Compounds for the Treatment of Malaria

Provided herein are compounds of the formula (I) as well as pharmaceutically acceptable salts thereof, wherein the substituents are as those disclosed in the specification. These compounds, and the pharmaceutical compositions containing them, are useful for the treatment of malaria.
COMPUNDS FOR THE TREATMENT OF MALARIA

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application No. 61/837,711, filed June 21, 2013, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Malaria is a vector-borne infectious disease caused by protozoan parasites and is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa. Of the five Plasmodium parasite species that can infect humans (P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi), the most serious forms of the disease are caused by P. falciparum and P. vivax. Of the approximately 515 million people infected yearly, between one and three million people, the majority of whom are young children in Sub-Saharan Africa, die from the disease. The current armament of approved anti-malarial drugs, such as chloroquine, atovaquone, pyrimethamine, and sulfadoxine, is limited to only a few targets within the human malaria parasite, and growing widespread resistance to current drugs is prompting the development of new antimalarial agents that have new biological targets.

SUMMARY OF THE INVENTION

The invention features a compound having the structure:

![Formula I](image)

wherein a and b are independently 0, 1, or 2;
c is 0, 1, 2, 3, or 4;
$R^1$ is hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_9$ heteroaryl, $C_3$-$C_{10}$ carbocyclyl $C_1$-$C_6$ alkyl, $C_6$-$C_{10}$ aryl $C_1$-$C_6$ alkyl, $C_2$-$C_9$ heteroaryl $C_1$-$C_6$ alkyl, $-C(O)NR^8R^9$, $-C(O)OR^9$, $-C(O)R^9$, or $-S(O)_2R^9$; each $R^2$ is independently hydroxyl, halogen, or $-OR^{12}$;
$R^3$ is hydrogen or $C_1$-$C_6$ alkyl;
$R^4$ is hydrogen or $C_1$-$C_6$ alkyl;
$R^5$ is $C_1$-$C_6$ alkyl, or $-(CH_2)_nX^1R^{13}$, or $R^5$ and $R^6$ together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a 5-8-membered heterocycle;
$R^6$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ perfluoroalkyl, $C_3$-$C_{10}$ carbocyclyl $C_1$-$C_6$ alkyl, $C_6$-$C_{10}$ aryl $C_1$-$C_6$ alkyl, $C_2$-$C_9$ heteroaryl $C_1$-$C_6$ alkyl, $C_2$-$C_9$ heterocyclyl $C_1$-$C_6$ alkyl, $N$-protecting group, $-C(O)R^{15}$, $-C(O)NR^{16}R^{17}$, or $-S(O)_2R^{18}$;
$R^7$ is hydrogen or $C_1$-$C_6$ alkyl;
$R^8$ is $C_6$-$C_{10}$ aryl, $C_2$-$C_9$ heteroaryl, $C_2$-$C_9$ heterocyclyl, or $C_2$-$C_{10}$ carbocyclyl;
$R^9$ is $C_1$-$C_6$ alkyl or $C_6$-$C_{10}$ aryl;

1
R\textsuperscript{10} is C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{6}-C\textsubscript{10} aryl, C\textsubscript{2}-C\textsubscript{9} heterocycyl, C\textsubscript{6}-C\textsubscript{10} aryl C\textsubscript{1}-C\textsubscript{6} alkyl, or C\textsubscript{2}-C\textsubscript{9} heteroaryl C\textsubscript{1}-C\textsubscript{6} alkyl;

R\textsuperscript{11} is C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{6}-C\textsubscript{10} aryl, or C\textsubscript{6}-C\textsubscript{10} aryl C\textsubscript{1}-C\textsubscript{6} alkyl;

each R\textsuperscript{12} is C\textsubscript{1}-C\textsubscript{6} alkyl or C\textsubscript{1}-C\textsubscript{6} acyl;

n is 1, 2, 3, 4, 5, or 6;

X\textsuperscript{1} is absent, O, or NR\textsuperscript{14};

R\textsuperscript{13} is hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{1}-C\textsubscript{6} heteroalkyl, C\textsubscript{1}-C\textsubscript{6} perfluoroalkyl, C\textsubscript{1}-C\textsubscript{6} acyl, C\textsubscript{6}-C\textsubscript{10} aryl C\textsubscript{1}-C\textsubscript{6} alkyl, an O- or N-protecting group, or R\textsuperscript{12} and R\textsuperscript{14} combine to form a 5-8-membered heterocycle;

R\textsuperscript{14} is hydrogen or C\textsubscript{1}-C\textsubscript{6} alkyl;

R\textsuperscript{15} is C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{1}-C\textsubscript{6} perfluoroalkyl, C\textsubscript{1}-C\textsubscript{6} heteroalkyl, C\textsubscript{2}-C\textsubscript{10} carbocycyl, C\textsubscript{2}-C\textsubscript{9} heterocycyl,

C\textsubscript{6}-C\textsubscript{10} aryl, C\textsubscript{6}-C\textsubscript{10} aryl C\textsubscript{1}-C\textsubscript{6} alkyl;

R\textsuperscript{16} and R\textsuperscript{17} are independently hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl, or C\textsubscript{6}-C\textsubscript{10} aryl; and

R\textsuperscript{18} is C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{1}-C\textsubscript{6} perfluoroalkyl, C\textsubscript{2}-C\textsubscript{10} carbocycyl, or C\textsubscript{6}-C\textsubscript{10} aryl; or a pharmaceutically acceptable salt thereof,

wherein the compound is not compound 12, compound 15, or any one of compounds 78-135 of Table 1 or a pharmaceutically acceptable salt thereof.

In some embodiments, c is 1. In other embodiments, c is 2.

In certain embodiments, the compound has a structure of Formula II:

\begin{center}
\includegraphics[width=0.5\textwidth]{formula2.png}
\end{center}

Formula II

In other embodiments, the compound has a structure of Formula III:

\begin{center}
\includegraphics[width=0.5\textwidth]{formula3.png}
\end{center}

Formula III
In some embodiments, the compound has a structure of Formula IV:

Formula IV

In certain embodiments, the compound has the structure:

In other embodiments, the compound has a structure of Formula V:

Formula V

In certain embodiments, the compound has the structure:

In some embodiments, the compound has a structure of Formula VI:

Formula VI
In certain embodiments, the compound has the structure:

In some embodiments, R³ is hydrogen. In other embodiments, R³ is C₁₋C₆ alkyl (e.g., methyl). In certain embodiments, R⁴ is hydrogen. In some embodiments, R⁴ is C₁₋C₆ alkyl (e.g., methyl).

In other embodiments, R² is hydroxyl. In certain embodiments, R² is halogen (e.g., fluoro). In some embodiments, R² is –OR¹₂ (e.g., R¹₂ is C₁₋C₆ alkyl, such as methyl or isopropyl or C₁₋C₆ acyl, such as acetyl).

In certain embodiments, R⁵ and R⁶ together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a 5-8-membered heterocycle (e.g., a 6-membered heterocycle substituted with an oxo).

In some embodiments, the compound has the structure of Formula VII:

In other embodiments, R⁵ is C₁₋C₆ alkyl (e.g., methyl).

In certain embodiments, R⁶ is –(CH₂)ₓX¹R¹². In some embodiments, n is 1. In other embodiments, n is 2. In certain embodiments, X¹ is absent. In some embodiments, R¹³ is C₁₋C₆ perfluoroalkyl (e.g., trifluoromethyl). In other embodiments, X¹ is O. In certain embodiments, R¹³ is hydrogen, C₁₋C₆ alkyl (e.g., methyl), C₁₋C₆ heteroalkyl (e.g., –CH₂OCH₃ or –CH₂OCH₂CH₂OCH₃), C₁₋C₆ acyl (e.g., acetyl), C₆₋C₁₀ aryl C₁₋C₆ alkyl (e.g., 4-methoxybenzyl), or an O-protecting group (e.g., tertbutyldimethylsilyl). In some embodiments, X¹ is NR¹⁴. In other embodiments, R¹³ and R¹⁴ combine to form a 5-8-membered heterocycle (e.g., morpholino). In certain embodiments, R¹⁴ is hydrogen. In some embodiments, R¹⁴ is C₁₋C₆ alkyl (e.g., methyl). In some embodiments, R¹³ is C₁₋C₆ alkyl (e.g., methyl).

In other embodiments, R² is hydrogen.

In certain embodiments, R¹ is C₁₋C₆ alkyl (e.g., methyl, ethyl, or n-propyl).

In some embodiments, R¹ is C₂₋C₉ heteroaryl (e.g., benzo-oxazolyl, benzo-imidazolyl, or benzo-thiazolyl).

In other embodiments, R¹ is C₂₋C₁₀ carbocyclyl C₁₋C₆ alkyl (e.g., cyclopropylmethyl, cyclopentylmethyl, or cyclohexylmethyl).

In certain embodiments, R¹ is C₂₋C₁₀ aryl C₁₋C₆ alkyl (e.g., 2-fluorophenyl-ethyl, 2-fluorobenzyl, 4-(2-pyridyl)-benzyl, 4-methoxybenzyl, or 3-fluorobenzyl).
In some embodiments, R^1 is C_{2-}C_{2} heteroaryl C_{1-}C_{6} alkyl (e.g., 2-pyridyl-methyl, 3-pyridyl-methyl, 3,5-pyrimidyl-methyl, thiazolyl-methyl, or (3-phenyl-oxazolyl)-methyl).

In other embodiments R^1 is -C(O)NR^3R^6. In certain embodiments, R^7 is hydrogen. In some embodiments, R^8 is C_{2-}C_{6} aryl (e.g., methyl). In some embodiments, R^8 is C_{6-}C_{10} aryl (e.g.,

2-chlorophenyl, 2-fluorophenyl, 2-trifluoromethylphenyl, 3-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, or 3,4-difluorophenyl). In other embodiments, R^6 is C_{2-}C_{9} heteroaryl (e.g., 2-pyridyl or 3-pyridyl). In certain embodiments, R^6 is C_{2-}C_{9} heterocyclyl (e.g., benzodioxolyl). In some embodiments, R^8 is C_{2-}C_{10} carbocyclyl (e.g., cyclohexyl).

In other embodiments, R^1 is -C(O)OR^9. In certain embodiments, R^9 is C_{1-}C_{6} alkyl (e.g., tertbutyl). In some embodiments, R^9 is C_{2-}C_{10} aryl (e.g., 4-nitrophenyl).

In other embodiments, R^1 is -C(O)R^{10}. In certain embodiments, R^{10} is C_{1-}C_{6} alkyl (e.g., ethyl or n-propyl). In some embodiments, R^{10} is C_{6-}C_{10} aryl (e.g., phenyl or 2-fluorophenyl). In other embodiments, R^{10} is C_{2-}C_{6} heterocyclyl (e.g., benzodioxolyl). In certain embodiments, R^{10} is C_{2-}C_{10} aryl C_{1-}C_{6} alkyl (e.g., 2-fluorobenzyl). In some embodiments, R^{10} is C_{2-}C_{6} heterocarlyl C_{1-}C_{6} alkyl (e.g., 3-pyridylmethyl).

In other embodiments, R^1 is -S(O)_{2}R^{11}. In certain embodiments, R^{11} is C_{1-}C_{6} alkyl (e.g., ethyl). In some embodiments, R^{11} is C_{6-}C_{10} aryl (e.g., phenyl, 2-fluorophenyl, 3-fluorophenyl, 3-methoxyphenyl, or 4-methoxyphenyl). In other embodiments, R^{11} is C_{6-}C_{10} aryl C_{1-}C_{6} alkyl (e.g., 2-fluorobenzyl).

In certain embodiments, R^6 is hydrogen. In some embodiments, R^6 is C_{1-}C_{6} alkyl (e.g., methyl, ethyl, n-propyl, or 2,2,2-trifluoroethyl). In certain embodiments, R^6 is C_{2-}C_{10} carbocyclyl C_{1-}C_{6} alkyl (e.g., cyclopropylmethyl or cyclohexylmethyl). In some embodiments, R^6 is C_{2-}C_{10} aryl C_{1-}C_{6} alkyl (e.g., benzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-chlorobenzyl, 2,5-difluorobenzyl, phenyl-ethyl, or phenyl-propyl). In other embodiments, R^6 is C_{2-}C_{9} heteroaryl C_{1-}C_{6} alkyl (e.g., 2-pyridyl-methyl). In certain embodiments, R^6 is C_{2-}C_{9} heterocyclyl C_{1-}C_{6} alkyl (e.g., benzodioxolyl-methyl). In some embodiments, R^6 is an N-protecting group (e.g., allyloxy carbonyl, i.e., alloc).

In other embodiments, R^6 is -C(O)R^{15}. In certain embodiments, R^{15} is C_{1-}C_{6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, or tertbutyl). In some embodiments, R^{15} is C_{1-}C_{6} perfluoroalkyl (e.g., trifluoromethyl). In other embodiments, R^{15} is C_{1-}C_{6} heteroalkyl (e.g.,-CH_{2}N(CH_{3})_{2}). In certain embodiments, R^{15} is C_{2-}C_{10} carbocyclyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In some embodiments, R^{15} is C_{2-}C_{9} heterocyclyl (e.g., pyranyl). In other embodiments, R^{15} is C_{6-}C_{10} aryl (e.g., phenyl or 4-fluorophenyl). In certain embodiments, R^{15} is C_{6-}C_{10} aryl C_{1-}C_{6} alkyl (e.g., benzyl).

In some embodiments, R^6 is -C(O)NR^{16}R^{17}. In other embodiments, R^{16} is hydrogen. In certain embodiments, R^{17} is C_{2-}C_{10} aryl (e.g., 4-fluorophenyl).

In some embodiments, R^6 is -S(O)_{2}R^{18}. In other embodiments, R^{18} is C_{1-}C_{6} alkyl (e.g., methyl, ethyl, or n-propyl). In certain embodiments, R^{18} is C_{1-}C_{6} perfluoroalkyl (e.g., trifluoromethyl). In some embodiments, R^{18} is C_{2-}C_{10} carbocyclyl (e.g., cyclopropyl). In other embodiments, R^{18} is C_{6-}C_{10} aryl (e.g., phenyl or 4-methylphenyl).

In another aspect, the invention features a compound selected from any one of compounds 1 to 11, 13, 14, 16 to 77, and 136 to 150 of Table 1 or a pharmaceutically acceptable salt thereof.
Table 1. Selected Compounds of the Invention

<table>
<thead>
<tr>
<th>Example Number</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure" /></td>
<td>(R)-2'-acetyl-N-(2-chlorophenyl)-1'- (hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure" /></td>
<td>2'-acetyl-N-(2-fluorophenyl)-7'-methoxy- 1',1'-dimethyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure" /></td>
<td>(R)-N-(2-fluorophenyl)-1'- (hydroxymethyl)-7'-methoxy-2'(2,2,2-trifluoroacetyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>(R)-1-(1'-(hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)ethanone</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure" /></td>
<td>(R)-2'-acetyl-N-(2-fluorophenyl)-1'- (hydroxymethyl)-7'-methoxy-9'-methyl- 1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure" /></td>
<td>(S)-2'-acetyl-N-(2-fluorophenyl)-7'- methoxy-1'-(methylamino)methyl- 1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
<td>Chemical Structure</td>
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</tr>
<tr>
<td>13</td>
<td>(R)-2'-acetyl-N-(3-chlorophenyl)-1'-((hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>tert-butyl 2'-acetyl-7'-methoxy-1',1'-dimethyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxylate</td>
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</tr>
<tr>
<td>15</td>
<td>(R)-2'-acetyl-N-(2-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>(R)-allyl 1-((2-fluorophenyl)carbamoyl)-1'-(hydroxymethyl)-7'-methoxy-3',9'-dihydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-2'(1'H)-carboxylate</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>(R)-(2'-acetyl-1-((2-fluorophenyl)carbamoyl)-7'-methoxy-9'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1'-yl)methyl acetate</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>(R)-2'-allyl 1-tert-butyl 1'-(((tert-butyl(dimethyl)silyl)oxy)methyl)-7'-methoxy-3',9'-dihydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1,2'(1'H)-dicarboxylate</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>(R)-1-((tert-butyldimethylsilyl)oxy)methyl)-1-(2-fluorophenethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)ethanone</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>(R)-N-(2-fluorophenyl)-1'- (hydroxymethyl)-7'-methoxy-2'-propionyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>(R)-1-((2-fluorobenzyl)-1'- (hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)ethanone</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>(R)-1'-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2-fluorophenyl)-7'-methoxy-2'-pivaloyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>(R)-N-(2-fluorophenyl)-1'- (hydroxymethyl)-7'-methoxy-2'-pivaloyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>(R)-tert-butyl 2'-acetyl-1'-(((tert-butyldimethylsilyl)oxy)methyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxylate</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>(R)-1-((tert-butyldimethylsilyl)oxy)methyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)ethanone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( (R)-\text{N-}[2\text{-fluorophenyl}]-1'\text{-}_\text{hydroxymethyl}])-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide )</td>
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</tr>
<tr>
<td>26</td>
<td>( (R)-1-\text{1-[2-fluorophenethyl]-1'}\text{-}_\text{hydroxymethyl}])-7'-methoxy</td>
<td>spiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl]ethanone) )</td>
</tr>
<tr>
<td>27</td>
<td>( (R)-2'\text{-allyl 1-[4-nitrophenyl]}) 1'-( (\text{hydroxymethyl}))-7'-methoxy-3',9'-dihydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1,2'(1'H)-dicarboxylate )</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>( (R)-\text{tert-butyl 2'}\text{-acetyl}-1'\text{-}[(\text{tert-butyl(dimethyl)silyl)}\text{oxy})\text{methyl}]\text{-7'}\text{-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxylate} )</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>( (S)\text{-tert-butyl 7'}\text{-methoxy-1'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxylate} )</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>( (R)\text{-allyl 1'}\text{-}[(\text{tert-butyl(dimethyl)silyl)}\text{oxy})\text{methyl}]-1-[(2-fluorophenyl)carbamoyl]-7'-methoxy-3',9'-dihydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-2'(1'H)-carboxylate )</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
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</tr>
<tr>
<td>32</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(S)-2'-acetyl-1'-(dimethylamino)methyl)-N-(2-fluorophenyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>33</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-2'-(cyclopropanecarbonyl)-N-(2-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>34</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(S)-tert-butyl 2'-acetyl-7'-methoxy-1'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxylate</td>
</tr>
<tr>
<td>35</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-2'-acetyl-1'-(hydroxymethyl)-7'-methoxy-N-phenyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>36</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-2'-butyryl-N-(2-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>37</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-2'-acetyl-N-(3-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-1-{1'-(((tert-butyl(dimethyl)silyloxy)methyl)-1-(2-fluorobenzyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)ethane}</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
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<tr>
<td>39</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-1-((2'-acetyl-1'-((hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-yl)-2-(2-fluorophenyl)ethanone)</td>
</tr>
<tr>
<td>40</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-1'-(((tert-butylimethyl)silyl)oxy)methyl)-N-(2-fluorophenyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>41</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-1-(1-(2-fluorobenzoyl)-1'-(hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indole]-2'(1'H,3'H,9'H)-yl)ethanone</td>
</tr>
<tr>
<td>42</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-N-(2-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-2'-phenethyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>43</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-2'-acetyl-N-cyclohexyl-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>44</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-1-(1-(2-fluorobenzyl)sulfonanyl)-1'-(hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indole]-2'(1'H,3'H,9'H)-yl)ethanone</td>
</tr>
<tr>
<td>45</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-2'-acetyl-N-(2,3-difluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>-----</td>
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<td>------------------</td>
</tr>
<tr>
<td>46</td>
<td><img src="image" alt="Structure 46" /></td>
<td>(S)-tert-butyl 2'-acetyl-7'-methoxy-1'-(morpholinomethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxylate</td>
</tr>
<tr>
<td>47</td>
<td><img src="image" alt="Structure 47" /></td>
<td>(R)-N-(2-fluorophenyl)-10-methoxy-4-oxo-1,3,4,6,12,12b-hexahydrospiro[1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-7,4'-piperidine]-1'-carboxamide</td>
</tr>
<tr>
<td>48</td>
<td><img src="image" alt="Structure 48" /></td>
<td>(S)-2'-acetyl-N-(2-fluorophenyl)-7'-methoxy-1'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>49</td>
<td><img src="image" alt="Structure 49" /></td>
<td>(R)-N-(2-fluorophenyl)-1'-[(hydroxymethyl)-7'-methoxy-2'-propyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>50</td>
<td><img src="image" alt="Structure 50" /></td>
<td>(R)-2'-benzoyl-N-(2-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>51</td>
<td><img src="image" alt="Structure 51" /></td>
<td>(R)-2'-acetyl-N-(2,6-difluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>52</td>
<td><img src="image" alt="Structure 52" /></td>
<td>(R)-2'-acetyl-1'-(hydroxymethyl)-7'-methoxy-N-(pyridin-3-yl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>---</td>
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<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>53</td>
<td><img src="image1" alt="Molecule 1" /></td>
<td>(R)-N-(2-fluorophenyl)-1'-hydroxymethyl-7'-methoxy-2'-methylsulfonyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>54</td>
<td><img src="image2" alt="Molecule 2" /></td>
<td>(R)-2'-acetyl-N-(2,4-difluorophenyl)-1'-hydroxymethyl-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>55</td>
<td><img src="image3" alt="Molecule 3" /></td>
<td>(R)-2'-acetyl-N-(2,5-difluorophenyl)-1'-hydroxymethyl-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>56</td>
<td><img src="image4" alt="Molecule 4" /></td>
<td>(R)-tert-butyl 1'-(tert-butyldimethylsilyl)oxy)methyl)-2'-ethyl-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxylate</td>
</tr>
<tr>
<td>57</td>
<td><img src="image5" alt="Molecule 5" /></td>
<td>(R)-2'-acetyl-1'-hydroxymethyl-7'-methoxy-N-(2-(trifluoromethyl)phenyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>58</td>
<td><img src="image6" alt="Molecule 6" /></td>
<td>(R)-2'-acetyl-N-(3,4-difluorophenyl)-1'-hydroxymethyl-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Molecular Formula</td>
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</tr>
<tr>
<td>59</td>
<td><img src="59.png" alt="Chemical Structure" /></td>
<td>(R)-1-(1-((2-fluorophenyl)sulfonyl)-1'-((hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)ethanone</td>
</tr>
<tr>
<td>60</td>
<td><img src="60.png" alt="Chemical Structure" /></td>
<td>(R)-2'-ethyl-N-((2-fluorophenyl)-1'-((hydroxymethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>61</td>
<td><img src="61.png" alt="Chemical Structure" /></td>
<td>(R)-N-((2-fluorophenyl)-1'-((hydroxymethyl)-7'-methoxy-2'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>62</td>
<td><img src="62.png" alt="Chemical Structure" /></td>
<td>(R)-N-((2-fluorophenyl)-1'-((hydroxymethyl)-7'-methoxy-2'-((2,2,2-trifluoroethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>63</td>
<td><img src="63.png" alt="Chemical Structure" /></td>
<td>(R)-2'-acetyl-N-((2-fluorophenyl)-1'-((hydroxymethyl)-7'-methoxy-N-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>64</td>
<td><img src="64.png" alt="Chemical Structure" /></td>
<td>(R)-2'-acetyl-N-((2-fluorophenyl)-7'-methoxy-1'-(1-(methoxyethoxy)methoxy)methyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Chemical Formula</td>
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<tr>
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</tr>
<tr>
<td>65</td>
<td><img src="image1" alt="Structure" /></td>
<td>(S)-2'-acetyl-N-(2-fluorophenyl)-7'-methoxy-1'-((morpholinomethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>66</td>
<td><img src="image2" alt="Structure" /></td>
<td>(R)-2'-acetyl-N-(2-fluorophenyl)-7'-methoxy-1'-'((4-methoxybenzyl)oxy)methyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>67</td>
<td><img src="image3" alt="Structure" /></td>
<td>(R)-2'-acetyl-N-(2-fluorophenyl)-7'-methoxy-1'-'((methoxymethoxy)methyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>68</td>
<td><img src="image4" alt="Structure" /></td>
<td>(R)-2'-acetyl-1'-((hydroxymethyl)-7'-methoxy-N-(pyridin-2-yl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>69</td>
<td><img src="image5" alt="Structure" /></td>
<td>(R)-2'-acetyl-N-(2-fluorophenyl)-7'-methoxy-1'-'(methoxymethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>70</td>
<td>(R)-2'-acetyl-7'-fluoro-N-(2-fluorophenyl)-1'-(hydroxymethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide compound with (S)-Mixture of 2'-acetyl-7'-fluoro-N-(2-fluorophenyl)-1'-(hydroxymethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide (1:1) and (R)-2'-acetyl-7'-fluoro-N-(2-fluorophenyl)-1'-(hydroxymethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide (1:1)</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>(R)-N-(2-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-2'-{(3-phenylpropyl)}-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>Mixture of (1R,3'S) and (1R,3's)-2-acetyl-N-(2-fluorophenyl)-1-(hydroxymethyl)-7-methoxy-1,2,3,9-tetrahydrospiro[pyrrolo[3,4-b]indole-4,3'-perrylidine]-1'-carboxamide compound with (1R,3'S)-2-acetyl-N-(2-fluorophenyl)-1-(hydroxymethyl)-7-methoxy-1,2,3,9-tetrahydrospiro[pyrrolo[3,4-b]indole-4,3'-pyrrolidine]-1'-carboxamide (1:1)</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>(S)-2'-acetyl-N-(2-fluorophenyl)-1'-(2-hydroxyethyl)-7'-methoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
<tr>
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</tr>
<tr>
<td>74</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(S)-2'-acetyl-N-(2-fluorophenyl)-7'-methoxy-1'-(2,2,2-trifluoroethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1'-carboxamide</td>
</tr>
<tr>
<td>75</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Mixture of (1R,3'R) and (1R,3'S)-2-acetyl-1-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2-fluorophenyl)-7-methoxy-1,2,3,9-tetrahydrospiro[pyrido[3,4-b]indole-4,3'-pyrrolidine]-1'-carboxamide, compound with (1R,3'S)-2-acetyl-1-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2-fluorophenyl)-7-methoxy-1,2,3,9-tetrahydrospiro[pyrido[3,4-b]indole-4,3'-pyrrolidine]-1'-carboxamide (1:1)</td>
</tr>
<tr>
<td>76</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Mixture of (1R,3'R) and (1R,3'S)-tert-butyl 2-acetyl-1-(((tert-butyldimethylsilyl)oxy)methyl)-7-methoxy-1,2,3,9-tetrahydrospiro[pyrido[3,4-b]indole-4,3'-pyrrolidine]-1'-carboxylate, compound with (1R,3'S)-tert-butyl 2-acetyl-1-(((tert-butyldimethylsilyl)oxy)methyl)-7-methoxy-1,2,3,9-tetrahydrospiro[pyrido[3,4-b]indole-4,3'-pyrrolidine]-1'-carboxylate (1:1)</td>
</tr>
<tr>
<td>77</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(R)-1-((1-benzo[d]oxazol-2-yl)-1'-(hydroxymethyl)-7'-methoxyspiropiperidine-4,4'-pyrido[3,4-b]indole]-2'(1'H,3'H,9'H)-yl)ethanone</td>
</tr>
<tr>
<td>78</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(R)-(2'-3-fluorobenzyl)-7'-methoxy-1'-(pyridin-2-ylmethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1'-yl)methanol</td>
</tr>
<tr>
<td>Number</td>
<td>Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
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</tr>
<tr>
<td>79</td>
<td><img src="image" alt="Structure 79" /></td>
<td>(R)-(7'-methoxy-9'-methyl-1-(4-(pyridin-2-yl)benzyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
</tr>
<tr>
<td>80</td>
<td><img src="image" alt="Structure 80" /></td>
<td>(R)-N-(4-fluorophenyl)-1'-hydroxymethyl)-7'-methoxy-1-(phenylsulfonyl)-3',9'-dihydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-2(1'H)-carboxamide</td>
</tr>
<tr>
<td>81</td>
<td><img src="image" alt="Structure 81" /></td>
<td>(R)-benzo[d][1,3]dioxol-5-yl(2'-benzo[d][1,3]dioxol-5-ylmethyl)-1'-hydroxy[methyl]-7'-methoxy-9'-methyl-1',2',3',9'-tetrahydrospiro[azetidine-3,4'-pyrido[3,4-b]indol]-1'-yl)methanone</td>
</tr>
<tr>
<td>82</td>
<td><img src="image" alt="Structure 82" /></td>
<td>(S)-(2'-(3-fluorobenzyl)-7'-methoxy-1-(pyridin-2-ylmethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
</tr>
<tr>
<td>83</td>
<td><img src="image" alt="Structure 83" /></td>
<td>(S)-(1-(cyclopropylmethyl)-7'-methoxy-2'-(2-methoxybenzyl)-9'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
</tr>
<tr>
<td>84</td>
<td><img src="image" alt="Structure 84" /></td>
<td>(S)-(7'-methoxy-1-((3-methoxyphenyl)sulfonyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
</tr>
<tr>
<td>85</td>
<td><img src="image" alt="Structure 85" /></td>
<td>(R)-(2'-(cyclohexylmethyl)-7'-methoxy-9'-methyl-1-(thiazol-2-ylmethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
</tr>
<tr>
<td>86</td>
<td><img src="image" alt="Structure 86" /></td>
<td>(S)-2'-(cyclobutane-carboxyl)-1'-hydroxymethyl)-7'-methoxy-N-(4-methoxyphenyl)-9'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>87</td>
<td>(R)-2′-(4-chlorobenzyl)-7′-methoxy-1′-(thiazol-2-ylmethyl)-1′,2′,3′,9′-tetrahydrospiro[piperidine-4,4′-pyrido[3,4-b]indol]-1′-yl)methanol</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>(R)-2′-(4-chlorobenzyl)-1′-(cyclopropylmethyl)-7′-methoxy-9′-methyl-1′,2′,3′,9′-tetrahydrospiro[piperidine-4,4′-pyrido[3,4-b]indol]-1′-yl)methanol</td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>(R)-1′-(1′-(cyclohexylmethyl)-1′-(hydroxymethyl)-7′-methoxyspiro[piperidine-4,4′-pyrido[3,4-b]indol]-2′)(1′H,3′H,9′H)-yl)-2′-(dimethylamino)ethaneone</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>(S)-2′-(dimethylamino)-1′-(1′-(hydroxymethyl)-7′-methoxy-9′-methyl-1′-(pyridin-3-ylmethyl)spiro[piperidine-4,4′-pyrido[3,4-b]indol]-2′)(1′H,3′H,9′H)-yl)ethaneone</td>
<td></td>
</tr>
<tr>
<td>91</td>
<td>(R)-1′-(1′-(cyclopentylmethyl)-7′-methoxy-9′-methyl-1′,2′,3′,9′-tetrahydrospiro[piperidine-4,4′-pyrido[3,4-b]indol]-1′-yl)methanol</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>(S)-7′-methoxy-2′-(2-methoxybenzyl)-9′-methyl-1′-propyl-1′,2′,3′,9′-tetrahydrospiro[piperidine-4,4′-pyrido[3,4-b]indol]-1′-yl)methanol</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>(S)-2′-(cyclopropanecarbonyl)-N-(3-fluorophenyl)-1′-(hydroxymethyl)-7′-methoxy-9′-methyl-1′,2′,3′,9′-tetrahydrospiro[azetidine-3,4′-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>(S)-2′-(benzyl-7′-methoxy-1′-(pyrimidin-5′-ylmethyl)-1′,2′,3′,9′-tetrahydrospiro[piperidine-4,4′-pyrido[3,4-b]indol]-1′-yl)methanol</td>
<td></td>
</tr>
</tbody>
</table>
| 95 | (R)-benzo[d][1,3]dioxol-5-yl(2'-
    cyclopropylmethyl)-1'-(hydroxymethyl)-
    7'-methoxy-9'-methyl-1',2',3',9'-
    tetrahydrospiro[azetidine-3,4'-pyrido[3,4-
    b]indole]-1-yl)methanone |
| 96 | (R)-N-(4-fluorophenyl)-1'-(
    hydroxymethyl)-7'-methoxy-1,9'-
    dimethyl-3',9'-dihydrospiro[piperidine-
    4,4'-pyrido[3,4-b]indole]-2'(1'H)-
    carboxamide |
| 97 | (S)-2-(dimethylamino)-1-(1'-(
    hydroxymethyl)-7'-methoxy-1-(4-
    methoxybenzyl)spiro[azetidine-3,4'-
    pyrido[3,4-b]indole]-2'(1'H,3'H,9'H)-
    yl)ethanone |
| 98 | (R)-1-(1'-(hydroxymethyl)-7'-methoxy-2'-
    tosyl-1',2',3',9'-tetrahydrospiro[piperidine-
    4,4'-pyrido[3,4-b]indole]-1-yl)butan-1-one |
| 99 | (S)-2'-(cyclopentanecarbonyl)-N-(3-
    fluorophenyl)-1'-(hydroxymethyl)-7'-
    methoxy-9'-methyl-1',2',3',9'-
    tetrahydrospiro[azetidine-3,4'-pyrido[3,4-
    b]indole]-1-carboxamide |
| 100 | (S)-2'-(cyclopentanecarbonyl)-N-(3-
    fluorophenyl)-1'-(hydroxymethyl)-7'-
    methoxy-9'-methyl-1',2',3',9'-
    tetrahydrospiro[piperidine-4,4'-pyrido[3,4-
    b]indole]-1-carboxamide |
| 101 | (S)-N-(4-fluorophenyl)-1'-(
    hydroxymethyl)-7'-methoxy-9'-methyl-1-
    (pyridin-2-ylmethyl)-3',9'-
    dihydrospiro[piperidine-4,4'-pyrido[3,4-
    b]indole]-2'(1'H)-carboxamide |
| 102 | (R)-N-(benzo[d][1,3]dioxol-5-yl)-1'-(
    hydroxymethyl)-7'-methoxy-1',2',3',9'-
    tetrahydrospiro[piperidine-4,4'-pyrido[3,4-
    b]indole]-1-carboxamide |
<p>| 103 | (R)-cyclohexyl(1'-(hydroxymethyl)-7'-methoxy-1-(thiazol-2-ylmethyl)spiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)methanone |
| 104 | (R)-(1'-(hydroxymethyl)-7'-methoxy-1-(thiazol-2-ylmethyl)spiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl)(tetrahydro-2H-pyran-4-yl)methanone |
| 105 | (R)-N-(2-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-2'-(2-phenylacetyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide |
| 106 | (S)-N-(4-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-9'-methyl-1-(pyridin-3-ylmethyl)-3',9'-dihydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-2'(1'H)-carboxamide |
| 107 | (R)-1-(1'-(hydroxymethyl)-7'-methoxy-2'-(3-methoxybenzyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-yl)propan-1-one |
| 108 | (S)-2'-(4-fluorobenzoyl)-N-(4-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-9'-methyl-1',2',3',9'-tetrahydrospiro[azetidine-3,4'-pyrido[3,4-b]indole]-1-carboxamide |
| 109 | (S)-(2'-(cyclohexylmethyl)-7'-methoxy-9'-methyl-1-(thiazol-2-ylmethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1'-yl)methanol |
| 110 | (S)-2'-(cyclobutane carbonyl)-N-(3-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-9'-methyl-1',2',3',9'-tetrahydrospiro[azetidine-3,4'-pyrido[3,4-b]indole]-1-carboxamide |</p>
<table>
<thead>
<tr>
<th></th>
<th>Molecular Structure</th>
<th>Chemical Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>119</td>
<td>(S)-(7'-methoxy-1-((4-methoxyphenyl)sulfonyl)-2'-(pyridin-4-ylmethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>(R)-1-((1'-(hydroxymethyl)-7'-methoxy-2'-tosyl-1',2',3',9'-tetrahydrospiro[azetidine-3,4'-pyrido[3,4-b]indol]-1'-yl)butan-1-one</td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>(S)-1-((1-cyclohexylmethyl)-1'-(hydroxymethyl)-7'-methoxy)spiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-ylo)-2-(dimethylamino)ethaneone</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>(R)-(1-(3-fluorobenzyl)-7'-methoxy-2'- (pyridin-2-ylmethyl)-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>(R)-1-((benzo[d][1,3]dioxole-5-carbonyl)-N-(4-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-9'-methyl-3',9'-dihydrospiro[azetidine-3,4'-pyrido[3,4-b]indole]-2'(1'H)-carboxamide</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>(R)-1-(ethylsulfonyl)-7'-methoxy-2'-tosyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl)methanol</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>(S)-2'-((cyclopropanecarbonyl)-N-(3-fluorophenyl)-1'-(hydroxymethyl)-7'-methoxy-9'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>(S)-2'-((cyclobutanecarbonyl)-1'- (hydroxymethyl)-7'-methoxy-N-(4-methoxyphenyl)-9'-methyl-1',2',3',9'-tetrahydrospiro[azetidine-3,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>127</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(R)-(7''-methoxy-2''-(3-methoxybenzyl)-1''-(pyridin-2''-ylmethyl)-1''',2'',3'',9''-tetrahydrospiro[piperidine-4,4''-pyrido[3,4-b]indole]-1''-yl)methanol</td>
</tr>
<tr>
<td>128</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(R)-N-(4-fluorophenyl)-1'-(3'-fluorophenyl)sulfonyl)-1'-(hydroxymethyl)-7''-methoxy-3'',9''-dihydrospiro[piperidine-4,4''-pyrido[3,4-b]indole]-2'(1'H)-carboxamide</td>
</tr>
<tr>
<td>129</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(S)-2''-(4-fluorobenzoyl)-N-(4'-fluorophenyl)-1''-(hydroxymethyl)-7''-methoxy-9''-methyl-1''',2'',3'',9''-tetrahydrospiro[piperidine-4,4''-pyrido[3,4-b]indole]-1''-carboxamide</td>
</tr>
<tr>
<td>130</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(S)-(7''-methoxy-9''-methyl-1''-(4-(pyridin-2''-yl)benzyl)-1''',2'',3'',9''-tetrahydrospiro[piperidine-4,4''-pyrido[3,4-b]indole]-1''-yl)methanol</td>
</tr>
<tr>
<td>131</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(R)-1'-(benzo[d][1,3]dioxole-5-carbonyl)-N-(4-fluorophenyl)-1''-(hydroxymethyl)-7''-methoxy-9''-methyl-3'',9''-dihydrospiro[piperidine-4,4''-pyrido[3,4-b]indole]-2'(1'H)-carboxamide</td>
</tr>
<tr>
<td>132</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>(S)-(2''-(4-chlorobenzyl)-1''-(cyclopropylmethyl)-7''-methoxy-9''-methyl-1''',2'',3'',9''-tetrahydrospiro[piperidine-4,4''-pyrido[3,4-b]indole]-1''-yl)methanol</td>
</tr>
<tr>
<td>133</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>(S)-(7''-methoxy-1''-(4-(pyridin-2''-yl)benzyl)-2''-(pyridin-4''-ylmethyl)-1''',2'',3'',9''-tetrahydrospiro[piperidine-4,4''-pyrido[3,4-b]indole]-1''-yl)methanol</td>
</tr>
<tr>
<td>134</td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>(R)-(7''-methoxy-1''-(4-(pyridin-2''-yl)benzyl)-2''-(pyridin-4''-ylmethyl)-1''',2'',3'',9''-tetrahydrospiro[azetidine-3,4''-pyrido[3,4-b]indole]-1''-yl)methanol</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>------</td>
<td>-------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>135</td>
<td><img src="image1.png" alt="Image" /></td>
<td>(R)-(2'-{(4-chlorobenzyl)-1-(cyclopropylmethyl)-7'-methoxy-9'-methyl-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indol]-1'-yl) methanol</td>
</tr>
<tr>
<td>136</td>
<td><img src="image2.png" alt="Image" /></td>
<td>(R)-1-{1-{1H-benzo[d]imidazol-2-yl)-1-[(hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl] ethanone</td>
</tr>
<tr>
<td>137</td>
<td><img src="image3.png" alt="Image" /></td>
<td>(R)-1-{1-(benzo[d]thiazol-2-yl)-1-[(hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl] ethanone</td>
</tr>
<tr>
<td>138</td>
<td><img src="image4.png" alt="Image" /></td>
<td>(R)-1-{1-(benzo[d]thiazol-2-yl)-1-[(hydroxymethyl)-7'-methoxyspiro[piperidine-4,4'-pyrido[3,4-b]indol]-7'-yl acetaterido[3,4-b]indol]-2'(1'H,3'H,9'H)-yl] ethanone</td>
</tr>
<tr>
<td>139</td>
<td><img src="image5.png" alt="Image" /></td>
<td>(R)-2'-acetyl-N-{(2-fluorophenyl)-1-[(hydroxymethyl)-6',7'-dimethoxy-1',2',3',9'-tetrahydrospiro[piperidine-4,4'-pyrido[3,4-b]indole]-1-carboxamide</td>
</tr>
<tr>
<td>140</td>
<td><img src="image6.png" alt="Image" /></td>
<td>(S)-N-{(2-fluorophenyl)-10-methoxy-4-oxo-1,3,4,6,12,12b-hexahydrospiro[1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-7,4'-piperidine]-1'-carboxamide</td>
</tr>
</tbody>
</table>
In some embodiments, the compound of Formula I has a structure of Formula Ia:
wherein:

a and b, independently of each other, are 0, 1 or 2;
c is 0, 1, 2, 3, or 4;
R¹ is  - hydrogen,
  - unsubstituted lower alkyl,
  - lower alkyl substituted with unsubstituted phenyl or phenyl mono- or di-substituted with halogen,
  - C(O)-R¹⁰,
  - S(O)₂-R¹,
  - benzo-oxazolyl
  - benzo-imidazolyl
  - benzo-thiazolyl or
  - CH₂-R¹⁰;
R² is  - alkoxy
  - hydroxyl or
  - halogen;
R³ is  - hydrogen or
  - methyl;
  one of R⁴ or R⁵ is hydrogen or methyl and the other is hydrogen, methyl, -CH₃OH, -CH₃NHCH₃, -OSi(CH₃)₃C(CH₃)₃, -CH₂OC(O)CH₃, -CH₂N(CH₃)₂, -CH₂-morpholinyl, -CH₂CH₃, -
CH₂OCH₂OCH₂CH₂OCH₃, - OCH₂-phenylmethoxy, -CH₂OCH₂OCH₃, -CH₂OCH₃, -CH₂CH₂OH or CH₂CF₃;
R⁵ is  - hydrogen,
  - lower alkyl, unsubstituted or substituted with phenyl or halophenyl,
  - C(O)-lower alkyl,
  - C(O)CF₃,
  - C(O)CH₂-phenyl,
  - C(O)OCH₂C≡CH₂,
  - C(O)-cycloalkyl,
  - S(O)₂CH₃,
  - CH₃OSi(CH₃)₂C(CH₃)₃,
  - CH₂CF₃,
  - C(O)NH-halophenyl,
  - CH₂-benzodioxolyl,
  - CH₂-phenylalkoxy,
  - CH₂-cycloalkyl,
  - C(O)CH₃N(CH₃)₂,
  - S(O)₂-phenylmethoxy,
  - C(O)-heterocyclyl,
  - C(O)-halophenyl,
  - CH₂-heterocyclyl,
  - C(O)-phenyl,
  - S(O)₂-phenyl,
  - CH₂-difluorophenyl
  - S(O)₂-cyclopentyl
  - S(O)₂-trifluoromethyl
  - S(O)₂-ethyl or
  - CH₂-heteroaryl,
or R⁵ and R⁶, together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a six-membered heterocyclul ring optionally substituted with an oxo group,

R¹⁰ is - unsubstituted lower alkyl,
- lower alkyl substituted with heteroaryl,
- unsubstituted phenyl,
- phenyl mono or bi-substituted with halogen,
- benzodioxolyl,
- cycloalkyl,
- NR²R⁶ or
- OR⁶;

one of R⁷ or R⁸ is hydrogen or lower alkyl and the other is heteroaryl, cycloalkyl, benzodioxolyl, unsubstituted phenyl or phenyl mono- or di-substituted independently with halogen, trifluoromethyl or alkoxy,

R⁹ is - lower alkyl or
- nitrophenyld;

R¹¹ is - lower alkyl,
- CH₂-phenyl,
- unsubstituted phenyl or
- phenyl mono or bi-substituted with halogen; and

R¹⁹ is - cycloalkyl,
- unsubstituted heteroaryl,
- heteroarylated substituted with phenyl,
- unsubstituted phenyl or
- phenyl substituted with heteroaryl or alkoxy;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the compound of Formula I has a structure of Formula Ila:

\[
\text{Formula Ila}
\]

wherein:

a and b, independently of each other, are 0, 1 or 2;

R¹ is - hydrogen,
- unsubstituted lower alkyl,
- lower alkyl substituted with unsubstituted phenyl or phenyl mono- or di-substituted with halogen,
- C(=O)-R¹⁰,
- S(=O)₂-R¹⁰,
- benzo-oxazolyl or
- CH₂-R¹⁰;

R² is - alkoxy or
- halogen;

R³ is - hydrogen or
- methyl;
one of R¹ or R⁵ is hydrogen or methyl and the other is hydrogen, methyl, -CH₃OH, -CH₂NHCH₃, -OSi(CH₃)₂C(CH₃)₃, -CH₂OC(O)CH₃, -CH₂N(CH₃)₂, -CH₂-morpholinyl, -CH₂CH₃, -CH₂OCH₂OCH₂CH₂OCH₃, -OCH₂-phenylmethoxy, -CH₂OCH₂OCH₃, -CH₂OCH₅, -CH₂CH₂OH or CH₂CF₃; 

R⁶ is  
- lower alkyl, unsubstituted or substituted with phenyl or halophenyl,  
- C(O)-lower alkyl,  
- C(O)CF₃,  
- C(O)CH₂-phenyl,  
- C(O)OCH₂C=CH₂,  
- C(O)-cycloalkyl,  
- S(O)₂CH₃,  
- CH₂OSi(CH₃)₂C(CH₃)₃,  
- CH₂CF₃,  
- C(O)NH-halophenyl,  
- CH₂-benzodioxolyl,  
- CH₂-phenylalkoxy,  
- CH₂-cycloalkyl,  
- C(O)CH₂N(CH₃)₂,  
- S(O)₂-phenylmethyl,  
- C(O)-heterocyclyl,  
- C(O)-halophenyl,  
- CH₂-heterocyclyl,  
- C(O)-phenyl,  
- S(O)₂-phenyl,  
- CH₂-difluorophenyl or  
- CH₂-heteroaryl,  

or R⁵ and R⁶, together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a six-membered heterocyclyl ring optionally substituted with an oxo group,  

R¹⁰ is  
- unsubstituted lower alkyl,  
- lower alkyl substituted with heteroaryl,  
- unsubstituted phenyl,  
- phenyl mono or bi-substituted with halogen,  
- benzodioxolyl,  
- cycloalkyl,  
- NR²R⁶ or  
- OR³,  

one of R⁷ or R⁸ is hydrogen or lower alkyl and the other is heteroaryl, cycloalkyl, benzodioxolyl, unsubstituted phenyl or phenyl mono- or di-substituted independently with halogen, trifluoromethyl or alkoxy,  

R⁸ is  
- lower alkyl or  
- nitrophenyl;  
R¹¹ is  
- lower alkyl,  
- CH₂-phenyl,  
- unsubstituted phenyl or  
- phenyl mono or di-substituted with halogen; and  
R¹⁹ is  
- cycloalkyl,  
- unsubstituted heteroaryl,  
- heteroaryl substituted with phenyl,  
- unsubstituted phenyl or  
- phenyl substituted with heteroaryl or alkoxy;  

or a pharmaceutically acceptable salt thereof.

In some embodiments of the compounds of Formula Ia or Formula Ila, R¹ is hydrogen, benzo-oxazolyl, benzo-imidazolyl, benzo-thiazolyl, unsubstituted lower alkyl, or lower alkyl substituted with unsubstituted phenyl or phenyl mono- or di-substituted with halogen.
In other embodiments of the compounds of Formula Ia or Formula IIa, R\(^1\) is hydrogen, benzo-
oxazolyl, unsubstituted lower alkyl, or lower alkyl substituted with unsubstituted phenyl or phenyl mono-
or di-substituted with halogen.

In certain embodiments of the compounds of Formula Ia or Formula IIa, R\(^1\) is \(-\text{C}(\text{O})\)-, \(-\text{S}(\text{O})\)\(^2\)-, \(-\text{CH}_2\)-, or \(-\text{OR}^9\), wherein:

- R\(^{10}\) is - unsubstituted lower alkyl,
  - lower alkyl substituted with heteroaryl,
  - unsubstituted phenyl,
  - phenyl mono or di-substituted with halogen,
  - benzodioxolyl,
  - cycloalkyl,
  - NR\(^2\)R\(^8\) or
  - OR\(^8\);

one of R\(^7\) or R\(^8\) is hydrogen or lower alkyl and the other is heteroaryl, cycloalkyl, benzodioxolyl, unsubstituted phenyl or phenyl mono- or di-substituted independently with halogen, trifluoromethyl or alkoxy,

- R\(^8\) is - lower alkyl or
  - nitrophenyl;
- R\(^{11}\) is - lower alkyl,
  - CH\(_2\)-phenyl,
  - unsubstituted phenyl or
  - phenyl mono or di-substituted with halogen; and
- R\(^{19}\) is - cycloalkyl,
  - unsubstituted heteroaryl,
  - heteroaryl substituted with phenyl,
  - unsubstituted phenyl or
  - phenyl substituted with heteroaryl or alkoxy.

In some embodiments of the compounds of Formula Ia or Formula IIa, R\(^2\) is methoxy, hydroxy, or fluoro. In other embodiments of the compounds of Formula Ia or Formula IIa, R\(^3\) is methoxy or fluoro.

In certain embodiments of the compounds of Formula Ia or Formula IIa, R\(^3\) is hydrogen.

In certain embodiments of the compounds of Formula Ia or Formula IIa, R\(^6\) is hydrogen or lower alkyl, unsubstituted or substituted with phenyl or halophenyl.

In some embodiments of the compounds of Formula Ia or Formula IIa, R\(^6\) is:

- \(-\text{C}(\text{O})\)-lower alkyl,
- \(-\text{C}(\text{O})\)CF\(_3\),
- \(-\text{C}(\text{O})\)CH\(_2\)-phenyl,
- \(-\text{C}(\text{O})\)OCH\(_2\)C=CH\(_2\),
- \(-\text{C}(\text{O})\)-cycloalkyl,
- \(-\text{C}(\text{O})\)NH-halophenyl,
- \(-\text{C}(\text{O})\)CH\(_2\)N(CH\(_3\))\(_2\),
- \(-\text{C}(\text{O})\)-heterocyclyl,
- \(-\text{C}(\text{O})\)-halophenyl,
- \(-\text{CH}_2\)-heterocyclyl
- \(-\text{S}(\text{O})\)\(_2\)-cyclopropyl
- \(-\text{S}(\text{O})\)\(_2\)-trifluoromethyl
- \(-\text{S}(\text{O})\)\(_2\)-ethyl or
- \(-\text{C}(\text{O})\)-phenyl.

In other embodiments of the compounds of Formula Ia or Formula IIa, R\(^6\) is:

- \(-\text{C}(\text{O})\)-lower alkyl,
- \(-\text{C}(\text{O})\)CF\(_3\),
- \(-\text{C}(\text{O})\)CH\(_2\)-phenyl,
- \(-\text{C}(\text{O})\)OCH\(_2\)C=CH\(_2\),
- \(-\text{C}(\text{O})\)-cycloalkyl,
- C(O)NH-halophenyl,
- C(O)CH₃Ν(CH₃)₂,
- C(O)-heterocyclyl,
- C(O)-halophenyl,
- C₂H₃-heterocyclyl or
- C(O)-phenyl.

In certain embodiments of the compounds of Formula Ia or Formula IIa, R⁶ is:
- CH₃OSi(CH₃)₂C(CH₃)₃,
- CH₂CF₃,
- CH₂-benzodioxolyl,
- CH₂-phenylalkoxy,
- CH₂-cycloalkyl,
- CH₂-difluorophenyl or
- CH₂-heteroaryl.

In some embodiments of the compounds of Formula Ia or Formula IIa, R⁶ is:
- S(O)₂CH₃,
- S(O)₂-phenylmethyl
- S(O)₂-cyclopropyl
- S(O)₂-trifluoromethyl
- S(O)₂-ethyl or
- S(O)₂-phenyl.

In other embodiments of the compounds of Formula Ia or Formula IIa, R⁶ is:
- S(O)₂CH₂,
- S(O)₂-ethyl or
- S(O)₂-phenyl.

In certain embodiments of the compounds of Formula Ia or Formula IIa, R¹₀ is:
- unsubstituted lower alkyl,
- lower alkyl substituted with heteroaryl,
- unsubstituted phenyl,
- phenyl mono or di-substituted with halogen,
- benzodioxolyl or
- cycloalkyl.

In some embodiments of the compounds of Formula Ia or Formula IIa, R¹₀ is – NR⁷R⁸ or – OR⁸.

In some embodiments of the compounds of Formula Ia or Formula IIa, R⁶ is lower alkyl.

In other embodiments of the compounds of Formula Ia or Formula IIa, R¹¹ is lower alkyl or
-CH₂-phenyl.

In certain embodiments of the compounds of Formula Ia or Formula IIa, R¹¹ is unsubstituted phenyl or phenyl mono or di-substituted with halogen.

In some embodiments of the compounds of Formula Ia or Formula IIa, R¹⁹ is cycloalkyl,

unsubstituted heteroaryl or heteroaryl substituted with phenyl.

In other embodiments of the compounds of Formula Ia or Formula IIa, R¹⁹ is unsubstituted phenyl or phenyl substituted with heteroaryl or alkoxy.

In certain embodiments of the compounds of Formula Ia or Formula IIa, a is 1. In some embodiments of the compounds of Formula Ia or Formula IIa, b is 1. In other embodiments of the compounds of Formula Ia or Formula IIa, a is 0. In certain embodiments of the compounds of Formula Ia or Formula IIa, b is 0. In some embodiments of the compounds of Formula Ia or Formula IIa, both a and b are 1. In other embodiments of the compounds of Formula Ia or Formula IIa, both a and b are 0. In certain embodiments of the compounds of Formula Ia or Formula IIa, a is 1 and b is 0.
In another aspect, the invention features a pharmaceutical composition, including a therapeutically effective amount of a compound of Formula VIII:

\[
\begin{align*}
\text{Formula VIII}
\end{align*}
\]

wherein a and b are independently 0, 1, or 2;
c is 0, 1, 2, 3, or 4;

R\(^1\) is hydrogen, C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_9\) heteroaryl, C\(_3\)-C\(_10\) carbocyclcyl C\(_1\)-C\(_6\) alkyl, C\(_6\)-C\(_10\) aryl C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_9\) heteroaryl C\(_1\)-C\(_6\) alkyl, -C(O)NR\(^7\)R\(^8\), -C(O)OR\(^9\), -C(O)R\(^10\), or -S(O)\(_2\)R\(^{11}\);
each R\(^8\) is independently hydroxy, halogen, or -OR\(^{12}\);

R\(^3\) is hydrogen or C\(_1\)-C\(_6\) alkyl;
R\(^1\) is hydrogen or C\(_1\)-C\(_6\) alkyl;
R\(^5\) is C\(_1\)-C\(_6\) alkyl, or -\((\text{CH}_2)_m\)X\(^{13}\), or R\(^5\) and R\(^6\) together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a 5-8-membered heterocycle;

R\(^6\) is hydrogen, C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) perfluoroalkyl, C\(_3\)-C\(_10\) carbocyclcyl C\(_1\)-C\(_6\) alkyl, C\(_6\)-C\(_10\) aryl C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_9\) heteroaryl C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_9\) heterocyclcyl C\(_1\)-C\(_6\) alkyl, N-protecting group, -C(O)R\(^{15}\), -C(O)NR\(^{16}\)R\(^{17}\), or -S(O)\(_2\)R\(^{18}\);
R\(^7\) is hydrogen or C\(_1\)-C\(_6\) alkyl;
R\(^8\) is C\(_6\)-C\(_10\) aryl, C\(_2\)-C\(_9\) heteroaryl, C\(_2\)-C\(_9\) heterocyclcyl, or C\(_3\)-C\(_10\) carbocyclcyl;
R\(^9\) is C\(_1\)-C\(_6\) alkyl or C\(_6\)-C\(_10\) aryl;

R\(^10\) is C\(_1\)-C\(_6\) alkyl, C\(_6\)-C\(_10\) aryl, C\(_2\)-C\(_9\) heterocyclcyl, C\(_6\)-C\(_10\) aryl C\(_1\)-C\(_6\) alkyl, or C\(_2\)-C\(_9\) heteroaryl C\(_1\)-C\(_6\) alkyl;
R\(^11\) is C\(_1\)-C\(_6\) alkyl, C\(_6\)-C\(_10\) aryl, or C\(_6\)-C\(_10\) aryl C\(_1\)-C\(_6\) alkyl;
each R\(^{12}\) is C\(_1\)-C\(_6\) alkyl or C\(_1\)-C\(_6\) acyl;
n is 1, 2, 3, 4, 5, or 6;

X\(^1\) is absent, O, or NR\(^{14}\);
R\(^{13}\) is hydrogen, C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) heterocyclcyl, C\(_1\)-C\(_6\) perfluoroalkyl, C\(_1\)-C\(_6\) acyl, C\(_6\)-C\(_10\) aryl C\(_1\)-C\(_6\) alkyl, an O- or N-protecting group, or R\(^{13}\) and R\(^{14}\) combine to form a 5-8-membered heterocycle;
R\(^{14}\) is hydrogen or C\(_1\)-C\(_6\) alkyl;
R\(^{15}\) is C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) perfluoroalkyl, C\(_1\)-C\(_6\) heterocyclcyl, C\(_2\)-C\(_10\) carbocyclcyl, C\(_2\)-C\(_9\) heterocyclcyl,
C\(_6\)-C\(_10\) aryl, C\(_6\)-C\(_10\) aryl C\(_1\)-C\(_6\) alkyl;
R\(^{16}\) and R\(^{17}\) are independently hydrogen, C\(_1\)-C\(_6\) alkyl, or C\(_6\)-C\(_10\) aryl; and
R\(^{18}\) is C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) perfluoroalkyl, C\(_2\)-C\(_10\) carbocyclcyl, or C\(_6\)-C\(_10\) aryl;
or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In another aspect, the invention features a method of treating malaria (e.g., malaria caused by \textit{P. falciparum}, \textit{P. vivax}, \textit{P. ovale}, \textit{P. malariae}, or \textit{P. knowlesi}) in a subject. This method includes the step of
administering to the subject a therapeutically effective amount of any of the foregoing compositions or a compound of Formula VIII:

\[
\begin{align*}
R^1 & \quad \text{is hydrogen, C}_{1-6} \text{ alkyl, C}_{2-6} \text{ heteroaryl, C}_{3-10} \text{ carbocycl} \text{y C}_{1-5} \text{ alkyl, C}_{6-10} \text{ aryl C}_{1-6} \\
R^2 & \quad \text{is C}_{2-9} \text{ heteroaryl C}_{1-2} \text{ alkyl, -C(O)NR^3R^4, -C(O)OR^5, -C(O)R^7, or -S(O)\_2R^{11}} \\
\text{each R^6 is independently hydroxyl, halogen, or -OR}^{12}; \\
R^3 & \quad \text{is hydrogen or C}_{1-6} \text{ alkyl; } \\
R^4 & \quad \text{is hydrogen or C}_{1-6} \text{ alkyl; } \\
R^5 & \quad \text{is C}_{1-6} \text{ alkyl, or -(CH}_2)_mX^\prime R^{13}, or R^5 \text{ and R}^{6} \text{ together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a 5-8-membered heterocycle; } \\
R^6 & \quad \text{is hydrogen, C}_{1-6} \text{ alkyl, C}_{1-6} \text{ perfluoroalkyl, C}_{3-10} \text{ carbocycl} \text{y C}_{1-6} \text{ alkyl, C}_{6-10} \text{ aryl C}_{1-6} \\
R^7 & \quad \text{is hydrogen or C}_{1-6} \text{ alkyl; } \\
R^8 & \quad \text{is C}_{6-10} \text{ aryl, C}_{2-6} \text{ heteroaryl, C}_{2-6} \text{ heterocycl} \text{y C}_{1-6} \text{ alkyl, or C}_{3-10} \text{ carbocycl} \text{y; } \\
R^9 & \quad \text{is C}_{1-6} \text{ alkyl or C}_{6-10} \text{ aryl; } \\
R^{10} & \quad \text{is C}_{1-6} \text{ alkyl, C}_{6-10} \text{ aryl, C}_{2-6} \text{ heterocycl} \text{y, C}_{6-10} \text{ aryl C}_{1-6} \text{ alkyl, or C}_{2-6} \text{ heteroaryl C}_{1-6} \text{ alkyl; } \\
R^{11} & \quad \text{is C}_{1-6} \text{ alkyl, C}_{6-10} \text{ aryl, or C}_{6-10} \text{ aryl C}_{1-6} \text{ alkyl; } \\
\text{each R^{12} is C}_{1-6} \text{ alkyl or C}_{1-6} \text{ acyl; } \\
n & \quad \text{is 1, 2, 3, 4, 5, or 6; } \\
X^\prime & \quad \text{is absent, O, or NR}^{14}; \\
R^{13} & \quad \text{is hydrogen, C}_{1-6} \text{ alkyl, C}_{1-6} \text{ heteroalkyl, C}_{1-6} \text{ perfluoroalkyl, C}_{1-6} \text{ acyl, C}_{6-10} \text{ aryl C}_{1-6} \text{ alkyl, an O- or N-protecting group, or R^{13} and R^{14} combine to form a 5-8-membered heterocycle; } \\
R^{14} & \quad \text{is hydrogen or C}_{1-6} \text{ alkyl; } \\
R^{15} & \quad \text{is C}_{1-6} \text{ alkyl, C}_{1-6} \text{ perfluoroalkyl, C}_{1-6} \text{ heteroalkyl, C}_{2-10} \text{ carbocycl} \text{y, C}_{2-6} \text{ heterocycl} \text{y; } \\
R^{16} & \quad \text{is C}_{6-10} \text{ aryl, C}_{6-10} \text{ aryl C}_{1-6} \text{ alkyl; } \\
R^{17} & \quad \text{are independently hydrogen, C}_{1-6} \text{ alkyl, or C}_{2-10} \text{ aryl; and } \\
R^{18} & \quad \text{is C}_{1-6} \text{ alkyl, C}_{1-6} \text{ perfluoroalkyl, C}_{3-10} \text{ carbocycl} \text{y, or C}_{6-10} \text{ aryl; or a pharmaceutically acceptable salt thereof to a patient in need thereof. } \\
\text{In some embodiments of any of the foregoing methods or compositions, the compound of} \\
\text{Formula VIII is not compound 12, compound 15, or any one of compounds 78-135 of Table 1.} \\
\end{align*}
\]
In some embodiments of any of the foregoing methods or compositions, c is 1. In other embodiments of any of the foregoing methods or compositions, c is 2.

In certain embodiments of any of the foregoing methods or compositions, the compound has a structure of Formula IX:

![Formula IX](image)

In other embodiments of any of the foregoing methods or compositions, the compound has a structure of Formula X:

![Formula X](image)

In some embodiments of any of the foregoing methods or compositions, the compound has a structure of Formula XI:

![Formula XI](image)

In certain embodiments of any of the foregoing methods or compositions, the compound has the structure:
In other embodiments of any of the foregoing methods or compositions, the compound has a structure of Formula XII:

![Formula XII](image)

In certain embodiments of any of the foregoing methods or compositions, the compound has the structure:

![Formula XIII](image)

In some embodiments of any of the foregoing methods or compositions, the compound has a structure of Formula XIII:

![Formula XIII](image)

In certain embodiments of any of the foregoing methods or compositions, the compound has the structure:

![Formula XIII](image)

In some embodiments of any of the foregoing methods or compositions, R³ is hydrogen. In other embodiments of any of the foregoing methods or compositions, R³ is C₁-C₆ alkyl (e.g., methyl). In certain embodiments of any of the foregoing methods or compositions, R⁴ is hydrogen. In some embodiments of any of the foregoing methods or compositions, R⁴ is C₁-C₆ alkyl (e.g., methyl).

In other embodiments of any of the foregoing methods or compositions, R² is hydroxyl. In certain embodiments of any of the foregoing methods or compositions, R² is halogen (e.g., fluoro). In some embodiments of any of the foregoing methods or compositions, R² is –OR¹⁰ (e.g., R¹² is C₁-C₆ alkyl, such as methyl or isopropyl or C₁-C₆ acyl, such as acetyl).
In certain embodiments of any of the foregoing methods or compositions, \( R^5 \) and \( R^6 \) together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a 5-8-membered heterocycle (e.g., a 6-membered heterocycle substituted with an oxo).

In some embodiments of any of the foregoing methods or compositions, the compound has the structure of Formula XIV:

![Formula XIV](image)

In other embodiments of any of the foregoing methods or compositions, \( R^6 \) is \( C_1-C_6 \) alkyl (e.g., methyl).

In certain embodiments of any of the foregoing methods or compositions, \( R^6 \) is \(-\text{CH}_2\text{OCH}_3\) or \(-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3\). In some embodiments of any of the foregoing methods or compositions, \( n \) is 1. In other embodiments of any of the foregoing methods or compositions, \( X^1 \) is absent. In some embodiments of any of the foregoing methods or compositions, \( X^{13} \) is \( C_1-C_6 \) perfluoroalkyl (e.g., trifluoromethyl). In other embodiments of any of the foregoing methods or compositions, \( X^1 \) is \( O \). In certain embodiments of any of the foregoing methods or compositions, \( X^{13} \) is hydrogen, \( C_1-C_6 \) alkyl (e.g., methyl), \( C_1-C_6 \) heteroalkyl (e.g., \(-\text{CH}_2\text{OCH}_3\) or \(-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3\)). In some embodiments of any of the foregoing methods or compositions, \( X^{14} \) is \( \text{NR}^{14} \). In other embodiments of any of the foregoing methods or compositions, \( R^{13} \) and \( R^{14} \) combine to form a 5-8-membered heterocycle (e.g., morpholino). In certain embodiments of any of the foregoing methods or compositions, \( R^{14} \) is \( C_1-C_6 \) alkyl (e.g., methyl). In some embodiments of any of the foregoing methods or compositions, \( R^{13} \) is \( C_1-C_6 \) alkyl (e.g., methyl).

In other embodiments of any of the foregoing methods or compositions, \( R^1 \) is \( C_1-C_6 \) alkyl (e.g., methyl, ethyl, or \( n \)-propyl).

In some embodiments of any of the foregoing methods or compositions, \( R^1 \) is \( C_2-C_6 \) heteroaryl (e.g., benzo-oxazolyl, benzo-imidazolyl, or benzo-thiazolyl).

In other embodiments of any of the foregoing methods or compositions, \( R^1 \) is \( C_2-C_{10} \) carbocyclyl \( C_1-C_6 \) alkyl (e.g., cyclopropylmethyl, cyclopentymethyl, or cyclohexylmethyl). In certain embodiments of any of the foregoing methods or compositions, \( R^1 \) is \( C_2-C_{10} \) aryl \( C_1-C_6 \) alkyl (e.g., 2-fluorophenyl-ethyl, 2-fluorobenzyl, 4-(2-pyridyl)-benzyl, 4-methoxybenzyl, or 3-fluorobenzyl).

In some embodiments of any of the foregoing methods or compositions, \( R^1 \) is \( C_2-C_6 \) heteroaryl \( C_1-C_6 \) alkyl (e.g., 2-pyridyl-methyl, 3-pyridyl-methyl, 3,5-pyrimidyl-methyl, thiazolyl-methyl, or (3-phenyl-oxazolyl)-methyl).
In other embodiments of any of the foregoing methods or compositions, R¹ is -C(O)NR²R³. In certain embodiments of any of the foregoing methods or compositions, R⁷ is hydrogen. In some embodiments of any of the foregoing methods or compositions, R⁷ is C₁₋₅ alkyl (e.g., methyl). In some embodiments of any of the foregoing methods or compositions, R⁸ is C₅₋₁₀ alkyl (e.g., 2-chlorophenyl, 2-fluorophenyl, 2-trifluoromethylphenyl, 3-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, or 3,4-difluorophenyl). In other embodiments of any of the foregoing methods or compositions, R⁸ is C₂₋₅ heteroaryl (e.g., 2-pyridyl or 3-pyridyl). In certain embodiments of any of the foregoing methods or compositions, R⁸ is C₂₋₅ heterocyclic (e.g., benzodioxolyl). In some embodiments of any of the foregoing methods or compositions, R⁸ is C₂₋₅ heteroaryl (e.g., cyclohexyl).

In other embodiments of any of the foregoing methods or compositions, R¹ is -C(O)OR⁹. In certain embodiments of any of the foregoing methods or compositions, R⁹ is C₁₋₅ alkyl (e.g., tertbutyl). In some embodiments of any of the foregoing methods or compositions, R⁹ is C₆₋₁₀ aryl (e.g., 4-nitrophenyl).

In other embodiments of any of the foregoing methods or compositions, R¹ is -C(O)R¹⁰. In certain embodiments of any of the foregoing methods or compositions, R¹⁰ is C₂₋₅ alkyl (e.g., ethyl or n-propyl). In some embodiments of any of the foregoing methods or compositions, R¹⁰ is C₆₋₁₀ aryl (e.g., phenyl or 2-fluorophenyl). In other embodiments of any of the foregoing methods or compositions, R¹⁰ is C₂₋₅ heterocyclic (e.g., benzodioxolyl). In certain embodiments of any of the foregoing methods or compositions, R¹⁰ is C₂₋₅ heterocyclic (e.g., 2-fluorobenzyl). In some embodiments of any of the foregoing methods or compositions, R¹⁰ is C₂₋₅ heteroaryl (e.g., 3-pyridylmethyl).

In other embodiments of any of the foregoing methods or compositions, R¹ is -S(O)₂R¹¹. In certain embodiments of any of the foregoing methods or compositions, R¹¹ is C₁₋₅ alkyl (e.g., ethyl). In some embodiments of any of the foregoing methods or compositions, R¹¹ is C₆₋₁₀ aryl (e.g., phenyl, 2-fluorophenyl, 3-fluorophenyl, 3-methoxyphenyl, or 4-methoxyphenyl). In other embodiments of any of the foregoing methods or compositions, R¹¹ is C₆₋₁₀ aryl (e.g., 2-fluorobenzyl). In certain embodiments of any of the foregoing methods or compositions, R⁶ is hydrogen. In some embodiments of any of the foregoing methods or compositions, R⁶ is C₁₋₅ alkyl (e.g., methyl, ethyl, n-propyl, or 2,2,2-trifluoroethyl). In certain embodiments of any of the foregoing methods or compositions, R⁶ is C₅₋₁₀ carbocyclic C₁₋₅ alkyl (e.g., cyclopropylmethyl or cyclohexylmethyl). In some embodiments of any of the foregoing methods or compositions, R⁶ is C₅₋₁₀ aryl C₁₋₅ alkyl (e.g., benzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-chlorobenzyl, 2,5-difluorobenzyl, phenyl-ethyl, or phenyl-propyl). In other embodiments of any of the foregoing methods or compositions, R⁶ is C₂₋₅ heteroaryl C₁₋₅ alkyl (e.g., 2-pyridyl-methyl). In certain embodiments of any of the foregoing methods or compositions, R⁶ is C₂₋₅ heterocyclic C₁₋₅ alkyl (e.g., benzodioxolyl-methyl). In some embodiments of any of the foregoing methods or compositions, R⁶ is an N-protecting group (e.g., allyloxycarbonyl, i.e., Alloc).

In other embodiments of any of the foregoing methods or compositions, R⁶ is -C(O)R¹⁵. In certain embodiments of any of the foregoing methods or compositions, R¹⁵ is C₁₋₅ alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, or tertbutyl). In some embodiments of any of the foregoing methods or compositions, R¹⁵ is C₁₋₅ perfluoroalkyl (e.g., trifluoromethyl). In other embodiments of any of the foregoing methods or compositions, R¹⁵ is C₁₋₅ heteroalkyl (e.g., -CH₂N(CH₃)₂). In certain embodiments of any of the foregoing methods or compositions, R¹⁵ is C₂₋₅ carbocyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or...
cyclohexyl). In some embodiments of any of the foregoing methods or compositions, R^{15} is C_{2}-C_{5} heterocycyl (e.g., pyranyl). In other embodiments of any of the foregoing methods or compositions, R^{15} is C_{6}-C_{10} aryl (e.g., phenyl or 4-fluorophenyl). In certain embodiments of any of the foregoing methods or compositions, R^{15} is C_{6}-C_{10} aryl C_{1}-C_{6} alkyl (e.g., benzyl).

In some embodiments of any of the foregoing methods or compositions, R^{8} is -C(O)NR^{16}R^{17}. In other embodiments of any of the foregoing methods or compositions, R^{16} is hydrogen. In certain embodiments of any of the foregoing methods or compositions, R^{17} is C_{6}-C_{10} aryl (e.g., 4-fluorophenyl).

In some embodiments of any of the foregoing methods or compositions, R^{8} is -S(O)_{2}R^{18}. In other embodiments of any of the foregoing methods or compositions, R^{18} is C_{1}-C_{6} perfluoroalkyl (e.g., trifluoromethyl). In some embodiments of any of the foregoing methods or compositions, R^{18} is C_{2}-C_{10} carbocycyl (e.g., cyclopropyl). In other embodiments of any of the foregoing methods or compositions, R^{18} is C_{6}-C_{10} aryl (e.g., phenyl or 4-methylphenyl).

In some embodiments of any of the foregoing compositions or methods, the compound is selected from any one of compounds 1 to 150 of Table 1 or a pharmaceutically acceptable salt thereof.

In some embodiments of any of the foregoing methods, the malaria is drug resistant (e.g., the malaria is resistant to chloroquine, quinine, pyrimethamine, sulfadoxine, meploquine, artemether, lumefantrine, artesunate, amodiaquine, dihydroartemisinin, piperaquine, proguanil, doxycycline, clindamycin, artemisinin, atovaquone, or any combination thereof).

In some embodiments, the malaria is liver stage.

Chemical Terms

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments, and is not intended to be limiting. Further, although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

The term “acyl,” as used herein, represents a hydrogen or an alkyl group, as defined herein, that is attached to the parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxylic acid group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons. In some embodiments, the alkyl group is further substituted with 1, 2, 3, or 4 substituents as described herein.

As used herein, the term “alkyl”, alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms (e.g., one to sixteen carbon atoms, one to ten carbon atoms, one to six carbon atoms).

The term “lower alkyl”, alone or in combination with other groups, refers to a branched or straight-chain alkyl radical of one to nine carbon atoms, preferably one to six carbon atoms, more preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, and 2-ethylbutyl.

As used herein, the term “alkenyl”, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having an olefinic bond.

The term “amino,” as used herein, represents -N(R^{N1})_{2}, wherein each R^{N1} is, independently, H, OH, NO_{2}, N(R^{N2})_{2}, SO_{2}OR^{N2}, SO_{2}R^{N2}, SOR^{N2}, an N-protecting group, alkyl, alkenyl, alkynyl, alkoxy, aryl,
alkaryl, cycloalkyl, alkycycloalkyl, carboxyalkyl (e.g., optionally substituted with an O-protecting group, such as optionally substituted arylalkoxy carbonyl groups or any described herein), sulfoalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), alkoxy carbonyl alkyll (e.g., optionally substituted with an O-protecting group, such as optionally substituted aryl alkoxycarbonyl groups or any described herein), heterocyclyl (e.g., heteroaryl), or heterocyclylalkyl (e.g., heteroarylalkyl), wherein each of these rected Rₙ groups can be optionally substituted, as defined herein for each group; or two Rₙ combine to form a heterocyclyl or an N-protecting group, and wherein each Rₙ is, independently, H, alkyl, or aryl. The amino groups of the invention can be an unsubstituted amino (i.e., –NH₂) or a substituted amino (i.e., –N(R¹)₂). In a preferred embodiment, amino is –NH₂ or –NHR¹, wherein R¹ is, independently, OH, NO₂, NH₂, NR², SO₂OR³, SO₂R³, SO₂N₂, alkyl, carboxyalkyl, sulfoalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), alkoxy carbonyl alkyll (e.g., t-butoxycarbonylalkyl) or aryl, and each R₂ can be H, C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), or C₆₋₁₀ aryl.

The term “aryl” refers to an aromatic mono- or polycyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene, 1,2-dihydronaphthalene, indanyl, and 1H-indenyl.

The “aryalkyl” group, which as used herein, represents an aryl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted aryalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁₋₆ alk-C₆₋₁₀ aryl, C₁₋₁₀ alk-C₆₋₁₀ aryl, or C₁₋₂₀ alk-C₆₋₁₀ aryl). In some embodiments, the alkylene and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups. Other groups preceded by the prefix “alk-“ are defined in the same manner, where “alk” refers to a C₁₋₆ alkylene, unless otherwise noted, and the attached chemical structure is as defined herein.

The alkyl, lower alkyl, carbocyclic, and aryl groups may be substituted or unsubstituted. When substituted, there will generally be, for example, 1 to 4 substituents present. These substituents may optionally form a ring with the alkyl, lower alkyl or aryl group with which they are connected. Substituents may include, for example: carbon-containing groups such as alkyl, aryl, aryalkyl (e.g., substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g., trifluoromethyl); oxygen-containing groups such as alcohols (e.g., hydroxyl, hydroxyalkyl, aryl(hydroxy)alkyl), ethers (e.g., alkoxy, arylxy, alkoxyalkyl, aryloxyalkyl, more preferably, for example, methoxy and ethoxy), aldehydes (e.g., carboxaldehyde), ketones (e.g., alkylcarbonyl, alkycarbonylalkyl, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, acid derivatives such as esters (e.g., alkoxy carbonyl), alkylalkoxycarbonylalkyl, alkylcarbonylalkyl, alkylcarbonylalkyl, alkylcarbonylalkyl, amides (e.g., aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, carbamates (e.g., alkoxy carbonylamino, arylxy carbonylamino, aminocarbonylxy, mono- or di-alkylaminocarbonylxy, aminocarboxy, mono- or di-alkylaminocarbonylxy, and ureas (e.g., mono- or di-alkylaminocarboxylamino or aminocarboxylamino); nitrogen-containing groups such as amines (e.g., amino, mono- or di-alkyl amino, amino alkyl, mono- or di-alkylaminoketyl), azides, nitriles (e.g., cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiois, thioethers, sulfoxides and sulfones (e.g., alkythio, alkylsulfanyl, alkylsulfonyl, alkylthioalkyl, alkylsulfanylalkyl, alkylsulfonfylalkyl, arythio, arylxyfynl, arylxyfynl, arythioalkyl, arythiofynlalkyl, arythiofynlalkyl); and heterocyclic groups containing one or more heteroatoms, (e.g., thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, and 1H-indenyl.
azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyranyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthenyl, benzofurananyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolyl, 7-aizandolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthidinyl, cinnolinyl, quinazolinyl, pyridopyriddy, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carboliny).

The term “azido” represents an –N\(_2\) group, which can also be represented as –N\(=\)N\(=\)N.

The terms “carbocyclic” and “carbocycl,” as used herein, refer to an optionally substituted non-aromatic C\(_3\) monocyclic, bicyclic, or tricyclic structure in which the rings are formed by carbon atoms.

Carbocyclic structures include cycloalkyl, cycloalkenyl, and cycloalkynyl groups.

The term “cycloalkyl” refers to a monovalent mono- or polycarbocyclic radical of three to ten, preferably three to six carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and indanyl. In a preferred embodiment, the “cycloalkyl” moieties can optionally be substituted with one, two, three or four substituents. Each substituent can independently be, alkyl, alkoxy, halogen, amino, hydroxyl or oxygen unless otherwise specifically indicated. Examples of cycloalkyl moieties include, but are not limited to, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclopentenyl, optionally substituted cyclohexyl, and optionally substituted cycloheptyl, or those which are specifically exemplified herein.

The “carbocyclalkyl” group, which as used herein, represents a carbocyclic group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein (e.g., an alkylene group of from 1 to 4, from 1 to 6, from 1 to 10, or form 1 to 20 carbons). In some embodiments, the alkylene and the cycloalkyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group.

The term “carbonyl,” as used herein, represents a C(O) group, which can also be represented as C\(=\)O.

The term “carboxy,” as used herein, means –CO\(_2\)H.

The term “cyano,” as used herein, represents an –CN group.

As used herein, the term “halogen” means a fluorine (fluoro), chlorine (chboro), bromine (bromo) or iodine (iodo) radical.

The term “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. The term “heteroalkenyl,” as used herein refers to alkenyl groups, as defined herein, respectively, in which one or more of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl groups can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an “alkoxy” which, as used herein, refers alkyl-O-; and “alkoyl” which, as used herein, refers to alkyl-CO--. Alkoy substituent groups or alkoxy-containing substituent groups may be substituted by, for example, one or more alkyl groups.

The term “heteroaryl,” refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the
remaining ring atoms being C. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are benzoazoxazolyl, benzoimidazolyl, and benzothiazolyl.

The term “heteroarylalkyl” refers to a heteroaryl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted heteroarylalkyl groups are from 2 to 32 carbons (e.g., from 2 to 22, from 2 to 18, from 2 to 17, from 2 to 16, from 3 to 15, from 2 to 14, from 2 to 13, or from 2 to 12 carbons, such as C₁₋₆ alk-C₁₋₁₂ heteroaryl, C₁₋₁₀ alk-C₁₋₁₂ heteroaryl, or C₁₋₂₀ alk-C₁₋₁₂ heteroaryl). In some embodiments, the alkylene and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group.

Heteroarylalkyl groups are a subset of heterocyclylalkyl groups.

The term “heterocyclyl” denotes a mono- or polycyclic alkyl ring, wherein one, two or three of the carbon ring atoms is replaced by a heteroatom such as N, O or S. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, pipеразинил, пiperidinyl, pyrrolidinyl, tetrahydropropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl. The heterocyclyl groups may be unsubstituted or substituted, and attachment may be through their carbon frame or through their heteroatom(s) where appropriate.

The “heterocyclylalkyl” group, which as used herein, represents a heterocyclyl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted heterocyclylalkyl groups are from 2 to 32 carbons (e.g., from 2 to 22, from 2 to 18, from 2 to 17, from 2 to 16, from 3 to 15, from 2 to 14, from 2 to 13, or from 2 to 12 carbons, such as C₁₋₁₂ heterocyclyl C₁₋₆ alkyl, C₁₋₁₂ heterocyclyl C₁₋₁₀ alkyl, or C₁₋₁₂ heterocyclyl C₁₋₂₀ alkyl). In some embodiments, the alkylene and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group.

The heterocyclyl, heterocyclylalkyl, and heteroaryl groups described above may be substituted independently with one, two, three, or more substituents. Substituents may include, for example: carbon-containing groups such as alkyI, aryl, aryalkyl (e.g., substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g., trifluoromethyl); oxygen-containing groups such as alcohols (e.g., hydroxyl, hydroxyalkyl, aryl(hydroxy)alkyl), ethers (e.g., alkoxy, aryloxy, aralkoxyalkyl, aralkyloxyalkyl), aldehydes (e.g., carboxaldehyde), ketones (e.g., alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl), acids (e.g., carboxy, carboxyalkyl), acid derivatives such as esters (e.g., alkoxycarbonyl, alkoxyalkyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g., aminocarboxyl, mono- or di-alkylaminoalkyl, aminocarboxyalkyl, mono- or di-alkylaminocarboxyalkyl, arylaminocarboxyl), carbamates (e.g., alkoxyaminocarbamyl, arloxyaminocarbamyl, aminocarboxyloxy, mono- or di-alkylaminocarbamyl, aminocarboxyl, mono- or di-alkylaminocarbamyl, aminocarboxylaminocarboxyl, aminocarboxylaminocarboxyl, monoo- or di-alkylaminocarboxylaminocarboxyl, aminocarboxylaminocarboxylaminocarboxyl); nitrogen-containing groups such as amines (e.g., amino, mono- or di-alkylamino, aminocarboxyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g., cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g., alkylthio, alkylsulfanyl, alkylsulfonyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfonylethyl, arythio, arylsulfanyl, arylthioalkyl, arylsulfonylethyl), arylsulfanyl, arylthioalkyl, arylsulfonylethyl); and heterocyclic groups containing one or more heteroatoms, (e.g., thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, azidinyl, azetidinyl, pyrrolidinyl, pyrrolyl, imidazolidinyl, imidazolyl,
pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperezinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoazoxinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzothiazolyl and carboliny).

The term “hydroxyl,” as used herein, represents an –OH group. In some embodiments, the hydroxyl group can be substituted with a O-protecting group as defined herein.

The term “N-protecting group,” as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, “Protective Groups in Organic Synthesis,” 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. N-protecting groups include acyloxy, arylxyloxy groups such as formyloxy, acetyl, propionyloxy, pivaloyloxy, t-butyloxy, 2-chloroacetoxy, 2-bromoacetoxy, trifluoroacetoxy, trichloroacetoxy, phthaloyloxy, o-nitrophenoxyacetoxy, α-chlorobutyryloxy, benzoyloxy, 4-chlorobenzyloxy, 4-bromobenzyloxy, 4-nitrobenzyloxy, and chiral auxiliaries such as protected or unprotected D, L or D, L-α-amino acids such as alanine, leucine, and phenylalanine; sulfonyloxy-containing groups such as benzenesulfonyloxy, and p-toluenesulfonyloxy; carbamate forming groups such as benzoxycarbonyl, p-chlorobenzoxycarbonyl, p-methoxybenzoxycarbonyl, p-nitrobenzoxycarbonyl, 2-nitrobenzoxycarbonyl, p-bromobenzoxycarbonyl, 3,4-dimethoxybenzoxycarbonyl, 3,5-dimethoxybenzoxycarbonyl, 2,4-dimethoxybenzoxycarbonyl, 4-methoxybenzoxycarbonyl, 2-nitro-4,5-dimethoxybenzoxycarbonyl, 3,4,5-trimethoxybenzoxycarbonyl, 1-(p-biphenylyloxy)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzoxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylmethoxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxy carbonyl, fluorenlyloxy-9-methoxycarbonyl, cyclopentylxoxycarbonyl, adamantoxycarbonyl, cyclohexylxoxycarbonyl, and phenylthiocarbonyl, alkaryl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred N-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butyloxycarbonyl (Boc), and benzoxycarbonyl (Cbz).

The term “nitro,” as used herein, represents an –NO₂ group.

The term “O-protecting group,” as used herein, represents those groups intended to protect an oxygen containing (e.g., phenol, hydroxyl, or carbonyl) group against undesirable reactions during synthetic procedures. Commonly used O-protecting groups are disclosed in Greene, “Protective Groups in Organic Synthesis,” 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. Exemplary O-protecting groups include acyloxy, arylxyloxy groups such as formyloxy, acetyl, propionyloxy, pivaloyloxy, t-butyloxy, 2-chloroacetoxy, 2-bromoacetoxy, trifluoroacetoxy, trichloroacetoxy, phthaloyloxy, o-nitrophenoxyacetoxy, α-chlorobutyryloxy, benzoyloxy, 4-chlorobenzyloxy, 4-bromobenzyloxy, t-butyldimethylsilyl, triiso-propylsilyloxymethyl, 4,4’-dimethoxytrityl, isobutyryloxy, phenoxyacetoxy, 4-isopropylphenoxyacetoxy, dimethylformamidino, and 4-nitrobenzoyl; alkylcarbonyl groups, such as acyl, acetyl, propionyloxy, and pivaloyloxy; optionally substituted arylcarbonyl groups, such as benzoyl; silyl groups, such as trimethylsilyl (TMS), tert-butylmethyldimethylsilyl (TBDMS), triiso-propylsilyloxymethyl (TOM), and triisopropylsilyl (TIPS); ether-forming groups with the hydroxyl, such methyl, methoxymethyl, tetrahydropyranyl, benzyl, p-methoxybenzyl, and trityl; alkoxycarbonyls, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-isopropoxycarbonyl, n-butyloxycarbonyl, isobutyloxycarbonyl, sec-
butyloxy carbonyl, t-butyloxy carbonyl, 2-ethylhexyloxycarbonyl, cyclohexyloxycarbonyl, and methylloxycarbonyl; alkoxyalkoxy carbonyl groups, such as methoxymethoxy carbonyl, ethoxymethoxy carbonyl, 2-methoxyethoxycarbonyl, 2-ethoxyethoxycarbonyl, 2-butoxyethoxycarbonyl, 2-methoxyethoxymethoxycarbonyl, allyloxycarbonyl, propargyloxycarbonyl, 2-butoxycarbonyl, and 3-methyl-2-butoxycarbonyl; haloalkoxy carbonyls, such as 2-chlorothoxycarbonyl, 2-chloroethoxycarbonyl, and 2,2,2-trichlorothoxycarbonyl; optionally substituted arylalkoxycarbonyl groups, such as benzyloxycarbonyl, p-methylbenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2,4-dinitrobenzyloxycarbonyl, 3,5-dimethylbenzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, and fluorenylmethoxycarbonyl; and optionally substituted aryloxycarbonyl groups, such as phenoxy carbonyl, p-nitrophenoxy carbonyl, o-nitrophenoxy carbonyl, 2,4-dinitrophenoxy carbonyl, p-methyl-phenoxy carbonyl, m-methylphenoxy carbonyl, o-bromophenoxy carbonyl, 3,5-dimethylphenoxy carbonyl, p-chlorophenoxy carbonyl, and 2-chloro-4-nitrophenoxy carbonyl; substituted alkyl, aryl, and alkaryl ethers (e.g., trityl; methylthiomethyl; methoxymethyl; benzyloxymethyl; silyloxymethyl; 2,2,2-trichloroethoxymethyl; tetrahydrofuranyl; tetrahydrofuranyl; ethoxyethyl; 1-[2-(trimethylsilyl)ethoxy]ethyl; 2-trimethylsilyl eth yl; t-butyl ether; p-chlorophenyl; p-methoxyphenyl; p-nitrophenyl; benzyl, p-methoxybenzyl, and nitrobenzyl); silyl ethers (e.g., trimethylsilyl; triethylsilyl; triisopropylsilyl; dimethylisopropylsilyl; t-butylidimethylsilyl; t-butylidiphenylsilyl; tribenzylsilyl; triphenylsilyl; and diphenylmethylsilyl); carbonates (e.g., methyl, methoxymethyl, 9-fluorenylmethyl; ethyl; 2,2,2-trichloroethyl; 2-(trimethylsilyl) ethyl; vinyl, allyl, nitrophenyl; benzyl; methoxybenzyl; 3,4-dimethoxybenzyl; and nitrobenzyl); carbonyl-protecting groups (e.g., acetal and ketal groups, such as dimethyl acetal, and 1,3-dioxolane; acy1 groups; and dithiane groups, such as 1,3-dithianes, and 1,3-dithiolane); carboxylic acid-protecting groups (e.g., ester groups, such as methyl ester, benzyl ester, t-butyl ester, and orthoesters; and oxazoline groups).  

The term "oxo" as used herein, represents =O.

The term "perfluoroalkyl," as used herein, represents alkyl group, as defined herein, where each hydrogen radical bound to the alkyl group has been replaced by a fluoride radical. For example, perfluoroalkyl groups are exemplified by trifluoromethyl and perfluoroethyl.

The term "sulfonyl," as used herein, represents an -SO2- group.

The term "thiol," as used herein, represents an SH group.

Compounds of formula I can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or
more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. “Racemate” or “racemic mixture” means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. “Geometric isomer” means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. “R,” “S,” “S*,” “R*,” “E,” “Z,” “cis,” and “trans,” indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9%) by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer
relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of
diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the
other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched
relative to the other diastereomers. The invention embraces all of these forms.

Definitions

In the practice of the method of the present invention, an "effective amount" of any one of the
compounds of this invention or a combination of any of the compounds of this invention or a
pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods
known in the art, either singly or in combination. The compounds or compositions can thus be
administered, for example, ocularly, orally (e.g., buccal cavity), sublingually, parenterally (e.g.,
intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings),
transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form or solid, liquid
or gaseous dosages, including tablets and suspensions. The administration can be conducted in a single
unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic
composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt
such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous
or intramuscular administration.

The dose of a compound of the present invention depends on a number of factors, such as, for
example, the manner of administration, the age and the body weight of the subject, and the condition of
the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such
an amount of the active compound as determined by the attending physician or veterinarian is referred to
herein, and in the claims, as a "therapeutically effective amount". For example, the dose of a compound
of the present invention is typically in the range of about 1 to about 1000 mg per day. Preferably, the
therapeutically effective amount is in an amount of from about 1 mg to about 500 mg per day.

As used herein, the term "patient" refers to any organism to which a composition in accordance
with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or
therapeutic purposes. Typical patients include any animal (e.g., mammals such as mice, rats, rabbits,
non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be
receiving treatment, may be receiving treatment in the future, or a human or animal who is under care by
a trained professional for a particular disease or condition.

The term "pharmaceutical composition," as used herein, represents a composition containing a
compound described herein formulated with a pharmaceutically acceptable excipient. In some
embodiments, the pharmaceutical composition is manufactured or sold with the approval of a
governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a
mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit
dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream,
gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli
and in a solvent system suitable for intravenous use); or in any other formulation described herein.
Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases. Thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g., binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, and aerosols. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, and sesame oil. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic with the blood) for injectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s) which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, and ethanol. The compositions may be subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, and buffers. Suitable pharmaceutical carriers and their formulation are described in Remington’s Pharmaceutical Sciences by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

As used herein, the term “pharmaceutically acceptable salt” means any pharmaceutically acceptable salt of the compound of formula (I). For example pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., J. Pharmaceutical Sciences 66:1-19, 1977 and in Pharmaceutical Salts: Properties, Selection, and Use, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, and various amines for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothentic, phosphoric, succinic, sulfonic, tartaric, oxalic, and p-toluenesulfonic.
Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g., sodium, potassium), alkaline earth metal (e.g., calcium, magnesium) and aluminum salts.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

As used herein, and as well understood in the art, "to treat" a condition or "treatment" of the condition (e.g., the conditions described herein such as malaria) is an approach for obtaining beneficial or desired results, such as clinical results. Beneficial or desired results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition (e.g., preventing the spread of Plasmodium infection beyond the liver, preventing systemic disease, preventing the symptomatic stage of malaria, and/or preventing establishment of Plasmodium infection); delay or slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or undetectable. "Palliating" a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

The term “unit dosage form” refers to a physically discrete unit suitable as a unitary dosage for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with any suitable pharmaceutical excipient or excipients. Exemplary, non-limiting unit dosage forms include a tablet (e.g., a chewable tablet), caplet, capsule (e.g., a hard capsule or a soft capsule), lozenge, film, strip, gelcap, and syrup.

**BRIEF DESCRIPTION OF THE DRAWING**

Figure 1 is an image illustrating the results of a liver stage in vivo assay utilizing transgenic parasites (P. berghei (ANKA GFP-luc) sporozoites), atovaquone (ATV), and compound 15.

**DETAILED DESCRIPTION OF THE INVENTION**

**Compounds**

The invention features compounds that are useful in the prevention and treatment of malaria. Exemplary compounds described herein include compounds 1-150 shown above in Table 1 and
compounds having a structure according to any of Formulae I-VII or a pharmaceutically acceptable salt thereof.

Other embodiments, as well as exemplary methods for the synthesis or production of these compounds, are described herein.

It will be appreciated, that the compounds of general formula I in this invention may be derivatized at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo. Physiologically acceptable and metabolically labile derivatives, which are capable of producing the parent compounds of general formula I in vivo are also within the scope of this invention.

Compounds of the present invention can be prepared beginning with commercially available starting materials and utilizing general synthetic techniques and procedures known to those skilled in the art. Chemicals may be purchased from companies such as Aldrich, Argonaut Technologies, VWR and Lancaster. Chromatography supplies and equipment may be purchased from such companies as for example AnaLogix, Inc, Burlington, Wis.; Biotage AB, Charlottesville, Va.; Analytical Sales and Services, Inc., Pompton Plains, N.J.; Teledyne Isco, Lincoln, Nebr.; VWR International, Bridgeport, N.J.; Varian Inc., Palo Alto, Calif., and Multigram II Mettler Toledo Instrument Newark, Del. Biotage, ISCO and Analogix columns are pre-packed silica gel columns used in standard chromatography.

Utility and Administration

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to inhibit the growth of or kill the parasitic protozoan which causes malaria (e.g., *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*). In some embodiments, the treatment of malaria includes causative prophylaxis, such as preventing the spread of plasmodium infection beyond the liver, preventing systemic disease, preventing the symptomatic stage of malaria, and/or preventing the establishment of the infection. In some embodiments, the treatment of malaria refers to treatment intended to achieve cure (e.g., of *P. vivax* or *P. malariae*), e.g., treatment for radical cure (i.e., clearing hypnozoites from the liver). In various examples,
the methods include preventing spread of infection of a malaria-causing parasite as described herein from
the liver.

The compounds of the invention may be useful in the treatment of drug resistant malaria, such as
malaria resistant to chloroquine, quinine, pyrimethamine, sulfadoxine, mefloquine, artemether,
lumefantrine, artesunate, amodiaquine, dihydroartemisinin, piperaquine, proguanil, doxycycline,
clindamycin, artemisinin, atovaquone, and any combination thereof.

For use as treatment of human and animal subjects, the compounds of the invention can be
formulated as pharmaceutical or veterinary compositions. Depending on the subject to be treated, the
mode of administration, and the type of treatment desired (e.g., prevention, prophylaxis, or therapy) the
compounds are formulated in ways consonant with these parameters. A summary of such techniques is
found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins,
(2005); and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999,
Marcel Dekker, New York, each of which is incorporated herein by reference.

The compounds described herein may be present in amounts totaling 1-95% by weight of the
total weight of the composition. The composition may be provided in a dosage form that is suitable for
intraarticular, oral, parenteral (e.g., intravenous, intramuscular), rectal, cutaneous, subcutaneous, topical,
transdermal, sublingual, nasal, vaginal, intravesicular, intraurethral, intrathecal, epidural, aural, or ocular
administration, or by injection, inhalation, or direct contact with the nasal, genital, gastrointestinal,
reproductive or oral mucosa. Thus, the pharmaceutical composition may be in the form of, e.g., tablets,
capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes,
ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables,
implants, sprays, preparations suitable for iontophoretic delivery, or aerosols. The compositions may be
formulated according to conventional pharmaceutical practice.

In general, for use in treatment, the compounds described herein may be used alone, as mixtures
of two or more compounds or in combination with other pharmaceuticals. An example of other
pharmaceuticals to combine with the compounds described herein would include pharmaceuticals for the
treatment of the same indication. Another example of a potential pharmaceutical to combine with the
compounds described herein would include pharmaceuticals for the treatment of different yet associated
or related symptoms or indications. Depending on the mode of administration, the compounds will be
formulated into suitable compositions to permit facile delivery. Each compound of a combination therapy
may be formulated in a variety of ways that are known in the art. For example, the first and second
agents of the combination therapy may be formulated together or separately. Desirably, the first and
second agents are formulated together for the simultaneous or near simultaneous administration of the
agents.

The compounds of the invention may be prepared and used as pharmaceutical compositions
comprising an effective amount of a compound described herein and a pharmaceutically acceptable
carrier or excipient, as is well known in the art. In some embodiments, the composition includes at least
two different pharmaceutically acceptable excipients or carriers.

Formulations may be prepared in a manner suitable for systemic administration or topical or local
administration. Systemic formulations include those designed for injection (e.g., intramuscular,
intravenous or subcutaneous injection) or may be prepared for transdermal, transmucosal, or oral
administration. The formulation will generally include a diluent as well as, in some cases, adjuvants,
buffers, and preservatives. The compounds can be administered also in liposomal compositions or as microemulsions.

For injection, formulations can be prepared in conventional forms as liquid solutions or suspensions or as solid forms suitable for solution or suspension in liquid prior to injection or as emulsions. Suitable excipients include, for example, water, saline, dextrose, and glycerol. Such compositions may also contain amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, and pH buffering agents, such as, for example, sodium acetate, sorbitan monolaurate, and so forth.

Various sustained release systems for drugs have also been devised. See, for example, U.S. Patent No. 5,624,677, which is herein incorporated by reference.

Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds of the invention. Suitable forms include syrups, capsules, and tablets, as is understood in the art.

 Each compound of a combination therapy, as described herein, may be formulated in a variety of ways that are known in the art. For example, the first and second agents of the combination therapy may be formulated together or separately.

The individually or separately formulated agents can be packaged together as a kit. Non-limiting examples include, but are not limited to, kits that contain, e.g., two pills, a pill and a powder, a suppository and a liquid in a vial, or two topical creams. The kit can include optional components that aid in the administration of the unit dose to subjects, such as vials for reconstituting powder forms, syringes for injection, customized IV delivery systems, or inhalers. Additionally, the unit dose kit can contain instructions for preparation and administration of the compositions. The kit may be manufactured as a single use unit dose for one subject, multiple uses for a particular subject (at a constant dose or in which the individual compounds may vary in potency as therapy progresses); or the kit may contain multiple doses suitable for administration to multiple subjects ("bulk packaging"). The kit components may be assembled in cartons, blister packs, bottles, and tubes.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with nontoxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or algic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, and buffering agents.

Two or more compounds may be mixed together in a tablet, capsule, or other vehicle, or may be partitioned. In one example, the first compound is contained on the inside of the tablet, and the second
compound is on the outside, such that a substantial portion of the second compound is released prior to the release of the first compound.

Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Dissolution or diffusion controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g., shellac, beeswax, glycogelax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylenmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methycellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Generally, when administered to a human, the oral dosage of any of the compounds of the combination of the invention will depend on the nature of the compound, and can readily be determined by one skilled in the art. Typically, such dosage is normally around 0.001 mg to 2000 mg per day, desirably about 1 mg to 1000 mg per day, and more desirably about 5 mg to 500 mg per day. Dosages up to 200 mg per day may be necessary.

Administration of each drug in a combination therapy, as described herein, can, independently, be one to four times daily for one day to one year, and may even be for the life of the subject. Chronic, long-term administration may be indicated.

Combination Therapies

In some embodiments, the pharmaceutical composition may further comprise an additional compound having anti-malarial activity. The additional compound having anti-malarial activity can be selected from any compound having anti-malarial activity, such as chloroquine, quinine, pyrimethamine, sulfadoxine, mefloquine, artemether, lumefantrine, artesunate, amodiaquine, dihydroartemisinin, piperaquine, proguanil, doxycycline, clindamycin, artemisinin, and atovaquone.

It will also be appreciated that the compounds and pharmaceutical compositions of the present invention can be formulated and employed in combination therapies, that is, the compounds and pharmaceutical compositions can be formulated with or administered concurrently with, prior to, or
subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder, or they may achieve different effects (e.g., control of any adverse effects).

Examples

The following Examples are intended to illustrate the synthesis of a representative number of compounds and the use of these compounds in the treatment of malaria. Accordingly, the Examples are intended to illustrate but not to limit the invention. Additional compounds not specifically exemplified may be synthesized using conventional methods in combination with the methods described herein.

Example 1. Synthesis of Compounds

The compounds of formula I can be prepared according to Schemes 1 to 9:

Compounds 1, 3, 5, 8-10, 12-13, 15, 16, 20-21, 23, 27, 33, 35-37, 39, 41-45, 49-55, 57-62, 68, 71, 78-135, 138, 139, and 141-150 can be prepared by the reactions shown in Scheme 1:
Compounds 4, 7, 17-19, 22, 24-25, 28, 29, 31, 34, 38, 46, 56, 64, 65 and 72-76 can be prepared by the reactions shown in Scheme 2:

Compounds 2, 11, 14, 30, 34 and 70 can be prepared by the reactions shown in Scheme 3:
Compound 47 and 140 can be prepared by the reactions shown in Scheme 4:

Compound 63 can be prepared according to the reactions shown in Scheme 5:

Compounds 64, 66-67 and 69 can be prepared according to the reactions shown in Scheme 6:

Compounds 6 and 32 can be prepared according to the reactions shown in Scheme 7:

Compounds 26 and 40 can be prepared according to the reactions shown in Scheme 8:
Compounds 77, 136, and 137 can be prepared according to the reactions shown in Scheme 9:

Example 2. Activity of Compounds Against the Dd2 strain of *P. falciparum*

The Dd2 strain of *P. falciparum* was cultured in complete medium (RPMI with L-glutamine, 4.3% heat-inactivated O-positive human serum, 2.08 mg/ml albumax, 0.013 mg/ml hypoxanthine, 1.17 mg/ml glucose, 0.18% NaHCO₃, 0.031 M Heps, 2.60 mM NaOH, and 0.043 mg/ml gentamicin) until the parasitemia reached 3–8%. Parasitemia was determined by checking at least 500 red blood cells from a Giemsa-stained blood smear. The Dd2 cultures along with tested O-positive red blood cells are centrifuged at room temperature at 2,000 rpm for 5 min using an Eppendorf centrifuge 5810R with an A-4-81 rotor. The medium was aspirated off. For the compound screening, a parasite dilution at a 1% parasitemia and 1.0% hematocrit was created with screening medium (RPMI with L-glutamine, 4.16 mg/ml albumax II, 0.013 mg/ml hypoxanthine, 1.73 mg/ml glucose, 0.18% NaHCO₃, 0.031M Heps, 2.60 mM NaOH, and 0.043 mg/ml gentamicin). The suspension was gassed with 93% nitrogen, 4% carbon dioxide, and 3% oxygen and placed at 37°C until needed. Using a liquid dispenser, 20 µl of screening medium was dispensed into 384-well, black, clear-bottom plates. With a PinTool, 100 nl of compounds dissolved in DMSO was transferred into the assay plates along with control compound (mefloquine). Next, 30 µl of the parasite suspension in screening medium was then dispensed into the assay plates such that the final parasitemia was 1%, and the final hematocrit was 1.0%. Final concentration of DMSO was 0.125%. Mefloquine at a final concentration of 20 µM and DMSO at a final concentration of 0.125% were used within the assay plates to serve as background and baseline controls, respectively. The assay plates were transferred to incubators (93% nitrogen, 4% carbon dioxide, and 3% oxygen during the 72-h incubation at 37°C). Ten microliters of detection reagent consisting of 10X SYBR Green I (Invitrogen; supplied in 10,000X concentration) in lysis buffer (20 mM Tris-HCl, 5 mM EDTA, 0.16% Saponin wt/vol, 1.6% Triton X vol/vol) was dispensed into the assay plates. For optimal staining, the assay plates were left at room temperature for 24 h in the dark. The assay plates were read by using an Envision (PerkinElmer) reader, with 505 dichroic mirrors with 485-nm excitation and 530-nm emission settings, and the plate reads were from the bottom.

**Results**

By following the above protocol, EC₅₀ Dd2 results for compounds 1-150 are shown in Table 2 below.
Table 2. Bioactivity of Selected Compounds

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<tr>
<th>Example Number</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; Dd2 (nM)</th>
<th>Example Number</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; Dd2 (nM)</th>
<th>Example Number</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; Dd2 (nM)</th>
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Example 3. In vitro *P. falciparum* blood-stage culture and assay

Strains of *Plasmodium falciparum* (Dd2, 3D7, D6, K1, NF54, V1/3, HB3, 7G8, FCB, TM90C2B) were obtained from Malaria Research and Reference Reagent Resource Center (MR4). *P. falciparum* isolates were maintained with O-positive human blood in an atmosphere of 93% N₂, 4% CO₂, 3% O₂ at 37°C in complete culturing medium (10.4 g/L RPMI 1640, 5.94 g/L HEPES, 5g/L albumax II, 50 mg/L hypoxanthine, 2.1 g/L sodium bicarbonate, 10% human serum and 43 mg/L gentamicin). Parasites were cultured in medium until the parasitemia reached 3–8%. Parasitemia was determined by checking at least 500 red blood cells from a Giemsa-stained blood smear. For the compound screening, a parasite suspension at 2.0% parasitemia and 2.0% hematocrit was created with medium. 25 μl of medium was dispensed into 384-well, black, clear-bottom plates. 100 nl of compounds in DMSO was transferred into the assay plates along with control compound (mefloquine). Next, 25 μl of the parasite suspension in medium was dispensed into the assay plates such that the final parasitemia was 1% and the final hematocrit was 1%. The assay plates were incubated for 72 hours at 37°C. 10 μl of detection reagent consisting of 10x SYBR Green I (Invitrogen; supplied at 10,000X concentration) in lysis buffer (20 mM Tris-HCl, 5 mM EDTA, 0.16% Saponin wt/vol, 1.6% Triton X vol/vol) was dispensed into the assay plates. For optimal staining, the assay plates were left at room temperature for 24 h in the dark. The assay plates were read with 505 dichroic mirrors with 485-nm excitation and 530-nm emission settings.

**Results**

Compound 15 was found to be equipotent against all field isolates (see Table 3).

Table 3. Activity of compound 15 against multiple drug resistant strains of *P. falciparum*

<table>
<thead>
<tr>
<th>Strain</th>
<th>Dd2</th>
<th>3D7</th>
<th>D6</th>
<th>K1</th>
<th>NF54</th>
<th>V1/3</th>
<th>HB3</th>
<th>7G8</th>
<th>FCB</th>
<th>TM90C2B</th>
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<tbody>
<tr>
<td>Activity (IC₅₀ nM)</td>
<td>73</td>
<td>65</td>
<td>70</td>
<td>91</td>
<td>88</td>
<td>98</td>
<td>147</td>
<td>113</td>
<td>130</td>
<td>104</td>
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</table>

Example 4. Activity against different stages of *P. falciparum*, *P. berghei* and *P. cynomolgi*.

**In vitro *P. berghei* liver-stage assay**

HepG2 cells were maintained in DMEM, 10% (vol/vol) FBS (Sigma), and 1% (vol/vol) antibiotic–antimycotic in a standard tissue culture incubator (37°C, 5% CO₂). *P. berghei* (ANKA GFP-luc) infected *Anopheles stephensi* mosquitoes were obtained from the New York University Langone Medical Center Insectary (New York). For assays, ~17,500 HepG2 cells per well were added to a 384-well microtiter plate in duplicate. After 18–24 h at 37°C the media was exchanged and compounds were added. After 1 hour, parasites obtained from freshly dissected mosquitoes were added to the plates (4,000 parasites per well), the plates were spun for 10 min at 1,000 rpm, and then the plates were incubated at 37°C. The final assay volume was 30 μL. After a 48 hour incubation at 37°C, Bright-Glo (Promega) was added to the parasite plate to measure relative luminescence. The relative signal intensity of each plate was evaluated with an EnVision (PerkinElmer) system.
In vitro P. cynomolgi liver stage assay
An in vitro P. cynomolgi liver stage assay was performed as described in Zeeman et al. Antimicrobial Agents and Chemotherapy, 2014, 58:1586-1595. 96-well plates are seeded with freshly isolated or thawed cryopreserved stocks of primary rhesus monkey hepatocytes one or two days before infection with 5 x 10^4 freshly dissected P. cynomolgi sporozoites per well. After 2-3 h of sporozoite invasion into the hepatocytes, culture medium is exchanged for culture medium containing appropriate compound dilutions. Initially, compounds are tested in duplicate in 3 dilutions: 0.1, 1 and 10 μM. Plates are incubated for 6 days with medium exchange (including compound dilutions) every other day. Plates are fixed in methanol and parasites are stained with rabbit anti-PcyHSP70 antiserum in the presence of DAPI to stain the nuclei. Plates are automatically counted in a high-content imager (Operetta®) and small parasites (hypnozoites, s.f.) and large schizonts (l.f.) are recorded, as well as number of hepatocytes as a measure for cytotoxic effects of the compounds. Controls include uninfected hepatocytes, sporozoite infected wells without compound and infected wells with primaquine and atovaquone. When activity is recorded and reported, a more extensive dilution curve can be evaluated: a 7-point 3-fold dilution series from days 0-6.

P. falciparum Gametocyte viability assay
P. falciparum 3D7 stage III-V gametocytes were isolated by discontinuous Percoll gradient centrifugation of parasite cultures treated with 50 mM N-acetyl-D-glucosamine for 3 days to kill asexual parasites. Gametocytes (1.0 x 10^5) were seeded in 96-well plates and incubated with compounds for 72 hours. In vitro anti-gametocyte activity was measured using Cell-titer glo (Promega).

Results
Compound 15 was found to inhibit the asexual stage and the sexual and transmission stage of the parasites (see Table 4).

Table 4. Activity of Compound 15 against different stages of Plasmodium (IC_{50}s reported in nM)

<table>
<thead>
<tr>
<th>erythrocytic stage (P. falciparum)</th>
<th>exo-erythrocytic stage</th>
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<tr>
<td>asexual</td>
<td>sexual (IV &amp; V)</td>
</tr>
<tr>
<td></td>
<td>P. berghei</td>
</tr>
<tr>
<td></td>
<td>P. cynomolgi (s.l/l.f)</td>
</tr>
<tr>
<td>64</td>
<td>643</td>
</tr>
<tr>
<td></td>
<td>459</td>
</tr>
<tr>
<td></td>
<td>344/832</td>
</tr>
</tbody>
</table>

Example 5. In vivo P. berghei blood-stage assay
CD-1 mice (n=4 per experimental group; female; 6-7-week-old; 20–24 g) were inoculated with 1x10^6 P. berghei (ANKA GFP-luc) blood stage parasites intravenously 24 hours before treatment and compounds were administered orally (at 0 hour). Parasitemia was monitored by the In vivo Imaging System (IVIS 100, Xenogen; Caliper Life Sciences) to acquire the bioluminescence signal. In addition, blood smear samples were obtained from each mouse on day 4 after inoculation, stained with Giemsa, and viewed under a microscope for visual detection of blood parasitemia. Animals with parasitemia exceeding 20% were euthanized.
Results

Compound 15 was found to inhibit the blood stage of *P. berghei in vivo* (see Table 5).

Table 5. *In vivo* activity of Compound 15 in blood-stage assay

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Route</th>
<th>Parasitized RBC</th>
<th>% of control</th>
<th>% Activity</th>
<th>Mouse survival in days</th>
<th>Avg. Mouse survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg</td>
<td></td>
<td>over 100</td>
<td>M1</td>
<td>M2</td>
<td>M3</td>
<td>M1</td>
</tr>
<tr>
<td>4x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>T/E</td>
<td>p.o.</td>
<td>3.70</td>
<td>3.20</td>
<td>2.80</td>
<td>5.80</td>
</tr>
</tbody>
</table>

T/E=7% Tween, 3% Ethanol, and 90% water

Example 6. *In vivo P. berghei* liver-stage assay

CD-1 mice (n=4 per experimental group; female; 6-7-week-old; 20–24 g) were inoculated intravenously with 1x10⁵ freshly isolated *P. berghei* (ANKA GFP-luc) sporozoites intravenously, and compounds were administered orally at 50 mg/kg two hours later. Bioluminescence signals from the transgenic parasites were monitored by the *In vivo* Imaging System (IVIS 100, Xenogen; Caliper Life Sciences). Animals with parasitemia exceeding 20% were euthanized.

Results

Compound 15 was found to inhibit the liver stage of *P. berghei in vivo* (Figure 1). Untreated control animals showed systemic (blood stage) parasitemia by day four, while atovaquone or Compound 15 treated animals remained parasite free.

Other Embodiments

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

What is claimed:
1. A compound according to Formula (I):

[Image of a chemical structure]

wherein a and b are independently 0, 1, or 2;
c is 0, 1, 2, 3, or 4;
R¹ is hydrogen, C₁₋C₆ alkyl, C₂₋C₉ heteroaryl, C₅₋C₁₀ carbocyclyl, C₁₋C₆ alkyl, C₆₋C₁₀ aryl C₁₋C₆ alkyl, C₂₋C₉ heteroaryl C₁₋C₆ alkyl, -(O)NR²R³, -(O)OR⁴, -(O)R⁵, or -(S)R⁶R⁷;
each R² is independently hydroxyl, halogen, or -OR⁸;
R³ is hydrogen or C₁₋C₆ alkyl;
R⁴ is hydrogen or C₁₋C₆ alkyl;
R⁵ is C₁₋C₆ alkyl, or -(CH₂)ₓX¹R¹⁴, or R⁶ and R⁷ together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a 5-8-membered heterocycle;
R⁶ is hydrogen, C₁₋C₆ alkyl, C₁₋C₆ perfluoroalkyl, C₃₋C₁₀ carbocyclyl, C₁₋C₆ alkyl, C₆₋C₁₀ aryl C₁₋C₆ alkyl, C₂₋C₉ heteroaryl C₁₋C₆ alkyl, C₂₋C₉ heterocyclyl C₁₋C₆ alkyl, N-protecting group, -(O)R¹⁰, -(O)NR¹⁰R¹¹, or -(S)R¹⁰R¹¹;
R⁷ is hydrogen or C₁₋C₆ alkyl;
R⁸ is C₆₋C₁₀ aryl, C₂₋C₉ heteroaryl, or C₃₋C₁₀ carbocyclyl;
R⁹ is C₁₋C₆ alkyl or C₆₋C₁₀ aryl;
R¹⁰ is C₁₋C₆ alkyl, C₆₋C₁₀ aryl, C₂₋C₉ heterocyclyl, C₆₋C₁₀ aryl C₁₋C₆ alkyl, or C₂₋C₉ heteroaryl C₁₋C₆ alkyl;
R¹¹ is C₁₋C₆ alkyl, C₂₋C₉ aryl, or C₂₋C₉ aryl C₁₋C₆ alkyl;
each R¹² is C₁₋C₆ alkyl or C₂₋C₆ acyl;
n is 1, 2, 3, 4, 5, or 6;
X¹ is absent, O, or NR¹⁴;
R¹⁴ is hydrogen, C₁₋C₆ alkyl, C₁₋C₆ heterocyclyl, C₁₋C₆ perfluoroalkyl, C₁₋C₆ acyl, C₆₋C₁₀ aryl C₁₋C₆ alkyl, an O- or N-protecting group, or R¹³ and R¹⁴ combine to form a 5-8-membered heterocycle;
R¹⁵ is hydrogen or C₁₋C₆ alkyl;
R¹⁶ is C₁₋C₆ alkyl, C₁₋C₆ perfluoroalkyl, C₁₋C₆ heterocyclyl, C₃₋C₁₀ carbocyclyl, C₂₋C₉ heterocyclyl,
C₆₋C₁₀ aryl, C₂₋C₉ aryl C₁₋C₆ alkyl;
R¹⁶ and R¹⁷ are independently hydrogen, C₁₋C₆ alkyl, or C₂₋C₉ aryl; and
R¹⁸ is C₁₋C₆ alkyl, C₁₋C₆ perfluoroalkyl, C₃₋C₁₀ carbocyclyl, or C₂₋C₉ aryl;
wherein the compound is not compound 12, compound 15, or any one of compounds 78-135 of Table 1,
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein c is 1.
3. The compound of claim 2, wherein the compound has a structure of Formula II:

![Formula II](image)

4. The compound of claim 1, wherein c is 2.

5. The compound of claim 4, wherein the compound has a structure of Formula III:

![Formula III](image)

6. The compound of any one of claims 1 to 5, wherein the compound has a structure of Formula IV:

![Formula IV](image)

7. The compound of claim 6, wherein said compound has the structure:
8. The compound of any one of claims 1 to 5, wherein the compound has a structure of Formula V:

![Formula V](image)

9. The compound of claim 8, wherein the compound has the structure:

![Formula VI](image)

10. The compound of any one of claims 1 to 5, wherein the compound has a structure of Formula VI:

![Formula VI](image)

11. The compound of claim 10, wherein the compound has the structure:

![Formula VI](image)

12. The compound of any one of claims 1 to 11, wherein R³ is hydrogen.

13. The compound of any one of claims 1 to 11, wherein R³ is C₁-C₆ alkyl.

14. The compound of claim 13, wherein said C₁-C₆ alkyl is methyl.
15. The compound of any one of claims 1 to 14, wherein R^4 is hydrogen.

16. The compound of any one of claims 1 to 14, wherein R^4 is C_1-C_6 alkyl.

17. The compound of claim 16, wherein said C_1-C_6 alkyl is methyl.

18. The compound of any one of claims 1 to 17, wherein R^2 is hydroxyl.

19. The compound of any one of claims 1 to 17, wherein R^2 is halogen.

20. The compound of claim 19, wherein said halogen is fluoro.

21. The compound of any one of claims 1 to 17, wherein R^2 is –OR^{12}.

22. The compound of claim 21, wherein R^{12} is C_1-C_6 alkyl.

23. The compound of claim 22, wherein said C_1-C_6 alkyl is methyl or isopropyl.

24. The compound of claim 21, wherein R^{12} is C_1-C_6 acyl.

25. The compound of claim 24, wherein said C_1-C_6 acyl is acetyl.

26. The compound of any one of claims 1 to 25, wherein R^5 and R^6 together with the carbon and nitrogen atoms to which they are respectively attached, combine to form a 5-8-membered heterocycle.

27. The compound of claim 26, wherein said 5-8-membered heterocycle is a 6-membered heterocycle substituted with an oxo.

28. The compound of claim 27, wherein the compound has the structure of Formula VII:

![Formula VII](image)

29. The compound of any one of claims 1 to 25, wherein R^5 is C_1-C_6 alkyl.

30. The compound of claim 29, wherein said C_1-C_6 alkyl is methyl.
31. The compound of any one of claims 1 to 25, wherein $R^5 = -(CH_2)_n X^1 R^{13}$.

32. The compound of claim 31, wherein $n$ is 1.

33. The compound of claim 31, wherein $n$ is 2.

34. The compound of any one of claims 31 to 33, wherein $X^1$ is absent.

35. The compound of claim 34, wherein $R^{13}$ is C$_1$-C$_6$ perfluoroalkyl.

36. The compound of claim 35, wherein said C$_1$-C$_6$ perfluoroalkyl is trifluoromethyl.

37. The compound of any one of claims 31 to 33, wherein $X^1$ is O.

38. The compound of claim 37, wherein $R^{13}$ is hydrogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ heteroalkyl, C$_1$-C$_6$ acyl, C$_6$-C$_{10}$ aryl C$_1$-C$_6$ alkyl, or an O-protecting group.

39. The compound of claim 38, wherein $R^{13}$ is hydrogen.

40. The compound of claim 38, wherein $R^{13}$ is C$_1$-C$_6$ alkyl.

41. The compound of claim 40, wherein said C$_1$-C$_6$ alkyl is methyl.

42. The compound of claim 38, wherein $R^{13}$ is C$_1$-C$_6$ acyl.

43. The compound of claim 42, wherein said C$_1$-C$_6$ acyl is acetyl.

44. The compound of claim 38, wherein $R^{13}$ is C$_6$-C$_{10}$ aryl C$_1$-C$_6$ alkyl.

45. The compound of claim 44, wherein said C$_6$-C$_{10}$ aryl C$_1$-C$_6$ alkyl is 4-methoxybenzyl.

46. The compound of claim 38, wherein $R^{13}$ is C$_1$-C$_6$ heteroalkyl.

47. The compound of claim 46, wherein said C$_1$-C$_6$ heteroalkyl is --CH$_2$OCH$_3$ or
   -CH$_2$OCH$_2$CH$_2$OCH$_3$.

48. The compound of claim 38, wherein $R^{13}$ is an O-protecting group.

49. The compound of claim 48, wherein said an O-protecting group is tertbutyldimethylsilyl.

50. The compound of any one of claims 31 to 33, wherein $X^1$ is NR$_{14}$.
51. The compound of claim 50, wherein R^{13} and R^{14} combine to form a 5-8-membered heterocycle.

52. The compound of claim 51, wherein said 5-8-membered heterocycle is morpholino.

53. The compound of claim 50, wherein R^{14} is hydrogen.

54. The compound of claim 50, wherein R^{14} is C_{1}-C_{6} alkyl.

55. The compound of claim 54, wherein said C_{1}-C_{6} alkyl is methyl.

56. The compound of any one of claims 53 to 55, wherein R^{13} is C_{1}-C_{6} alkyl.

57. The compound of claim 56, wherein said C_{1}-C_{6} alkyl is methyl.

58. The compound of any one of claims 1 to 57, wherein R^{1} is hydrogen.

59. The compound of any one of claims 1 to 57, wherein R^{1} is C_{1}-C_{6} alkyl.

60. The compound of claim 59, wherein said C_{1}-C_{6} alkyl is methyl, ethyl, or n-propyl.

61. The compound of any one of claims 1 to 57, wherein R^{1} is C_{2}-C_{9} heteroaryl.

62. The compound of claim 62, wherein said C_{2}-C_{9} heteroaryl is benzo-oxazolyl, benzo-imidazolyl, or benzo-thiazolyl.

63. The compound of any one of claims 1 to 57, wherein R^{1} is C_{5}-C_{10} carbocyclic C_{1}-C_{6} alkyl.

64. The compound of claim 63, wherein said C_{5}-C_{10} carbocyclic C_{1}-C_{6} alkyl is cyclopropyl-methyl, cyclopentyl-methyl, or cyclohexyl-methyl.

65. The compound of any one of claims 1 to 57, wherein R^{1} is C_{6}-C_{10} aryl C_{1}-C_{6} alkyl.

66. The compound of claim 65, wherein said C_{6}-C_{10} aryl C_{1}-C_{6} alkyl is 2-fluorophenyl-ethyl, 2-fluorobenzyl, 4-(2-pyridyl)-benzyl, 4-methoxybenzyl, or 3-fluorobenzyl.

67. The compound of any one of claims 1 to 57, wherein R^{1} is C_{2}-C_{9} heteroaryl C_{1}-C_{6} alkyl.

68. The compound of claim 67, wherein said C_{2}-C_{9} heteroaryl C_{1}-C_{6} alkyl is 2-pyridyl-methyl, 3-pyridyl-methyl, 3,5-pyrimidyl-methyl, thiazolyl-methyl, or (3-phenyl-oxazolyl)-methyl.
69. The compound of any one of claims 1 to 57, wherein \( R^1 \) is \(-\text{C}(\text{O})\text{NR}^7\text{R}^8 \).

70. The compound of claim 69, wherein \( R^7 \) is hydrogen.

71. The compound of claim 69, wherein \( R^7 \) is \( \text{C}_1\text{-C}_6 \) alkyl.

72. The compound of claim 71, wherein said \( \text{C}_1\text{-C}_6 \) alkyl is methyl.

73. The compound of any one of claims 69 to 72, wherein \( R^8 \) is \( \text{C}_6\text{-C}_{10} \) aryl.

74. The compound of claim 73, wherein said \( \text{C}_6\text{-C}_{10} \) aryl is 2-chlorophenyl, 2-fluorophenyl, 2-trifluoromethylphenyl, 3-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, or 3,4-difluorophenyl.

75. The compound of claim 74, wherein said \( \text{C}_6\text{-C}_{10} \) aryl is 2-fluorophenyl.

76. The compound of any one of claims 69 to 72, wherein \( R^8 \) is \( \text{C}_2\text{-C}_9 \) heteroaryl.

77. The compound of claim 76, wherein said \( \text{C}_2\text{-C}_9 \) heteroaryl is 2-pyridyl or 3-pyridyl.

78. The compound of any one of claims 69 to 72, wherein \( R^8 \) is \( \text{C}_2\text{-C}_9 \) heterocycl reduced 

79. The compound of claim 78, wherein said \( \text{C}_2\text{-C}_9 \) heterocycl reduced 

80. The compound of any one of claims 69 to 72, wherein \( R^8 \) is \( \text{C}_3\text{-C}_{10} \) carbocycl reduced 

81. The compound of claim 80, wherein said \( \text{C}_3\text{-C}_{10} \) carbocycl reduced 

82. The compound of any one of claims 57, wherein \( R^1 \) is \(-\text{C}(\text{O})\text{OR}^9 \).

83. The compound of claim 82, wherein \( R^9 \) is \( \text{C}_1\text{-C}_6 \) alkyl.

84. The compound of claim 83, wherein said \( \text{C}_1\text{-C}_6 \) alkyl is tertbutyl.

85. The compound of claim 82, wherein \( R^9 \) is \( \text{C}_6\text{-C}_{10} \) aryl.

86. The compound of claim 85, wherein said \( \text{C}_6\text{-C}_{10} \) aryl is 4-nitrophenyl.

87. The compound of any one of claims 1 to 57, wherein \( R^1 \) is \(-\text{C}(\text{O})\text{R}^{10} \).

88. The compound of claim 87, wherein \( \text{R}^{10} \) is \( \text{C}_1\text{-C}_6 \) alkyl.
89. The compound of claim 88, wherein said C₁-C₆ alkyl is ethyl or n-propyl.

90. The compound of claim 87, wherein R¹⁰ is C₆-C₁₀ aryl.

91. The compound of claim 90, wherein said C₆-C₁₀ aryl is phenyl or 2-fluorophenyl.

92. The compound of claim 87, wherein R¹⁰ is C₂-C₉ heterocyclil.

93. The compound of claim 92, wherein said C₂-C₉ heterocyclil is benzodioxolyl.

94. The compound of claim 87, wherein R¹⁰ is C₆-C₁₀ aryl C₁-C₆ alkyl.

95. The compound of claim 94, wherein said C₆-C₁₀ aryl C₁-C₆ alkyl is 2-fluorobenzyl.

96. The compound of claim 87, wherein R¹⁰ is C₂-C₉ heteroaryl C₁-C₆ alkyl.

97. The compound of claim 96, wherein said C₂-C₉ heteroaryl C₁-C₆ alkyl is 3-pyridyl-methyl.

98. The compound of any one of claims 1 to 57, wherein R¹ is –S(O)₂R¹¹.

99. The compound of claim 98, wherein R¹¹ is C₁-C₆ alkyl.

100. The compound of claim 99, wherein said C₁-C₆ alkyl is ethyl.

101. The compound of claim 98, wherein R¹¹ is C₆-C₁₀ aryl.

102. The compound of claim 101, wherein said C₆-C₁₀ aryl is phenyl, 2-fluorophenyl, 3-fluorophenyl, 3-methoxyphenyl, or 4-methoxyphenyl.

103. The compound of claim 98, wherein R¹¹ is C₆-C₁₀ aryl C₁-C₆ alkyl.

104. The compound of claim 103, wherein said C₆-C₁₀ aryl C₁-C₆ alkyl is 2-fluorobenzyl.

105. The compound of any one of claims 1 to 104, wherein R⁶ is hydrogen.

106. The compound of any one of claims 1 to 104, wherein R⁶ is C₁-C₆ alkyl.

107. The compound of claim 106, wherein said C₁-C₆ alkyl is methyl, ethyl, n-propyl, or trifluoroethyl.

108. The compound of any one of claims 1 to 104, wherein R⁶ is C₃-C₁₀ carbocyclil C₁-C₆ alkyl.
109. The compound of claim 108, wherein said C₃⁻C₁₀ carbocyclyl C₁⁻C₆ alkyl is cyclopropyl-methyl or cyclohexyl-methyl.

110. The compound of any one of claims 1 to 104, wherein R⁶ is C₆⁻C₁₀ aryl C₁⁻C₆ alkyl.

111. The compound of claim 110, wherein said C₆⁻C₁₀ aryl C₁⁻C₆ alkyl is benzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-chlorobenzyl, 2,5-difluorobenzyl, phenyl-ethyl, or phenyl-propyl.

112. The compound of any one of claims 1 to 104, wherein R⁶ is C₂⁻C₉ heteroaryl C₁⁻C₆ alkyl.

113. The compound of claim 112, wherein said C₂⁻C₉ heteroaryl C₁⁻C₆ alkyl is 2-pyridylmethyl.

114. The compound of any one of claims 1 to 104, wherein R⁶ is C₂⁻C₉ heterocyclyl C₁⁻C₆ alkyl.

115. The compound of claim 114, wherein said C₂⁻C₉ heterocyclyl C₁⁻C₆ alkyl is benzodioxolyl-methyl.

116. The compound of any one of claims 1 to 104, wherein R⁶ is an N-protecting group.

117. The compound of claim 116, wherein said N-protecting group is allyloxycarbonyl (alloc).

118. The compound of any one of claims 1 to 104, wherein R⁶ is -C(O)R¹⁵.

119. The compound of claim 118, wherein R¹⁵ is C₁⁻C₆ alkyl.

120. The compound of claim 119, wherein said C₁⁻C₆ alkyl is methyl, ethyl, n-propyl, isopropyl, or tertbutyl.

121. The compound of claim 120, wherein said C₁⁻C₆ alkyl is methyl.

122. The compound of claim 118, wherein R¹⁵ is C₁⁻C₆ perfluoroalkyl.

123. The compound of claim 122, wherein said C₁⁻C₆ perfluoroalkyl is trifluoromethyl.

124. The compound of claim 118, wherein R¹⁵ is C₁⁻C₆ heteroalkyl.

125. The compound of claim 124, wherein said C₁⁻C₆ heteroalkyl is –CH₂N(CH₃)₂.

126. The compound of claim 118, wherein R¹⁵ is C₃⁻C₁₀ carbocyclyl.

127. The compound of claim 126, wherein said C₃⁻C₁₀ carbocyclyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.
128. The compound of claim 118, wherein R^{15} is C_2-C_9 heterocyclyl.

129. The compound of claim 128, wherein said C_2-C_9 heterocyclyl is pyranyl.

130. The compound of claim 118, wherein R^{15} is C_6-C_{10} aryl.

131. The compound of claim 130, wherein said C_6-C_{10} aryl is phenyl or 4-fluorophenyl.

132. The compound of claim 118, wherein R^{15} is C_6-C_{10} aryl C_1-C_6 alkyl.

133. The compound of claim 132, wherein said C_6-C_{10} aryl C_1-C_6 alkyl is benzyl.

134. The compound of any one of claims 1 to 104, wherein R^6 is -C(O)NR^{16}R^{17}.

135. The compound of claim 134, wherein R^{16} is hydrogen.

136. The compound of claim 134 or 135, wherein R^{17} is C_6-C_{10} aryl.

137. The compound of claim 136, wherein said C_6-C_{10} aryl is 4-fluorophenyl.

138. The compound of any one of claims 1 to 104, wherein R^6 is -S(O)_2R^{18}.

139. The compound of claim 138, wherein R^{18} is C_1-C_6 alkyl.

140. The compound of claim 139, wherein said C_1-C_6 alkyl is methyl, ethyl, or n-propyl.

141. The compound of claim 138, wherein R^{18} is C_1-C_6 perfluoroalkyl.

142. The compound of claim 141, wherein said C_1-C_6 perfluoroalkyl is trifluormethyl.

143. The compound of claim 138, wherein R^{18} is C_3-C_{10} carbocyclyl.

144. The compound of claim 143, wherein said C_3-C_{10} carbocyclyl is cyclopropyl.

145. The compound of claim 138, wherein R^{18} is C_6-C_{10} aryl.

146. The compound of claim 145, wherein said C_6-C_{10} aryl is phenyl or 4-methylphenyl.

147. A compound selected from any one of compounds 1 to 11, 13, 14, 16 to 77, or 136 to 150 of Table 1 or a pharmaceutically acceptable salt thereof.
148. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1 to 147 or any one of compounds 12, 15, or 78-135 of Table 1 and a pharmaceutically acceptable excipient.

149. A method of preventing or treating malaria in a subject, comprising the step of administering to the subject an effective amount of a compound of any one of claims 1 to 147, any one of compounds 12, 15, or 78-135 of Table 1, or a composition of claim 148 to a patient in need thereof.

150. The method of claim 149, wherein said malaria is drug resistant malaria.

151. The method of claim 150, wherein said drug resistant malaria is resistant to chloroquine, quinine, prymethamine, sulfadoxine, mefloquine, artemether, lumefantrine, artesunate, amodiaquine, dihydroartemisinin, piperaquine, proguanil, doxycycline, clindamycin, artemisinin, atovaquone, or any combination thereof.

152. The method of any one of claims 149 to 151, wherein said malaria is liver stage malaria.

153. The method of any one of claims 149 to 152, wherein the liver of said subject is infected with a malaria-causing parasite and said treatment prevents spread of said infection from their liver.