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Potential Antimalarials. VI*
Mannich Bases Derived from 4-[7′-Bromo(and chloro)-1′,5′-naphthyridin-4′-ylamino]phenols and 4-(7′-Trifluoromethylquinolin-4′-ylamino)phenol

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Abstract

Eleven di-Mannich bases derived from 4-[7′-bromo(and chloro)-1′,5′-naphthyridin-4′-ylamino]phenols and 4-(7′-trifluoromethylquinolin-4′-ylamino)phenol have been prepared. Each of these compounds showed very good antimalarial activity w en injected intraperitoneally in a single dose of 50–100 mg/kg to mice infected with *Plasmodium vinckei vinckei*.

Introduction

In earlier parts[1–3] of this series we reported the synthesis and significant antimalarial activity (against *P. vinckei vinckei* in mice) of a series of N^4-substituted 7-bromo(and chloro)-1,5-naphthyridin-4-amines,[1,2] 4-[7′-bromo(and chloro)-1′,5′-naphthyridin-4′-ylamino]phenols[1,2] and 4-(7′-trifluoromethylquinolin-4′-ylamino)phenols.[3] Apparent cures were effected when many of these test chemicals were injected intraperitoneally in a single dose of 100 or 200 mg/kg to infected mice.

In tests *in vitro* against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* three of the compounds described in Parts III[1] and IV,[2] namely 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(dimethylaminomethyl, dipropylaminomethyl and pyrrolidin-1″-ylmethyl)phenol, were more effective than chloroquine and similar in activity to amodiaquine and mefloquine.[4]

In this paper we report the preparation of further 'symmetrical' di-Mannich bases (1a–c), (1e–h) and (2a–c), derived from 4-[7′-bromo(and chloro)-1′,5′-naphthyridin-4′-ylamino]phenols (1; X = Br, $R^1 = R^2 = H$) and (1; X = Cl, $R^1 = R^2 = H$), and 4-(7′-trifluoromethylquinolin-4′-ylamino)phenol (2; R = H), and an 'unsymmetrical' di-Mannich base (1d) derived from (1; X = Br, $R^1 = R^2 = H$) and incorporating two amines found to be most effective in our tests against chloroquine-resistant *P. falciparum*.[4]

* Part V, *Aust. J. Chem.*, 1985, **38**, 1827.

[1] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1985, **38**, 459.
[2] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1985, **38**, 905.
[3] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1985, **38**, 1827.
[4] Scott, H. V., Tan, W.-L., and Barlin, G. B., unpublished data.

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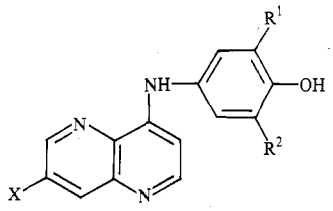
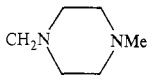
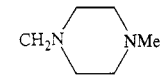
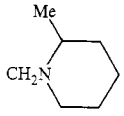
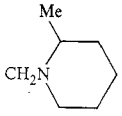
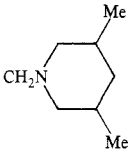
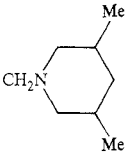
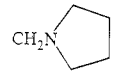
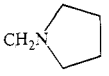
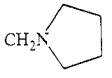
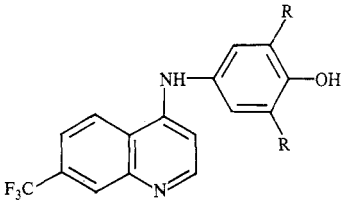
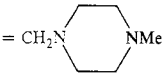
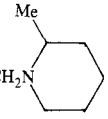


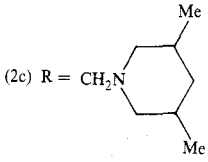
	X	R^1	R^2
(1a)	Br		
(1b)	Br		
(1c)	Br		

	X	R^1	R^2
(1d)	Br	CH_2NMe_2	
(1e)	Cl	CH_2NMe_2	CH_2NMe_2
(1f)	Cl	CH_2NEt_2	CH_2NEt_2
(1g)	Cl	CH_2NPr_2	CH_2NPr_2
(1h)	Cl		



(2a) R = 

(2b) R = 

(2c) R = 

Testing of these di-Mannich bases against *P. vinckei vinckei* in mice also revealed significant antimalarial activity by all these new compounds.

Synthesis

The di-Mannich bases (1a–c,e,f,h) and (2a–c), which were symmetrically substituted about the *p*-aminophenol, were prepared by refluxing the *N*-substituted *p*-aminophenol (1; X = Cl, $R^1 = R^2 = H$), (1; X = Br, $R^1 = R^2 = H$) or (2; R = H) with excess formaldehyde and amine in ethanol for 20 h, but the preparation of the 2,6-bis(dipropylaminomethyl) analogue (1g) required a reflux time of 40 h to complete the formation of the di-Mannich base. The 'unsymmetrical' di-Mannich base (1d) was prepared from 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(pyrrolidin-1″-ylmethyl)phenol[2] by refluxing with excess formaldehyde and ethanolic dimethylamine for 10 h.

Table 1. Preliminary antimalarial screening results against *Plasmodium vinckei vinckei* in mice

For details of test procedures see Experimental section. Times given are those after injection of the chemical under test. Time: h, hours; d, days; 0 h denotes pretreatment

Compound	Solvent	Dose (mg/kg)	Mean percentage of parasite-infected red cells															
			0 h	9 h	24 h	48 h	3 d	4 d	5 d	6 d	7 d	8 d	9 d	10 d	11 d	12 d	14 d	19 d
(1a)	peanut oil	100	10	4	1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	3[A]	
(1b)	peanut oil	100	9	3	<1	<1	<1	<1	<1	<1	<1	<1	1	14	28	55	[B]	
(1c)	peanut oil	100	14	20	13	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
(1d)	peanut oil	100	9	6	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
(1e)	peanut oil	100	13	11	1	<1	<1	<1	<1	<1	<1	<1	<1	3	5	19	[C]	
(1f)	peanut oil	100	4	1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
(1g)	peanut oil	100	10	7	2	1	<1	<1	<1	2	6	17	21	27	7	3	2	<1[D]
(1h)	peanut oil	100	9	5	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	[E]
(2a)	peanut oil	50	7	4	2	<1	<1	<1	<1	<1	<1	5	14	33	40	[F]		
(2b)	peanut oil	100	18	18	4	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	3	26	[G]
(2c)	peanut oil	100	12	12	6	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Normal saline			11	19	28	57	[H]											
Peanut oil			8	13	31	63	[H]											
Chloroquine[I]	normal saline	40	24	18	3	<1	<1	<1	<1	2	2	<1	<1	<1	<1	<1	<1	<1

[A] Parasitaemia of one mouse 12% at 14 days. This mouse dead at 19 days, parasitaemia of other two mice <1%.
[B] Two mice dead at 14 days, parasitaemia of remaining mouse 8% at 14 days and <1% at 19 days.
[C] One mouse dead at 14 days, parasitaemia of other two average 11%.
[D] Parasitaemia rose in one mouse only, to 80%, then declined.
[E] One mouse dead at 19 days, parasitaemia of other two mice <1%.
[F] Two mice dead at 12 days, parasitaemia of other mouse <1% at 19 days.
[G] All mice dead at 19 days.
[H] One mouse dead at 3 days, all mice dead at 4 days.
[I] Diphosphate.

Transaminations rendered unsatisfactory the attempted preparation of 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminomethyl)-6-(pyrrolidin-1″-ylmethyl)phenol from 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminomethyl)phenol by reflux with formaldehyde and pyrrolidine; and the attempted preparation of 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminomethyl)-6-(dimethylaminomethyl)phenol from 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminomethyl)phenol with formaldehyde and dimethylamine, or from 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(dimethylaminomethyl)phenol with formaldehyde and diethylamine.

Biological Activities

Compounds reported in this paper were examined for toxicity and safe dosage levels prior to testing for antimalarial activity. Each compound was then examined for activity against *P. vinckei vinckei* in mice and the results, averaged for the three mice at each time point, are summarized in Table 1. All Mannich bases reported in this paper showed strong antimalarial activity under the test conditions. Parasitaemia values were significantly reduced within 24 h from treatment with the chemical, and in all cases was reduced to 1% or less within 48 h.

Comparison of the antimalarial test results reported here for the chloro compounds (1f,h) with those of their bromo analogues reported previously[2] at the same dose levels did not reveal any significant differences. Although the dose levels for chloro compounds (1e,g) were not the same as for their bromo analogues reported previously,[2] similar resuslts were observed.

The 7-trifluoromethylquinolines (2a–c) exhibited antimalarial activity comparable with that of their analogues reported in Part V[3] of this series.

Experimental

General

Solids and oils for analysis were dried at 100°/20 mmHg unless otherwise specified, and melting points were taken in Pyrex capillaries. Analyses were performed by the Australian National University Analytical Services Unit. ^{1}H n.m.r. spectra were recorded at 90 MHz and 30° with a Jeol FX90Q Fourier-transform spectrometer with digital resolution of 0·12 Hz, with tetramethylsilane in $CDCl_3$ or CD_3SOCD_3 as internal standards.

Syntheses

(a) 4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(4″-methylpiperazin-1″-ylmethyl)phenol (1a)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol[2] (0·2 g), formalin (2·0 ml), *N*-methylpiperazine (2·0 ml) and ethanol (10·0 ml) were refluxed with stirring for 20 h. Excess amine was distilled off under vacuum and the oily residue purified by t.l.c. (alumina; chloroform) to give (1a) as a yellow *oil* (0·17 g) (Found: C, 54·9; H, 6·2; N, 16·8. $C_{26}H_{34}BrN_7O.1·8H_2O$ requires C, 54·5; H, 6·6; N, 17·1%). ^{1}H n.m.r. ($CDCl_3$): δ 2·31, s, CH_3; 2·55, complex, H 2″,3″,5″,6″; 3·68, s, CH_2N; 6·87, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·09, s, H 3,5; 8·18, br s, NH; 8·42, d, $J_{6',8'}$ 2 Hz, H 8′; 8·49, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·74, d, $J_{6',8'}$ 2 Hz, H 6′.

(b) 4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(2″-methylpiperidin-1″-ylmethyl)phenol (1b)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol[2] (0·2 g), formalin (2·0 ml), 2-methylpiperidine (2·0 ml) and ethanol (10 ml) were treated as in (*a*). Traces of 2-methylpiperidine

were removed by triturating with water (50 ml) before the oily residue was purified by t.l.c. (alumina; chloroform) to give (1b) as a yellow *oil* (0·2 g) (Found: C, 62·9; H, 6·9; N, 12·8. $C_{28}H_{36}BrN_5O$ requires C, 62·5; H, 6·7; N, 13·0%). ^{1}H n.m.r. ($CDCl_3$): δ 1·18, d, *J* 6·5 Hz, CH_3; 1·58, complex, H 3″,4″,5″; 2·34, complex, H 2″; 2·85, complex, H 6″; 3·36, d, *J* 14 Hz, 4·10, d, *J* 14 Hz, CH_2N; 6·90, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·12, s, H 3,5; 8·19, br s, NH; 8·41, d, $J_{6',8'}$ 2 Hz, H 8′; 8·48, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·73, d, $J_{6',8'}$ 2 Hz, H 6′.

(c) 4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(3″,5″-dimethylpiperidin-1″-ylmethyl)phenol (1c)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·2 g), formalin (2·0 ml), 3,5-dimethylpiperidine (2·0 ml) and ethanol (10·0 ml) were treated as in (*a*), and the oily residue purified on t.l.c. (alumina; chloroform, then silica; methanol) to give (1c) as a yellow *oil* (0·12 g) (Found: C, 63·1; H, 7·2; N, 12·1. $C_{30}H_{40}BrN_5O$ requires C, 63·6; H, 7·1; N, 12·4%). ^{1}H n.m.r. ($CDCl_3$): δ 0·85, d, *J* 6·5 Hz, CH_3; 1·68, complex, H 3″,4″,5″; 2·90, complex, H 2″,6″; 3·63, s, CH_2N; 6·92, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·08, s, H 3,5; 8·22, br s, NH; 8·41, d, $J_{6',8'}$ 2 Hz, H 8′; 8·48, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·73, d, $J_{6',8'}$ 2 Hz, H 6′.

(d) 4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2-(dimethylaminomethyl)-6-(pyrrolidin-1″-ylmethyl)phenol (1d)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2-(pyrrolidin-1″-ylmethyl)phenol[2] (0·15 g), formalin (2·0 ml) and ethanolic dimethylamine (10 ml; 33%) were refluxed with stirring for 10 h. The reaction mixture was evaporated to dryness in a vacuum to leave an oil which was purified by t.l.c. (alumina; chloroform) to give (1d) as a yellow *oil* (0·11 g) (Found: C, 57·5; H, 5·8; N, 14·9. $C_{22}H_{26}BrN_5O$ requires C, 57·9; H, 5·7; N, 15·3%). ^{1}H n.m.r. ($CDCl_3$): δ 1·85, complex, H 3″,4″; 2·33, s, CH_3; 2·67, complex, H 2″,5″; 3·57, s, 6-CH_2; 3·79, s, 2-CH_2; 6·88, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·07, s, H 3,5; 8·20, br s, NH; 8·41, d, $J_{6',8'}$ 2 Hz, H 8′; 8·49, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·72, d, $J_{6',8'}$ 2 Hz, H 6′.

(e) 4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)phenol (1; X = Cl, R^1 = R^2 = H)

A mixture (*c.* 1 : 1·5) of 4,7-dichloro-1,5-naphthyridine[2] (0·66 g), and *p*-aminophenol hydrochloride (0·72 g), in methanol (20·0 ml) and water (20·0 ml) was refluxed with stirring for 2 h. The methanol was then evaporated under reduced pressure and the aqueous solution adjusted to pH 8 with ammonium hydroxide. The yellow precipitate was collected, washed with water and recrystallized from methanol to give *4-(7′-chloro-1′,5′-naphthyridin-4′-ylamino)phenol* (0·7 g), m.p. 240–241° (Found: C, 61·9; H, 3·8; N, 15·1. $C_{14}H_{10}ClN_3O$ requires C, 61·9; H, 3·7; N, 15·5%). ^{1}H n.m.r. (CD_3SOCD_3): δ 6·81, d, $J_{2',3'}$ 5·5 Hz, H 3′; 6·83, d, $J_{2,3}$ 8·5 Hz, H 2,6; 7·23, d, $J_{2,3}$ 8·5 Hz, H 3,5; 8·35, d, $J_{6',8'}$ 2 Hz, H 8′; 8·44, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·81, d, $J_{6',8'}$ 2 Hz, H 6′; 9·18, br s, NH; 9·45, br s, OH.

(f) 4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(dimethylaminoethyl)phenol (1e)

4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)phenol (0·2 g), formalin (2·0 ml) and ethanolic dimethylamine (20·0 ml; 33%) were treated as in (*a*) to give (1e) as a yellow *oil* (0·22 g) (Found: C, 61·2; H, 6·4; N, 17·7. $C_{20}H_{24}ClN_5O.\frac{1}{2}H_2O$ requires C, 60·8; H, 6·4; N, 17·7%). ^{1}H n.m.r. ($CDCl_3$): δ 2·34, s, CH_3; 3·58, s, CH_2N; 6·86, d, $J_{2',3'}$ 5·5 Hz, H 3′; 6·07, s, H 3,5; 8·18, br s, NH; 8·23, d, $J_{6',8'}$ 2 Hz, H 8′; 8·50, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·64, d, $J_{6',8'}$ 2 Hz, H 6′.

(g) 4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(diethylaminomethyl)phenol (1f)

4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)phenol (0·2 g), formalin (2·0 ml), diethylamine (2·0 ml) and ethanol (10·0 ml) were treated as in (*a*), and the residue purified by t.l.c. (silica; methanol) to give (1f) as a yellow *oil* which slowly crystallized (0·19 g), m.p. 106–107° (Found: C, 65·0; H, 7·5; N, 15·7. $C_{24}H_{32}ClN_5O$ requires C, 65·2; H, 7·3; N, 15·8%). ^{1}H n.m.r. ($CDCl_3$): δ 1·10, t, *J* 7 Hz, CH_3CH_2; 2·63, q, *J* 7 Hz, CH_3CH_2 3·71, s, CH_2N; 6·88, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·11, s, H 3,5; 8·20, br s, NH; 8·23, d, $J_{6',8'}$ 2 Hz, H 8′; 8·49, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·65, d, $J_{6',8'}$ 2 Hz, H 6′.

(h) 4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(dipropylaminomethyl)phenol (1g)

4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)phenol (0·2 g), formalin (2·0 ml), dipropylamine (2·0 ml) and ethanol (10·0 ml) were refluxed with stirring for 40 h (the reaction was incomplete at 20 h). The solution was evaporated to dryness under reduced pressure and the residue purified on t.l.c. (silica; methanol) to give (1g) as a yellow *oil* (0·20 g) (Found: C, 66·4; H, 8·1; N, 13·8. $C_{28}H_{40}ClN_5O.\frac{1}{2}H_2O$ requires C, 66·3; H, 8·1; N, 13·8%). ^{1}H n.m.r. ($CDCl_3$): δ 0·89, t, J 7 Hz, $CH_3CH_2CH_2$; 1·50, complex, $CH_3CH_2CH_2$; 2·48, complex, $CH_3CH_2CH_2$; 3·70, s, CH_2N; 6·89, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·12, s, H 3,5; 8·20, br s, NH; 8·23, d, $J_{6',8'}$ 2 Hz, H 8′; 8·49, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·65, d, $J_{6',8'}$ 2 Hz, H 6′.

(i) 4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(pyrrolidin-1″-ylmethyl)phenol (1h)

A mixture of 4-(7′-chloro-1′,5′-naphthyridin-4′-ylamino)phenol (0·2 g), formalin (2·0 ml), pyrrolidine (2·0 ml) and ethanol (10·0 ml) was treated as in (*b*), and the residue purified by t.l.c. (silica; methanol) to give (1h) as a yellow *oil* (0·21 g) (Found: C, 64·6; H, 6·6; N, 15·4. $C_{24}H_{28}ClN_5O.\frac{1}{2}H_2O$ requires C, 64·5; H, 6·5; N, 15·7%). ^{1}H n.m.r. ($CDCl_3$): δ 1·84, complex, H 3″,4″; 2·64, complex, H 2″,5″; 3·77, s, CH_2N; 6·87, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·09, s, H 3,5; 8·18, br s, NH; 8·23, d, $J_{6',8'}$ 2 Hz, H 8′; 8·50, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·65, d, $J_{6',8'}$ 2 Hz, H 6′.

(j) 2,6-Bis(4″-methylpiperazin-1″-ylmethyl)4-(7′-trifluoromethylquinolin-4′-ylamino)phenol (2a)

4-(7′-Trifluoromethylquinolin-4′-ylamino)phenol[3] (0·2 g), formalin (2·0 ml), *N*-methylpiperazine (2·0 ml) and ethanol (10·0 ml) were treated as in (*a*). The product was purified by column (alumina; chloroform) and thin-layer chromatography (silica; methanol) to give (2a) as a yellow *oil* which crystallized m.p. 163–164° (Found: C, 62·9; H, 7·2; N, 15·7. $C_{28}H_{35}F_3N_6O.\frac{1}{2}H_2O$ requires C, 62·6; H, 6·8; N, 15·6%). ^{1}H n.m.r. ($CDCl_3$): δ 2·30, s, CH_3; 2·53, complex, H 2″,3″,5″,6″; 3·67, s, CH_2N; 6·73, d, $J_{2',3'}$ 5·5 Hz, H 3′; 6·86, br s, NH; 7·04, s, H 3,5; 7·63, d, $J_{5',6'}$ 8·5 Hz, H 6′; 8·85, d, $J_{5',6'}$ 8·5 Hz, H 5′; 8·30, s, H 8′; 8·55, d, $J_{2',3'}$ 5·5 Hz, H 2′.

(k) 2,6-Bis(2″-methylpiperidin-1″-ylmethyl)-4-(7′-trifluoromethylquinolin-4′-ylamino)phenol (2b)

A mixture of 4-(7′-trifluoromethylquinolin-4′-ylamino)phenol (0·2 g), formalin (2·0 ml), 2-methylpiperidine (2·0 ml) and ethanol (10·0 ml) was treated as in (*b*). The oily residue was purified by t.l.c. (alumina; chloroform) to give a solid which was recrystallized from aqueous ethanol to give (2b) as yellow *crystals* (0·18 g), m.p. 102–104° (Found: C, 68·5; H, 7·3; N, 10·4. $C_{30}H_{37}F_3N_4O$ requires C, 68·4; H, 7·1; N, 10·6%). ^{1}H n.m.r. ($CDCl_3$): δ 1·18, d, J 6·5 Hz, CH_3; 1·58, complex, H 3″,4″,5″; 2·32, complex, H 2″; 2·90, complex, H 6″; 3·36, d, J 14 Hz, 4·10, d, J 14 Hz, CH_2N; 6·68, br s, NH; 6·76, $J_{2',3'}$ 5·5 Hz, H 3′; 7·07, s, H 3,5; 7·64, q, $J_{5',6'}$ 8·5, $J_{6',8'}$ 1·5 Hz, H 6′; 8·02, d, $J_{5',6'}$ 8·5 Hz, H 5′; 8·30, s, H 8′; 8·56, d, $J_{2',3'}$ 5·5 Hz, H 2′.

(l) 2,6-Bis(3″,5″-dimethylpiperidin-1″-ylmethyl)-4-(7′-trifluoromethylquinolin-4′-ylamino)phenol (2c)

4-(7′-Trifluoromethylquinolin-4′-ylamino)phenol (0·2 g), formalin (2·0 ml), 3,5-dimethylpiperidine (2·0 ml) and ethanol (10·0 ml) were treated as in (*a*). The product was purified by t.l.c. (alumina; chloroform) to give (2c) as a yellow *oil* (0·19 g) (Found: C, 67·0; H, 7·5; N, 9·7. $C_{32}H_{41}F_3N_4O.H_2O$ requires C, 67·1; H, 7·6; N, 9·8%). ^{1}H n.m.r. ($CDCl_3$): δ 0·86, d, J 6·5 Hz, CH_3; 1·65, complex, H 3″,4″,5″; 2·90, complex, H 2″,6″; 3·64, s, CH_2N; 6·78, br s, NH; 6·79, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·04, s, H 3,5; 7·63, q, $J_{5',6'}$ 8·5, $J_{6',8'}$ 1·5 Hz, H 6′; 8·02, br s, OH; 8·03, d, $J_{5',6'}$ 8·5 Hz, H 5′; 8·30, s, H 8′; 8·56, d, $J_{2',3'}$ 5·5 Hz, H 2′.

Toxicity Testing

Each 1,5-naphthyridine and quinoline used for antimalarial screening was tested for acute toxicity in mice by intraperitoneal injection in normal saline or peanut oil. Each test chemical was injected in a single dose of 100 mg/kg of body weight [except for 2,6-bis(4″-methylpiperazin-1″-ylmethyl)-4-(7′-trifluoromethylquinolin-4′-ylamino)phenol (2a) which, due to the death of one mouse at a dose of 100 mg/kg, was run at 50 mg/kg] to three mice.

No apparent ill effects were observed, and all mice survived to and beyond 30 days in the above tests, and in control experiments with normal saline and peanut oil.

Preliminary Antimalarial Screen

This was carried out as described previously.[1,5] Each test chemical was given at a dosage of 100 mg/kg of body weight except for 2,6-bis(4″-methylpiperazin-1″-ylmethyl)-4-(7′-trifluoromethylquinolin-4′-ylamino)phenol (2a) which was at 50 mg/kg, and blood counts were made at 9, 24, 48, and 72 h and thereafter as shown in Table 1.

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