ANTIFUNGAL AND ANTIPARASITIC INDOLOQUINOLINE DERIVATES

Inventor: Seth Y. Aborderpepy, Tallahassee, FL (US)

Assignee: Florida Agricultural and Mechanical University, Tallahassee, FL (US)

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Primary Examiner — Charanjit Aulakh
Attorney, Agent, or Firm — Thomas, Kayden, Horstemeyer & Risley, LLP

ABSTRACT

An indoloquinoline wherein the quarternary N-5 atom is a straight C(1-5) chain, a branched C(1-5) chain, a heterocum chain, a straight chain substituted terminally by a cycloalkyl or aromatic ring, a branched chain substituted terminally by a cycloalkyl or aromatic ring, a heteroatom chain substituted terminally by a cycloalkyl or aromatic ring; the 10 position is N—R10, O, S—O, CH2 or C—O, where R10 is a branched C(1-5) chain, a heteroatom chain, a straight chain substituted terminally by a cycloalkyl or aromatic ring, a branched chain substituted terminally by a cycloalkyl or aromatic ring, a heteroatom chain substituted terminally by a cycloalkyl or aromatic ring. In one embodiment the quarternary N-5 atom is —CH3 and the 10 position is N—(CH2)3—Ph.

7 Claims, No Drawings
OTHER PUBLICATIONS
* cited by examiner
1. ANTIFUNGAL AND ANTIPARASITIC INDOQUINOLINE DERIVATIVES

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BACKGROUND OF THE INVENTION


The structures of quinolone and its basic and salt forms are:

![Quinoline (1)](image1)

Cryptopine, 2a (Basic form)

![Cryptopine, 2b (Salt form)](image2)

It has been shown that alkylolation of the N-5 atom in quinolone is necessary for several of the therapeutic activities associated therewith [a] Ablordepepe, S. Y.; Fan, P.; Clark, A. M.; Nimrod, A. Bioorg Med Chem, 1999, 7, 343-349. b] Mardenborough L. G.; Fan, P. C.; Ablordepepe, S. Y.; Nimrod, A.; Clark A M. Med Chem Res, 1999, 9, 118-132. c] Oyeken, A. O.; Ablordepepe, S. Y. Med Chem Res 1996, 6, 602-610]. In particular, it has been reported that co-phenylpentyl and cyclohexylpentyl moieties on the N-5 atom of the quinoline ring produce a high antifungal potency and broadens the spectrum of activities. It is interesting to note that N-5 alkylolation produces an anthyronium base in which the N-5 nitrogen becomes positively charged, i.e., aromatic quaternary nitrogen (2b), under acidic conditions but reverts to S,3 type nitrogen under basic conditions (2a). This physical characteristic of cryptopine is also accompanied by a color change from pink in a basic medium to orange in an acidic environment. This unique behavior may allow for easy entry into cells in the basic form, despite its quaternary nature, and yet produce its pharmacological effect in the salt form.

It is an object of the present invention to provide novel quinolone compounds having one or more of a variety of therapeutic properties.

SUMMARY OF THE INVENTION

The above and other objects are realized by the present invention, one embodiment of which relates to compounds having the formula: 
wherein: \( R \) is an electron withdrawing or electron donating moiety;

\( R_5 \) and \( R_{10} \) may be the same or different and are a straight or branched 1-5 carbon or heteroatom chain substituted terminally by a cycloalkyl or aromatic ring, or other structural isomer or complex thereof;

\( n \) is the position of substitution of \( R \);

\( Z \) is \( N-R_{10}, O, S, S=O, CH_2 \) or \( C=O \);

\( y \) is 1-5 and

\( Q \) is \( Z \) or \( NH \),

with the proviso that, where \( Z \) is \( NH \), \( N-CH_3 \), \( S \) or \( O \) and \( R_n \) is \( H \), \( R_5 \) may not be \( CH_3 \).

Another embodiment of the invention relates to quaternary salts of the above compounds having the formula:

wherein: \( x \) is an anion.

A still further embodiment of the invention concerns pharmaceutical composition comprising a pharmacologically effective amount of a compound having one of the above formulas and a pharmaceutically acceptable carrier therefore.

An additional embodiment of the invention relates to a method of treating a mammal in need of therapy comprising administering thereto a pharmacologically effective amount of a compound having one of the above formulas.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention is predicated on the discovery that the substitution of certain groups at certain locations on the quindoline group produces compounds having a wide variety of pharmacological utilities, e.g., antifungal, antileishmanial, antimycobacterial, antimalarial, antituberculosis or anticancer.

To test the hypothesis that a charged N-5 atom is necessary for producing biological activity in the quinidine moiety, the N-10 atom was alkylated (see Chart I) to prevent an anhydrohrom base formation and to produce a compound with a
permanently charged N-5 atom (3a). Because compound 3a showed antifungal activity, it was previously reported that the active form of the indolquinoline ring system is the salt form in which N-5 is positively charged [Ablordepppey, S. Y.; Fan, P.; Li, S.; Clark, A. M.; Hufford, C. D. Bioorg Med Chem, 2002, 10, 1337-1346]. This view is consistent with the binding mode of cryptoplepine to DNA fragments reported by Aymami et al. [Lisgarten, J. N.; Pous, J.; Coll, M.; Wright, C. W.; Aymami, J. Acta Crystallogr D Biol Crystallogr, 2002, D58, 312-313] on the basis of x-ray crystallographic work.

Chart 1: Compounds synthesized and tested for biological activity

Thus, it was decided to investigate the effect of various combinations of substituents, on the N-5 and N-10 atoms, as well as other portions of the molecule, including bis-quinoindolines, on the pharmacological properties of these compounds.


Herein a previously reported method [Holt, et al, supra] was employed to construct the quindoline unit. A substituted or unsubstituted anthranilic acid was acylated with 2-bromoacetyl chloride and the resulting alkyl halide was used in alkylating aniline. The alkylated aniline in the presence of polyphosphoric acid (PPA) underwent a double cyclization reaction to yield a quindoline which was chlorinated with phosphorous oxychloride (POCl). The resulting chloride was dechlorinated with hydrogen on palladium to obtain the desired quindoline. (Scheme 1).
Reagents: i) BrCH₂COBr₂, NaOH; ii) DMF, PhNH₂; iii) a) PPA, 130°; b) POCl₃; c) H₂/10% Pd — C Scheme 1: The general synthetic method for substituted quinolines.

Specifically alkylating either the N-5 or N-10 atoms was accomplished using methods previously reported [Fan et al, supral]. However, the synthesis of the bis-quinolines, where they were joined on the N-5 atoms was accomplished by heating quinoline with 1,4-diiodobutane (9) or the corresponding 1,5-diiodopentane (10). The formation of bis-quinolines, where the N-10 atoms were joined together required a strongly basic medium and was achieved by the introduction of sodamide and the subsequent alkylation was accomplished in a similar manner (Scheme 2).
acid-albumin-dextrose-catalase enrichment for *M. intracellularare* to afford recommended inoculum sizes. Microbial inocula were added to the samples to achieve a final volume of 200 μl and final sample concentrations starting with 100 μg/ml. Growth, solvent, and medium controls were included on each test plate. The plates were read at either 630 nm or excitation and emission wavelengths of 544 and 590 nm (for Mi) prior to and after incubation. Percent growth was calculated and plotted with the concentration tested to afford the concentration that inhibits 50% of growth (IC50). Antimarial and cytotoxicity procedures were conducted in a similar manner as previously reported [a] Muhammad, I.; Bedir, E.; Khan, S. I.; Tekwani, B. L.; Khan, I. A.; Takamatsu, S.; Pelletier, 1.; Walker, L. A. J Nat Prod. 2004, 67, 772-7. [b] Muhammad, I.; Dunbar, D. C.; Khan, S. I.; Tekwani, B. L.; Bedir, E.; Takamatsu, S.; Ferreira, D., Walker L. A., J Nat Prod. 2003, 66, 96-92.-]

The results were as follows. Re-evaluation of N-10 methylated cryptolepines (3a-3c), confirmed that substitution at the 2-position with bromine, an electron withdrawing group while enhancing anticytotoxic activity, had no effect on antacandida action. On the other hand, the electron-donating methoxy group has little or no effect on both activities when compared to 3a, it had previously been shown that alkylation of the N-5 in quindoline with O-phenylpentyl or cyclohexylpentyl moiety as in 4a and 4b enhances antifungal activity (Table 1). In this form, the positively charged N5 atom is retained. Thus, it became of interest to investigate the contribution of the positively charged N5 atom.

**TABLE 1**

<table>
<thead>
<tr>
<th>Recrystallization</th>
<th>Empirical</th>
<th>K&lt;sup&gt;50&lt;/sup&gt; (μg/ml)&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>% Yield&lt;sup&gt;e&lt;/sup&gt;</td>
<td>MP (°C)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2a MeOH·2H2O</td>
<td>73</td>
<td>265-268</td>
</tr>
<tr>
<td>3a MeOH·2H2O</td>
<td>100</td>
<td>304-306</td>
</tr>
<tr>
<td>3b MeOH·2H2O</td>
<td>57</td>
<td>285-288</td>
</tr>
<tr>
<td>3c MeOH·2H2O</td>
<td>27</td>
<td>262-264</td>
</tr>
<tr>
<td>4a MeOH·2H2O</td>
<td>67</td>
<td>218-219</td>
</tr>
<tr>
<td>4b MeOH·2H2O</td>
<td>34</td>
<td>262-264</td>
</tr>
<tr>
<td>5a Hexane·EthOAc</td>
<td>94</td>
<td>110-112</td>
</tr>
<tr>
<td>5b Hexane·EthOAc</td>
<td>62</td>
<td>160-162</td>
</tr>
<tr>
<td>5c MeOH·2H2O</td>
<td>54</td>
<td>223-224</td>
</tr>
<tr>
<td>5d MeOH·2H2O</td>
<td>64</td>
<td>202-204</td>
</tr>
<tr>
<td>6a MeOH·2H2O</td>
<td>71</td>
<td>235-234</td>
</tr>
<tr>
<td>7a MeOH·2H2O</td>
<td>67</td>
<td>215-217</td>
</tr>
<tr>
<td>7b MeOH·2H2O</td>
<td>30</td>
<td>203-204</td>
</tr>
<tr>
<td>7c MeOH·2H2O</td>
<td>100</td>
<td>217-220</td>
</tr>
<tr>
<td>8a MeOH·2H2O</td>
<td>22</td>
<td>195-198</td>
</tr>
<tr>
<td>8b EtOH·2H2O</td>
<td>65</td>
<td>79-83</td>
</tr>
<tr>
<td>8c MeOH·2H2O</td>
<td>45</td>
<td>86-89</td>
</tr>
<tr>
<td>9 MeOH·HCl·C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>78</td>
<td>252-254</td>
</tr>
<tr>
<td>10 MeOH·2H2O</td>
<td>76</td>
<td>250-258</td>
</tr>
<tr>
<td>11 MeOH·2H2O</td>
<td>87</td>
<td>-</td>
</tr>
<tr>
<td>12 MeOH·2H2O</td>
<td>75</td>
<td>238-240</td>
</tr>
</tbody>
</table>

One way a non-N-5 alkylated quindoline can produce a positively charged N-5 atom is to form the salt. Hence, two N-10 methylated analogs in their salt form (5a & 5b) were synthesized for evaluation. The results showed that these compounds were only weakly active against *C. neoformans* and *C. albicans*. Compound 5c was synthesized to explore the possibility that antifungal potency might be enhanced the same way α-phenylpentyl group enhanced the potency of quindoline. Indeed, a moderate increase in potency (≈10-8a-8c in order to dispel the notion that the antifungal activity of these compounds was intricately associated with any functionality with a quaternary N+ atom and an alkyl function such as the (O)-cyclohexylpentyl moiety. As shown in Table 1, there was little antifungal activity associated with 8a-c suggesting that the A and B rings may be important for the activities observed in the quindolines.

As a result of the fact that phenyl and cyclohexyl moieties placed five carbon atoms away from N*-5 display high anti-
fungal potency, it became necessary to investigate the possibility that bisquinolines five carbons from each other might similarly enhance antifungal potency perhaps by interacting with two adjoining DNA molecules. In this regard, compounds 9 and 10 (n=4 and 5 respectively) in which the pyridine nitrogens are connected, and 11 and 12, where the tetracycles are joined by the indole N-atoms were synthesized, and evaluated for biological activity. The results show that the positively charged quaternary amine is required for activity even in the bis-quinolines. However, there was little difference in the antifungal activities of 10 and 12 when compared together and with the mono-quinolines.

A selected number of the compounds (7a, 9, 10 and 12) was further evaluated in additional assays with cryptolepine as the benchmark, to explore their antimicrobial spectrum. Their cytotoxicities to mammalian cells were also determined. The results are reported in Tables 2 and 3. Evaluation of these results show that compounds 7a, 10 and 12 show more expansive antimicrobial/antiparasitic spectra than cryptolepine. All three compounds also display activity against methicillin-resistant Staphylococcus aureus (MRSA). Similarly, all four compounds displayed significant activity against Mycobacterium intracellulare (Mi). Among the four compounds tested however, only 7a showed significant potency against Aspergillus fumigatus (Af), Candida krusei (Ck) and Plasmodium falciparum (Pf) and only compound 10 displayed activity against Pseudomonas aeruginosa (Pa). Thus, among the bi-quinolines, joining the pyridine nitro groups (compounds 9 and 10) by an alkyl chain appears to be more effective than through the indole nitrogen (compound 11). In addition, the 5 chain compound (10) was more potent than the 4 chain structure (9). Interestingly, cryptolepine was more potent than any of the four selected compounds against the malaria parasite P. falciparum while all four compounds were less cytotoxic to mammalian cells than cryptolepine. It is important to note that these compounds may not be acting through their monomeric units since that would have resulted in similar or higher toxicity and decreased potency per unit weight of compound. The fact that compounds 10 and 12 displayed no cytotoxicity up to 23.8 µg/ml and are potent against a wide spectrum of microorganisms, suggest that these bis-quinolines may have therapeutic advantage over their monomeric counterparts as new anti-infectives.

**TABLE 2**

The effect of N-allylation on the antimicrobial activity of selected quinolines

<table>
<thead>
<tr>
<th>Compound</th>
<th>Af</th>
<th>Ck</th>
<th>MRSA</th>
<th>Mi</th>
<th>Pa</th>
<th>Sa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptolepine</td>
<td>&gt;20</td>
<td>4.5</td>
<td>20</td>
<td>15.0</td>
<td>NA</td>
<td>NT</td>
</tr>
<tr>
<td>7a</td>
<td>2.5</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
<td>NA</td>
<td>NT</td>
</tr>
<tr>
<td>9</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>5.5</td>
<td>NA</td>
<td>NT</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>NT</td>
<td>3.0</td>
<td>7.0</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>15</td>
<td>6.0</td>
<td>15.0</td>
<td>NA</td>
<td>NT</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.31</td>
<td>0.60</td>
<td></td>
<td></td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.15</td>
<td>0.20</td>
<td>0.06</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3**

Antimalarial activity and Cytotoxicity of selected quinolines

<table>
<thead>
<tr>
<th>Compound</th>
<th>Pf (D6)</th>
<th>SI</th>
<th>Pf (W2)</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptolepine</td>
<td>44</td>
<td>54</td>
<td>130</td>
<td>18.5</td>
</tr>
<tr>
<td>7a</td>
<td>62</td>
<td>145</td>
<td>28</td>
<td>321</td>
</tr>
<tr>
<td>9</td>
<td>&gt;528</td>
<td>NA</td>
<td>NA</td>
<td>NC</td>
</tr>
<tr>
<td>10</td>
<td>1300</td>
<td>&gt;18.3</td>
<td>1000</td>
<td>&gt;23.8</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>260</td>
<td>&gt;91.5</td>
<td>140</td>
<td>&gt;170</td>
</tr>
<tr>
<td>Artemisinin</td>
<td>17.0</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>NT</td>
<td>NT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evaluation of the above indoloquinolines confirms the importance of N-5 alkylation. The basicity of this nitrogen and consequently the formation of the positive charge appear to be important. On the other hand, alkylation of the non-basic indole nitrogen appears not to lead to activity. Despite this observation, it appears that simultaneous alkylation of both nitrogen atoms results in improved potency and extension in the antiinfective spectrum. Similarly, bis-quinolines obtained by double alkylation of the pyridine N-5 atoms produce a broad spectrum antimicrobial activity while connection through the indole N10 atoms led to compounds without activity. Subsequent alkylation of the N9 in this type of bio-quinolines however, resulted in similar antifungal properties. The broad spectrum of antimicrobial actions and the lower cytotoxicity displayed by the bis-quinolines indicates this group may be acting through a different mechanism of action from that of their monomeric counterparts.

The active agents identified by the present invention may be employed in the treatment of pathological conditions in the same manner and in approximately the same dosages utilized when employing those quinolines presently known in the art for similar purposes.

There are few efficacious drugs on the market to treat new and emerging opportunistic infections (OIs) such as those associated with HIV/AIDS and other immunocompromised conditions. The present invention identifies certain substituted indoloquinolines, benzothienoquinolines, phenylisalicylyquinolines and their analogs as novel agents against these opportunistic infections.

**Synthesis of [Ph3Bi(OAc)2]**:

To a solution of Ph3Bi (5 g, 11.3 mmol) in 30 ml of dichloromethane/THF (7:3) at 0°C, was added drop wise CH3CO2H (2.9 ml of a 32% solution in CH3COOH, 1.2 eq). The mixture was stirred at room temperature for 1 hr. Et2O (50 ml) was added to form a precipitate which was filtered, washed with Et2O, collected and dried, (mp: 192-194°C). The isolated yield was (5.7 g). 1H NMR (CDCl3): δ 1.82 (S, 6H), 7.45-7.60 (m, 9H), 8.15 (d, J=3.1 Hz, 6H).

**Scheme 3**

**Synthesis of 3-Anilinoquinoline**
To a solution of 2-aminoquinoline (800 mg, mmol) in 30 ml of CH₂Cl₂, Cu powder (272 mg), and triphenylobismuth diacetate (4.64 gm) were added. The reaction was stirred at room temperature overnight and progress was monitored subsequently by TLC. The crude reaction mixture was diluted with CH₂Cl₂ (20 ml), filtered, the filtrate washed with water and brine. The organic phase was dried over anhydrous Na₂SO₄; and solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc and hexane (1:9) as eluent to obtain a pale green solid (800 mg). ¹H NMR (CDCl₃): δ 6.00 (bs, NH), 7.05 (t, 1H, J=7.2 Hz), 7.15 (d, 2H, J=8.10 Hz), 7.35 (t, 2H, J=8.4 Hz), 7.45-7.55 (m, 2H), 7.60 (dd, 1H, J=1.8, 7.5 Hz), 7.70 (d, 1H, J=2.7 Hz), 8.00 (d, 1H, J=7.8 Hz), 8.70 (d, 1H, J=2.7 Hz). Synthesis of 1-Methyl-3-phenylamino-quinolinium iodide

A mixture of 3-anilinoquinoline (100 mg), methyl iodide (0.3 ml) and toluene (3 ml) in a sealed pressure tube was stirred at 110°C for 24 hours. The reaction mixture was cooled to room temperature and diluted with Et₂O (15 ml) to precipitate the product. The product was filtered and washed with ether (3x20 ml) before purification by column chromatography using methanol as an eluent to yield the pure product as an orange solid (80 mg, mp: 182-183°C). ¹H NMR (CD₃OD): δ 4.64 (s, 3H), 7.14 (m, 1H), 7.36 (dd, 2H, J=0.9, 7.5 Hz), 7.44 (m, 2H), 7.82 (t, 2H, J=6.30 Hz), 7.94 (m, 2H), 8.10 (d, 1H, J=8.4 Hz), 8.26 (d, 1H, J=8.6 Hz), 8.46 (d, 1H, J=2.4 Hz), 9.04 (d, 1H, J=2.7 Hz). Anal Calcd for: C₁₃H₁₄N⁺I⁻ 0.13 H₂O: C, 46.98; H, 4.34; N, 6.85 Found: C, 46.81; H, 3.95; N, 6.54

Synthesis of 5-(Bromo-pentyl)-cyclohexene: A mixture of 1,5-dibromopentane (16 gm, 69.97 mmol) in THF (20 ml) and a solution of (Li₂CuCl₄ in ether, 14 ml) under nitrogen at 5-10°C. The reaction mixture was cooled to 0°C, stirred for 24 hours, and then cyclohexyl magnesium bromide (10 gm, 69.97 mmol) was added dropwise over 30 minutes. The reaction was stirred at 0°C for another 1 h, then at room temperature for 12 h. The reaction mixture was cooled to 0°C, saturated with NH₄Cl solution (20 ml), diluted with ethyl acetate (100 ml) and the combined organic layer was separated, washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using hexane as an eluent. The pure product was an oily liquid (12.84 gm). ¹H NMR (CDCl₃): δ 0.8 (t, 2H, J=10.2 Hz), 1.00-1.38 (m, 9H), 1.52-1.68 (m, 6H), 1.70-1.80 (m, 2H), 3.38 (t, 2H, J=7.2 Hz).

Synthesis of 5-(Iodo-pentyl)-cyclohexene: A mixture of 5-(bromo-pentyl)-cyclohexene (2 gm, 8.58 mmol) in acetonitrile (20 ml), and sodium iodide (2.57 g, 17.15 mmol) was heated at 60°C for 12 hrs and then cooled to room temperature. The solvent was evaporated, the residue was taken up in EtOAc (30 ml), washed with water (20 ml) and then brine (30 ml), and then dried to room temperature. The organic layer was separated, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude product was purified by column chromatography using hexane as an eluent to yield an oily liquid (1.36 gm). ¹H NMR (CDCl₃): δ 0.30-1.70 (m, 4H), 1.60 (m, 2H), 2.6 (t, 2H, J=7.2 Hz), 3.10 (t, 2H, J=7.8 Hz), 4.00-4.34 (m, 5H).
Synthesis of 1-(5-Cyclohexyl-pentyl)-3-phenyl-quinolinium iodide:

A solution of Phenyl-quinolin-3-yl-amine (100 mg, 0.45 mmol) toluene (2 ml) and 5-iodo-pentyl-benzene (375 mg, 1.36 mmol) in a sealed pressure tube was stirred at 110° C. for 24 hours. The reaction mixture was cooled to room temperature, diluted with Et₂O (15 ml) and the precipitated compound was filtered and washed with Et₂O (3×20 ml). The crude product was purified on a chromatographic column using methanol as an eluent to yield a pure product as an orange solid (75 mg, mp 140-141° C.). ¹H NMR (CD₂OD): δ 1.42-1.56 (m, 2H), 1.66-1.78 (m, 2H), 2.04-2.18 (m, 2H), 2.58-2.68 (t, 2H, J=7.2 Hz), 4.88-5.04 (t, 2H, J=7.8 Hz), 7.08-7.24 (m, 6H), 7.14 (dd, 2H, J=0.9, 7.5 Hz), 7.40-7.44 (t, 2H, J=8.4 Hz), 7.76-7.84 (t, 1H, J=7.5 Hz), 7.86-7.94 (m, 1H), 8.08 (d, 1H, J=8.4 Hz), 8.30 (d, 1H, J=9.0 Hz), 8.46 (d, 1H, J=2.4 Hz), 9.04 (d, 1H, J=2.7 Hz). Anal. Calcd for: C₂₃H₁₇IN₂·H₂O: C, 60.92; H, 5.70; N, 5.47. Found: C, 60.79; H, 5.33; N, 6.38.

Reactions Conditions:
(i) Aqueous KOH, 10 days.
(ii) Parfin Oil, 300° C., 4 hr.
(iii) 1,5-Diiodopentane, Tetramethylethylene, 110° C., 36 hr.
(iv) THF, NaH, 1,5-Dibromopentane, Reflux, 24 hr.
(v) Methyl iodide, Tetramethylethylene, 110° C., 36 hr.
Synthesis of 2-Bromo-1,5-bis (10-indolo-[3,2-b] quinolin-5-ium pentane) diiodide: A mixture of 2-bromo-10H-indole [3,2-b] quinoline (4) (300 mg, 0.67 mmol), 1,5-diodopentane (160 mg, 0.40 mmol), and tetramethylene sulfone (3 mL) was sealed in a pressure tube and the solution was heated at 110°C for 24 hrs. The mixture was allowed to cool to room temperature and diluted with Et₂O (15 mL) to precipitate a yellow solid, which was collected by filtration. The solid was recrystallized from methanol-dichloromethane to give compound 5 (150 mg, mp 273-274°C). ¹H NMR (DMSO-d₆): δ 1.80 (m, 2H), 2.20 (m, 4H), 5.40 (m, 4H), 7.50 (t, 2H, J=8.1 Hz), 7.80 (d, 2H, J=8.1 Hz), 8.00 (t, 2H, J=7.5 Hz), 8.20 (dd, 2H, J=2.1, 7.5 Hz), 8.50 (d, 2H, J=8.7 Hz), 8.70 (d, 2H, J=9.6 Hz), 8.90 (d, 2H, J=2.1 Hz), 9.20 (s, 2H). Anal. Calc'd for: C₃₀H₂₅Br₃N₆S₂O₆C₃0₂H₂₅Br₃N₆S₂O₆. Found: C, 38.92; H, 2.71; N, 4.96.

Synthesis of 2-Bromo-1,5-bis (10-indolo-[3,2-b] quinolin-10-yl)pentane (6):

To a mixture of 2-bromo-10H-indole [3,2-b] quinoline (4) (850 mg, 2.86 mmol) and NaH (242 mg, 6.06 mmol) dissolved in DME (15 mL) was added 1,5-diodopentane (463 mg, 1.43 mmol) with stirring. After addition was completed, the reaction mixture was refluxed for 12 h at 60°C, allowed to cool to room temperature and DME was removed under reduced pressure. The residue is taken up in Et₂OAc (20 mL), washed with water (20 mL) then with brine (20 mL) and dried over anhydrous sodium sulfate. The organic solvent was removed, and the crude product was purified by column chromatography to give a solid yellow compound 6 (260 mg). ¹H NMR (DMSO-d₆): δ 1.40 (m, 2H), 1.80-2.00 (m, 4H), 4.20-4.36 (m, 4H), 7.20-7.38 (m, 4H), 7.50-7.60 (m, 2H), 7.64 (s, 2H), 7.68 (d, 1H, J=2.4 Hz), 7.72 (d, 1H, J=1.8 Hz), 8.00 (d, 2H, J=2.1 Hz), 8.18-8.20 (d, 2H, J=9.0 Hz), 8.48-8.54 (d, 2H, J=7.8 Hz).

Scheme 2

1  COOH
    NH₂ + Br + COBr

(i)

1  COOH
    NH₂ + Br + COBr

(ii)

1  COOH
    NH₂ + Br + COBr

(iii)

1  COOH
    NH₂ + Br + COBr

(iv)

1  COOH
    NH₂ + Br + COBr

(v)
Compound 2a: A mixture of crude product 1 (10 gm, 38.75 mmol), 2-chlorobenzene-thiol (5.6 gm, 38.75 mmol), acetone (100 ml), K₂CO₃ (2.0 gm) and KI (200 mg) was refluxed for one day, cooled to room temperature and acetone was removed on a rotary vapor. The colorless precipitate was dissolved in water (200 ml) and 10% aqueous hydrochloric acid (100 ml) was added and solids were separated by filtration. The solid was washed with water (2×100 ml) and dried to give compound 2a as a colorless solid (8 gm). Compounds 2b and 2c were similarly prepared. ¹H NMR: (CD₃OD): δ 3.90 (s, 2H), 7.00-7.08 (m, 1H), 7.12-7.18 (m, 1H), 7.20-7.23 (m, 1H), 7.30-7.52 (m, 1H), 7.33-7.40 (m, 1H), 7.46-7.52 (dd, 1H, J=1.5, 6.3 Hz), 8.00-8.04 (dd, 1H, J=1.5, 6.3 Hz), 8.38-8.44 (d, 1H, J=8.1 Hz). (2b) ¹H NMR: (CD₃OD): δ 3.80 (s, 2H), 7.00-7.08 (m, 1H), 7.14-7.18 (m, 1H), 7.22-7.28 (t, 1H, J=7.8 Hz), 7.30-7.38 (m, 2H), 7.44 (t, 1H, J=2.1 Hz), 7.88-8.04 (dd, 1H, J=1.5, 6.0 Hz), 8.40-8.44 (dd, 1H, J=0.9, 7.5 Hz). (2c) ¹H NMR: (CD₃OD): δ 3.90 (s, 2H), 7.10-7.16 (m, 1H), 7.24-7.30 (m, 2H), 7.38-7.44 (m, 2H), 7.48 (m, 1H), 8.02-8.04 (dd, 1H, J=1.5, 6.6 Hz), 8.50-8.56 (dd, 1H, J=0.9, 7.8 Hz).

Compound 3a: A mixture of crude 2-[2-(2-Chloro-phenyl)-sulfanylacetylaminol-benzoic acid (8.0 gm), and PPA (120 gm) was stirred at 130°C for 6 h. and then was poured onto ice/water (150 ml) and neutralized with aqueous sodium hydroxide solution until the pH=7. The solids were filtered, washed with water (2×100 ml), and dried. The crude product was used without further purification. Compounds 3b, 3c were similarly prepared.

(3b) ¹H NMR: (DMSO-d₆): δ 7.32-7.34 (m, 1H), 7.60-7.64 (dd, 1H, J=2.1, 6.9 Hz), 7.70-7.80 (m, 2H), 8.18-8.24 (d, 1H, J=8.1 Hz), 8.26-8.28 (d, 1H, J=2.1 Hz), 8.48-8.54 (d, 1H, J=8.4 Hz), 12.80 (s, 1H).

Compound 4a:

A mixture of crude 3a (4 gm) and POCl₃ (30 ml) was stirred under reflux at 120°C for 6 h. The reaction mixture was allowed to cool then was poured onto ice/water (200 ml). The resulting mixture was neutralized with aqueous sodium hydroxide solution until the pH=7, the solid was filtered, washed with water (2×100 ml) and dried. The crude product was purified by column chromatography using ethyl acetate: hexanes (1:9) as eluent to yield a colorless solid (500 mg). Compounds 4b, 4c were similarly prepared.

¹H NMR: (CDCl₃): δ 7.52-7.58 (m, 1H), 7.62-7.68 (dd, 1H, J=0.9, 6.9 Hz), 7.70-7.76 (m, 1H), 7.82-7.88 (m, 1H), 8.30-8.38 (d, 2H, J=8.4 Hz), 8.54-8.60 (d, 1H, J=7.8 Hz). (4b) ¹H NMR: (CDCl₃): δ 7.52-7.58 (dd, 1H, J=1.8, 6.6 Hz), 7.68-7.74 (m, 1H), 7.80-7.88 (m, 2H), 8.26-8.36 (m, 2H), 8.50-8.56 (d, 1H, J=8.4 Hz). (4c) ¹H NMR: (CDCl₃): δ 7.58-7.62 (dd, 1H, J=2.1, 6.3 Hz), 7.68-7.74 (m, 1H), 7.76-7.88 (m, 2H), 8.26-8.38 (t, 2H, J=7.8 Hz), 8.60 (d, 1H, J=1.5 Hz).

Compound 5a:

A mixture of compound 4a (500 mg), in ethyl acetate (150 ml) and Pd/C (10%) (500 mg), was hydrogenated for 6 h. The reaction mixture was filtered through celite, washed with ethyl acetate (2×50 ml) and solvent was removed under reduced pressure. The pure product was obtained by column chromatography using ethyl acetate and hexane to yield the desired compound 5a as a colorless solid (160 mg). Compounds 5b, 5c were similarly prepared.

¹H NMR: (CDCl₃): δ 7.50-7.56 (t, 1H, J=7.5 Hz), 7.58-7.64 (m, 2H), 7.76-7.82 (m, 1H), 7.90-7.96 (d, 1H, J=8.4 Hz), 8.56-8.62 (d, 1H, J=7.8 Hz), 8.64 (s, 1H). (5b) ¹H NMR: (CDCl₃): δ 7.52-7.56 (dd, 1H, J=1.8, 6.6 Hz), 7.58-7.64 (m, 1H), 7.74-7.82 (m, 1H), 7.90-7.94 (d, 1H, J=8.1 Hz), 8.26-8.30 (d, 1H, J=8.7 Hz), 8.56-8.58 (d, 1H, J=8.7 Hz), 8.60 (s, 1H). (5c) ¹H NMR: (CDCl₃): δ 8.75-8.70 (m, 2H), 7.76-7.86 (m, 2H), 7.92-7.98 (d, 1H, J=8.4 Hz), 8.44-8.50 (d, 1H, J=8.7 Hz), 8.68 (s, 1H), 8.86 (s, 1H).

Compound 6a:

A solution of 5a (150 mg) in tetramethylene sulfone (3 ml) and methyl iodide (0.3 ml) in a sealed tube was stirred at 110°C for 36 hours. The reaction mixture was cooled to room temperature, diluted with diethyl ether (15 ml) to form a precipitate which was filtered and washed with ether (3×20 ml). The crude product purified by recrystallization using
dichloromethane and methanol to yield the pure product as an orange solid (65 mg, mp 192-193°C). Compound 6b (140 mg, mp: 218-219°C) and 6c (130 mg, mp: 203-204°C) were similarly prepared. 1H NMR (CD3OD): δ 5.20 (s, 3H), 7.88-7.94 (t, 1H, J=7.8 Hz), 8.04-8.14 (m, 2H), 8.34-8.42 (m, 1H), 8.50-8.54 (d, 1H, J=8.1 Hz), 8.78-8.80 (d, 1H, J=9.3 Hz), 9.02-9.04 (d, 1H, J=8.4 Hz), 9.88 (s, 1H). Anal Calcd for: C16H12ClN0.3CH3OH: C, 45.24; H, 2.88; N, 3.23. Found: C, 44.90; H, 2.56; N, 3.22. (6b) 1H NMR (CD3OD): δ 5.20 (s, 3H), 7.86-7.94 (dd, 1H, J=1.8, 7.2 Hz), 8.04-8.10 (t, 1H, J=7.5 Hz), 8.30-8.40 (m, 1H), 8.44 (d, 1H, J=2.1 Hz), 8.48-8.52 (d, 1H, J=8.7 Hz), 8.72-8.80 (d, 1H, J=9.0 Hz), 9.00-9.06 (d, 1H, J=9.6 Hz), 9.80 (s, 1H). (6c) 1H NMR (CD3OD): δ 5.20 (s, 3H), 7.98-8.04 (dd, 1H, J=2.1, 6.6 Hz), 8.06-8.12 (t, 1H, J=7.8 Hz), 8.32-8.40 (m, 2H), 8.48-8.54 (d, 1H, J=8.4 Hz), 8.76-8.82 (d, 1H, J=9.0 Hz), 9.04 (d, 1H, J=1.5 Hz), 9.84 (s, 1H).

The invention claimed is:
1. A compound having the formula:

![Chemical structure](image)

wherein:
R6 is —CH3, and
Z is N—(CH2)3—Ph.

2. The compound of claim 1, wherein said compound is a quaternary salt.

3. A pharmaceutical composition comprising a pharmacologically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

4. The pharmaceutical composition of claim 3 comprising a pharmacologically antinociceptive, antimalarial, or anti-inflammatory effective amount of a compound and a pharmaceutically acceptable carrier.

5. A method of treating a mammal in need of antinociceptive, antimalarial, or anti-inflammatory therapy comprising administering thereto a pharmacologically effective amount of a compound of claim 1.

6. An article of manufacture comprising packaging material and a pharmaceutical agent contained within said packaging material, wherein said pharmaceutical agent is effective for the treatment of a subject suffering from one or more conditions of a fungal infection, a mycobacterial infection, or malaria, and wherein said packaging material comprises a label which indicates that said pharmaceutical agent can be used for ameliorating the symptoms associated with said condition and wherein said pharmaceutical agent is a compound of claim 1.

7. The compound of claim 2 wherein said quaternary salt has the formula:

![Chemical structure](image)

wherein: X is an anion, wherein X is l or tosylate.

* * * * *
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In Column 1, Lines 4-8 should read:
This invention was made with government support under grants AI379760 and RR003020 which was awarded by the National Institutes of Health. The government has certain rights in the invention.