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# Synthesis and biological evaluation of the first pentafluorosulfanyl analogs of mefloquine†

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## Abstract

Two novel $SF_5$ analogs of the antimalarial agent mefloquine were synthesized in 5 steps and 10–23% overall yields and found to have improved activity and selectivity against malaria parasites. This work also represents the first report of $SF_5$-substituted quinolines.

Malaria remains a major global health problem with approximately 300 million clinical cases and as many as 2.7 million casualties per year.[1] One of the major factors contributing to the continued presence of malaria is the emergence of parasites that are resistant to one or more antimalarial compounds.[2] Mefloquine (Fig. 1) is an orally-administered drug used as a prophylaxis and treatment for malaria, especially against chloroquine-resistant strains.[3] It was until recently the drug of choice for U.S. military deployments in regions where malaria is endemic, primarily because its long half-life allows weekly administration. However, association of mefloquine with adverse neuropsychiatric effects, including anxiety, depression, halucinations and seizures[4] has effectively curtailed its use. The ability of mefloquine to inhibit human P-glycoprotein and cross the blood–brain barrier has been suggested as an explanation for these adverse neurological events.[5] We seek to reengineer the quinoline methanol scaffold to yield derivatives that, ultimately, should exhibit fewer adverse neurological effects but retain their antimalarial efficacy. In addition to optimizing the 4-position aminoalcohol moiety to reduce absorption through the blood–brain barrier, we were also interested in replacements of the $CF_3$ groups in mefloquine with pentafluorosulfanyl ($-SF_5$) substituents in order to probe slight perturbations of the electron density of the heteroaromatic scaffold.

The physicochemical and pharmacological properties of small organic molecules are often significantly modified by the incorporation of fluorine atoms.[6] While the synthesis of highly fluorinated and yet rigid octahedral $SF_5$ derivatives is still emerging, recent studies are starting to exploit their unique potential in materials, pharmaceutical and agrochemical applications.[7] The volume of the $SF_5$ group is slightly less than that of a *tert*-butyl group, but considerably larger than $CF_3$.[8] The electronegativity of the $SF_5$ function has been proposed to be as high as

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3.65, *vs.* 3.36 for the $CF_3$ group.[9,10] In electrophilic aromatic substitutions, the $SF_5$ group was found to have a Hammet $\sigma_p$ value of 0.68 *vs.* $\sigma_p = 0.54$ for $CF_3$.[11] As our first foray into the chemistry and biology of $SF_5$ derivatives, we are exploring the replacement of the $CF_3$ groups in mefloquine with $SF_5$ substituents. In agreement with the afore-mentioned parameters, the electron-density surface encoded with the electrostatic potential for 4-methyl-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline *vs.* 4-methyl-2,8-bis(trifluoromethyl)-quinoline in Fig. 2 shows higher steric crowding around the quinoline nitrogen, a slightly decreased electron density in the benzene ring, and a more positive nitrogen electrostatic charge (−0.64 *vs.* −0.66). In both model compounds, the nitrogen atoms are completely buried in between *ortho*- and *peri*-substituents.

Other noteworthy features of the $SF_5$ group include its remarkable chemical stability. Aromatic $SF_5$ groups tolerate even harsh acidic conditions; their hydrolytic stability equals or exceeds that of the $CF_3$ group.[12]

Despite their origins dating back half a century ago,[13] only a limited number of aromatic pentafluorosulfanes have been prepared, and there is still a considerable need for practical synthetic routes. In particular, there are only a few heterocyclic derivatives, and there is no report in the literature on $SF_5$ -containing quinolines. In this communication, we report efficient syntheses of 6-$SF_5$ and 7-$SF_5$ analogs of mefloquine, as well as the evaluation of their biological activities against malaria parasites.

The first synthesis of mefloquine was published in 1971,14 and since then, several other routes have been developed.[15] A straightforward and high yielding synthesis is based on the oxidative decyanation of 2-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-(pyridin-2-yl)acetonitrile,[16] and we selected this route to access analogs **2** and **3**, which were each obtained in 5 steps from the commercially available amino-(pentafluorosulfanyl)-benzenes **4a** and **4b** (Scheme 1). Condensation of **4a** and **4b** with ethyl 4,4,4-trifluoroacetoacetate in the presence of polyphosphoric acid led to the 4-hydroxyquinolines **6a** and **6b**.[17] In the conversion of **4b**, only the desired 4-hydroxy-7-(pentafluorosulfanyl)quinoline **6b** was isolated in 75% yield. The absence of the 5-pentafluorosulfanylquinoline isomer is probably due to the large steric demand of the $SF_5$ group and/or electrostatic repulsion of the 4-oxygen substituent. Chlorination with phosphorus oxychloride gave the corresponding 4-chloroquinolines **7a** and **7b** in good yields. Subsequent nucleophilic aromatic substitution by 2-pyridylacetonitrile carbanion provided **8a** and **8b**. Exposure to a mixture of hydrogen peroxide and acetic acid then afforded the 4-quinolylketones **9a** and **9b** in excellent yields.

The concomitant reduction of the carbonyl and pyridyl groups in the presence of the quinoline moiety was achieved using catalytic hydrogenation under acidic conditions. This step of the synthesis proved to be problematic. After screening different solvents and acids, and varying hydrogen pressure and catalyst equivalents, optimal conditions for substrate **9a** were found to be 0.4 equivalents of platinum oxide in ethanol containing hydrochloric acid, followed by recrystallization of crude **2** in MeOH. In contrast, **9b** was best converted to target compound **3** in the presence of the milder acetic acid. Gratifyingly, both reactions were highly selective and afforded the desired *anti*-diastereomers. Furthermore, slow evaporation of a MeOH solution of **3** afforded needle-like crystals suitable for X-ray diffraction analysis (Fig. 3).[18] The sulfur atom of the $SF_5$ group is situated in an octahedral environment, and the disposition of the two stereocenters is *anti* as in mefloquine.

The antimalarial activities and selectivities of **2** and **3** were compared to **1** and mefloquine analogs in which the quinoline ring was substituted at the 6- and 7-positions with a trifluoromethyl group (**10** and **11**, Fig. 4).[14,21] The 50% and 90% inhibitory concentrations ($IC_{50}$ s and $IC_{90}$ s) against four drug resistant strains of *Plasmodium falciparum*, and the

$LC_{50}$ s against a mammalian cell line were determined as previously described.[20] Compound **2** exhibited generally equivalent or lower $IC_{50}$ and $IC_{90}$, and greater selectivity than its $CF_3$ -congener **10** and mefloquine (Table 1). The $IC_{50}$ and $IC_{90}$ of **3** were generally equivalent to those of $CF_3$ -analog **11** and mefloquine. These data demonstrate the effective biological mimicry as well as the considerable pharmaceutical potential of the $CF_3$ –$SF_5$ switch in quinoline containing antimalarials.

## Conclusions

We have synthesized two novel pentafluorosulfanyl analogs of mefloquine and demonstrated their equivalent or improved biological activities *vs.* the parent drug and the corresponding C-6 and C-7 trifluoromethyl isomers. Further studies on other $SF_5$-substituted analogs, in particular at the 8-position of the heterocyclic ring, are in progress and will be reported in due course. Our synthetic strategy also represents the first report on an $SF_5$–quinoline construction, and thus expands the repertoire of pentafluorosulfanyl chemistry.[22]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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19. The relative configurations of **10** and **11** have not been assigned, but since a catalytic reduction was used, it is likely that they are also predominantly *anti*.
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22. This manuscript was reviewed by the Walter Reed Army Institute of Research and the U. S. Army Medical Research and Materiel Command, and there is no objection to its publication or dissemination. The opinions expressed herein are those of the authors and do not reflect the views or opinions of the Department of the Army or the Department of Defense.

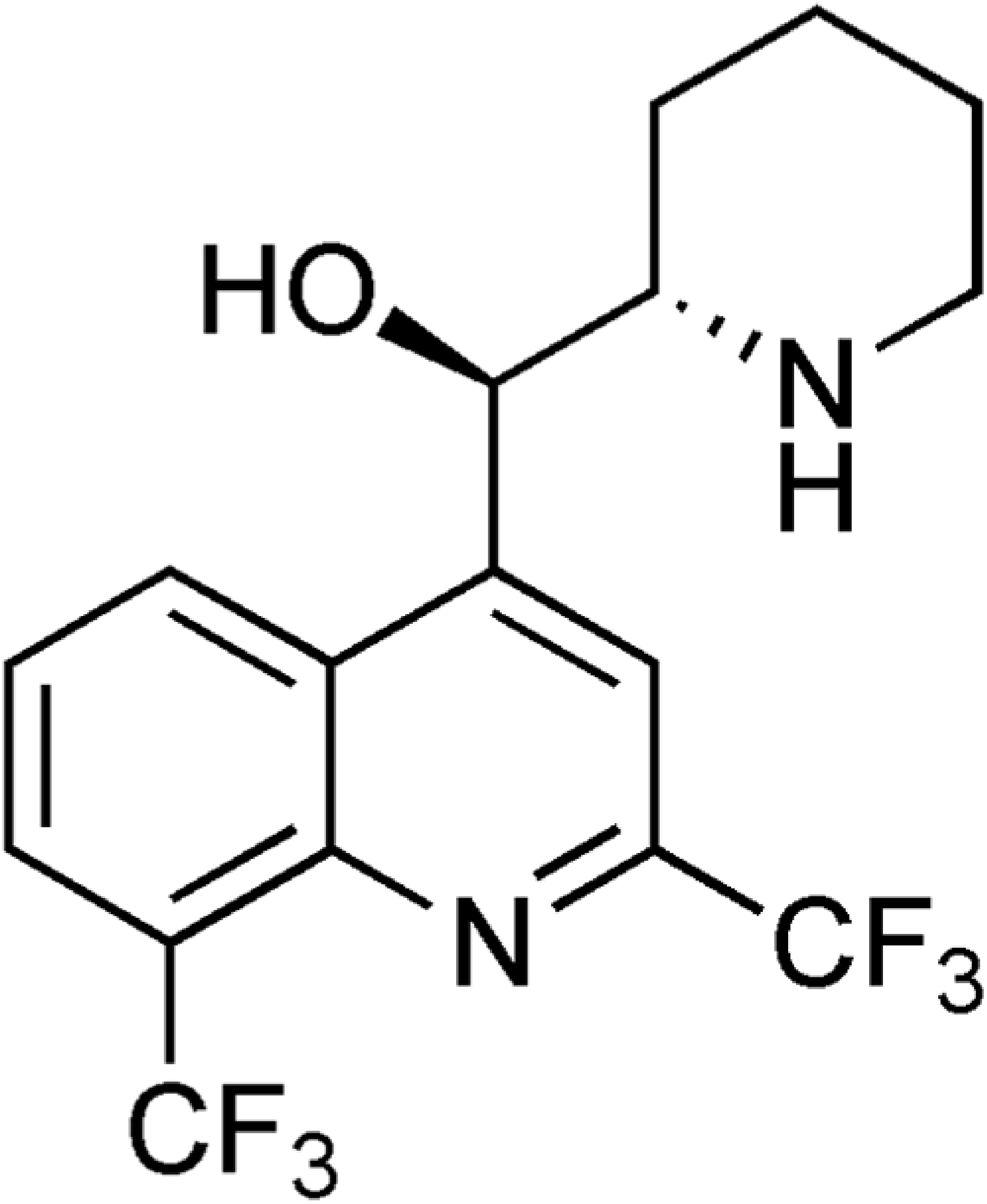


**Fig. 1.**
Mefloquine (**1**).

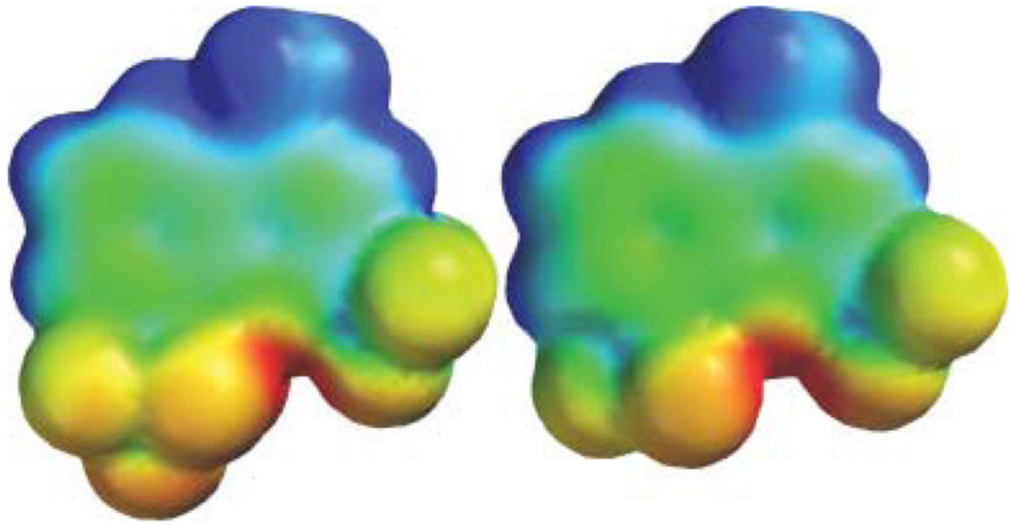

**Fig. 2.**
Electron-density surfaces/electrostatic potential maps calculated with Spartan 08 (HF/6–31G*) for 2 analogs of **1**, 4-methyl-8-penta-fluorosulfanyl-2-trifluoromethylquinoline (left) and 4-methyl-2,8-bis-(trifluoromethyl)quinoline (right).

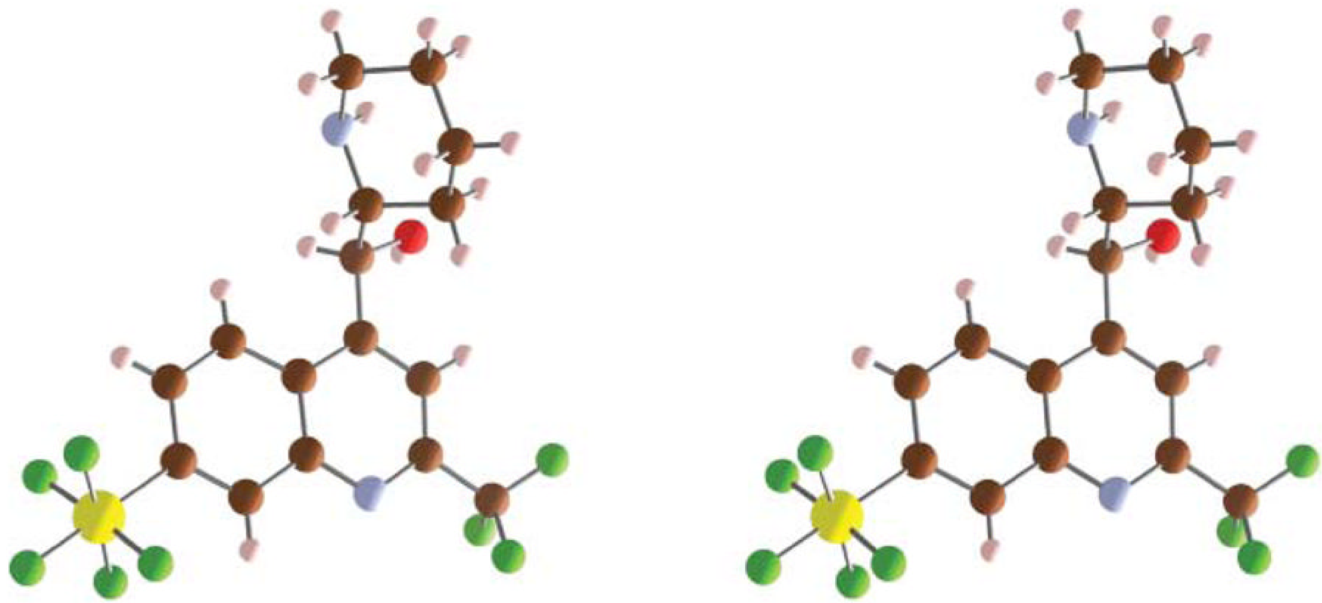

**Fig. 3.**
Stereoview of the X-ray structure of **3**.

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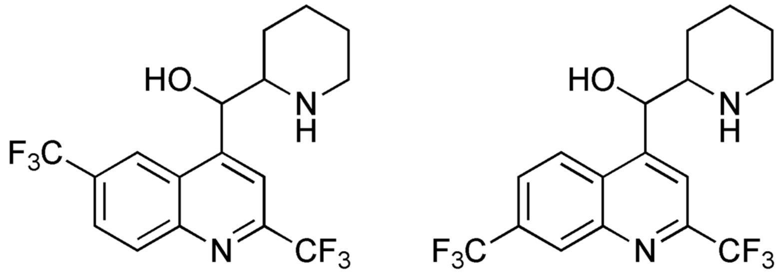
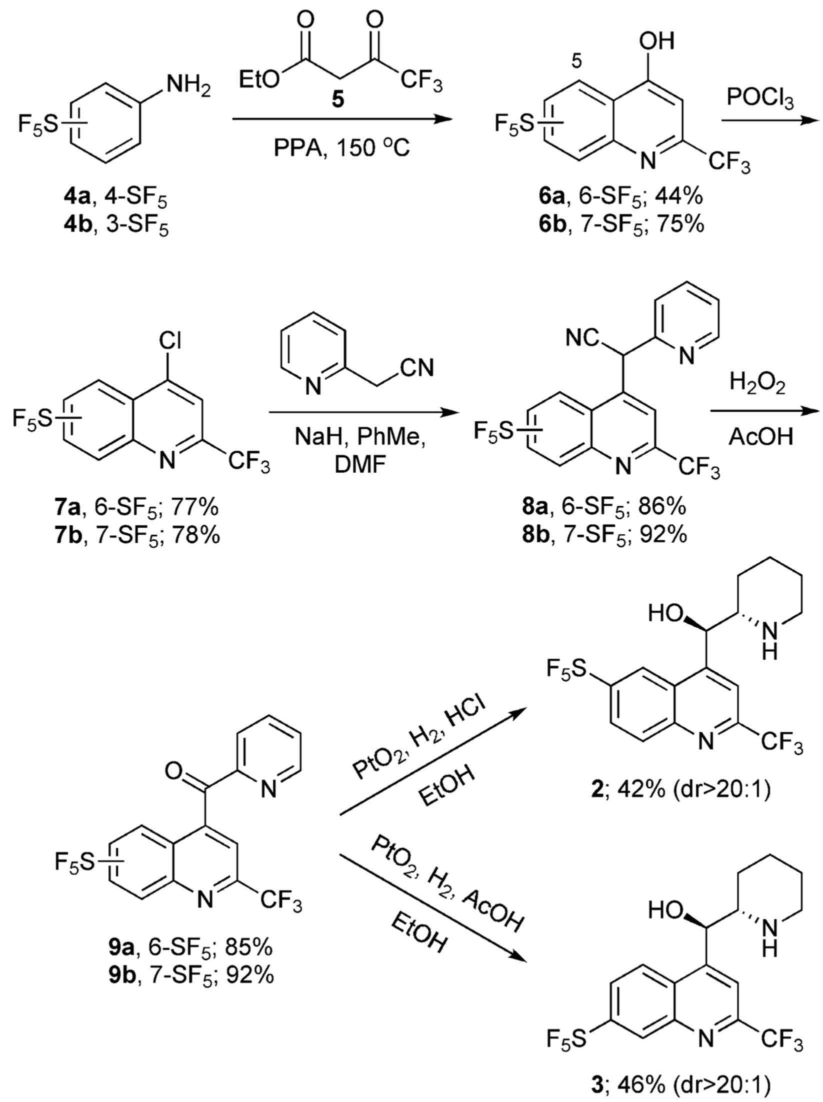



**10** **11**

**Fig. 4.**
Structures of trifluoromethylated quinoline methanols **10**[19] and **11**[19] used as references in the biological assays.




**Scheme 1.**
Synthesis of mefloquine analogs **2** and **3**.

**Table 1**

Antimalarial activity and toxicity of selected quinoline methanols.[20] The units are ng/mL for $IC_{50}$, $IC_{90}$ and $LC_{50}$ data. The selectivity index (SI) is the ratio of the $LC_{50}$ against RAW macrophages relative to the PfW2 $IC_{50}$

| | Pf W2 | | Pf D6 | | Pf C235 | | Pf C2A | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Analog** | **$IC_{50}$** | **$IC_{90}$** | **$IC_{50}$** | **$IC_{90}$** | **$IC_{50}$** | **$IC_{90}$** | **$IC_{50}$** | **$IC_{90}$** | **RAW $LC_{50}$** | **SI** |
| **1** | 2.5 | 9.8 | 8.0 | 20 | 18 | 63 | 22 | 87 | 5064 | 2026 |
| **2** | 3.3 | 11 | 9.2 | 33 | 9.8 | 39 | 14 | 52 | 13740 | 4164 |
| **3** | 3.3 | 13 | 12 | 45 | 10 | 47 | 16 | 80 | ND | ND |
| **10** | 5.0 | 16 | 17 | 67 | 53 | 140 | 21 | 130 | ND | ND |
| **11** | 3.0 | 17 | 12 | 37 | 30 | 86 | 13 | 60 | ND | ND |