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Potential Antimalarials. XXII*
Some 2,4-Diamino-5-(3- and 4-trifluoromethylphenyl and 3,4-methylenedioxyphenyl)pyrimidines

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A series of 10 pyrimethamine analogues containing 3′- and 4′-trifluoromethyl and 3′,4′-methylenedioxy groups has been prepared and tested for *in vitro* antimalarial activity against the FC-27 and K-1 isolates of *Plasmodium falciparum*. Several of these compounds were almost as active as pyrimethamine against the drug-sensitive FC-27 isolate, and like pyrimethamine, they were much less active against the drug-resistant K-1 isolate. The 4′-trifluoromethyl compunds, however, showed much smaller differences.

Introduction

In earlier work[1,2] we have shown that compound (1; X = H), with a 7-trifluoromethyl group in place of the 7-chloro substituent in amodiaquine, possesses comparable antimalarial activity to amodiaquine, and that this activity is enhanced further in the di-Mannich base derivatives (1; X = CH_2NR_2).[1,2] The antimalarial pyrimethamine (2a) also contains a chloro substituent, and we have now prepared analogous and isomeric compounds which contain the trifluoromethyl group, as in 2,4-diamino-5-(3′- and 4′-trifluoromethylphenyl)pyrimidines, for testing for antimalarial activity.

In unrelated work we have shown that a 3′,4′-methylenedioxyphenyl group in imidazo[1,2-*b*]pyridazines[3] is beneficial to biological activity so we have also prepared some 2,4-diamino-5-(3′,4′-methylenedioxyphenyl)pyrimidines for testing as antimalarials.

Syntheses

The compounds described in this work were prepared by a modification of the procedures described by Russell and Hitchings.[4] This is illustrated by the condensation of α-(3′-trifluoromethylphenyl)acetonitrile (3; X = 3-CF_3) with ethyl acetate in ethanolic sodium ethoxide to give α-acetyl-α-(3′-trifluoromethylphenyl)acetonitrile (4; X = 3-CF_3, R = Me) which, when methylated with diazomethane, gave β-methoxy-α-(3′-trifluoromethylphenyl)crotononitrile (5; X = 3-CF_3, R = Me). When compound (5) was treated with guanidine it cyclized to give 6-methyl-5-(3′-trifluoromethylphenyl)pyrimidine-2,4-diamine (2c).

The arylacetonitriles used in this work were α-(3′- and 4′-trifluoromethylphenyl and 3′,4′-methylenedioxyphenyl)acetonitriles; the esters were ethyl formate, ethyl acetate, ethyl propionate and α,α,α-trifluoroacetate. The polymerization of arylacetonitriles under alkaline reaction conditions has been discussed by Rogers, Leanza and Sarett.[5] In our reactions, the trifluoromethyl compounds [particularly α-(4′-trifluoromethylphenyl)acetonitrile] with esters and sodium ethoxide at elevated temperatures resulted in considerable decomposition/polymerization and we found it necessary to conduct such reactions at room temperature (20°). Under these reaction conditions the yields were relatively low in the initial condensation (some starting material was recovered) but subsequent reactions to the pyrimidines proceeded satisfactorily.

Condensations of α-(3′,4′-methylenedioxyphenyl)acetonitrile with esters in ethanolic sodium ethoxide, however, were carried out at reflux and gave good yields of the intermediate compounds (4; X = 3,4-OCH_2O) and ultimately of the pyrimidine-2,4-diamines (2h–k).

In these ways were prepared 5-(3′- and 4′-trifluoromethylphenyl)-6-(ethyl, methyl and unsubstituted)pyrimidine-2,4-diamines (2b–d) and (2e–g), and 5-(3′,4′-methylenedioxyphenyl)-6-(ethyl, methyl, trifluoromethyl and unsubstituted)pyrimidine-2,4-diamines (2h–k).

Biological Activity

The series of new pyrimethamine analogues described in this paper were examined for their antimalarial activity *in vitro* against both pyrimethamine and chloroquine sensitive (FC-27) and resistant (K-1) strains of

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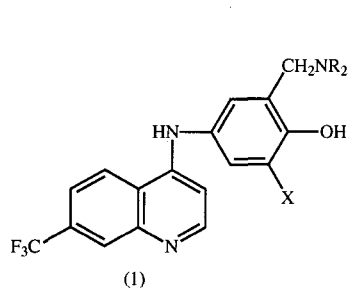

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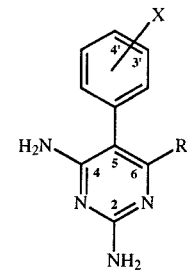

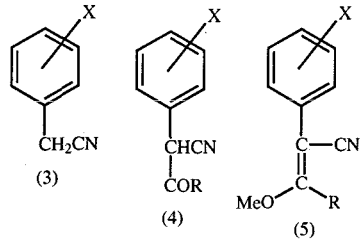

(3) (4) (5)

	X	R
(2a)	4'-Cl	Et
(2b)	3'-CF_3	H
(2c)	3'-CF_3	Me
(2d)	3'-CF_3	Et
(2e)	4'-CF_3	H
(2f)	4'-CF_3	Me
(2g)	4'-CF_3	Et
(2h)	3',4'-OCH_2O	H
(2i)	3',4'-OCH_2O	Me
(2j)	3',4'-OCH_2O	Et
(2k)	3',4'-OCH_2O	CF_3

Plasmodium falciparum. Pyrimethamine belongs to the class of antimalarials that inhibit dihydrofolate reductase (DHFR), the enzyme responsible for converting dihydrofolate into the biologically active tetrahydrofolate cofactor and in consequence inhibits DNA synthesis by malaria parasites. Milhous *et al.*[6] reported that antimalarial activity of DHFR inhibitors is antagonized by the presence of folic acid (FA) and *p*-aminobenzoic acid (PABA); therefore, *in vitro* assessment of their antimalarial activity requires control of these factors in the culture medium. Accordingly, in these studies, *in vitro* assays were conducted by using two types of culture medium; LPLF RPMI 1640, containing physiological levels of FA and PABA (physiological RPMI), and RPMI 1640, FA- and PABA-free (depleted RPMI).

Three independent test procedures were carried out; the microscopic (M) test at physiological RPMI and the radioisotopic (R) test at physiological and depleted RPMI. The results (as IC_{50} and IC_{90} values) for the FC-27 strain are given in Fig. 1, and those for the K-1 strain in Fig. 2.

Statistical analysis of the results showed a high positive correlation between the results obtained from the three different methods. The correlation coefficients were as follows:

Strain FC-27

M-LPLF RPMI/R-LPLF RPMI	0·99 (IC_{50});	0·98 (IC_{90})
M-LPLF RPMI/R-depleted RPMI	0·96 (IC_{50});	0·98 (IC_{90})
R-LPLF RPMI/R-depleted RPMI	0·95 (IC_{50});	1·00 (IC_{90})

Strain K-1

M-LPLF RPMI/R-LPLF RPMI	0·91 (IC_{50});	1·00 (IC_{90})
M-LPLF RPMI/R-depleted RPMI	0·87 (IC_{50});	0·91 (IC_{90})
R-LPLF RPMI/R-depleted RPMI	0·87 (IC_{50});	0·91 (IC_{90})

The abnormal appearance of the malarial parasites in the microscopic test after exposure to the test drugs and the comparatively lower IC_{50} and IC_{90} values observed in depleted RPMI suggest that the mode of action of all test compounds was similar to that of pyrimethamine.

The results for tests against the FC-27 isolate show that the activities of the compounds prepared in this work approached, but were generally less than, that

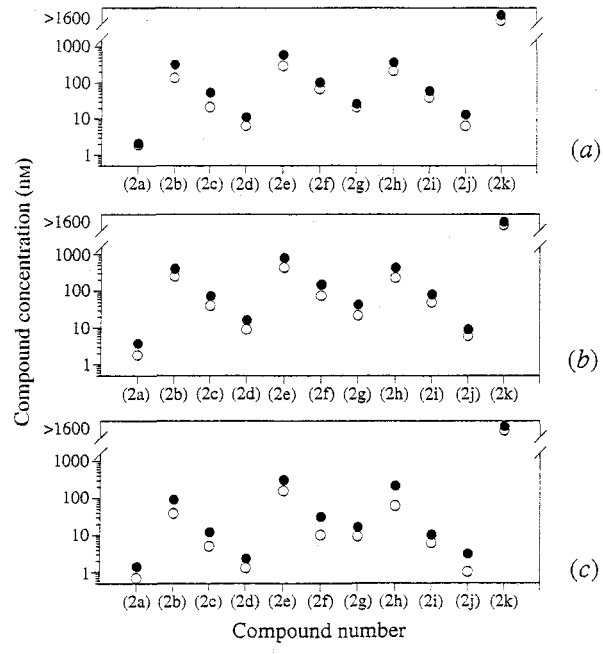

Fig. 1. Results for tests of compounds (2a–k) against the FC-27 isolate of *P. falciparum*: (*a*) microscopic-LPLF RPMI; (*b*) radioisotopic-LPLF RPMI; (*c*) radioisotopic-depleted RPMI. ○ IC_{50}; ● IC_{90}.

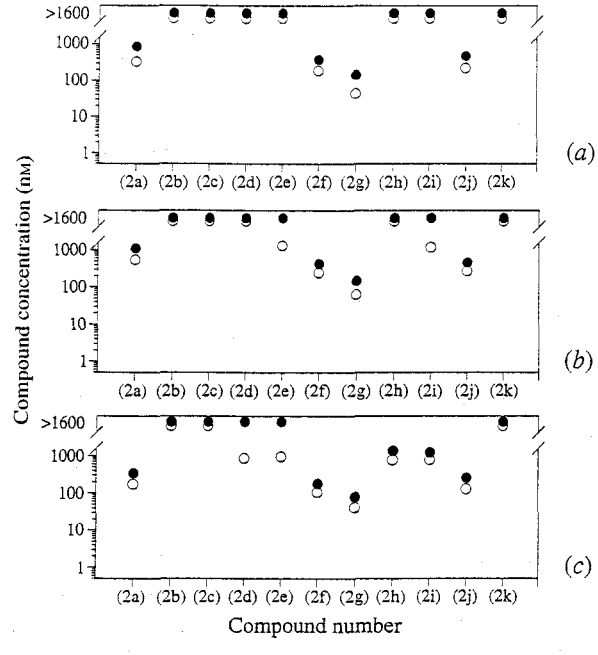

Fig. 2. Results for tests of compounds (2a–k) against the K-1 isolate of *P. falciparum*: (*a*) microscopic-LPLF RPMI; (*b*) radioisotopic-LPLF RPMI; (*c*) radioisotopic-depleted RPMI. ○ IC_{50}; ● IC_{90}.

of pyrimethamine (2a). Amongst the trifluoromethyl compounds (2d), with the 3′-trifluoromethyl group, and (2g), the 4′-trifluoromethyl isomer, both with C 6–ethyl substituents as in pyrimethamine, were the most active whereas compounds (2c,f) (the C 6–methyl analogues) were slightly less active; the C 6-unsubstituted compounds (2b,e) were least active. Similar results have been obtained with 5-(4′-chlorophenyl)pyrimidine-2,4-diamines.[4] The 3′-trifluoromethyl compounds (2b–d) were also slightly more active than the 4′-trifluoromethyl isomers (2e–g) against the FC-27 isolate.

Amongst the methylenedioxy compounds (2h–k), the 6-ethyl compound (2j) was the most active; and lower activities were found for the 6-methyl and 6-unsubstituted analogues (2i) and (2h), respectively. The 6-trifluoromethyl compound (2k) was inactive. In all tests against the FC-27 isolate compounds (2d,j) were the most active of all the compounds prepared in this work, and their activities approached that of pyrimethamine.

Whereas pyrimethamine (2a) contains an electron-attracting 4′-chloro substituent and compound (2d) contains the electron-attracting 3′-trifluoromethyl substituent, compound (2j) contains the electron-donating methylenedioxy group. Russell and Hitchings[4] have reported that in 5-arylpyrimidine-2,4-diamines, maximal antimalarial activity was found with a 5-phenyl group substituted by an electron-attracting group in the *para* position (and an alkyl radical in the pyrimidine 6-position). Clearly, our results show that in 5-arylpyrimidine-2,4-diamines, factors other than electronic effects are also important in determining antimalarial activity.

The results presented for tests against the K-1 isolate in Fig. 2 indicate that all of these new compounds examined were less active against the pyrimethamine-resistant strain K-1 than against the sensitive strain FC-27; and that three compounds (2b,c,k) did not show any activity under the conditions applied. However three test compounds (2f,g,j) demonstrated stronger antimalarial activity (from two- to nine-fold) against the K-1 strain than pyrimethamine, and of these compounds (2g) was the most active.

The data for the 4′-trifluoromethyl compound (2g) showed a two- to five-fold difference in activity against the two isolates whereas those for the 3′-trifluoromethyl isomer (2d) and the methylenedioxy compound (2j) showed a much larger difference in activity.

Experimental

All products were examined for the presence of impurities by thin-layer chromatography on alumina. Analytical samples were dried at 100–110°/710 mmHg for 2–3 h unless otherwise specified. Melting points were taken in Pyrex capillaries. Analyses were performed by the Australian National University Analytical Services Unit. ^{1}H n.m.r. spectra (δ values) were recorded in CD_3SOCD_3 solutions unless otherwise stated, at 90 MHz and 30° on a Jeol FX90Q Fourier-transform spectrometer.

Low-resolution mass spectra were recorded on an Incos data system attached to a VG-Micromass 7070 double-focusing mass spectrometer by using electron ionization (e.i.) at 70 eV (under the supervision of Dr J. K. MacLeod at the Research School of Chemistry).

Syntheses

6-Methyl-5-(3′-trifluoromethylphenyl)pyrimidine-2,4-diamine (2c) and Related Compounds

A mixture of α-(3′-trifluoromethylphenyl)acetonitrile (1·0 g), sodium ethoxide solution (3·0 ml; from 0·13 g sodium and 10·0 ml ethanol) and ethyl acetate (0·53 ml) was allowed to stand at 20° for 3 days. The orange-coloured solution was poured into water and the solution (pH *c.* 11) was adjusted with 10 M sodium hydroxide to pH 12·5–13. An ethereal extract of this mixture gave unchanged α-(3′-trifluoromethylphenyl)acetonitrile (0·858 g). The aqueous solution was acidified to pH 0·5 with concentrated sulfuric acid and the mixture, on extraction with ether, gave crude solid α-acetyl-α-(3′-trifluoromethylphenyl)acetonitrile (0·177 g) [^{1}H n.m.r. ($CDCl_3$): δ 2·33, s, Me; 4·78, s, CH; 7·51–7·67, complex, H 2′,4′,5′,6′].

This product in ether was stirred with excess ethereal diazomethane (from 1·0 g nitrosomethylurea), initially at <5° and then at 20° overnight. Excess reagent and ether were then evaporated to give, as an oil, the crude β-methoxy-α-(3′-trifluoromethylphenyl)acrylonitrile [^{1}H n.m.r. ($CDCl_3$): δ 2·48, s, Me; 3·90, s, MeO; 7·47–7·90, complex, H 2′,4′,5′,6′].

This compound and guanidine hydrochloride (0·3 g) with sodium ethoxide solution (5·6 ml; prepared above) were refluxed on a steam bath for 4 h. The solvent was then evaporated under reduced pressure, the residue was diluted with a little water, 10 M sodium hydroxide was added to pH 12, the solution removed with a Pasteur pipette and the residue twice washed similarly with water. After evaporation to dryness on a rotary evaporator the residue was recrystallized from ethanol and gave the *title compound* (0·056 g), m.p. 212–214° (Found: C, 53·4; H, 4·1; N, 20·8. $C_{12}H_{11}F_3N_4$ requires C, 53·7; H, 4·1; N, 20·9%). ^{1}H n.m.r.: δ 1·83, s, Me; 5·60, br, 5·87, br, 2×NH_2; 7·48–7·71, complex, H 2′,4′,5′,6′.

The following compounds were prepared by similar procedures from α-(3′ or 4′-trifluoromethylphenyl)acetonitrile (1·0 g) and ethyl formate, ethyl acetate or ethyl propionate; and from α-(3′,4′-methylenedioxyphenyl)acetonitrile (0·5 g) with ethyl trifluoroacetate. Variations to these procedures are noted under individual preparations.

5-(3′-Trifluoromethylphenyl)pyrimidine-2,4-diamine (2b) (0·037g), m.p. 196–197·5° (from aqueous ethanol) (Found: C, 52·1; H, 3·6; N, 21·6. $C_{11}H_9F_3N_4$ requires C, 52·0; H, 3·6; N, 22·0%). ^{1}H n.m.r.: δ 6·04, br, 6·13, br, 2×NH_2; 7·62–7·69, complex, H 6,2′,4′,5′,6′.

6-Ethyl-5-(3′-trifluoromethylphenyl)pyrimidine-2,4-diamine (2d) (0·041g), m.p. 203·5–205° (from aqueous ethanol) (Found: C, 55·6; H, 4·7; N, 19·6. $C_{13}H_{13}F_3N_4$ requires C, 55·3; H, 4·6; N, 19·9%). ^{1}H n.m.r.: δ 0·95, t, *J* 7 Hz, CH_3; 2·08, q, *J* 7 Hz, CH_2; 5·57, br, 5·88, br, 2×NH_2; 7·45–7·67, complex, H 2′,4′,5′,6′. The intermediate crude α-propionyl-α-(3′-trifluoromethylphenyl)acetonitrile (0·069 g) was prepared from α-(3′-trifluoromethylphenyl)acetonitrile (0·5 g) and ethyl propionate in ethanolic sodium ethoxide at reflux for 1·5 h. It had ^{1}H n.m.r. ($CDCl_3$): δ 1·07, t, *J* 7 Hz, Me; 2·70, q, *J* 7 Hz, CH_2; 4·80, s, CH; 7·59–7·68, complex, H 2′,4′,5′,6′.

5-(4′-Trifluoromethylphenyl)pyrimidine-2,4-diamine (2e) (0·028g), m.p. 215° (from ethanol) (Found: C, 52·1; H, 3·4; N, 21·8. $C_{11}H_9F_3N_4$ requires C, 52·0; H, 3·6; N, 22·0%). ^{1}H n.m.r.: δ 6·66, br, NH_2; 7·50–7·79, complex, H 6,2′,4′,5′,6′. The condensation reaction of α-(4′-trifluoromethylphenyl)-acetonitrile (1·0 g) with ethyl formate in ethanolic sodium ethoxide was carried out at 20° for 21 days and gave α-formyl-α-(4′-trifluoromethylphenyl)acetonitrile (0·075 g).

6-Methyl-5-(4′-trifluoromethylphenyl)pyrimidine-2,4-diamine (2f) (0·018g), m.p. 233–234° (from ethanol) (Found: C, 53·8; H, 3·9; N, 21·0. $C_{12}H_{13}F_3N_4$ requires C, 53·7; H, 4·1; N, 20·9%). ^{1}H n.m.r.: δ 1·85, s, Me; 5·61, br, 5·89, br, 2×NH_2; 7·42, d, *J* 9 Hz, 7·76, d, *J* 9 Hz, H 2′,3′,5′,6′. The intermediate crude α-acetyl-α-(4′-trifluoromethylphenyl)acetonitrile (0·052 g) had ^{1}H n.m.r. ($CDCl_3$): δ 2·34, s, Me; 4·75, s, CH; 7·50–7·77, complex, H 2′,3′,5′,6′.

6-Ethyl-5-(4′-trifluoromethylphenyl)pyrimidine-2,4-diamine (2g) (0·011g), m.p. 198–200° (from aqueous ethanol) (Found: C, 55·8; H, 4·3. $C_{13}H_{13}F_3N_4$ requires C, 55·3; H, 4·6). ^{1}H n.m.r.: δ 0·96, t, CH_3; 2·09, q, *J* 7 Hz, CH_2; 5·57, br, 5·88, br, 2×NH_2; 7·40, d, *J* 8 Hz, 7·77, d, *J* 8 Hz, H 2′,3′,5′,6′. Mass spectrum *m/z* 282 (M, 60%), 281 (100), 263 (10), 253 (25). The condensation of α-(4′-trifluoromethylphenyl)acetonitrile with ethyl propionate in ethanolic sodium ethoxide was at 20° for 33 days. The intermediate crude α-propionyl-α-(4′-trifluoromethylphenyl)acetonitrile (0·045 g) had ^{1}H n.m.r. ($CDCl_3$): δ 1·07, t, *J* 7 Hz, CH_3; 2·70, q, *J* 7 Hz, CH_2; 4·76, s, CH; 7·52, d, *J* 8 Hz, 7·72, d, J 8 Hz, H 2′,3′,5′,6′.

5-(3′,4′-Methylenedioxyphenyl)-6-trifluoromethylpyrimidine-2,4-diamine (2k) (0·242g), m.p. 245–250° (Found: C, 47·8; H, 2·8; N, 18·9. $C_{12}H_9F_3N_4O_2$ requires C, 48·3; H, 3·0; N, 19·1%). ^{1}H n.m.r.: δ 6·05, s, OCH_2O; 6·40, br, NH_2; 6·72, d, *J* 8 Hz, 6·95, d, *J* 8 Hz, H 5′,6′; 6·71, s, H 2′. The condensation of α-(3′,4′-methylenedioxyphenyl)acetonitrile with ethyl trifluoroacetate in ethanolic sodium ethoxide was carried out at 20° for 33 days. The crude intermediate α-(3′,4′-methylenedioxyphenyl)-α-(trifluoroacetyl)acetonitrile (1·234 g) had ^{1}H n.m.r. ($CDCl_3$): δ 4·19, s, CH; 5·97, s, OCH_2O; 6·82–6·97, complex, H 2′,5′,6′.

5-(3′,4′-Methylenedioxyphenyl)pyrimidine-2,4-diamine (2h) and Related Compounds

A mixture of α-(3′,4′-methylenedioxyphenyl)acetonitrile (0·5 g), ethanolic sodium ethoxide (2·0 ml; from 0·44 g sodium and 20·0 ml ethanol) and ethyl formate (0·6 ml) was heated at 62° for 20 h. It was diluted with water, adjusted with 10 M sodium hydroxide to pH 12, and extracted with ether which gave unchanged α-(3′,4′-methylenedioxyphenyl)acetonitrile (0·256 g). The aqueous solution at pH 12 was adjusted by the addition of concentrated sulfuric acid to pH 1 and the mixture extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, water, and dried (Na_2SO_4). Evaporation of the solvent gave crude α-formyl-α-(3′,4′-methylenedioxyphenyl)acetonitrile (0·206 g).

This product was then converted by the procedures described above into the *title compound* (0·133 g), m.p. 224·5–226·5° (Found: C, 57·3; H, 4·4; N, 24·6. $C_{11}H_{10}N_4O_2$ requires C, 57·4; H, 4·4; N, 24·3%). ^{1}H n.m.r.: δ 5·88, br, 5·95, br, 2×NH_2; 6·01, s, OCH_2O; 6·69–6·90, complex, H 2′,5′,6′; 7·57, s, H 6. Mass spectrum *m/z* 230 (M, 100%), 229 (300), 188 (15).

In a similar manner from α-(3′,4′-methylenedioxyphenyl)acetonitrile (0·5 g) with ethyl acetate or ethyl propionate in ethanolic sodium ethoxide at reflux for 7 h, were made the α-acetyl-α-(3′,4′-methylenedioxyphenyl)acetonitrile and its α-propionyl homologue; these, by the procedures described above, gave the following compounds.

6-Methyl-5-(3′,4′-methylenedioxyphenyl)pyrimidine-2,4-diamine (2i) (0·040g), m.p. 265–267° (Found, for a sample dried at 134°/710 mmHg for 5 h: C, 58·8; H, 4·9. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 5·0%). ^{1}H n.m.r.: δ 1·86, s, Me; 5·56, br, 5·75, br, 2×NH_2; 6·03, s, OCH_2O; 6·56–6·99, complex, H 2′,5′,6′. Mass spectrum *m/z* 244 (M, 100%), 243 (60), 185 (10). The intermediate crude α-acetyl-α-(3′,4′-methylenedioxyphenyl)acetonitrile (0·214 g) had ^{1}H n.m.r. ($CDCl_3$): δ 2·23, s, Me; 4·66, s, CH; 5·99, s, OCH_2O; 6·84, s, H 2′,5′,6′.

6-Ethyl-5-(3′,4′-methylenedioxyphenyl)pyrimidine-2,4-diamine (2j) (0·100 g), m.p. 238° (from ethanol) (Found: C, 60·9; H, 5·7; N, 21·6. $C_{13}H_{14}N_4O_2$ requires C, 60·5; H, 5·5; N, 21·7%). ^{1}H n.m.r.: δ 0·97, t, *J* 7 Hz, Me; 2·14, q, *J* 7 Hz, CH_2; 5·46, br, 5·77, br, 2×NH_2; 6·04, s, OCH_2O; 6·55–7·00, complex, H 2′,5′,6′. Mass spectrum *m/z* 258 (M, 90%), 257 (100), 229 (25), 199 (15). The intermediate α-(3′,4′-methylenedioxyphenyl)-α-(propionyl)acetonitrile (0·341 g) had ^{1}H n.m.r. ($CDCl_3$): δ 1·05, t, *J* 7 Hz, CH_3; 2·61, q, *J* 7 Hz, CH_2; 4·58, s, CH; 6·00, s, OCH_2O; 6·84, br s, H 2′,5′,6′.

Antimalarial Testing

The compounds described in this paper were examined for their antimalarial activity against both pyrimethamine and chloroquine sensitive (FC-27) and resistant (K-1) strains of *Plasmodium falciparum* maintained in continuous culture at the Army Malaria Research Unit.[7] Two types of culture medium were employed; LPLF RPMI 1640, containing physiological levels of folic acid (FA), and *p*-aminobenzoic acid (PABA) (physiological RPMI), and RPMI 1640 FA- and PABA-free (depleted RPMI).

The test compounds were dissolved in 100% methanol at concentrations of 1·6 mM and subsequently diluted in adequate (physiological or depleted) culture medium to obtain a final concentration range of 0·1–1600 nM. All tests were performed in triplicate and pyrimethamine was used as a reference drug.

At the start the compounds were screened by the microscopic test[8] by using physiological RPMI with a drug exposure time of 30 h. The number of ring forms of the parasites that mature to normal-looking schizonts containing eight or more nuclei per 200 asexual parasites was determined in the microcultures containing different drug concentrations. The values obtained were divided by the values for the corresponding control and the results were expressed as a percentage of growth.

Radioisotopic tests[6] were performed in both types of culture medium. Drug exposure time was 48 h followed by an 18 h pulse with [G-^{3}H]hypoxanthine. The counts per minute (cpm) in the wells which contained different concentrations of drug were compared to those obtained from the control. The percentage of parasite growth was calculated as follows: [cpm in test wells/cpm in control wells]×100.

Assessment of the antimalarial activity *in vitro* of the test compounds was based on IC_{50} and IC_{90} values obtained from concentration–response curves generated by the TableCurve (Jandel Scientific) computer program. Statistical comparisons were made by using Spearman's rank test (r_s).

The results for the FC-27 strain are given in Fig. 1, and those for the K-1 strain in Fig. 2.

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