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Synthesis and evaluation of naphthyridine compounds as antimalarial agents

Shuren Zhu,[a,*] Quan Zhang,[a] Chandrashekar Gudise,[b] Li Meng,[a] Lai Wei,[a] Erika Smith[a] and Yuliang Kong[c]

[a]*Radix Pharmaceuticals Inc., 880 College Pkwy, Rockville, MD 20850, USA*
[b]*Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India*
[c]*Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China*

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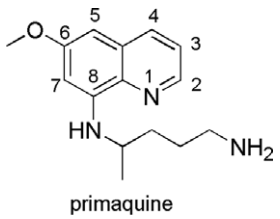
Abstract—Primaquine is the drug of choice for the radical cure of *Plasmodium vivax* malaria, but possesses serious side effects. In this study novel primaquine analogues were designed and synthesized. Lower toxicity was achieved by reducing or eliminating the tendency of forming chemically reactive and toxic intermediates and metabolites. In vitro and in vivo studies found that synthesized compounds were less toxic than the parent compound primaquine, while preserving the desired antimalarial activity. Some of these compounds possess a therapeutic index over 10 times superior to that of the commonly used antimalarial drug chloroquine. These compounds, as well as the underlying design rationale, may find usefulness in the discovery and development of new antimalarial drugs.

Malaria is the best known protozoal disease, caused by one of four species of the sporazoa type—*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. The malaria parasite has now become resistant to the best antimalarial drugs, and can now be found in at least 100 tropical and subtropical countries. Worldwide, malaria infects 300–600 million people and kills about three million in a year.[1]

Primaquine (Fig. 1) is the drug of choice for the radical cure of *P. vivax* malaria for over 40 years.[2] Primaquine mode of action could be based in the capacity of primaquine to bind to the parasite's DNA and modify its properties.[3] Primaquine, however, like all its predecessors, is by no means non-oxic. Among the serious side effects it could produce are acute hemolysis in patients with certain types of glucose 6-phosphate dehydrogenase deficiency, methemoglobinemia, and severe gastrointestinal disturbances.[4]

Over the years, several attempts have been made to improve the therapeutic index of primaquine through modification of its chemical structure. Introduction of 4-methyl and 5-phenoxy[5,6] or alkoxy groups[7] have produced analogues with much superior tissue and blood schizonticidal activity. However, toxicity studies have shown that these analogues also have a greater potential of producing methemoglobin.[8] Tafenoquine (also known as WR 238605) is a primaquine analogue and is underdevelopment for the treatment of relapsing malaria.[9] However, tafenoquine would also cause hemolysis in persons with G6PD deficiency, and must not be used during pregnancy because of its potential effect on the fetus.[10] Therefore, further research in the discovery and development of novel molecule entities as safe, effective, and low cost replacement for primaquine is urgently needed.



primaquine

Figure 1.

Keywords: Primaquine; Antimalarial.
* Corresponding author. Tel.: +1 301 675 3714; fax: +1 301 424 1927; e-mail: shuren.zhu@gmail.com

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Early mechanistic studies of primaquine have established that primaquine hemotoxicity was due to metabolites of the drug, rather than the parent compound. Phenolic metabolites of primaquine have been identified in the biological fluids of experimental animals and have long been suggested as candidate hemotoxic species.[11–13] These compounds were shown to induce a variety of oxidative effects in both normal and G6PD-deficient red cells, including stimulation of hexose monophosphate shunt activity, hemoglobin oxidation, and glutathione depletion.[14–16] Both 5-hydroxyprimaquine and 5-hydroxy-6-desmethylprimaquine are direct-acting hemolytic agents. These mechanistic studies have suggested that 5-hydroxyprimaquine forms a redox pair with its *p*-quinoneimine analogue and that the 5,6-diphenolic metabolite forms a redox pair with either an *o*-quinone or a *p*-quinoneimine. It has also been suggested that the hemotoxicity of primaquine is associated with arylhydroxylamine metabolites.[17] Primaquine is known to undergo N-dealkylation (oxidative deamination) in humans to yield 6-methoxy-8-aminoquinoline (MAQ). It has been concluded that MAQ could be converted to the corresponding 8-hydroxylamino metabolite (i.e., MAQ–NOH) and that this metabolite could be capable of inducing methemoglobinemia and hemolytic damage by forming a redox pair with its nitroso analogue.[17]

As continued efforts in antimalarial drug discovery at our laboratory, novel primaquine analogues were designed and synthesized. These compounds (**1**–**12**) are shown in Figure 2. Lower toxicity will be achieved by reducing the tendency to form chemically reactive and toxic intermediates and metabolites. To achieve this goal, the following strategies are employed: (I) Replacing the quinoline moiety with a [1,5]naphthyridine core to prevent hydroxylation at C-5 position.[18,19] Toxic phenolic metabolites arise when C-5 position of the quinoline ring becomes oxidized and this process can be made unfavorable by blocking the C-5 position of the quinoline ring. Naphthyridine closely resembles quinoline, yet possesses higher oxidation potential due to the introduction of the second nitrogen on the aromatic system. Although a naphthyridine analogue of primaquine has previously been synthesized,[18,19] there was no systemic evaluation of naphthyridine analogues of primaquine to date. (II) Introducing a second substitution at the α position of the aliphatic side chain so that oxidative deamination will be disfavored. These compounds (**1**–**12**) now bear a dimethyl group at the α position, or the α position is part of a new cyclopropane unit. (III) Compounds **7**–**12** also bear a substitution at position 2 of the aromatic ring. It has been reported that introducing an alkyl or alkoxy group at position 2 of the aromatic ring reduces the toxicity of a compound (induction of methemoglobin).[20,21]

Scheme 1 describes the synthesis of compound **1**. Compounds **2**–**6** were synthesized in similar routes. The synthesis began with 6-methoxy-pyridin-3-ylamine (**13**). Condensation of **13** with propane-1,2,3-triol under strong acidic condition[22] furnished 2-methoxy-[1,5]-naphthyridine (**14**), which underwent oxidation with 3-chloroperbenzoic acid to give 2-methoxy-[1,5]-naphthyridine 1-oxide (**15**). Compound **15** then reacted with phosphorus(III) oxychloride,[23] to furnish 4-chloro-2-methoxy-[1,5]naphthyridine (**16**). After deprotonation with sodium hydride, 2-(4-amino-4-methyl-pentyl)-isoindole-1,3-dione (**17**) reacted with compound **16** in a S_N2 type mode, which is followed by removal of the protective group on the terminal amine, to furnish N^4-(2-methoxy-[1,5]naphthyridin-4-yl)-4-methyl-pentane-1,4-diamine (**1**).[24,25]

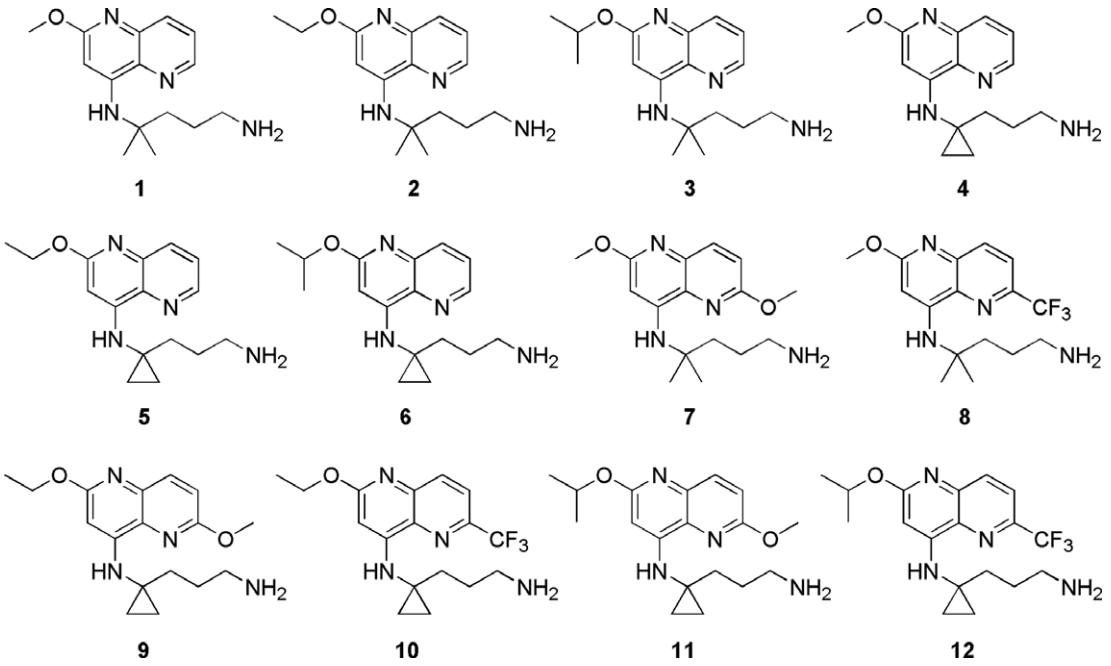
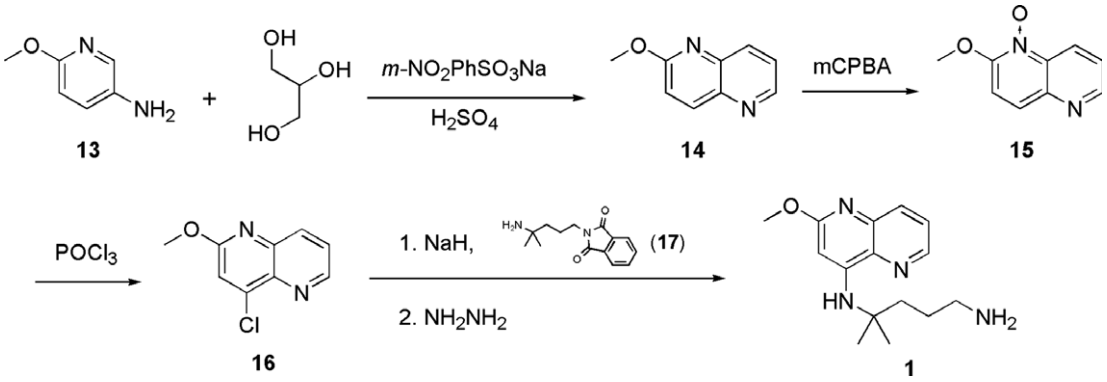


Figure 2.



Scheme 1.

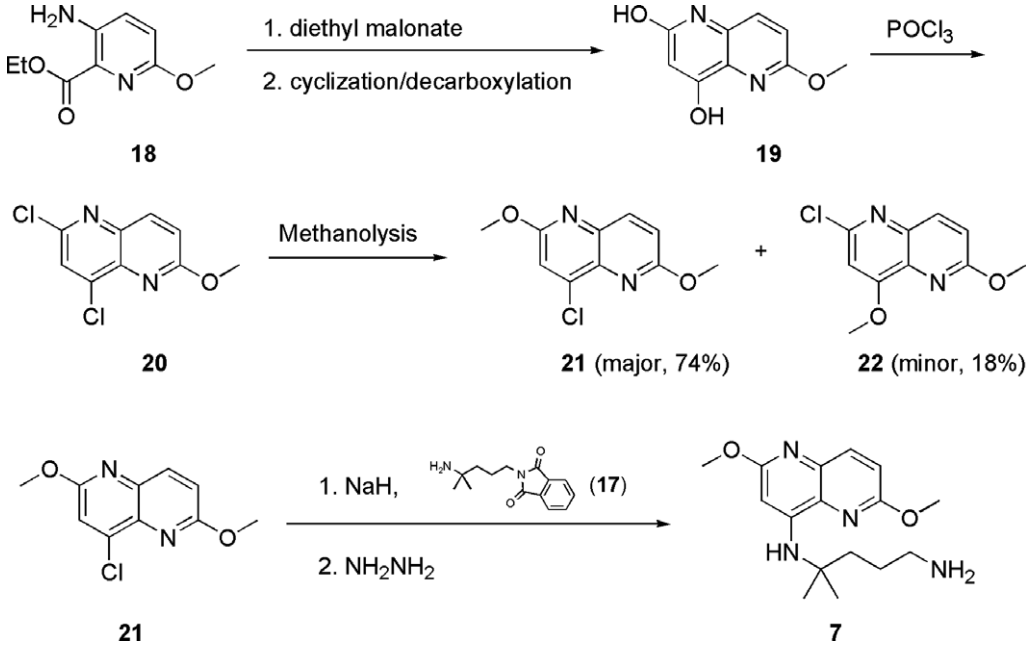
The synthesis of compounds **7**–**12** follows a different route. Scheme 2 describes the synthesis of compound **7**. Compounds **8**–**12** were synthesized in similar procedures. Condensation of 3-amino-pyridine-2-carboxylic acid ethyl ester (**18**) with diethyl malonate followed by cyclization and decarboxylation afforded [1,5]-naphthyridine-2,4-diol (**19**), which then reacted with phosphorus oxychloride to furnish 2,4-dichloro-[1,5]-naphthyridine (**20**). Acid methanolysis of **20** gave 4-chloro-2-methoxy-[1,5]-naphthyridine (**21**) as the major isomer and 2-chloro-4-methoxy-[1,5]naphthyridine (**22**) as the minor one. The synthesis of **21** is a modified method of McCaustland and Cheng[19] Compound **7** was then synthesized from intermediate **21**, using the method described above.[26]

In vitro antimalarial activities of compounds **1**–**12** as IC_{50} values for the inhibition of chloroquine-resistant *P. falciparum* strain W2 were determined (Table 1), using previously reported protocols.[27,28] Most compounds in this class exhibited potent antimalarial activity (IC_{50} <= 0.11 μM), superior to that of chloroquine (IC_{50} = 0.31 μM).

The target compounds were also evaluated for the blood-schizontocidal antimalarial activity against *P. berghei* (sensitive strain) and *P. yoelii nigeriensis* (multidrug-resistant strain) in a rodent model (Table 1), using previously reported protocols.[29]

The objective of this investigation was to prepare less toxic analogue of primaquine. As mentioned earlier, primaquine and related metabolites are capable of inducing methemoglobinemia and hemolytic damage. Therefore, in vivo MetHb-inducing properties estimation of compounds **1**–**12** was carried out in *Mastomys coucha* (Table 2), a rodent animal model using previously reported protocols.[30] Primaquine was used as the standard drug for the test.

Replacing the quinoline moiety in primaquine with 1,5-naphthyridine clearly offers advantages. Primaquine



Scheme 2.

Table 1. In vitro (*P. falciparum*) and in vivo (*P. berghei* and *P. yoelii nigeriensis*) antimalarial studies[a]

Compound	IC_{50} for *P. falciparum* W2 (μM)	LD_{50}[b] (mg/kg)	ED_{50}[c] (mg/kg)	ED_{50}[d] (mg/kg)	TI[e]
1	0.065	130	1.8	2.1	72
2	0.077	155	0.95	0.89	163
3	0.11	167	0.33	0.28	506
4	0.057	145	1.6	1.4	91
5	0.072	161	0.88	1.0	183
6	0.10	175	0.29	0.38	603
7	0.033	>200	1.6	2.0	>125
8	0.021	>200	1.5	1.7	>133
9	0.045	>200	0.72	0.65	>278
10	0.058	>200	0.75	0.68	>267
11	0.047	>200	0.31	0.41	>645
12	0.055	>200	0.26	0.23	>769
PQ	>10	55	ND	ND	ND
CQ	0.31	70	2.0	ND	35

[a] Antimalarial activities were determined after ip administration of the compounds once daily for 4 days to infected mice. The first drug administration began 1 h after ip inoculation with malarial strain. PQ, primaquine. CQ, chloroquine. ND, not determined.
[b] Acute toxicity was determined after one single drug injection into four non-infected random-bred Swiss mice and expressed as the 50% lethal dose (LD_{50}), which corresponds to the dose leading to deaths of 50% of the subjects 10 days after the drug injection.
[c] The 50% efficient dose (ED_{50}), which is the dose leading to 50% parasite (*P. berghei*) growth inhibition compared to the control (treated with an equal volume of vehicle), was evaluated from a plot of activity (expressed as a percentage of the control) versus the log dose.
[d] The parasite is *P. yoelii nigeriensis*.
[e] TI (therapeutic index) was calculated on the basis of the acute LD_{50}/ED_{50} (*P. berghei*) ratios.

Table 2. In vivo methemoglobin (MetHb) toxicity estimation in *Mastomys coucha*[a]

Compound	% of MetHb
1	0.10
2	−0.12
3	−0.15
4	0.10
5	−0.12
6	−0.10
7	0.13
8	−0.11
9	−0.10
10	0.095
11	−0.12
12	0.14
PQ	3.4
Vehicle	−0.14

[a] Compound was administered at a dose of 15 mg/kg per day for 3 days. Data are means ± SEM for each group of animals (set of three experiments). PQ, primaquine.

itself is not active against *P. falciparum* strains in vitro. However, all new compounds (**1**–**12**) exhibited potent in vitro antimalarial activity against chloroquine-resistant *P. falciparum* strain W2. It is not clear why this series of compounds are effective against *P. falciparum* while primaquine, the compound on which the work is based, is ineffective. It is believed that changing the structure of the aromatic core of primaquine will change the mode of action, hence rendering the compound active in vitro against *P. falciparum*. Previous studies have also found that analogues with an alkyl substitution at position 2 of the aromatic ring possess in vitro antimalarial activity against *P. falciparum*.[21]

Compounds **1**–**12** have also shown excellent in vivo blood-schizontocidal antimalarial activity against both *P. berghei* (sensitive strain) and *P. yoelii nigeriensis* (multidrug-resistant strain). They were over three times less toxic than the parent compound primaquine, as measured by the in vivo LD_{50}. These compounds did not show any increase in MetHb, whereas primaquine induced 3.4% increase in MetHb. Replacing the α,α-dimethyl group in compounds **1**–**3** with a bioisosteric cyclopropyl group gives compounds **4**–**6**. This modification did not significantly alter the efficacy and toxicity of a compound. However, introducing a substitution at position 2 of the naphthyridine ring further reduces the toxicity, while preserving the desired antimalarial activity.

Variation of the side chain substitution at the position 6 of the naphthyridine ring did not have profound effect on their toxicity. However, an increase in the lipophilicity of a compound has consequently improved the efficacy. For example, when the methyl group in compound **1** is replaced by the more lipophilic isopropyl group as in compound **3**, efficacy is increased by sixfold, while toxicity is more or less flat.

In conclusion, new primaquine analogues were designed and synthesized. Some of these compounds (**3**, **6**, **11**, **12**) possess a therapeutic index over ten times superior to that of the commonly used antimalarial drug chloroquine. These compounds, as well as the underlying design rationale, may find usefulness in the discovery and development of new antimalarial drugs.

Acknowledgments

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24. Synthesis procedure: *2-Methoxy-[1,5]naphthyridine* (***14***). 12.4 g of 6-methoxy-pyridin-3-ylamine (**13**) and 18.4 g of propane-1,2,3-triol were dissolved in 180 mL of methanol. Sodium 3-nitrobenzenesulfonate (4.5 g) and sulfuric acid (98%, 0.98 g) were added in. The resulting solution was heated at 140 °C in a sealed tube for 12 h. It was allowed to cool down, and methanol was evaporated in a rotary evaporator under reduced pressure to give a slurry, which was re-dissolved in 100 mL of 6 N aqueous NaOH. The resulting solution was continuously extracted with chloroform. Concentration of the chloroform extracts furnished **14** as essentially pure compound. *2-Methoxy-[1,5]naphthyridine 1-oxide* (***15***). Compound **14** (6.4 g) and 3-chloroperbenzoic acid (10.4 g) were dissolved in 150 mL of chloroform. The resulting solution was heated at reflux for 3 h. It was cooled, washed with 6 N aqueous NaOH (50 mL), and dried over anhydrous sodium sulfate. Silica gel flash chromatography (10% methanol/chloroform, with 0.5% ammonia) furnished **15**. *4-Chloro-2-methoxy-[1,5]naphthyridine* (***16***). Compound **15** (600 mg) was dissolved in 5 mL of phosphorus(III) oxychloride. The resulting solution was heated at reflux for 2 h. It was cooled, slowly poured into 6 N aqueous NaOH (200 mL) with ice-water cooling, and extracted with ethyl acetate (4× 60 mL). The combined organic extracts were concentrated and purified by silica gel flash chromatography (5% methanol/chloroform, with 0.5% ammonia) to give **16**. *N^4-(2-Methoxy-[1,5]naphthyridin-4-yl)-4-methyl-pentane-1,4-diamine* (***1***). One hundred and sixty-five milligrams of sodium hydride was suspended in 10 mL of anhydrous *N*,*N*-dimethyl-formamide. It was cooled in an ice-water bath. Six hunderd and sixty-five milligrams of 2-(4-amino-4-methyl-pentyl)-isoindole-1,3-dione (**17**) was added in. This solution was maintained at 0 °C for 30 min. 1.2 g of 4-chloro-2-methoxy-[1,5]naphthyridine (**16**) was then added in. The resulting solution was heated at 80 °C for 2 h. At this time, condensation between **16** and **17** was completed. The reaction mixture was quenched with the addition of saturated aqueous sodium bicarbonate (15 mL), and extracted with chloroform (3× 25 mL). The combined chloroform extracts were concentrated, the resulting oil was re-dissolved in 5 mL of methanol, and 1 mL of hydrazine is added in 2 h later, the reaction mixture was partitioned between water (25 mL) and chloroform (25 mL), aqueous layer was then further extracted with chloroform (4× 20 mL). The combined organic extracts were concentrated and purified by silica gel flash chromatography (20% methanol/chloroform, with 0.5% ammonia) to furnish **1**.
25. Newly synthesized compounds possess satisfactory spectroscopic and analytical data. Compound **1** (hydrochloride salt): mp 277–278 °C. ^{1}H NMR (D_2O): 9.05 (d, J = 7.2 Hz, 1H), 8.48 (d, J = 7.2 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 6.67 (s, 1H), 4.11 (s, 3H), 2.85 (m, 2H), 1.84 (m, 2H), 1.64 (t, J = 5.8 Hz, 2H), 1.19 (s, 6H). ^{13}C NMR: 168.4, 160.2, 150.3, 148.9, 137.2, 127.6, 110.3, 105.7, 58.8, 52.1, 45.5, 43.6, 28.9, 27.1. Anal. Calcd for $C_{15}H_{22}N_4O$·HCl: C, 57.96; H, 7.46; Cl, 11.41; N, 18.03. Found: C, 57.88; H, 7.51; Cl, 11.37; N, 18.11. Compound **2** (hydrochloride salt): mp 285–286 °C. ^{1}H NMR (D_2O): 9.08 (d, J = 7.1 Hz, 1H), 8.51 (d, J = 7.1 Hz, 1H), 7.59 (t, J = 7.1 Hz, 1H), 6.72 (s, 1H), 4.33 (q, J = 7.5 Hz, 2H), 2.86 (m, 2H), 1.82 (m, 2H), 1.66 (t, J = 7.5 Hz, 3H), 1.62 (t, J = 5.9 Hz, 2H), 1.20 (s, 6H). ^{13}C NMR: 166.1, 161.8, 151.4, 147.4, 138.1, 127.9, 111.2, 107.5, 68.1, 53.2, 44.7, 43.1, 28.8, 26.2, 18.9. Anal. Calcd for $C_{16}H_{24}N_4O$·HCl: C, 59.16; H, 7.76; Cl, 10.91; N, 17.25. Found: C, 59.22; H, 7.71; Cl, 10.97; N, 17.31. Compound **3** (hydrochloride salt): mp 291–292 °C. ^{1}H NMR (D_2O): 9.11 (d, J = 7.3 Hz, 1H), 8.44 (d, J = 7.3 Hz, 1H), 7.67 (t, J = 7.3 Hz, 1H), 6.63 (s, 1H), 4.48 (m, 1H), 2.83 (m, 2H), 1.85 (m, 2H), 1.75 (d, J = 7.7 Hz, 6H), 1.65 (t, J = 5.8 Hz, 2H), 1.11 (s, 6H). ^{13}C NMR: 169.1, 160.7, 149.8, 147.7, 138.0, 128.5, 109.4, 106.3, 73.5, 53.4, 44.9, 43.2, 29.0, 27.4, 23.9. Anal. Calcd for $C_{17}H_{26}N_4O$·HCl: C, 60.25; H, 8.03; Cl, 10.46; N, 16.53. Found: C, 60.33; H, 7.99; Cl, 10.50; N, 16.48. Compound **4** (hydrochloride salt): mp 269–270 °C. ^{1}H NMR (D_2O): 9.01 (d, J = 7.0 Hz, 1H), 8.43 (d, J = 7.0 Hz, 1H), 7.71 (t, J = 7.0 Hz, 1H), 6.72 (s, 1H), 4.09 (s, 3H), 2.83 (m, 2H), 1.86 (m, 2H), 1.61 (t, J = 5.9 Hz, 2H), 0.41 (d, J = 5.1 Hz, 2H), 0.33 (d, J = 5.1 Hz, 2H). ^{13}C NMR: 169.9, 162.1, 151.8, 148.1, 138.7, 127.1, 111.6, 104.9, 59.2, 46.8, 43.1, 39.8, 27.9, 12.1. Anal. Calcd for $C_{15}H_{20}N_4O$·HCl: C, 58.34; H, 6.85; Cl, 11.48; N, 18.14. Found: C, 58.41; H, 6.82; Cl, 11.43; N, 18.21. Compound **5** (hydrochloride salt): mp 274–275 °C. ^{1}H NMR (D_2O): 9.06 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 7.2 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 6.78 (s, 1H), 4.35 (q, J = 7.4 Hz, 2H), 2.81 (m, 2H), 1.82 (m,

2H), 1.68 (t, J = 7.4 Hz, 3H), 1.62 (t, J = 5.9 Hz,2H), 0.40 (d, J = 5.2 Hz, 2H), 0.34 (d, J = 5.2 Hz, 2H). ^{13}C NMR: 168.3, 161.7, 152.4, 147.3, 139.1, 128.4, 113.1, 106.1, 69.2, 47.3, 42.7, 38.5, 28.1, 19.5, 12.4. Anal. Calcd for $C_{16}H_{22}N_4O$·HCl: C, 59.53; H, 7.18; Cl, 10.98; N, 17.35. Found: C, 59.60; H, 7.14; Cl, 10.89; N, 17.41. Compound **6** (hydrochloride salt): mp 279–280 °C. ^{1}H NMR (D_2O): 9.11 (d, J = 7.3 Hz, 1H), 8.40 (d, J = 7.3 Hz, 1H), 7.67 (t, J = 7.3 Hz, 1H), 6.62 (s, 1H), 4.43 (m, 1H), 2.91 (m, 2H), 1.89 (m, 2H), 1.71 (d, J = 7.5 Hz, 6H), 1.67 (t, J = 5.7 Hz, 2H), 0.38 (d, J = 5.2 Hz, 2H), 0.31 (d, J = 5.2 Hz, 2H). ^{13}C NMR: 168.3, 162.6, 150.9, 148.7, 137.8, 127.5, 111.9, 105.6, 72.6, 48.1, 44.2, 38.3, 28.2, 22.7, 13.2. Anal. Calcd for $C_{17}H_{24}N_4O$·HCl: C, 60.61; H, 7.48; Cl, 10.52; N, 16.63. Found: C, 60.54; H, 7.52; Cl, 10.48; N, 16.71.

26. Newly synthesized compounds possess satisfactory spectroscopic and analytical data. Compound **7** (hydrochloride salt): mp 286–287 °C. ^{1}H NMR (D_2O): 8.63 (d, J = 6.9 Hz, 1H), 7.18 (d, J = 6.9 Hz, 1H), 6.37 (s, 1H), 4.34 (s, 3H), 4.15 (s, 3H), 2.81 (m, 2H), 1.91 (m, 2H), 1.67 (t, J = 5.9 Hz, 2H), 1.22 (s, 6H). ^{13}C NMR: 170.3, 167.3, 159.1, 150.9, 148.6, 138.4, 119.7, 107.3, 60.4, 58.5, 52.9, 44.3, 42.5, 28.6, 26.9. Anal. Calcd for $C_{16}H_{24}N_4O_2$·HCl: C, 56.38; H, 7.39; Cl, 10.40; N, 16.44. Found: C, 56.32; H, 7.41; Cl, 10.42; N, 16.39. Compound **8** (hydrochloride salt): mp 278–279 °C. ^{1}H NMR (D_2O): 8.54 (d, J = 7.1 Hz, 1H), 7.42 (d, J = 7.1 Hz, 1H), 6.29 (s, 1H), 4.17 (s, 3H), 2.87 (m, 2H), 1.84 (m, 2H), 1.64 (t, J = 5.7 Hz, 2H), 1.20 (s, 6H). ^{13}C NMR: 168.5, 160.4, 158.3, 151.2, 147.2, 139.1, 124.3, 118.7, 106.9, 59.2, 52.4, 43.9, 41.8, 29.1, 26.7. Anal. Calcd for $C_{16}H_{21}F_3N_4O$·HCl: C, 50.73; H, 5.85; Cl, 9.36; F, 15.05; N, 14.79. Found: C, 50.81; H, 5.82; Cl, 9.29; F, 15.14; N, 14.82. Compound **9** (hydrochloride salt): mp 284–285 °C. ^{1}H NMR (D_2O): 8.58 (d, J = 7.1 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 6.31 (s, 1H), 4.38 (q, J = 7.3 Hz, 2H), 4.27 (s, 3H), 2.86 (m, 2H), 1.86 (m, 2H), 1.72 (t, J = 7.3 Hz, 3H), 1.65 (t, J = 5.9 Hz, 2H), 0.41 (d, J = 5.3 Hz, 2H), 0.32 (d, J = 5.3 Hz, 2H). ^{13}C NMR: 169.8, 166.5, 159.4, 150.7, 149.3, 138.6, 118.4, 106.8, 69.9, 61.3, 44.9, 41.9, 37.7, 26.5, 19.2, 11.7. Anal. Calcd for $C_{17}H_{24}N_4O_2$·HCl: C, 57.87; H, 7.14; Cl, 10.05; N, 15.88. Found: C, 57.91; H, 7.11; Cl, 10.11; N, 15.94. Compound **10** (hydrochloride salt): mp 276–277 °C. ^{1}H NMR (D_2O): 8.58 (d, J = 6.8 Hz, 1H), 7.38 (d, J = 6.8 Hz, 1H), 6.25 (s, 1H), 4.39 (q, J = 7.2 Hz, 2H), 2.84 (m, 2H), 1.91 (m, 2H), 1.71 (t, J = 7.2 Hz, 3H), 1.69 (t, J = 5.6 Hz, 2H), 0.42 (d, J = 5.3 Hz, 2H), 0.32 (d, J = 5.3 Hz, 2H). ^{13}C NMR: 169.1, 161.1, 158.8, 150.9, 148.1, 138.3, 126.7, 119.7, 108.2, 68.4, 44.3, 40.9, 38.1, 27.6, 19.1, 12.9. Anal. Calcd for $C_{17}H_{21}F_3N_4O$·HCl: C, 52.24; H, 5.67; Cl, 9.07; F, 14.58; N, 14.34. Found: C, 52.27; H, 5.63; Cl, 9.12; F, 14.51; N, 14.41. Compound **11** (hydrochloride salt): mp 290–291 °C. ^{1}H NMR (D_2O): 8.51 (d, J = 6.9 Hz, 1H), 7.29 (d, J = 6.9 Hz, 1H), 6.25 (s, 1H), 4.52 (m, 1H), 4.29 (s, 3H), 2.81 (m, 2H), 1.91 (m, 2H), 1.78 (d, J = 7.4 Hz, 6H), 1.69 (t,J = 5.8 Hz, 2H), 0.38 (d, J = 5.4 Hz, 2H), 0.30 (d, J = 5.4 Hz, 2H). ^{13}C NMR: 170.2, 164.8, 159.1, 151.2, 148.7, 138.9, 117.8, 106.2, 72.7, 61.9, 45.4, 40.5, 38.1, 27.8, 22.8, 12.2. Anal. Calcd for $C_{18}H_{26}N_4O_2$·HCl: C, 58.93; H, 7.42; Cl, 9.66; N, 15.27. Found: C, 58.88; H, 7.45; Cl, 9.63; N, 15.33. Compound **12** (hydrochloride salt): mp 283–284 °C. ^{1}H NMR (D_2O): 8.69 (d, J = 7.1 Hz, 1H), 7.31 (d, J = 7.1 Hz, 1H), 6.29 (s, 1H), 4.59 (m, 1H), 2.80 (m, 2H), 1.87 (m, 2H), 1.72 (d, J = 7.3 Hz, 6H), 1.63 (t, J = 5.8 Hz, 2H), 0.35 (d, J = 5.4 Hz, 2H), 0.29 (d, J = 5.4 Hz, 2H). ^{13}C NMR: 169.9, 162.4, 157.9, 152.1, 149.4, 137.1, 128.3, 118.5, 107.1, 71.9, 45.0, 40.3, 39.2, 27.1, 22.2, 12.3. Anal. Calcd for $C_{18}H_{23}F_3N_4O$·HCl: C, 53.40; H, 5.98; Cl, 8.76; F, 14.08; N, 13.84. Found: C, 53.44; H, 5.95; Cl, 8.82; F, 14.02; N, 13.90.

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