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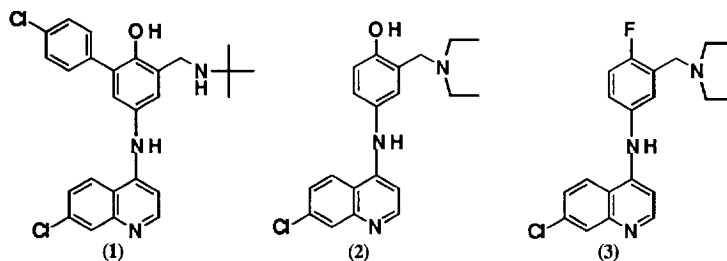
The Effect of Fluorine Substitution on the Antimalarial Activity of Tebuquine

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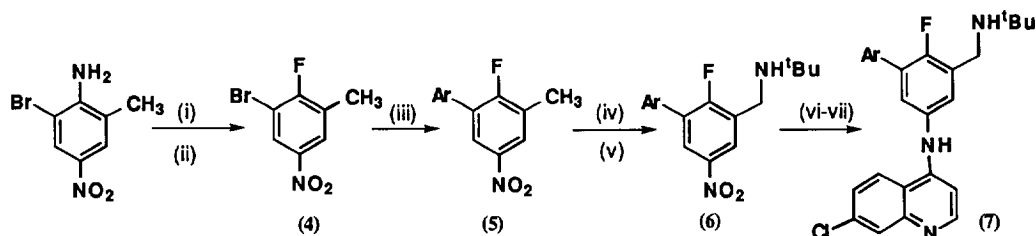
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Abstract: A novel synthetic route has been developed for the synthesis of fluorotebuquine which was active against the chloroquine resistant K1 strain of *Plasmodium Falciparum*, but less potent than both chloroquine and tebuquine against the 3D7 strain.

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.



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 Reaction⁵ 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, $\text{Pd}(\text{O})(\text{PPh}_3)_4$, toluene, 4-chlorophenylboronic acid, $2\text{M Na}_2\text{CO}_3$ (iv) NBS, AIBN, CCl_4 (v) $t\text{-BuNH}_2$ (vi) Sn, HCl (vii) 4,7-dichloroquinoline, ethanol, reflux $\text{Ar} = p\text{-C}_6\text{H}_4\text{Cl}$

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 [^3H]- 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 (IC ₅₀)/nmolar	K1 (IC ₅₀)/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 ; ^1H NMR (CDCl_3 , 200MHz) δ 8.55 (1H, dd, $J_{\text{H-F}} = 4.95$ Hz, $J_{\text{H-H}} = 2.20$ Hz Ar-H), 8.02 (1H, dd, $J_{\text{H-F}} = 4.95$ Hz, $J_{\text{H-H}} = 2.20$ 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, $J_{\text{H-H}} = 6.05$ and 2.20 Hz), 6.85 (1H, d, $J_{\text{H-H}} = 5.50$ Hz) 3.85 (2H, s, CH_2NHtBu), 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, ($\text{C}_{26}\text{H}_{24}\text{N}_3\text{FCl}_2$) requires 467.13315
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