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The Effect of Fluorine Substitution on the Antimalarial Activity of Tebuquine

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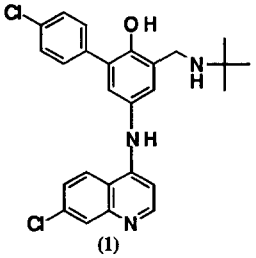
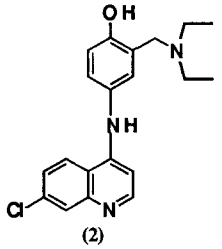
Abstract: A novel synthetic route has been developed for the synthesis of fluorotebuquine which was active against the chloroquine resistant K1 strain of *Plasmodium Falciparum*, but less potent than both chloroquine and tebuquine against the 3D7 strain.

Tebuquine (1) is a 4-aminoquinoline drug that is significantly more potent than amodiaquine (2) and chloroquine.[1] Tebuquine contains the 4-aminophenol moiety and therefore would be expected to undergo P450 mediated oxidation to a toxic quinoneimine. Since oxidation of the antimalarial amodiaquine is implicated in the toxicity of this drug, we proposed that chemical manipulation of the 4-aminophenol functionality in tebuquine would result in the generation of a highly potent antimalarial agent, devoid of the toxicity associated with amodiaquine.[2] We have recently shown that replacement of the 4-hydroxy-function in amodiaquine with fluorine produced an amodiaquine analogue (3) which had antimalarial activity against chloroquine resistant and sensitive *Plasmodium Falciparum*. Furthermore, this analogue was not susceptible to bioactivation to a toxic quinoneimine. [3] In this communication we describe the synthesis and effect of fluorine substitution on the *in vitro* antimalarial activity of tebuquine.



(1)



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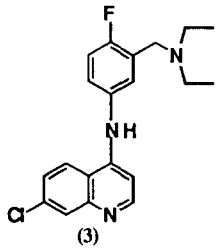
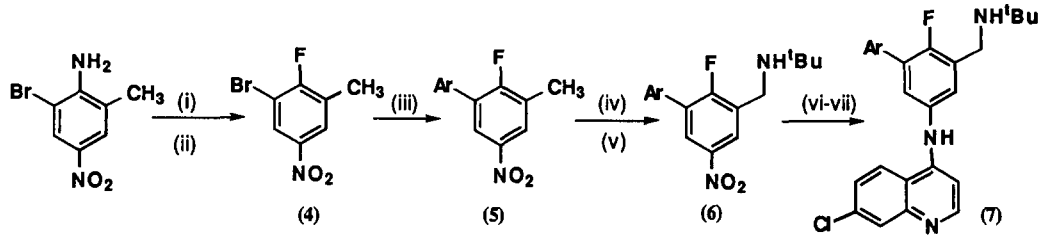


(3)

The required intermediate (4) for the synthesis of fluorotebuquine was obtained by the Balz-Schiemann reaction of 2-amino-3-bromo-5-nitrotoluene.[4] The diazonium tetrafluoroborate salt obtained from this amine was mixed with acid-washed sand and decomposed at 140°C under a constant flow of nitrogen to give the required fluoro compound (4) in 50% yield after flash column chromatography to remove tar and decomposition products. This was then subjected to the palladium catalysed Suzuki Reaction [5] to introduce the 4-chlorophenyl function. Bromination followed by reaction of the benzyl bromide (5) with t-butylamine gave the substitution product (6) which was purified by flash column chromatography. Reduction of the nitro-function of (6) furnished the corresponding amine which was allowed to react with 4,7-dichloroquinoline to give the required target molecule (7). [6]



(i) HNO_2, HBF_4 (ii) Δ, 150°C (iii) Suzuki Coupling, $Pd(0)(PPh_3)_4$, toluene, 4-chlorophenylboronic acid, 2M Na_2CO_3 (iv) NBS, AIBN, CCl_4 (v) *t*-$BuNH_2$ (vi) Sn, HCl (vii) 4,7-dichloroquinoline, ethanol, reflux

Antimalarial testing

Two strains of *Plasmodium falciparum* were used in this study: a) the uncloned K1 strain which is known to be chloroquine resistant and b) the 3D7 strain. Parasites were maintained in continuous culture using a method derived from that of Jensen and Trager. [7] Antimalarial activity was assessed using an adaptation of the 48 hour sensitivity assay of Desjardins et al [8] using [^{3}H]- hypoxanthine incorporation as an assessment of parasite growth. The Table shows clearly that fluorotebuquine is considerably more potent than chloroquine against the K1 strain of *P. Falciparum*. However, fluorotebuquine is less potent than both chloroquine and tebuquine in the chloroquine sensitive 3D7 strain.

Drug	3D7 (IC50)/nmolar	K1 (IC50)/nmolar
Chloroquine	**20**	**250**
Tebuquine	**18**	**21**
Fluorotebuquine	**58**	**74**

Conclusion

Fluorotebuquine has been synthesised and shown to be active against the chloroquine resistant K1 strain and the chloroquine sensitive 3D7 strain of *Plasmodium Falciparum*. Further studies are in progress to determine the effect of fluorine substitution on the *in vivo* antimalarial activity of tebuquine.

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References and Notes

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(6) **Fluorotebuquine 7**: m.p. = 179°C; ^{1}H NMR ($CDCl_3$, 200MHz) δ 8.55 (1H, dd, J_{H-F} = 4.95 Hz, J_{H-H} =2.20Hz Ar-H), 8.02 (1H, dd, J_{H-F} = 4.95 Hz, J_{H-H} = 2.20 Hz Ar-H), 7.89 (1H, d, 8.80 Hz, Ar-H), 7.31-7.51 (6H, m, p-Ar-Cl and Ar-H), 7.20 (1H, dd, J_{H-H} = 6.05 and 2.20 Hz), 6.85 (1H, d, J_{H-H} = 5.50 Hz) 3.85 (2H, s, $\underline{CH_2}$NHtBu), 1.07 (9H, s, tBu); MS m/z 467 (M^+, 4.2%), 455 (15 %), 452 (100 %), 395 (32 %), 380 (47 %), 360 (47 %), 227 (21 %), 170 (41 %), 162 (33 %); HRMS 467.13153, ($C_{26}H_{24}N_3FCl_2$) requires 467.13315)

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