d, J = 4.8 Hz), 7.89 (1H, d, J = 8.8), 7.53 (1H, d, J = 4.4), 7.25 (3H, m), 6.77 (1H, s), 6.67 (1H, d, J = 2), 6.25 (1H, d, J = 15.6), 5.90 (3H, m), 5.79 (1H, s), 3.86 (3H, s), 3.73 (1H, m), 3.24 (2H, m), 2.76 (2H, m), 2.50 (1H, m), 1.90 (3H, m), 1.57 (2H, m). $^{13}$C-NMR (CDCl$_3$): $\delta$ 157.90 ppm, 147.93, 147.29, 147.08, 146.96, 143.92, 131.40, 131.31, 130.50, 130.28, 128.51, 126.35, 126.04, 121.68, 120.53, 118.60, 108.21, 105.43, 101.12, 101.00, 70.21, 60.21, 57.20, 56.17, 43.37, 38.89, 28.13, 26.77, 20.94.

11-(3-fluorophenyl)-quinine (entry 15, Table 2). m-Bromofluorobenzene (111.7 µL, 1.0 mmol) was used with all other general synthesis conditions and reacted for 24 hours. The filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography with
the solvent system of 92% DCM, and 8% MeOH to yield 0.053g (51%). HRMS:
Calculated for C_{26}H_{27}FN_{2}O_{2}: 419.2135 (M+H\(^{+}\)), found 419.2132. \(^{1}\)H-NMR (CDCl\(_{3}\)): \(\delta\)
8.51 ppm (1H, d, J = 4.4 Hz), 7.88 (1H, d, J = 9.2), 7.52 (1H, d, J = 4.4), 7.2 (3H, m),
6.98 (1H, d, J = 7.6), 6.92 (1H, dt, J = 2, 10), 6.85 (1H, td, J = 2.8, 8.4), 6.29 (1H, d, J =
15.6), 6.08 (1H, dd, J = 8, 15.6), 5.71 (1H, s), 3.84 (3H, s), 3.65 (1, m), 3.20 (2H, m),
2.70 (2H, m), 2.48 (1H, m), 1.89 (3H, m), 1.56 (2H, m). \(^{13}\)C-NMR (CDCl\(_{3}\)): \(\delta\) 164.23
ppm, 161.80, 157.79, 147.29, 143.88, 139.44, 134.16, 131.26, 129.89, 129.46, 126.40,
121.87, 121.50, 118.55, 114.12, 112.61, 101.18, 70.65, 60.17, 57.02, 55.80, 43.18, 39.15,
28.11, 26.96, 21.05.
REFERENCES


Appendix 1.
Appendix 2.
Appendix 3.
Appendix 5.
Appendix 6.
Appendix 7.
Appendix 8.
Appendix 9.
Appendix 10.
Appendix 11.
Appendix 13.
Appendix 14.
Appendix 15.
Appendix 16.
Appendix 17.
Appendix 18.
Appendix 19.
Appendix 20.
Appendix 21.
Appendix 22.
Appendix 23.
Appendix 24.
Appendix 25.
Appendix 26.
Appendix 27.
Appendix 28.
Appendix 29.
Appendix 30.