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Potential Antimalarials. XII*
4-Chloro-3-(substituted amino)methyl-5-[7-bromo (and 7-trifluoromethyl)-1,5-naphthyridin-4-ylamino]biphenyl-2-ols and 4-Chloro-3-(substituted amino)methyl-5-(7-trifluoromethylquinazolin-4-ylamino)biphenyl-2-ols

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Abstract

The mono-Mannich bases 3-(t-butylamino)methyl-4′-chloro-, 3-(4-benzylpiperidin-1-yl)methyl-4′-chloro-, 3-(4-benzylpiperazin-1-yl)methyl-4′-chloro-, 4′-chloro-3-diethylaminomethyl-, 4′-chloro-3-(pyrrolidin-1-yl)methyl-, 4′-chloro-3-(piperidin-1-yl)methyl- and 4′-chloro-3-(3- and 4-methylpiperidin-1-yl)methyl-5-[7-bromo (and 7-trifluoromethyl)-1,5-naphthyridin-4-ylamino]-biphenyl-2-ol, and the corresponding substituted 5-(7-trifluoromethylquinazolin-4-ylamino)biphenyl-2-ols, have been prepared by condensation of the 5-amino-3-(*N*-substituted aminomethyl)-4′-chlorobiphenyl-2-ols and the appropriate 4-chloro heterocycle.

The antimalarial activity of these products against the chloroquine-sensitive isolate (FCQ-27) of *Plasmodium falciparum* revealed that the 1,5-naphthyridines reported here were less active than the corresponding di-Mannich bases, e.g. (6), derived from 4-[7-bromo (and 7-trifluoromethyl)-1′,5′-naphthyridin-4′-ylamino]phenol, a feature not shared by the corresponding quinazolines.

Introduction

Previously we have reported the preparation of compounds (1),[1] Mannich bases derived from 4′-chloro-5-(7″-trifluoromethylquinolin-4″-ylamino)biphenyl-2-ol, which are analogues of the experimental antimalarial 'Tebuquine' (2).[2] We now describe the preparation of a range of such compounds derived from 4′-chloro-5-(7″-trifluoromethyl-1″-5″-naphthyridin-4″-yl)amino-, 5-(7″-bromo-1″,5″-naphthyridin-4″-yl)amino-4′-chloro- and 4′-chloro-5-(7″-trifluoromethylquinazolin-4″-yl)amino-biphenyl-2-ol.

Werbel and coworkers[2] have published an extensive structure–activity study of 'Tebuquine' and a series of related 3-(alkylamino)methyl-5-(7″-chloroquinolin-4″-ylamino)biphenyl-2-ols and $N^{1''}$-oxides; and we have described Mannich base derivatives of 4-[7′-bromo (7′-chloro and 7′-trifluoromethyl)-1′,5′-naphthyridin-

* Part XI, *Aust. J. Chem.*, 1990, **43**, 1301.

[1] Barlin, G. B., and Jiravinyu, C., *Aust. J. Chem.*, 1990, **43**, 1301.

[2] Werbel, L. M., Cook, P. D., Elslager, E. F., Hung, J. H., Johnson, J. L., Kesten, S. J., McNamara, D. J., Ortwine, D. F., and Worth, D. F., *J. Med. Chem.*, 1986, **29**, 924.

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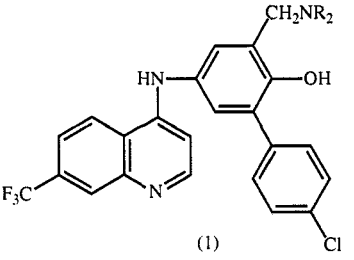
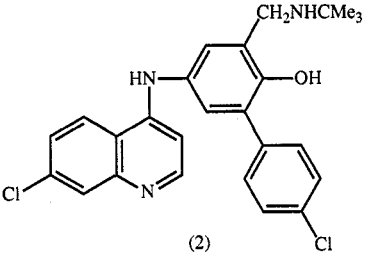
4′-ylamino]phenols[3–6] and 4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol,[7] including some results of antimalarial testing against the human malaria *Plasmodium falciparum*.[8,9]



(1)



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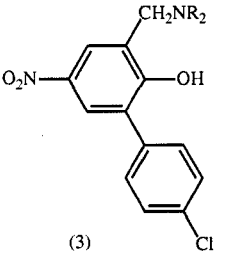

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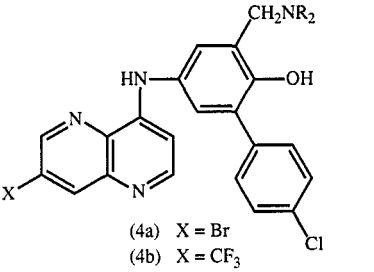
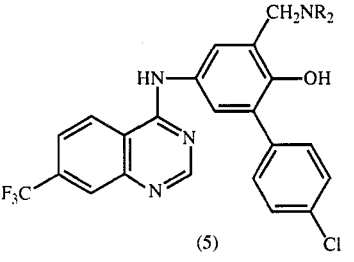
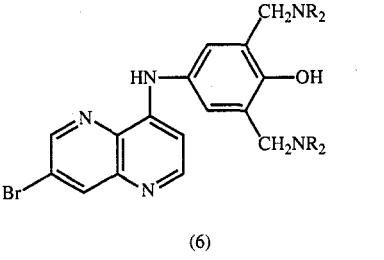


(4a) X = Br
(4b) X = CF_3



(5)



(6)

Syntheses

The compounds described in this paper were prepared from the appropriate 4′-chloro-3-(substituted amino)methyl-5-nitrobiphenyl-2-ols[1] [e.g. (3)] by catalytic reduction to the corresponding 5-aminobiphenyl-2-ol and subsequent condensation with the relevant 4-chloro-7-bromo(or 7-trifluoromethyl)-1,5-naphthyridine or 4-chloro-7-trifluoromethylquinazoline in aqueous methanol (containing a little hydrochloric acid) to give the Mannich base derivatives, e.g. (4a,b) or (5), of 4′-chloro-5-[7″-bromo (and 7″-trifluoromethyl)-1″,5″-naphthyridin-4″-ylamino]biphenyl-2-ols or 4′-chloro-5-(7″-trifluoromethylquinazolin-4″-yl)amino-biphenyl-2-ol, respectively.

[3] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1985, **38**, 459.
[4] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1985, **38**, 905.
[5] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1985, **38**, 51.
[6] Barlin, G. B., and Ireland, S. J., *Aust. J. Chem.*, 1988, **41**, 1727.
[7] Barlin, G. B., and Jiravinyu, C., *Aust. J. Chem*, 1990, **43**, 311.
[8] Scott, H. V., Tan, W.-L., and Barlin, G. B., *Ann. Trop. Med. Parasitol.*, 1987, **81**, 85.
[9] Scott, H. V., Tan, W.-L., and Barlin, G. B., *Ann. Trop. Med. Parasitol.*, 1988, **82**, 127.

Biological Activity

Antimalarial activity of the compounds reported in this paper was measured by *in vitro* tests against the chloroquine-sensitive (FCQ-27) isolate of the human malaria parasite *Plasmodium falciparum*; details of these are recorded in the Experimental section. In this procedure the incorporation of [G-^{3}H]hypoxanthine was used as the index of parasite growth and development.[10]

Table 1. Antimalarial activity *in vitro* of a series of Mannich base derivatives (4a,b) and (5), and chloroquine against the FCQ-27 isolate of *Plasmodium faciparum*

Results are expressed in nmol l^{-1}

Inhibitor	IC_{50}	Inhibitor	IC_{50}
(4a; NR_2 = diethylamino)	60	(4b; NR_2 = 4-methylpiperidin-1-yl)	40
(4a; NR_2 = t-butylamino)	30	(4b; NR_2 = 4-benzylpiperidin-1-yl)	>200
(4a; NR_2 = pyrrolidin-1-yl)	70	(4b; NR_2 = 4-benzylpiperazin-1-yl)	>200
(4a; NR_2 = piperidin-1-yl)	80		
(4a; NR_2 = 3-methylpiperidin-1-yl)	90	(5; NR_2 = diethylamino)	80
(4a; NR_2 = 4-methylpiperidin-1-yl)	160	(5; NR_2 = t-butylamino)	20
(4a; NR_2 = 4-benzylpiperidin-1-yl)	>200	(5; NR_2 = pyrrolidin-1-yl)	30
(4a; NR_2 = 4-benzylpiperazin-1-yl)	145	(5; NR_2 = piperidin-1-yl)	120
		(5; NR_2 = 3-methylpiperidin-1-yl)	75
(4b; NR_2 = diethylamino)	170	(5; NR_2 = 4-methylpiperidin-1-yl)	140
(4b; NR_2 = t-butylamino)	50	(5; NR_2 = 4-benzylpiperidin-1-yl)	>200
(4b; NR_2 = pyrrolidin-1-yl)	70	(5; NR_2 = 4-benzylpiperazin-1-yl)	>200
(4b; NR_2 = piperidin-1-yl)	90		
(4b; NR_2 = 3-methylpiperidin-1-yl)	150	chloroquine	12

The results are recorded in Table 1. Inspection reveals that in each of the three series of compounds the Mannich base containing a t-butylamino group was the most active, followed closely by those containing a pyrrolidin-1-yl group. Generally the least active compounds were those containing the benzylpiperidin-1-yl or benzylpiperazin-1-yl groups, but this may be related to solubility under the test conditions. A comparison of the results in Table 1 for the compounds (4a) with those published[8,9] for the di-Mannich bases (6) of 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)phenol reveals that the di-Mannich bases have higher activities. For example, the IC_{50} value recorded[9] for compound (6; NR_2 = pyrrolidin-1-yl) was 3·6 nmol l^{-1} whereas that for the corresponding compound (4a; NR_2 = pyrrolidin-1-yl) reported in this paper was 70 nmol l^{-1}.

A comparison of the antimalarial activity of the compounds (4b) with the as yet unpublished results for the di-Mannich bases of 4-(7′-trifluoromethyl-1′,5′-naphthyridin-4′-ylamino)phenol revealed a similar pattern. The quinazolines (5), however, did not show consistent or marked differences in activity from the published[7] data for the corresponding di-Mannich bases. For example, the quinazoline (5; $NR_2 = NEt_2$) was more active and others such as (5; NR_2 = 4-methylpiperidin-1-yl) were less active than the corresponding di-Mannich bases.

[10] Desjardins, R. E., Canfield, C. J., Haynes, J. D., and Chulay, J. D., *Antimicrob. Agents Chemother.* 1979, **16**, 710.

Experimental

All products were examined by thin-layer chromatography for the presence of impurities. Melting points were taken in Pyrex capillaries and are uncorrected. Unless otherwise stated samples for analysis were dried at 70–90°/0·2 mmHg for 20–40 h. Analyses were performed by the Australian National University Analytical Services Unit. ^{1}H n.m.r. spectra were recorded in $CDCl_3$ solutions with tetramethylsilane as internal standard and at 90 MHz and 30° with a Jeol FX90Q Fourier-transform spectrometer possessing digital resolution of 0·12 Hz.

4′-Chloro-3-diethylaminomethyl-5-(7″-trifluoromethyl-1″,5″-naphthyridin-4″-yl)aminobiphenyl-2-ol

4′-Chloro-3-diethylaminomethyl-5-nitrobiphenyl-2-ol[1] (0·122 g) was dissolved in half-saturated ethanolic ammonia (10 ml), and shaken with hydrogen over Raney nickel at room temperature until uptake ceased. The catalyst was filtered off on Celite, and the filtrate evaporated to give crude 5-amino-4′-chloro-3-diethylaminomethylbiphenyl-2-ol (0·085 g).

This amine (0·085 g, 0·28 mmol) and 4-chloro-7-trifluoromethyl-1,5-naphthyridine[11] (0·061 g, 0·26 mmol) in a mixture of methanol (1·5 ml), water (0·5 ml) and concentrated hydrochloric acid (3 drops) at pH 2·5 was refluxed in an oil bath at 95–100° for 5 h. The solvent was evaporated, the residue diluted with water (5·0 ml) and adjusted with 0·9 N sodium hydroxide to give a yellow precipitate. The product was extracted into chloroform; the extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a yellow oil. It was purified by t.l.c. (alumina; 20% ethyl acetate in hexane) to give the *title compound* (0·118 g), m.p. 140–142° (Found: C, 62·6; H, 5·0; N, 11·1. $C_{26}H_{24}ClF_3N_4O$ requires C, 62·3; H, 4·8; N, 11·3%). ^{1}H n.m.r. δ 1·16, t, J 7 Hz, Me; 2·73, q, J 7 Hz, Me**C**$\mathbf{H_2}$; 3·88, s, CH_2N; 7·01, d, J 5·5 Hz, H3″; 7·04, 7·26, br s, H4,6; 7·38, d, 7·59, d, J 9 Hz, H2′,3′,5′,6′; 8·36, br s, NH; 8·58, br s, H8″; 8·61, d, J 5·5 Hz, H2″; 8·95, d, J 2 Hz, H6″.

3-(4″-Benzylpiperidin-1″-ylmethyl)-5-(7‴-bromo-1‴,5‴-naphthyridin-4‴-yl)amino-4′-chlorobiphenyl-2-ol

A mixture of 7-bromo-4-chloro-1,5-naphthyridine[3] (0·059 g, 0·24 mmol) and crude 5-amino-3-(4″-benzylpiperidin-1″-yl)-4′-chlorobiphenyl-2-ol [0·100 g, 0·24 mmol; prepared by reduction, as above, of 3-(4″-benzylpiperidin-1″-yl)-4′-chloro-5-nitrobiphenyl-2-ol[1]] in a mixture of methanol (1·8 ml), water (0·6 ml) and concentrated hydrochloric acid (2 drops) was refluxed at 100° for 8 h. The product was isolated as above and purified by t.l.c. (alumina, methylene chloride), and recrystallized from a mixture of methylene chloride and hexane with concentration to give as a pale yellow solid the *title compound* (0·10 g), m.p. 169–170·5° (Found: C, 64·7; H, 4·8; N, 9·0. $C_{33}H_{30}BrClN_4O$ requires C, 64·6; H, 4·9; N, 9·1%). ^{1}H n.m.r. δ 1·63, complex, 2·09, complex, 3·04, complex, H2″,3″,4″,5″,6″; 2·49, d, J 5·5 Hz, C$\mathbf{H_2}$Ph; 3·73, s, CH_2N; 6·90, d, J 5·5 Hz, H3‴; 6·96, d, 7·17, d, J 3 Hz, H4,6; 7·38, d, 7·58, d, J 9 Hz, H2′,3′,5′,6′; 8·21, br, NH; 8·41, d, J 2 Hz, H8‴; 8·48, d, J 5·5 Hz, H2‴; 8·72, d, J 2 Hz, H6‴.

3-(t-Butylaminomethyl)-4′-chloro-5-(7″-trifluoromethylquinazolin-4″-ylamino)biphenyl-2-ol and Related Compounds

Crude 5-amino-3-(t-butylaminomethyl)-4′-chlorobiphenyl-2-ol (0·102 g; prepared by reduction of the corresponding nitro compound[1]) and 4-chloro-7-trifluoromethylquinazoline[7] (0·078 g) in a mixture of methanol (1·8 ml), water (0·8 ml) and concentrated hydrochloric acid (2 drops) were refluxed in an oil bath at 100° for 8 h. The crude product (0·153 g) was subjected to t.l.c. (alumina; 35% ethyl acetate in hexane) and then reprecipitated from dilute acetic acid solution by addition of 0·9 N ammonium hydroxide to give the *title compound*, m.p. 180° (dec.) (Found: C, 59·6; H, 4·9; N, 10·5. $C_{26}H_{24}ClF_3N_4O.1·3H_2O$ requires C, 59·6; H, 5·1; N, 10·7%). ^{1}H n.m.r. δ 1·30, s, Me; 4·01, s, CH_2N; 7·46, complex, H4,6,2′,3′,5′,6′; 7·66, d, J 9 Hz, H6″; 8·11, s, H8″; 8·14, d, J 9 Hz, H5″; 8·68, s, H2″.

[11] Barlin, G. B., and Jiravinyu, C., *Aust. J. Chem.*, 1990, **43**, 1175.

In a similar manner the following compounds were prepared from the corresponding chloro-substituted heterocycle and 3-substituted 4′-chloro-5-nitrobiphenyl-2-ol.[1]

3-(t-Butylaminomethyl)-4′-chloro-5-(7″-trifluoromethyl-1″,5″-naphthyridin-4″-yl)aminobiphenyl-2-ol (68%) after t.l.c. (alumina; 30% ethyl acetate/hexane) and reprecipitation from aqueous acid by neutralization with ammonium hydroxide gave a yellow solid, m.p. 189–192° (Found: C, 61·6; H, 4·6; N, 10·8. $C_{26}H_{24}ClF_3N_4O.0{\cdot}25H_2O$ requires C, 61·8; H, 4·9; N, 11·1%). ^{1}H n.m.r. δ 1·25, s, Me; 4·05, s, CH_2N; 7·14, d, J 5·5 Hz, H3″; 7·18, br s, 7·24, d, J 2 Hz, H4,6; 7·40, d, 7·59, d, J 9 Hz, H2′,3′,5′,6′; 8·34, br s, NH; 8·54, d, J 2 Hz, H8″; 8·64, d, J 5·5 Hz, H2″; 8·95, d, J 2 Hz, H6″.

4′-Chloro-3-(pyrrolidin-1″-ylmethyl)-5-(7‴-trifluoromethyl-1‴,5‴-naphthyridin-4‴-yl)-aminobiphenyl-2-ol (78%) [after t.l.c. (alumina; 20% ethyl acetate in hexane)], m.p. 125–127° (Found: C, 62·5; H, 4·3; N, 11·2. $C_{26}H_{22}ClF_3N_4O$ requires C, 62·6; H, 4·4; N, 11·2%). ^{1}H n.m.r. δ 1·89, complex, 2·73, complex, H2″,3″,4″,5″; 3·93, s, CH_2N; 7·01, d, J 5·5 Hz, H3‴; 7·04, br s, 7·27, br s, H4,6; 7·38, d, 7·59, d, J 9 Hz, H2′,3′,5′,6′; 8·32, br s, NH; 8·54, br s, H8‴; 8·61, d, J 5·5 Hz, H2‴; 8·93, br s, H6‴.

4′-Chloro-3-(piperidin-1″-ylmethyl)-5-(7‴-trifluoromethyl-1‴,5‴-naphthyridin-4‴-yl)aminobiphenyl-2-ol (77%), m.p. 165–166° [after t.l.c. (alumina; 25% ethyl acetate in hexane)] (Found: C, 63·3; H, 4·8; N, 10·6. $C_{27}H_{24}ClF_3N_4O$ requires C, 63·3; H, 4·7; N, 10·9%). ^{1}H n.m.r. δ 1·64, complex, 2·63, complex, H2″,3″,4″,5″,6″; 3·77, s, CH_2N; 7·01, d, J 5·5 Hz, H3‴; 7·00, br s, 7·27, br s, H4,6; 7·40, d, 7·60, d, J 9 Hz, H2′,3′,5′,6′; 8·32, br s, NH; 8·55, br s, H8‴; 8·59, d, J 5·5 Hz, H2‴; 8·94, br s, H6‴.

4′-Chloro-3-(3″-methylpiperidin-1″-ylmethyl)-5-(7‴-trifluoromethyl-1‴,5‴-naphthyridin-4‴-yl)aminobiphenyl-2-ol was obtained after t.l.c. (alumina; 25% ethyl acetate in hexane) as a yellow oil (87%) (Found, for a sample dried at 60°/0·2 mmHg for 24 h: C, 63·9; H, 5·1, N, 10·3. $C_{28}H_{26}ClF_3N_4O$ requires C, 63·8; H, 5·0; N, 10·6%). ^{1}H n.m.r. δ 0·90, d, J 5·5 Hz, Me; 1·73, complex, 2·35, complex, 2·98, complex, H2″,3″,4″,5″,6″; 3·79, s, CH_2N; 7·01, J 5·5 Hz, H3‴; 7·04, br s, 7·26, br s, H4,6; 7·38, d, 7·58, d, J 9 Hz, H2′,3′,5′,6′; 8·36, br s, NH; 8·57, br s, H8‴; 8·60, d, J 5·5 Hz, H2‴; 8·93, br s, H6‴.

4′-Chloro-3-(4″-methylpiperidin-1″-ylmethyl)-5-(7‴-trifluoromethyl-1‴,5‴-naphthyridin-4‴-yl)aminobiphenyl-2-ol (84%) after t.l.c. (alumina; 20% ethyl acetate in hexane), m.p. 164–167° (Found: C, 64·0; H, 5·2; N, 10·5. $C_{28}H_{26}ClF_3N_4O$ requires C, 63·8; H, 5·0; N, 10·6%). ^{1}H n.m.r. δ 0·94, d, J 4·5 Hz, Me; 1·54, complex, 2·19, complex, 3·05, complex, H2″,3″,4″,5″,6″; 3·78, s, CH_2N; 6·99, d, J 5·5 Hz, H3‴; 7·03, br s, 7·24, br s, H4,6; 7·38, d, 7·58, d, J 9 Hz, H2′,3′,5′,6′; 8·32, br s, NH; 8·55, br s, H8‴; 8·60, d, J 5·5 Hz, H2‴; 8·93, br s, H6‴.

3-(4″-Benzylpiperidin-1″-ylmethyl)-4′-chloro-5-(7‴-trifluoromethyl-1‴,5‴-naphthyridin-4‴-yl)aminobiphenyl-2-ol (82%) after reprecipitation and t.l.c. (alumina; methylene chloride), m.p. *c.* 95° (Found: C, 68·0; H, 5·3; N, 9·2. $C_{34}H_{30}ClF_3N_4O$ requires C, 67·7; H, 5·0; N, 9·3%). ^{1}H n.m.r. δ 1·64, complex, 2·13, complex, 3·05, complex, H2″,3″,4″,5″,6″; 2·53, d, J 5·5 Hz, C**H**$_2$Ph; 3·76, s, CH_2N; 6·98, d, J 3 Hz, H3‴; 7·02, br s, 7·16, br s, H4,6; 7·39, d, 7·59, d, J 9 Hz, H2′,3′,5′,6′; 8·32, br s, NH; 8·54, br s, H8‴; 8·57, d, J 5·5 Hz, H2‴; 8·93, br s, H6‴.

3-(4″-Benzylpiperazin-1″-ylmethyl)-4′-chloro-5-(7‴-trifluoromethyl-1‴,5‴-naphthyridin-4‴-yl)aminobiphenyl-2-ol (87%) after t.l.c. (alumina; 30% ethyl acetate in hexane). It crystallized as a yellow solid from a mixture of methylene chloride and hexane and had m.p. 181–183° (Found: C, 63·8; H, 4·8; N, 11·0. $C_{33}H_{29}ClF_3N_5O.H_2O$ requires, C, 63·7; H, 5·0; N, 11·3%). ^{1}H n.m.r. δ 2·67, complex, H2″,3″,5″,6″; 3·60, s, PhC**H**$_2$N; 3·82, s, ArC**H**$_2$N; 7·00, d, J 7 Hz, H3‴; 7·04, br s, 7·28, br s, H4,6; 7·39, d, 7·58, d, J 9 Hz, H2′,3′,5′,6′; 8·32, br s, NH; 8·54, br s, H8‴; 8·60, d, J 5·5 Hz, H2‴; 8·94, d, J 2 Hz, H6‴.

5-(7″-Bromo-1″,5″-naphthyridin-4″-ylamino)-4′-chloro-3-diethylaminomethylbiphenyl-2-ol (96%) after t.l.c. (alumina; 20% ethyl acetate in hexane). Recrystallization from a mixture of ether and light petroleum (b.p. 60–80°) gave a pale yellow solid, m.p. 171–173° (Found: C, 59·0; H, 4·8; N, 11·1. $C_{25}H_{24}BrClN_4O$ requires C, 58·7; H, 4·7; N, 11·0%). ^{1}H n.m.r. δ 1·14, t, J 7 Hz, Me; 2·68, q, J 7 Hz, MeC**H**$_2$; 3·85, s, CH_2N; 6·92, d, J 5·5 Hz, H3″; 7·00, d, 7·24, d, J 3 Hz, H4,6; 7·38, d, 7·59, d, J 9 Hz, H2′,3′,5′,6′; 8·24, br, NH; 8·44, d, J 2 Hz, H8″; 8·50, d, J 5·5 Hz, H2″; 8·75, d, J 2 Hz, H6″.

5-(7″-Bromo-1″,5″-naphthyridin-4″-ylamino)-3-(t-butylaminomethyl)-4′-chlorobiphenyl-2-ol (66%), m.p. *c.* 97° [after t.l.c. (alumina; methylene chloride)] (Found, for a sample dried at 65°/0·2 mmHg for 20 h: C, 58·7; H, 4·8; N, 10·8. $C_{25}H_{24}BrClN_4O$ requires C, 58·7; H, 4·7;

N, 10·9%). ^{1}H n.m.r. δ 1·23, s, Me; 3·98, s, CH_2N; 6·87, d, *J* 5·5 Hz, H3″; 6·96, d, *J* 2 Hz, 7·18, d, *J* 2 Hz, H4,6; 7·35, d, 7·56, d, *J* 9 Hz, H2′,3′,5′,6′; 8·20, br, NH; 8·38, d, *J* 2 Hz, H8″; 8·47, d, *J* 5·5 Hz, H2″; 8·70, d, *J* 2 Hz, H6″.

5-(7″-Bromo-1″,5″-naphthyridin-4″-ylamino)-4′-chloro-3-(pyrrolidin-1‴-ylmethyl)biphenyl-2-ol (68%), m.p. 198–201° [from t.l.c. (alumina; 20% ethyl acetate in hexane)] (Found: C, 58·5; H, 4·3; N, 10·7. $C_{25}H_{22}BrClN_4O$ requires C, 58·9; H, 4·3; N, 11·0%). ^{1}H n.m.r. δ 1·90, complex, H3‴,4‴; 2·76, complex, H2‴,5‴; 3·96, s, CH_2N; 6·95, d, *J* 5·5 Hz, H3″; 7·05, d, 7·27, d, *J* 3 Hz, H4,6; 7·40, d, 7·60, d, *J* 9 Hz, H2′,3′,5′,6′; 8·30, br, NH; 8·49, br s, H8″; 8·53, d, *J* 5·5 Hz, H2″.

5-(7″-Bromo-1″,5″-naphthyridin-4″-ylamino)-4′-chloro-3-(piperidin-1‴-ylmethyl)biphenyl-2-ol (91%), m.p. 173–175° [after t.l.c. (alumina; 30% ethyl acetate in hexane, developed twice)] (Found: C, 59·5; H, 4·7; N, 10·4. $C_{26}H_{24}BrClN_4O$ requires C, 59·6; H, 4·6; N, 10·7%). ^{1}H n.m.r. δ 1·59, complex, 2·60, complex, H2‴,3‴,4‴,5‴,6‴; 3·75, s, CH_2N; 6·92, d, *J* 5·5 Hz, H3″; 6·99, d, 7·24, d, *J* 3 Hz, H4,6; 7·37, d, 7·59, d, *J* 9 Hz, H2′,3′,5′,6′; 8·24, br, NH; 8·47, s, H8″; 8·48, d, *J* 5·5 Hz, H2″; 8·75, d, *J* 2 Hz, H6″.

5-(7″-Bromo-1″,5″-naphthyridin-4″-ylamino)-4′-chloro-3-(3‴-methylpiperidin-1‴-ylmethyl)-biphenyl-2-ol (78%) after t.l.c. (alumina; 30% ethyl acetate in hexane; then alumina; methylene chloride), m.p. 86–88° (Found: C, 60·3; H, 4·7; N, 10·3. $C_{27}H_{26}BrClN_4O$ requires C, 60·3; H, 4·9; N, 10·4%). ^{1}H n.m.r. δ 0·90, d, *J* 5·5 Hz, Me; 1·69, complex, 2·92, complex, H2‴,3‴,4‴,5‴,6‴; 3·75, s, C**H**$_2$N; 6·93, d, *J* 5·5 Hz, H3″; 7·00, d, 7·24, d, *J* 3 Hz, H4,6; 7·39, d, 7·59, d, *J* 9 Hz, H2′,3′,5′,6′; 8·24, br s, NH; 8·44, d, *J* 2 Hz, H8″; 8·51, d, *J* 5·5 Hz, H2″; 8·74, d, *J* 2 Hz, H6″.

5-(7″-Bromo-1″,5″-naphthyridin-4″-ylamino)-4′-chloro-3-(4‴-methylpiperidin-1‴-ylmethyl)-biphenyl-2-ol (95%), m.p. 207–209° [after t.l.c. (alumina; 33% ethyl acetate in hexane)] (Found: C, 60·5; H, 5·0; N, 10·3. $C_{27}H_{26}BrClN_4O$ requires C, 60·3; H, 4·9; N, 10·4%). ^{1}H n.m.r. δ 0·93, d, *J* 4·5 Hz, Me; 1·25, complex, 3·04, complex, H2‴,3‴,4‴,5‴,6‴; 3·77, s, CH_2N; 6·92, d, *J* 5·5 Hz, H3″; 7·00, d, 7·26, d, *J* 3 Hz, H4,6; 7·39, d, 7·58, d, *J* 9 Hz, H2′,3′,5′,6′; 8·33, br, NH; 8·48, br s, H8″; 8·51, d, *J* 5·5 Hz, H2″; 8·76, br s, H6″.

3-(4″-Benzylpiperazin-1″-ylmethyl)-5-(7‴-bromo-1‴,5‴-naphthyridin-1‴-ylamino)-4′-chlorobiphenyl-2-ol (81%), m.p. *c.* 107–110° [after t.l.c. (alumina; methylene chloride; and alumina; 25% ethyl acetate in hexane, developed twice)] (Found: C, 62·5; H, 4·8; N, 11·2. $C_{32}H_{29}BrClN_5O$ requires C, 62·5; H, 4·8; N, 11·4%). ^{1}H n.m.r. δ 2·66, complex, H2″,3″,5″,6″; 3·56, s, PhC**H**$_2$N; 3·80, s, ArC**H**$_2$N; 6·92, d, *J* 5·5 Hz, H3‴; 7·02, d, 7·26, d, *J* 3 Hz, H4,6; 7·39, d, 7·58, d, *J* 9 Hz, H2′,3′,5′,6′; 8·26, br, NH; 8·46, d, *J* 2 Hz, H8‴; 8·50, d, *J* 5·5 Hz, H2‴; 8·75, d, *J* 2 Hz, H6‴.

4′-Chloro-3-diethylaminomethyl-5-(7″-trifluoromethylquinazolin-4″-ylamino)biphenyl-2-ol (73%), m.p. *c.* 110° [after t.l.c. (alumina; 34% ethyl acetate in hexane)] (Found: C, 62·4; H, 5·0; N, 11·2. $C_{26}H_{24}ClF_3N_4O$ requires C, 62·3; H, 4·8; N, 11·2%). ^{1}H n.m.r. δ 1·14, t, *J* 7 Hz, Me; 2·70, q, *J* 7 Hz, MeC**H**$_2$; 3·87, s, CH_2N; 7·42, s, H4,6; 7·36, d, 7·58, d, *J* 9 Hz, H2′,3′,5′,6′; 7·57, d, *J* 9 Hz, H6″; 8·00, d, *J* 9 Hz, H5″; 8·17, br s, H8″; 8·76, s, H2″.

4′-Chloro-3-(pyrrolidin-1″-ylmethyl)-5-(7‴-trifluoromethylquinazolin-4‴-ylamino)biphenyl-2-ol (72%), m.p. 115–120° [after t.l.c. (alumina; methylene chloride)] (Found: C, 62·8; H, 4·5; N, 10·9. $C_{20}H_{22}ClF_3N_4O$ requires C, 62·6; H, 4·4; N, 11·2%). ^{1}H n.m.r. δ 1·86, complex, 2·72, complex, H2″,3″,4″,5″; 3·93, s, CH_2N; 5·53, br, NH; 7·42, s, H4,6; 7·37, d, 7·57, d, *J* 9 Hz, H2′,3′,5′,6′; 7·69, d, *J* 9 Hz, H6‴; 8·02, d, *J* 9 Hz, H5‴; 8·17, br s, H8‴; 8·76, s, H2‴.

4′-Chloro-3-(piperidin-1″-ylmethyl)-5-(7‴-trifluoromethylquinazolin-4‴-ylamino)biphenyl-2-ol (81%), m.p. *c.* 135° with sublimation [after t.l.c. (alumina; 30% ethyl acetate in hexane; then alumina; methylene chloride)] (Found: C, 63·0; H, 4·6; N, 10·6. $C_{27}H_{24}ClF_3N_4O$ requires C, 63·3; H, 4·7; N, 10·9%). ^{1}H n.m.r. δ 1·59, complex, 2·60, complex, H2″,3″,4″,5″,6″; 3·78, s, CH_2N; 4·42, br s, NH; 7·43, s, H4,6; 7·38, d, 7·57, d, *J* 9 Hz, H2′,3′,5′,6′; 7·70, d, *J* 9 Hz, H6‴; 8·03, d, *J* 9 Hz, H5‴; 8·17, br s, H8‴; 8·72, s, H2‴.

4′-Chloro-3-(3″-methylpiperidin-1″-ylmethyl)-5-(7‴-trifluoromethylquinazolin-4‴-ylamino)-biphenyl-2-ol (69%), m.p. 118–122° [after t.l.c. (alumina; 30% ethyl acetate in hexane)] (Found: C, 63·8; H, 5·2; N, 10·3. $C_{28}H_{26}ClF_3N_4O$ requires C, 63·8; H, 5·0; N, 10·6%). ^{1}H n.m.r. δ 0·87, d, *J* 5·5 Hz, Me; 1·72, complex, 3·02, complex, H2″,3″,4″,5″,6″; 3·75, s, CH_2N; 7·43, s, H4,6; 7·38, d, 7·59, d, *J* 9 Hz, H2′,3′,5′,6′; 7·68, d, *J* 9 Hz, H6‴; 8·01, d, *J* 9 Hz, H5‴; 8·19, br s, H8‴; 8·77, s, H2‴.

4′-Chloro-3-(4″-methylpiperidin-1″-ylmethyl)-5-(7‴-trifluoromethylquinazolin-4‴-ylamino)-biphenyl-2-ol (56%), m.p. 119–123° [after t.l.c. (alumina; 36% ethyl acetate in hexane)] (Found: C, 63·8; H, 5·0; N, 10·3. $C_{28}H_{26}ClF_3N_4O$ requires C, 63·8; H, 5·0; N, 10·6%). ^{1}H n.m.r. δ 0·93, d, J 3·5 Hz, Me; 1·51, complex, 2·20, complex, 3·06, complex, H 2″,3″,4″,5″,6″; 3·80, s, CH_2N; 7·42, s, H 4,6; 7·39, d, 7·58, d, J 9 Hz, H 2′,3′,5′,6′; 7·68, d, J 9 Hz, H 6‴; 8·01, d, J 9 Hz, H 5‴; 8·19, br s, H 8‴; 8·77, s, H 2‴.

3-(4″-Benzylpiperidin-1″-ylmethyl)-4′-chloro-5-(7‴-trifluoromethylquinazolin-4‴-ylamino)-biphenyl-2-ol (78%) after t.l.c. (alumina; methylene chloride; then alumina; 80% methylene chloride in hexane, developed twice), m.p. *c.* 140° (after filtration from dilute hydrochloric acid) (Found: C, 67·9; H, 5·3; N, 9·0. $C_{34}H_{30}ClF_3N_4O$ requires C, 67·7; H, 5·0; N, 9·2%). ^{1}H n.m.r. δ 1·62, complex, 2·14, complex, 3·07, complex, H 2″,3″,4″,5″,6″; 2·52, d, J 5·5 Hz, C**H**$_2$Ph; 3·78, s, CH_2N; 7·41, s, H 4,6; 7·39, d, 7·58, d, J 9 Hz, H 2′,3′,5′,6′; 7·69, d, J 9 Hz, H 6‴; 8·01, d, J 9 Hz, H 5‴; 8·16, s, H 8‴; 8·75, s, H 2‴.

3-(4″-Benzylpiperazin-1″-ylmethyl)-4′-chloro-5-(7‴-trifluoromethylquinazolin-4‴-ylamino)-biphenyl-2-ol (64%) [after t.l.c. (alumina; 40% ethyl acetate in hexane)]. It was dissolved in dilute hydrochloric acid and reprecipitated with aqueous ammonium hydroxide to give a yellow solid, m.p. 144–150° (Found: C, 63·2; H, 4·7; N, 10·9. $C_{33}H_{29}ClF_3N_5O.1·4H_2O$ requires C, 63·0; H, 5·1; N, 11·1%). ^{1}H n.m.r. δ 2·71, complex, H 2″,3″,5″,6″; 3·63, s, C**H**$_2$Ph; 3·83, s, CH_2N; 7·44, complex, H 4,6,2″,3″,5″,6″; 7·73, d, J 9 Hz, H 6‴; 8·06, d, J 9 Hz, H 5‴; 8·19, br s, H 8‴; 8·78, s, H 2‴.

Antimalarial Activity

The compounds reported in this paper were examined for antimalarial activity *in vitro* against the chloroquine-sensitive isolate (FCQ-27) of *P. falciparum* in the laboratories of Dr G. A. Butcher, Zoology Department, Australian National University. This procedure, in which the incorporation of [G-^{3}H]hypoxanthine was used as an index of parasite growth and development, was first described by Desjardines *et al.*,[10] and has been employed in our work previously.[7,8,12]

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