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# Synthesis and evaluation of febrifugine analogues as potential antimalarial agents

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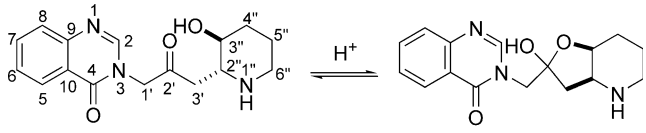
**Abstract**—Febrifugine is an alkaloid isolated from *Dichroa febrifuga* Lour as the active component against *Plasmodium falciparum*. Strong liver toxicity has precluded febrifugine as a potential clinical drug. In this study novel febrifugine analogues were designed and synthesized. Lower toxicity was achieved by reducing or eliminating the tendency of forming chemically reactive and toxic intermediates and metabolites. Synthesized compounds were evaluated in vitro against chloroquine sensitive (D6) and chloroquine resistant (W2) *P. falciparum* strains for efficacy and in freshly isolated rat hepatocytes for potential cytotoxicity. The $IC_{50}$'s of the best compounds were superior to their parent compound febrifugine. Noticeably, these compounds were also over 100 times less toxic than febrifugine. These compounds, as well as the underlying design rationale, may find usefulness in the discovery and development of new antimalarial drugs.


Malaria is one of the major parasitic infections in many tropical and subtropical regions. Worldwide, malaria infects 300–600 million people and kills about three million in a year.[1] The malaria parasite has now become resistant to the best antimalarial drugs.[2,3] Therefore, medicinal agents based on novel mode of action are required to overcome the emergence of resistance and to control an ever-increasing number of epidemics caused by the malaria parasite.

Febrifugine (**1**) and isofebrifugine (**2**), as shown in Figure 1, were isolated as the active components against malaria in the Chinese herb Chang Shan (*Dichroa febrifuga* Lour),[4,5] which has been employed by the local people as medicine against fevers caused by malaria parasites for a long time. Febrifugine acts by impairing haemazoin formation required for maturation of the parasite at the trophozoite stage.[6] Subsequent pre-clinical researches have found that febrifugine possesses adverse side effects. Strong liver toxicity has precluded febrifugine as a potential clinical drug.[7,8]

Some febrifugine analogues have been synthesized; most of the structural modifications were focused on side-chain alterations. It is known that the 4-quinazolinone moiety plays an essential role in the appearance of activity; and that the presence of a 1″-amino group and C-2′, C-3″ O-functionalities is crucial in the antimalarial activity of febrifugine.[9–11] Structure–activity relationship studies have also demonstrated that attaching any electron-withdrawing group to the 1″-nitrogen decreases activity.[10]




Febrifugine (**1**) Isofebrifugine (**2**)

**Figure 1.**

Febrifugine could be metabolized to the corresponding arene oxide **3** by cytochrome P-450 enzymes (Scheme 1). When arene oxide **3** escapes deactivation process by certain enzymes such as epoxide hydrase or glutathione *S*-transferase, toxicity can result because this reactive electrophile will form covalent adducts with DNA, RNA, proteins, or other biomolecules of the host. Such binding can cause mutations and result in cell damage. In a recent metabolic study of febrifugine, Oshima and co-workers isolated metabolite **4**.[12] This study indicates that arene oxide **3** is most probably a short-lived reactive metabolic intermediate because metabolite **4** would have

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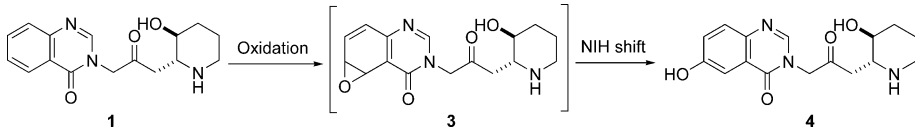



**Scheme 1.**

been derived from intermediate **3** through the rearrangement known as *NIH shift*.[13]

There are two possible ways to make this process unfavorable: (I) Blocking the C-5 or C-6 position of the quinazolinone ring; and (II) increasing the oxidation potential of the molecule. As part of an ongoing malaria chemotherapy project in our laboratory, we undertook the synthesis and antimalarial activity evaluation of the following febrifugine analogues (compounds **5**–**20**, shown in Fig. 2). Compounds **5**–**16** are designed to block the aforementioned unwarranted metabolic pathway. Introduction of an extra nitrogen atom on position 5 or 6 of the quinazolinone ring in febrifugine furnishes compounds **5** and **6**. Compounds **7**–**11** each bear one or two electron-withdrawing group(s), while compounds **12** and **13** bear a bulky group on C-5 or C-6 position of the quinazolinone ring. Compounds **14** and **15** have an extra nitrogen atom on position 7 or 8 of the aromatic ring, and compound **16** has an electron-withdrawing group (fluoride) attached to C-8 position of the quinazolinone ring. For compounds **14**–**16**, the C-5 and C-6 positions are now exposed to oxidation, but such a process will be hampered because the oxidation potential of the molecule is increased due to the introduction of an extra nitrogen atom or an electron-withdrawing group on the quinazolinone ring. Overall, these compounds closely resemble febrifugine itself by possessing a planar aromatic ring, a 1″-amino group, and C-2′, C-3″ O-functionality, and are therefore expected to possess the same or a similar mode of action. Meanwhile, they would be much less likely to produce toxic intermediates because of the blocking of C-5 and C-6 positions (compounds **5**–**13**) or the increase of the oxidation potential of the molecule (compounds **5**–**11**, **14**–**16**).

As a comparative study, compounds **17**–**20** were also designed. These compounds have a methyl group or an electron-donating methoxy group attached to the C-7 or C-8 of the aromatic ring. These compounds have comparable or even greater tendency to undergo oxidation. Biological data from these compounds should further validate, or nullify, the hypothesis that some oxidized febrifugine metabolites have contributed to the observed toxicity.

The synthesis of compound **5** is shown in Scheme 2. Previously published procedure was adopted to synthesize the aromatic moiety: 3H-pyrido[3,2-*d*]pyrimidin-4-one (**21**).[14] Compound **21** condensed with the known epoxide **22**,[15] to furnish corresponding alcohol **23**, as a pair of diastereomers, which follows the methods of Taniguchi and Ogasawara.[15] Compound **23** then underwent TPAP oxidation[16] to give ketone **24** as a single enantiomer. Finally, compound **24** underwent hydrogenolysis to afford compound **5**.[17,18] The synthesis of compounds **6**–**20**[18] follows a similar route. The respective aromatic moieties are available from previously published procedures.[19–21]

Synthesized compounds (**5**–**20**) were tested in vitro against two *P. falciparum* malaria parasite clones: W2 and D6, following the procedures of Desjardins et al.[22] and Chulay et al.[23] Both strains are from the Malaria Research and Reference Reagent Resource Center (MR4). The W2 clone is susceptible to mefloquine but

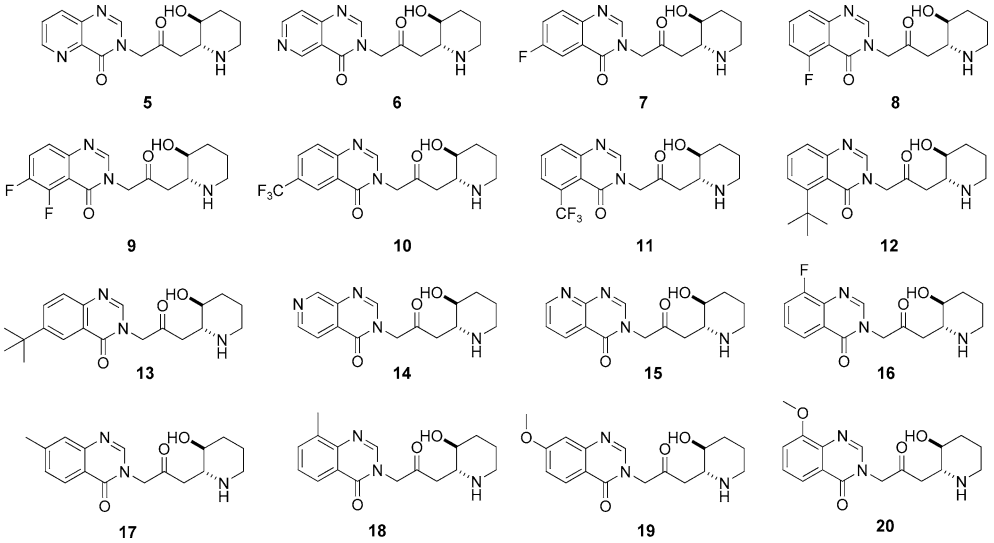
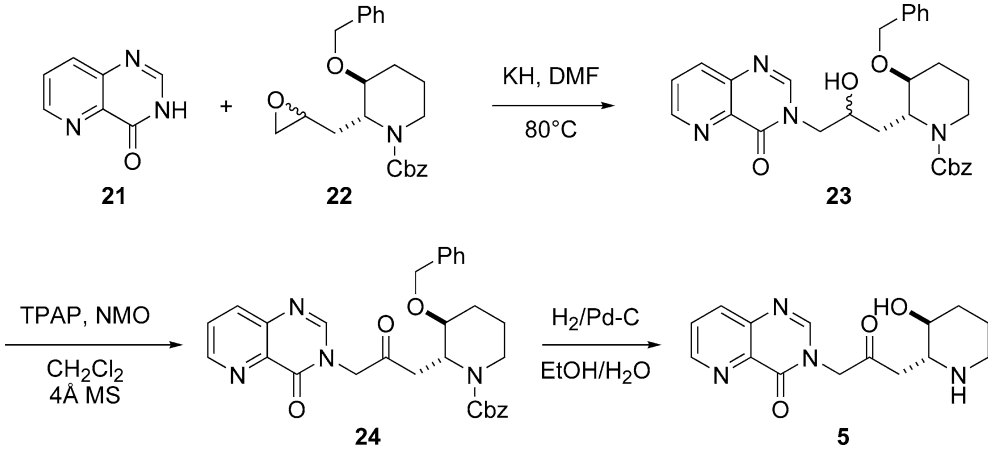



**Figure 2.**




**Scheme 2.**

resistant to chloroquine, sulfadoxine, pyrimethamine, and quinine, whereas the D6 clone is naturally resistant to mefloquine but susceptible to chloroquine, sulfadoxine, pyrimethamine and quinine. For in vitro toxicological studies, synthesized compounds were evaluated in freshly isolated rat hepatocytes by the measuring of lysosomal (neutral red assay) functions as cytotoxicity parameter, as described by Fontaine et al.[24] Freshly isolated rat hepatocytes are widely used in drug metabolism and toxicity studies. Chloroquine and febrifugine were also screened in W2, D6, and rat hepatocytes as positive controls. Their $IC_{50}$ values are summarized in Table 1.

Compounds **5** and **6** with an extra nitrogen atom on the position 5 or 6 of the aromatic ring and compound **8** with a fluoride substitution on C-5 possess antimalarial activity comparable to that of febrifugine. Compounds **9** and **11** with difluoride attached to C-5 and C-6 or trifluoromethyl substitution at C-5 have antimalarial activity superior to that of parent compound febrifugine. These compounds showed potency against both chloroquine-sensitive malarial strain (D-6) and chloroquine-resistant malarial strain (W-2). Noticeably, these compounds were over 100 times less toxic than febrifugine. On the other hand, compounds with an electron-withdrawing group on C-6 alone (**7** and **10**) or a bulky substitution (**12** and **13**) have both decreased antimalarial activity and toxicity.

**Table 1.** In vitro activity against malarial parasite and rat hepatocytes [$IC_{50}$ (nM)]

| Compound | D6 clone | W2 clone | Rat hepatocytes |
|---|---|---|---|
| **5** | 1.2 | 1.3 | $1.8 \times 10^4$ |
| **6** | 1.5 | 1.8 | $1.7 \times 10^4$ |
| **7** | 4.7 | 5.0 | $1.3 \times 10^4$ |
| **8** | 1.3 | 1.3 | $1.9 \times 10^4$ |
| **9** | 0.33 | 0.39 | $1.7 \times 10^4$ |
| **10** | 14 | 16 | $1.5 \times 10^4$ |
| **11** | 0.43 | 0.41 | $1.9 \times 10^4$ |
| **12** | 132 | 160 | $7.0 \times 10^3$ |
| **13** | 165 | 188 | $9.8 \times 10^3$ |
| **14** | 63 | 73 | $1.9 \times 10^4$ |
| **15** | 70 | 109 | $2.2 \times 10^4$ |
| **16** | 103 | 100 | $1.6 \times 10^4$ |
| **17** | 2.0 | 2.2 | 117 |
| **18** | 1.7 | 1.9 | 140 |
| **19** | 1.4 | 1.3 | 15 |
| **20** | 1.2 | 1.3 | 16 |
| Chloroquine | 23 | 338 | $1.9 \times 10^3$ |
| Febrifugine | 1.6 | 1.9 | 169 |

Although compounds **14**–**16** were also much less toxic than febrifugine, these compounds were less active, suggesting that increasing the oxidation potential of the molecule alone reduces both toxicity and antimalarial activity.

Compounds **17**–**20** possess antimalarial activity comparable to that of parent compound febrifugine, suggesting that introducing a small alkyl or alkoxy substitution on C-7 or C-8 of the aromatic ring does not change the biological potency of the molecule. Nevertheless, compounds **19** and **20**, with an electron-donating methoxy substitution at C-7 or C-8 of the aromatic ring and hence possess greater tendency to undergo oxidation, have become 10 times more toxic. A weak electron-donating methyl substitution (compounds **17** and **18**) only increases the toxicity slightly.

In conclusion, new febrifugine analogues were designed and synthesized. Lower toxicity was achieved by reducing or eliminating the tendency of forming chemically reactive and toxic intermediates and metabolites. Some of these compounds (**5**, **6**, **8**, **9**, and **11**) possess significantly low cytotoxicity, while retaining potent antimalarial activity against both chloroquine-sensitive and -resistant strains. 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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Institutes for Biological Sciences, Chinese Academy of Sciences, for a sample of febrifugine. This research was partially supported by a grant from the National Institutes of Health (AI63734 to S.Z.).

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17. Synthesis procedure: Potassium hydride (30% in mineral oil, 1.33 g) was suspended in 10 mL DMF. It was cooled in an ice-water bath, and solid 3H-pyrido[3,2-*d*]pyrimidin-4-one (**21**, 1.47 g) was added in. After 30 min, a solution of oxirane **22** (1.91 g) in 2 mL DMF was added in. The reaction mixture was then heated at 80 °C for 12 h under nitrogen atmosphere. It was partitioned between EtOAc (80 mL) and water (80 mL), and separated organic layer was washed with water (3 × 60 mL), then brine (40 mL), dried over anhydrous sodium sulfate, and evaporated in a rotary evaporator under reduced pressure to furnish the crude product. Flash chromatography (5% MeOH/EtOAc) furnished **23**. A solution of alcohol **23** (2.1 g) in 5 mL of $CH_2Cl_2$ was added into a stirred slurry of tetrapropylammonium perruthenate (TPAP, 70 mg), *N*-methylmorpholine *N*-oxide (NMO, 936 mg), and ground molecular sieve (800 mg) in 10 mL of $CH_2Cl_2$ at room temperature. After 1 h, the reaction mixture was loaded directly into a short column of silica gel and eluted with 5% MeOH/EtOAc. Concentration of the eluant under reduced pressure afforded **24**. Ketone **24** (1.88 g) was dissolved in 15 mL of 95% EtOH/$H_2O$. 300 mg of 10% Pd on carbon was added in. It was then treated with hydrogen (60 psi) in a Parr apparatus for 12 h. Solid was filtered off and the solution was evaporated under vacuum to dryness. Recrystallization from ethanol–water (with addition of dilute aqueous HCl solution, 4–5 equiv of HCl) furnished compound **5** (dil HCl salt) as pale-yellow crystals. Yield: 1.15 g, 61% (three steps from oxirane **22**).
18. All new compounds possess satisfactory analytical data. Compound **5** (dihydrochloride salt): mp: 347–348 °C (dec). $[\alpha]_D^{25}$ +31.4 (*c* 0.3, EtOH). $^1$H NMR (DMSO-$d_6$): 9.11 (d, *J* = 7.4 Hz, 1H), 8.48 (d, *J* = 7.4 Hz, 1H), 8.24 (s, 1H), 7.85 (t, *J* = 7.4 Hz, 1H), 5.01 (d, *J* = 16.8 Hz, 1H), 4.89 (d, *J* = 16.8 Hz, 1H), 3.45 (m, 1H), 3.23 (m, 1H), 3.15 (dd, *J* = 17.1 and 5.8 Hz, 1H), 2.85 (m, 2H), 2.80 (dd, *J* = 17.1 and 4.7 Hz, 1H), 1.83 (m, 2H), 1.69 (m, 2H). $^{13}$C NMR: 202.8, 168.4, 163.0, 153.1, 149.8, 143.8, 139.1, 132.5, 80.7, 71.4, 66.3, 53.4, 51.2, 37.2, 32.9. Anal. Calcd for $C_{15}H_{18}N_4O_3{\cdot}2HCl$: C, 48.01; H, 5.37; N, 14.93. Found: C, 47.82; H, 5.43; N, 14.80. Compound **6** (dihydrochloride salt): mp: 336–337 °C (dec). $[\alpha]_D^{25}$ +21.8 (*c* 0.5, EtOH). $^1$H NMR: 9.04 (s, 1H), 8.68 (d, *J* = 7.3 Hz, 1H), 8.22 (s, 1H), 7.84 (d, *J* = 7.3 Hz, 1H), 5.04 (d, *J* = 16.9 Hz, 1H), 4.85 (d, *J* = 16.9 Hz, 1H), 3.45 (m, 1H), 3.26 (m, 1H), 3.11 (dd, *J* = 17.0 and 5.9 Hz, 1H), 2.83 (m, 2H), 2.78 (dd, *J* = 17.0 and 4.6 Hz, 1H), 1.81 (m, 2H), 1.64 (m, 2H). $^{13}$C NMR: 203.1, 167.5, 163.6, 158.0, 154.8, 148.8, 133.1, 129.4, 81.3, 70.6, 65.9, 54.1, 51.8, 36.7, 31.3. Anal. Calcd for $C_{15}H_{18}N_4O_3{\cdot}2HCl$: C, 48.01; H, 5.37; N, 14.93. Found: C, 48.11; H, 5.27; N, 15.04. Compound **7** (hydrochloride salt): mp: 306–307 °C. $[\alpha]_D^{25}$ +26.3 (*c* 0.5, EtOH). $^1$H NMR: 8.24 (s, 1H), 7.86 (d, *J* = 7.1 Hz, 1H), 7.55 (s, 1H), 7.48 (d, *J* = 7.1 Hz, 1H), 5.04 (d, *J* = 16.7 Hz, 1H), 4.91 (d, *J* = 16.7 Hz, 1H), 3.46 (m, 1H), 3.29 (m, 1H), 3.26 (dd, *J* = 17.1 and 5.6 Hz, 1H), 2.91 (m, 2H), 2.79 (dd, *J* = 17.1 and 4.8 Hz, 1H), 1.81 (m, 2H), 1.67 (m, 2H). $^{13}$C NMR: 202.9, 167.9, 163.6, 147.1, 133.2, 129.7, 128.9, 128.0, 127.7, 81.1, 71.3, 64.5, 55.6, 51.3, 37.3, 32.2. Anal. Calcd for $C_{16}H_{18}FN_3O_3{\cdot}HCl$: C, 54.01; H, 5.38; N, 11.81; Cl, 9.96. Found: C, 54.19; H, 5.34; N, 11.75; Cl, 9.82. Compound **8** (hydrochloride salt): mp: 302–303 °C. $[\alpha]_D^{25}$ +21.5 (*c* 0.5, EtOH). $^1$H NMR: 8.20 (s, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 5.05 (d, *J* = 16.8 Hz, 1H), 4.85 (d, *J* = 16.8 Hz, 1H), 3.44 (m, 1H), 3.31 (m, 1H), 3.29 (dd, *J* = 17.2 and 5.5 Hz, 1H),2.93 (m, 2H), 2.82 (dd, *J* = 17.2 and 4.7 Hz, 1H), 1.84 (m, 2H), 1.71 (m, 2H). $^{13}$C NMR: 205.4, 167.5, 164.1, 146.9, 141.2, 133.1, 129.9, 128.1, 127.9, 81.0, 72.1, 63.5, 55.8, 51.5, 37.4, 31.8. Anal. Calcd for $C_{16}H_{18}FN_3O_3{\cdot}HCl$: C, 54.01; H, 5.38; N, 11.81; Cl, 9.96. Found: C, 54.15; H, 5.32; N, 11.70; Cl, 9.79. Compound **9** (hydrochloride salt): mp: 294–295 °C. $[\alpha]_D^{25}$ −11.5 (*c* 0.45, EtOH). $^1$H NMR: 8.25 (s, 1H), 7.88 (d, *J* = 6.9 Hz, 1H), 7.71 (d, *J* = 6.9 Hz, 1H), 5.09 (d, *J* = 16.7 Hz, 1H), 4.88 (d, *J* = 16.7 Hz, 1H), 3.41 (m, 1H), 3.35 (m, 1H), 3.27 (dd, *J* = 17.3 and 5.6 Hz, 1H), 2.90 (m, 2H), 2.86 (dd, *J* = 17.3 and 4.8 Hz, 1H), 1.86 (m, 2H), 1.69 (m, 2H). $^{13}$C NMR: 203.8, 166.8, 164.7, 158.9, 152.5, 147.6, 136.9, 129.1, 128.9, 81.2, 71.9, 63.7, 55.4, 52.0, 37.6, 31.6. Anal. Calcd for $C_{16}H_{17}F_2N_3O_3{\cdot}HCl$: C, 51.41; H, 4.85; N, 11.24; Cl, 9.48. Found: C, 51.33; H, 4.82; N, 11.20; Cl, 9.39. Compound **10** (hydrochloride salt): mp: 326–327 °C (dec). $[\alpha]_D^{25}$ +16.7 (*c* 0.5, EtOH). $^1$H NMR: 8.23 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 5.05 (d, *J* = 16.9 Hz, 1H), 4.93 (d, *J* = 16.9 Hz, 1H), 3.48 (m, 1H), 3.26 (m, 1H), 3.20 (dd, *J* = 17.3 and 5.7 Hz, 1H), 2.82 (m, 2H), 2.77 (dd, *J* = 17.3 and 4.9 Hz, 1H), 1.80 (m, 2H), 1.68 (m, 2H). $^{13}$C NMR: 203.3, 167.8, 162.6, 147.3, 137.1, 133.5, 129.8, 128.1, 127.4, 119.2, 80.1, 70.7, 64.2, 54.7, 51.0, 36.9, 33.1. Anal. Calcd for $C_{17}H_{18}F_3N_3O_3{\cdot}1.5HCl$: C, 48.15; H, 4.64; N, 9.91. Found: C, 47.92; H, 4.73; N, 9.81. Compound **11** (hydrochloride salt): mp: 320–321 °C (dec). $[\alpha]_D^{25}$ −10.5 (*c* 0.45, EtOH). $^1$H NMR: 8.18 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 5.06

(d, $J$ = 16.8 Hz, 1H), 4.84 (d, $J$ = 16.8 Hz, 1H), 3.43 (m, 1H), 3.30 (m, 1H), 3.27 (dd, $J$ = 17.2 and 5.6 Hz, 1H), 2.92 (m, 2H), 2.84 (dd, $J$ = 17.2 and 4.8 Hz, 1H), 1.83 (m, 2H), 1.70 (m, 2H). $^{13}$C NMR: 203.4, 166.5, 163.3, 146.7, 134.2, 133.1, 128.9, 128.0, 126.9, 118.4, 80.7, 72.0, 63.3, 54.8, 51.2, 37.1, 31.4. Anal. Calcd for $C_{17}H_{18}F_3N_3O_3 \cdot 1.5HCl$: C, 48.15; H, 4.64; N, 9.91. Found: C, 47.97; H, 4.60; N, 9.98. Compound **12** (hydrochloride salt): mp: 293–294 °C.$[\alpha]_D^{25}$ +12.4 ($c$ 0.51, EtOH). $^1$H NMR: 8.24 (d, $J$ = 7.2 Hz, 1H), 8.18 (s, 1H), 7.75 (d, $J$ = 7.2 Hz, 1H), 7.64 (t, $J$ = 7.2 Hz, 1H), 5.05 (d, $J$ = 16.8 Hz, 1H), 4.85 (d, $J$ = 16.8 Hz, 1H), 3.44 (m, 1H), 3.31 (m, 1H), 3.29 (dd, $J$ = 17.2 and 5.5 Hz, 1H), 2.93 (m, 2H), 2.85 (dd, $J$ = 17.2 and 4.7 Hz, 1H), 1.82 (m, 2H), 1.71 (m, 2H), 1.31 (s, 9H). $^{13}$C NMR: 202.3, 169.5, 165.1, 152.9, 147.2, 143.1, 133.9, 130.1, 129.9, 81.0, 72.1, 63.5, 56.8, 51.5, 37.3, 35.6, 31.8, 30.5. Anal. Calcd for $C_{20}H_{27}N_3O_3 \cdot HCl$: C, 60.98; H, 7.16; N, 10.67; Cl, 9.00. Found: C, 60.91; H, 7.19; N, 10.56; Cl, 9.09. Compound **13** (hydrochloride salt): mp: 290–291 °C. $[\alpha]_D^{25}$ −10.3 ($c$ 0.45, EtOH). $^1$H NMR: 8.21 (s, 1H), 7.96 (d, $J$ = 7.1 Hz, 1H), 7.68 (d, $J$ = 7.1 Hz, 1H), 7.55 (s, 1H), 5.06 (d, $J$ = 16.8 Hz, 1H), 4.90 (d, $J$ = 16.8 Hz, 1H), 3.44 (m, 1H), 3.29 (m, 1H), 3.25 (dd, $J$ = 17.2 and 5.7 Hz, 1H), 2.89 (m, 2H), 2.77 (dd, $J$ = 17.2 and 4.8 Hz, 1H), 1.80 (m, 2H), 1.71 (m, 2H), 1.34 (s, 9H). $^{13}$C NMR: 202.9, 167.9, 164.6, 154.1, 143.2, 134.7, 129.9, 128.8, 128.4, 81.1, 71.2, 65.5, 55.7, 52.3, 37.4, 35.5, 32.7, 30.2. Anal. Calcd for $C_{20}H_{27}N_3O_3 \cdot HCl$: C, 60.98; H, 7.16; N, 10.67; Cl, 9.00. Found: C, 60.89; H, 7.13; N, 10.60; Cl, 9.12. Compound **14** (dihydrochloride salt): mp: 341–342 °C (dec). $[\alpha]_D^{25}$ +27.4 ($c$ 0.43, EtOH). $^1$H NMR: 9.25 (s, 1H), 8.76 (d, $J$ = 7.3 Hz, 1H), 8.48 (d, $J$ = 7.3 Hz, 1H), 8.26 (s, 1H), 5.07 (d, $J$ = 16.7 Hz, 1H), 4.93 (d, $J$ = 16.7 Hz, 1H), 3.42 (m, 1H), 3.27 (m, 1H), 3.28 (dd, $J$ = 17.3 and 5.8 Hz, 1H), 2.92 (m, 2H), 2.78 (dd, $J$ = 17.3 and 4.7 Hz, 1H), 1.81 (m, 2H), 1.70 (m, 2H). $^{13}$C NMR: 202.6, 167.9, 164.6, 159.1, 155.2, 154.7, 139.9, 134.8, 81.0, 71.9, 66.5, 55.6, 52.1, 37.6, 32.5. Anal. Calcd for $C_{15}H_{18}N_4O_3 \cdot 2HCl$: C, 48.01; H, 5.37; N, 14.93. Found: C, 48.12; H, 5.33; N, 14.84. Compound **15** (dihydrochloride salt): mp: 341–342 °C (dec). $[\alpha]_D^{25}$ −19.6 ($c$ 0.42, EtOH). $^1$H NMR: 8.93 (d, $J$ = 6.8 Hz, 1H), 8.78 (d, $J$ = 6.8 Hz, 1H), 8.31 (s, 1H), 8.25 (t, $J$ = 6.8 Hz, 1H), 4.92 (d, $J$ = 17.2 Hz, 1H), 4.81 (d, $J$ = 17.2 Hz, 1H), 3.51 (m, 1H), 3.33 (m, 1H), 3.21 (dd, $J$ = 17.2 and 5.6 Hz, 1H), 2.81 (m, 2H), 2.78 (dd,$J$ = 17.2 and 4.5 Hz, 1H), 1.89 (m, 2H), 1.67 (m, 2H). $^{13}$C NMR: 204.1, 171.8, 167.3, 162.8, 152.1, 142.6, 133.1, 130.9, 81.4, 70.8, 65.8, 52.7, 50.9, 37.6, 31.8. Anal. Calcd for $C_{15}H_{18}N_4O_3 \cdot 2HCl$: C, 48.01; H, 5.37; N, 14.93. Found: C, 47.90; H, 5.45; N, 14.81. Compound **16** (hydrochloride salt): mp: 298–299 °C. $[\alpha]_D^{25}$ +14.6 ($c$ 0.5, EtOH). $^1$H NMR: 8.21 (s, 1H), 7.85 (d, $J$ = 7.2 Hz, 1H), 7.64 (t, $J$ = 7.2 Hz, 1H), 7.55 (d, $J$ = 7.2 Hz, 1H), 5.03 (d, $J$ = 16.8 Hz, 1H), 4.87 (d, $J$ = 16.8 Hz, 1H), 3.41 (m, 1H), 3.34 (m, 1H), 3.26 (dd, $J$ = 17.1 and 5.5 Hz, 1H), 2.90 (m, 2H), 2.84 (dd, $J$ = 17.1 and 4.7 Hz, 1H), 1.83 (m, 2H), 1.70 (m, 2H). $^{13}$C NMR: 204.4, 167.8, 164.8, 149.9, 142.2, 134.3, 130.9, 129.1, 127.6, 81.1, 72.4, 64.5, 54.8, 51.8, 37.2, 31.6. Anal. Calcd for $C_{16}H_{18}FN_3O_3 \cdot HCl$: C, 54.01; H, 5.38; N, 11.81; Cl, 9.96. Found: C, 54.11; H, 5.30; N, 11.74; Cl, 9.85. Compound **17** (hydrochloride salt): mp: 276–277 °C. $[\alpha]_D^{25}$ +15.4 ($c$ 0.45, EtOH). $^1$H NMR: 8.17 (s, 1H), 7.81 (s, 1H), 7.62 (d, $J$ = 7.1 Hz, 1H), 7.47 (d, $J$ = 7.1 Hz, 1H), 5.02 (d, $J$ = 16.7 Hz, 1H), 4.93 (d, $J$ = 16.7 Hz, 1H), 3.45 (m, 1H), 3.29 (m, 1H), 3.21 (dd, $J$ = 17.3 and 5.8 Hz, 1H), 2.80 (m, 2H), 2.74 (dd, $J$ = 17.3 and 4.9 Hz, 1H), 2.65 (s, 3H), 1.82 (m, 2H), 1.70 (m, 2H). $^{13}$C NMR: 202.3, 167.4, 161.6, 146.3, 138.5, 133.4, 129.5, 128.6, 127.9, 80.5, 77.7, 66.2, 53.7, 51.8, 36.7, 33.0, 26.8. Anal. Calcd for $C_{17}H_{21}N_3O_3 \cdot HCl$: C, 58.03; H, 6.30; N, 11.94; Cl, 10.08. Found: C, 58.13; H, 6.28; N, 11.85; Cl, 10.15. Compound **18** (hydrochloride salt): mp: 272–273 °C. $[\alpha]_D^{25}$ −11.6 ($c$ 0.45, EtOH). $^1$H NMR: 8.18 (s, 1H), 7.85 (d, $J$ = 7.2 Hz, 1H), 7.64 (t, $J$ = 7.2 Hz, 1H), 7.45 (d, $J$ = 7.2 Hz, 1H), 5.04 (d, $J$ = 16.7 Hz, 1H), 4.89 (d, $J$ = 16.7 Hz, 1H), 3.40 (m, 1H), 3.39 (m, 1H), 3.25 (dd, $J$ = 17.1 and 5.7 Hz, 1H), 2.92 (m, 2H), 2.81 (dd, $J$ = 17.1 and 4.9 Hz, 1H), 2.61 (s, 3H), 1.80 (m, 2H), 1.71 (m, 2H). $^{13}$C NMR: 202.4, 167.2, 161.3, 147.3, 137.4, 134.4, 129.9, 129.0, 128.3, 80.2, 77.1, 66.0, 53.4, 51.5, 36.3, 33.2, 26.9. Anal. Calcd for $C_{17}H_{21}N_3O_3 \cdot HCl$: C, 58.03; H, 6.30; N, 11.94; Cl, 10.08. Found: C, 58.09; H, 6.35; N, 11.80; Cl, 10.25. Compound **19** (hydrochloride salt): mp: 281–282 °C.$[\alpha]_D^{25}$ +18.3 ($c$ 0.5, EtOH). $^1$H NMR: 8.11 (s, 1H), 7.71 (s, 1H), 7.22 (d, $J$ = 7.2 Hz, 1H), 7.42 (d, $J$ = 7.2 Hz, 1H), 5.05 (d, $J$ = 16.7 Hz, 1H), 4.90 (d, $J$ = 16.7 Hz, 1H), 3.81 (s, 3H), 3.49 (m, 1H), 3.28 (m, 1H), 3.20 (dd, $J$ = 17.1 and 5.8 Hz, 1H), 2.80 (m, 2H), 2.74 (dd, $J$ = 17.1 and 4.9 Hz, 1H), 1.82 (m, 2H), 1.72 (m, 2H). $^{13}$C NMR: 202.5, 168.3, 165.5, 161.3, 188.5, 138.4, 134.5, 130.6, 128.9, 81.5, 77.5, 66.0, 58.7, 53.5, 52.8, 37.1, 32.2. Anal. Calcd for $C_{17}H_{21}N_3O_4 \cdot HCl$: C, 55.51; H, 6.03; N, 11.42; Cl, 9.64. Found: C, 55.63; H, 6.08; N, 11.55; Cl, 9.75. Compound **20** (hydrochloride salt): mp: 282–283 °C. $[\alpha]_D^{25}$ −15.6 ($c$ 0.5, EtOH). $^1$H NMR: 8.13 (s, 1H), 7.54 (t, $J$ = 7.3 Hz, 1H), 7.35 (d, $J$ = 7.3 Hz, 1H), 7.15 (d, $J$ = 7.3 Hz, 1H), 5.02 (d, $J$ = 16.9 Hz, 1H), 4.89 (d, $J$ = 16.9 Hz, 1H), 3.77 (s, 3H), 3.41 (m, 1H), 3.36 (m, 1H), 3.27 (dd, $J$ = 17.4 and 5.7 Hz, 1H), 2.92 (m, 2H), 2.81 (dd, $J$ = 17.4 and 4.9 Hz, 1H), 2.64 (s, 3H), 1.79 (m, 2H), 1.68 (m, 2H). $^{13}$C NMR: 203.1, 166.2, 162.3, 160.5, 147.3, 137.4, 132.9, 129.9, 128.7, 80.1, 76.1, 66.5, 58.9, 53.1, 51.3, 36.7, 33.0. Anal. Calcd for $C_{17}H_{21}N_3O_4 \cdot HCl$: C, 55.51; H, 6.03; N, 11.42; Cl, 9.64. Found: C, 55.44; H, 6.05; N, 11.52; Cl, 9.55.


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