Structure−Activity Relationships for the Antileishmanial and Antitrypanosomal Activities of 1′-Substituted 9-Anilinoacridines

Swarna A. Gamage,[†] David P. Figgitt,[‡] Stanley J. Wojcik,[‡] Raymond K. Ralph,[‡] Adriana Ransijn,[§] Jacques Mauel,[§] Vanessa Yardley,[∥] Diane Snowdon,[∥] Simon L. Croft,[∥] and William A. Denny*,[†]

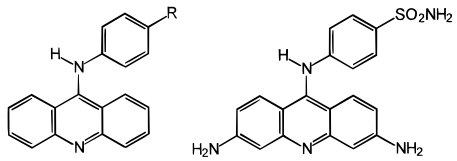
Cancer Research Laboratory, Faculty of Medicine and Health Sciences, and Cancer Research and Developmental Biology, School of Biological Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand, Institute of Biochemistry, University of Lausanne, CH-1066 Epalinges, Switzerland, and London School of Hygiene and Tropical Medicine, University of London, Keppel Street, London WC1E 7HT, U.K.

Received April 7, 1997[⊗]

Members of the class of 9-anilinoacridine topoisomerase II inhibitors bearing lipophilic electron-donating 1′-anilino substituents are active against both the promastigote and amastigote forms of the parasite *Leishmania major*. A series of analogues of the known 1′-NHhexyl lead compound were prepared and evaluated against *L. major* in macrophage culture to further develop structure−activity relationships (SAR). Toxicity toward mammalian cells was measured in a human leukemia cell line, and the ratio of the two IC_{50} values (IC_{50}(J)/IC_{50}(L)) was used as a measure of the *in vitro* therapeutic index (IVTI). A 3,6-diNMe_2 substitution pattern on the acridine greatly increased toxicity to *L. major* without altering mammalian toxicity, increasing IVTIs over that of the lead compound. The 2-OMe, 6-Cl acridine substitution pattern used in the antimalarial drug mepacrine also resulted in potent antileishmanial activity and high IVTIs. Earlier suggestions of the utility of 2′-OR groups in lowering mammalian cytotoxicity were not borne out in this wider study. A series of very lipophilic 1′-NRR (symmetric dialkylamino)-substituted analogues showed relatively high antileishmanial potency, but no clear trend was apparent across the series, and none were superior to the 1′-N$H(CH_2)_5$Me subclass. Subsets of the most active 1′-N(R)$(CH_2)_5$Me- and 1′-N(alkyl)$_2$-substituted compounds against *L. major* were also evaluated against *Leishmania donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei*, but no consistent SAR could be discerned in these physiologically diverse test systems. The present study has confirmed earlier conclusions that lipophilic electron-donating groups at the 1′-position of 9-anilinoacridines provide high activity against *L. major*, but the SAR patterns observed do not carry over to the other parasites studied.

Diseases caused by protozoal parasites remain an important human health problem, despite much progress in understanding the biology of these organisms. In particular, while progress has been made[1] in the drug treatment of leishmania (caused in humans primarily by the organisms *Leishmania donovani*, *Leishmania tropica*, and *Leishmania braziliensis*), better drugs are still required. Following reports[2,3] that inhibitors of the enzyme topoisomerase II show activity against *Leishmania donovani* and *Leishmania mexicana*, we investigated[4] the antileishmanial activity of 9-anilinoacridines. Members of this general class are known to inhibit topoisomerase II enzymes from a wide variety of sources, including mammalian cells,[5] trypanosomes,[6] and malaria parasites,[7,8] but with varying structure−activity relationships.

Our previous study of the activity of derivatives of 9-anilinoacridine (**1**) against both promastigote and amastigote forms of *Leishmania major* and mammalian cells reinforced the observations that structure−activity relationships vary considerably between different organisms. For example, while substitution with 1′-electron-donating substituents favored activity against both *L. major* and mammalian cells (e.g., **32**),[4,7] overall high lipophilicity lowered potency against mammalian cells and malaria parasites without affecting antileishmanial activity (e.g., **13**).[4] Similarly, 3,6-diNH_2 substitution of the acridine ring (e.g., **43**) abolished antileishmanial activity while greatly improving potency against *Plasmodium falciparum*.[8]



1: R = H
13: R = $NH(CH_2)_5Me$
32: R = CH_2NMe_2

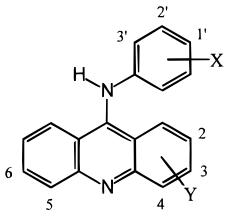
43

The above study[4] identified the 1′-NHhexyl analogue **13** (Table 1) as the most effective compound of the set against *L. major* in macrophage culture and indicated the possible effectiveness of 2′-OMe substitution to improve the *in vitro* therapeutic index. However, detailed structure−activity relationships (SAR) were difficult to discern because of the limited range of variations studied. We now report the synthesis and evaluation against *L. major* of additional 1′-substituted 9-anilinoacridines, designed to improve the effectiveness of this class of drugs by exploring the parameters previously identified as possibly beneficial for antileishmanial activity. A subset of the most active compounds were also evaluated against *L. donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei in vitro* (Table 2).

[†] Cancer Research Laboratory, University of Auckland.
[‡] Cancer Research and Developmental Biology, University of Auckland.
[§] University of Lausanne.
[∥] University of London.
[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1997.

S0022-2623(97)00232-X CCC: $14.00

Table 1. Activity of 9-Anilinoacridines against *L. major* in Murine Macrophages



no.	substituents X (aniline)	substituents Y (acridine)	lipophilicity[a] ($\Sigma\pi$)	IC_{50} (μM) Jurkat[b]	IC_{50} (μM) *L. major*[c]	IVTI[d]
1[e]	1′-H	H	0.0	2.7	2.7	1
2[e]	1′-H	3,6-diNMe_2	0.36	1.4	0.03	47
3[e]	1′-$NHSO_2Me$, 3′-OMe	H	−1.20	0.2	1.5	0.1
4[e]	1′-$NHSO_2Me$, 3′-OMe	3,6-diNH_2	−3.66	0.8	>3	<0.25
5[e]	1′-$NHSO_2Me$, 3′-OMe	3,6-diNMe_2	−0.84	3	>3	<1
6[e]	1′-NH_2	H	−1.23	0.75	2.1	0.4
7	1′-NH_2, 2′-aza	H	−2.74	3.6	3.9	0.9
8[e]	1′-NHMe	H	−0.47	1.5	1.5	1
9	1′-NHMe, 2′-OMe	H	−0.49	11	3.6	3
10	1′-NHMe, 2′-OiPr	H	0.38	8	1.3	6
11	1′-NHcyclopentyl	H	ca. 1.8	5	0.45	11
12	1′-NHcyclohexyl	H	ca. 2	>15	0.55	>27
13[f]	1′-$NH(CH_2)_5Me$	H	2.38	17	0.55 ± 0.21	31
14	1′-$NH(CH_2)_5Me$, 2′-OMe	H	2.36	3.5	0.4	9
15	1′-$NH(CH_2)_5Me$	2-OMe, 6-Cl	3.07	4	0.2	20
16	1′-$NH(CH_2)_5Me$, 2′-OMe	2-OMe, 6-Cl	3.71	>20	0.5	>40
17	1′-$NH(CH_2)_5Me$	3,6-diNMe_2	2.74	1.75	0.16	11
18	1′-$NH(CH_2)_3NEt_2$	H	3.29	1.3	0.2	6.5
19	1′-$NH(CH_2)_2NEt_2$, 2′-OMe	H	3.27	1.5	1.6	0.9
20	1′-N(Me)Et	H	0.68	4.0	1.0	4.0
21	1′-N(Me)Et, 2′-OMe	H	0.66	16.5	>3	>5
22	1′-$N(Me)(CH_2)_5Me$	H	3.04	3	0.3	10
23	1′-$N(Me)(CH_2)_5Me$, 2′-OMe	H	3.02	6.5	0.6	11
24	1′-$N(Me)(CH_2)_5Me$	2-OMe, 6-Cl	3.73	>20	1.8	>11
25	1′-$N(Me)(CH_2)_5Me$	3,6-diNMe_2	3.40	1.75	0.07	25
26[f]	1′-$N(Me)_2$	H	0.18	1.0	0.9	1.1
27[f]	1′-$N(Et)_2$	H	1.18	1.0	0.4	<4
28	1′-$N(Pr)_2$	H	2.24	1.5	0.2	7
29	1′-$N(Bu)_2$	H	3.56	2.0	0.35	7
30	1′-$N(Pt)_2$	H	4.88	2.3	0.16	14
31	1′-$N(Hx)_2$	H	6.20	6.5	0.24	27
32[e]	1′-CH_2NMe_2	H	−0.15	7.5	1.0	7.5
33[e]	1′-CH_2NMe_2	3,6-diNH_2	−2.61	12	5.0	2.4
34[e]	1′-CH_2NMe_2	3,6-diCl	1.27	5	2	2.5
35	1′-$CH_2NH(CH_2)_4Me$	H		1.53	2	0.25
36	1′-CH_2Npyrrole	H		2	0.2	10
37[e]	1′-CH_2Npyrrole	3,6-diNH_2		>20	>3	ND[g]
38	1′-$(CH_2)_6CH_3$	H	3.99	13	0.8	16
39	1′-$(CH_2)_3NEt_2$	H	4.22	<1	0.3	<3
40[h]	1′-$(CH_2)_2NH(CH_2)_2NH_2$	H		4	0.7	5.7
41	1′-$O(CH_2)_5Me$	H	2.87	5	1.0	5
42[e]	1′-SO_2NH_2	H	−1.82	5	>3	<1.7
43[f]	1′-SO_2NH_2	3,6-diNH_2	−4.28	20	>3	<7
44[e]	1′-$SO_2NH(CH_2)_6NH_2$	H		>20	>3	ND

[a] Relative lipophilicities determined where possible by computation of $\Sigma\pi$ values for all 1′- and nuclear substituents, by the fragment constant method of ref 13. These calculations are for the free base forms of potentially cationic side chains. [b] Concentration of drug to reduce the growth of human Jurkat leukemia cells to 50% of control cultures, using a 72 h continuous exposure. Values are averages of at least two independent determinations; variation was typically ±15%. [c] Concentration of drug to reduce the incorporation of [^{3}H]TdR in drug-treated cultures of intracellular *L. major* to 50% of controls (see text). Values are averages of at least two independent determinations; variation was typically ±15%. Data for **13** is the average ± SEM for 15 determinations. [d] IVTI, *in vitro* therapeutic index = IC_{50}(Jurkat)/IC_{50}(*L. major*). [e] Reference 8. [f] Reference 9. [g] Not determinable. [h] Reference 26.

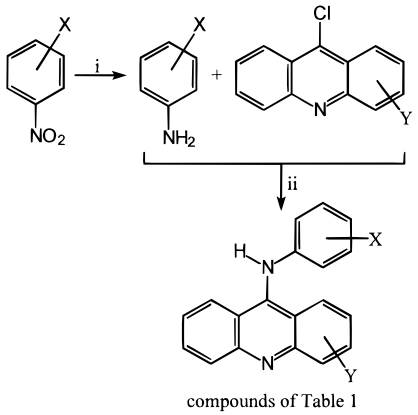
Chemistry

Some of the required 1′-substituted 9-anilinoacridines were available from previous work,[8,9] and these are referenced in Table 1. Most of the new analogues were prepared (Scheme 1) by acid-catalyzed coupling of either appropriate 9-chloroacridines or 9-(methylthio)-3,6-bis-(dimethylamino)acridine (**45**)[10] with anilines. Many of the anilines were unstable and were prepared immediately prior to use by catalytic hydrogenation of the corresponding nitro compounds.

The latter were made by a variety of different methods, and the preparations of unreported analogues are outlined. Acylation of nitroanilines and $Me_2S{\cdot}BH_3$ reduction of the corresponding amides (Scheme 3) gave *N*-hexyl-*N*-methyl-4-nitroaniline (**49**; for the preparation of **22**, **24**, and **25**), *N*-hexyl-*N*-methyl-2-methoxy-4-nitroaniline (**51**; for the preparation of **23**), and *N*-ethyl-2-methoxy-*N*-methyl-4-nitroaniline (**53**; for the preparation of **21**).

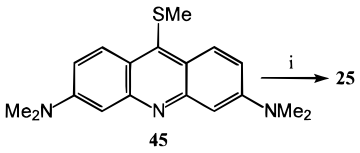
N-[2-(Diethylamino)ethyl]-2-methoxy-4-nitroaniline (**56**; for the preparation of **19**) was produced from 2-methoxy-

Scheme 1[a]



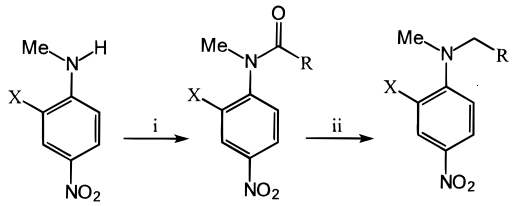
[a] (i) Pd−C/H_2/MeOH; (ii) MeOH/trace HCl/20 °C/15−45 min.

Scheme 2[a]



[a] (i) Phenol/100 °C/15 min, then freshly reduced **49**.

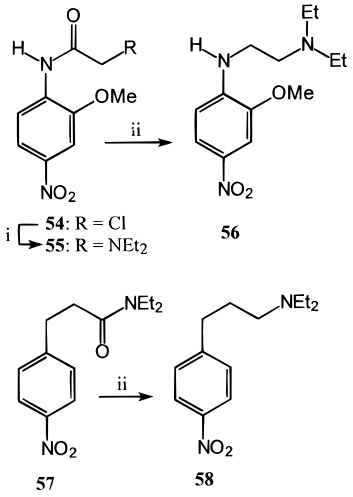
Scheme 3[a]



46: X=H
47: X=OMe
48: X=H, R=$(CH_2)_4$Me
50: X=OMe, R=$(CH_2)_4$Me
52: X=H, R=Me
49: X=H, R=$(CH_2)_4$Me
51: X=OMe, R=$(CH_2)_4$Me
53: X=H, R=Me

[a] (i) RCOCl/THF/reflux/2 h; (ii) BH_3·Me_2S/THF/reflux/1 h.

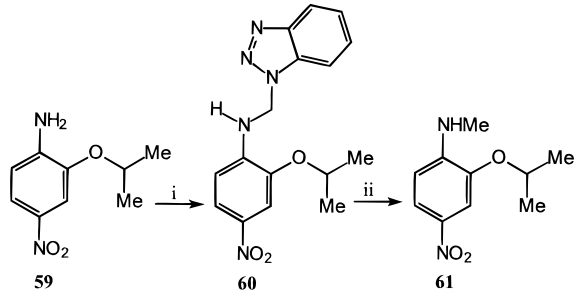
Scheme 4[a]



[a] (i) Et_2NH/EtOH/reflux/2 h; (ii) BH_3·Me_2S/THF/reflux/15 h.

4-nitroaniline by reaction with 2-chloroacetyl chloride to give **54** followed by displacement of chlorine with diethylamine and reduction of the resulting amide **55** with Me_2S·BH_3 (Scheme 4). Similar reaction of 3-(4-nitrophenyl)propanoyl chloride with diethylamine and Me_2S·BH_3 reduction of the resulting amide **57** gave *N*-[3-(diethylamino)propyl]-4-nitrobenzene (**58**; for the preparation of **39**) (Scheme 4).

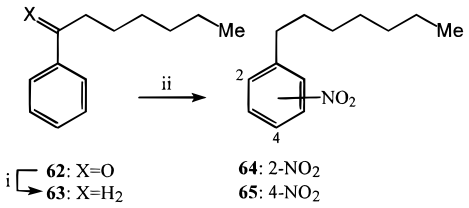
Scheme 5[a]



59 **60** **61**

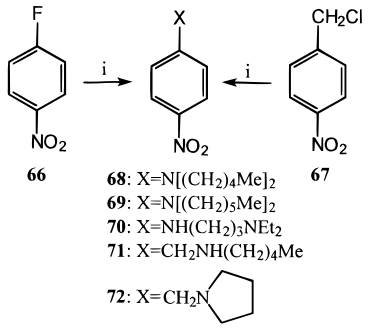
[a] (i) Benzotriazole/HCHO/EtOH/20 °C/3 h; (ii) $NaBH_4$/dioxane/reflux/3 h.

Scheme 6[a]



[a] (i) NH_2NH_2·H_2O/diethylene glycol/KOH/100 °C/1 h; (ii) fuming HNO_3/20 °C/24 h.

Scheme 7[a]



[a] (i) EtOH/reflux/1 h.

N-Methyl-2-isopropoxy-4-nitroaniline (**61**; for the preparation of **10**) was made by *N*-methylation of 2-isopropoxy-4-nitroaniline[11] (**59**) with formaldehyde/benzotriazole to give the benzotriazole **60**, which was reduced with $NaBH_4$ (Scheme 5). 7-(4-Nitrophenyl)-heptane (**65**; for the preparation of **38**) was prepared from 7-phenylheptan-7-one (**62**) by Wolf−Kishner reduction followed by regioselective nitration (Scheme 6). Finally, *N*,*N*-dialkyl-4-nitroanilines **68**−**70** (for the preparation of **30**, **31**, and **18**) and 4-nitrobenzylamines **71** and **72** (for the preparation of **35** and **36**) were made by direct displacement of 4-fluoronitrobenzene (**66**) or 4-nitrobenzyl chloride (**67**), respectively (Scheme 7).

Biological Evaluation

Toxicity toward mammalian cells was measured using the Jurkat human leukemia cell line; the IC_{50}(J) values are the concentrations of drug required to inhibit the growth of Jurkat cells by 50%.[4] Antileishmanial activity was determined using bone marrow-derived macrophages isolated from CBA/H mice and infected *in vitro* with *L. major* promastigotes. Following drug treatment the macrophages were lyzed and the level of surviving parasites was measured by uptake of tritiated thymidine;[4,12] IC_{50}(L) values were determined from the best-fit straight line from log/linear plots of parasite numbers

Table 2. Comparative Activity of 1′-NH$(CH_2)_5$Me- and 1′-N(alkyl)$_2$-Substituted 9-Anilinoacridines of Table 1 against *L. donovani*, *T. cruzi*, and *T. brucei*

		IC_{50} (μm)		ED_{50} (μm)		
no.	substituents	Jurkat[a]	*L. major*[b]	*L. donovani*[c]	*T. cruzi*[d]	*T. brucei*[e]
13	1′-NH$(CH_2)_5$Me	17	0.55	12.3	2.2	3.9
14	1′-NH$(CH_2)_5$Me, 2′-OMe	3.5	0.4	1.2	1.8	0.65
15[f]	1′-NH$(CH_2)_5$Me	4	0.2	4	>10	>0.3
16[f]	1′-NH$(CH_2)_5$Me, 2′-OMe	>20	0.5	3.2	9.3	0.6
17[g]	1′-NH$(CH_2)_5$Me	1.75	0.16	0.25	>3	0.2
22	1′-N(Me)$(CH_2)_5$Me	3	0.3	1.2	>1	0.33
23	1′-N(Me)$(CH_2)_5$Me, 2′-OMe	4	0.6	1.9	>0.3	1.8
24[f]	1′-N(Me)$(CH_2)_5$Me	>20	2.0	>3	>3	4.3
25[g]	1′-N(Me)$(CH_2)_5$Me	1.75	0.07	0.03	0.12	>0.3
20	1′-N(Me)Et	4.0	1.0	4.4	3.3	0.88
26	1′-N$(Me)_2$	1	0.9	3.6	>3	1.3
27	1′-N$(Et)_2$	1	0.4	0.76	>3	>0.3
28	1′-N$(Pr)_2$	1.5	0.2	>10	2.5	0.37
29	1′-N$(Bu)_2$	2.0	0.35	>10	>10	1.46
30	1′-N$(Pt)_2$	2.3	0.16	>90	>0.3	0.2
31	1′-N$(Hx)_2$	6.5	0.24	1.35	>3	>0.3

[a] Concentration of drug to reduce the growth of human Jurkat leukemia cells to 50% of control cultures, using a 72 h continuous exposure. Values are averages of at least two independent determinations; variation was typically ±15%. [b] Concentration of drug to reduce the incorporation of [^{3}H]TdR in drug-treated cultures of intracellular *L. major* to 50% of untreated controls (see text). Values are averages of at least two independent determinations; variation was typically ±15%. [c] *L. donovani* ED_{50}: concentration of compound required to reduce the number of macrophages infected with amastigotes to 50% of untreated controls. [d] *T. cruzi* ED_{50}: concentration of compound required to reduce the number of macrophages infected with amastigotes to 50% of untreated controls. [e] *T. brucei* ED_{50}: concentration of compound required to inhibit the growth of extracellular bloodstream form tryptomastigotes to 50% of untreated controls. [f] 2-OMe, 6-Cl-substituted acridine. [g] 3,6-DiNMe_2-substituted acridine.

versus concentration. The *in vitro* therapeutic index (IVTI = IC_{50}(J)/IC_{50}(L)), the ratio of these two values, was used as a measure of how changes in drug structure differentially affect potencies in these two biological systems. Selected compounds were also evaluated against intracellular *L. donovani* and *Tr. cruzi* amastigotes in mouse peritoneal macrophages and against extracellular *T. brucei* bloodstream form trypomastigotes in culture (Table 2).

Results and Discussion

The structures of the substituted 9-anilinoacridines are listed in Table 1, together with relevant physicochemical and biological properties. Relative lipophilicities were determined by computation of π values for all substituents on the 9-anilinoacridine ring system, by the fragment constant method.[9,13] While these calculations allow for the proximity of polar functionality, they are for the free base forms in all cases. For compounds with potentially fully ionizable side chains, π values will be lower by approximately 3 units.[13] Full dose−response curves were determined for the activity of the compounds against *L. major*, allowing a more accurate determination of antileishmanial activity than before,[4] in terms of ED_{50} values.

Compounds **1** and **2** in Table 1 are the parent 9-anilinoacridines (X = H); comparison suggests a positive effect for the (lipophilic) 3,6-diNMe_2 grouping, which greatly increased toxicity to *L. major* without altering mammalian toxicity. Thus **2** has a larger therapeutic index (IVTI = 47) than the lead compound **13** (IVTI = 31) which showed greatest activity in an earlier study.[4] Compounds **4** and **5** are acridine-substituted analogues of the clinical antileukemic drug and topoisomerase II inhibitor amsacrine (**3**).[9] As expected, the amsacrine side chain confers high mammalian toxicity, leading to low IVTIs (even for **5**).

While compounds **6**−**8** had IVTIs of about unity, compounds **9** and **10** have improved (but still modest) IVTIs, consistent with earlier studies[4] suggesting the positive effect of a 2′-OR group in lowering mammalian cytotoxicity, presumably by reducing its ability to inhibit mammalian topo II.[14] Compounds **11**−**13** compare the effects of cyclic and linear lipophilic 1′-NHR groups, with either showing good activity (**13** is the previous lead compound).[4] Analogues **14**−**17** explored the effects of 2′-OMe groups and various acridine substitutions on this 1′-NH$(CH_2)_5CH_3$ series. However, no clear SAR patterns emerge (for example, the 2′-OMe group does not always improve the IVTI; e.g., **13** and **14**). The 2-OMe, 6-Cl substitution pattern (as in the antimalarial drug mepacrine) resulted in potent antileishmanial activity and high IVTIs for **15** and **16**. Again (compare with **2**), 3,6-diNMe_2 substitution in **17** increased antileishmanial potency (IC_{50} = 0.16 μM, compared with IC_{50} = 0.55 μM for **13**). Because the 1′-NH$(CH_2)_3NEt_2$ side chain had previously[4] shown modest activity (**18**), the 2′-OMe analogue **19** was also evaluated, but toxicity to Jurkat cells was not reduced and the IVTI was low.

Because 1′-NHR-substituted 9-anilinoacridines are known to undergo facile oxidation to the quinonimines,[15,16] the use of less easily oxidized side chains (that cannot form quinonimines) was explored with the 1′-NRR derivatives **20**−**25**. The simple 1′-N(Me)Et derivative **20** shows some antileishmanial activity, but the more lipophilic 1′-N(Me)hexyl analogue **22** was more potent and more selective. The corresponding 2′-OMe derivatives **21** and **23** were less toxic to mammalian cells but had only marginal improvements in IVTI. Again, the 3,6-diNMe_2 derivative **25** showed the highest antileishmanial potency (IC_{50} = 0.07 μM).

The series **26**−**31** further explores the utility of 1′-NRR substitution, covering the symmetric dialkylamino groups from methyl to hexyl. The latter members of this series are very lipophilic compounds. All showed relatively high antileishmanial potency, but no clear trend was apparent across the series. Compounds **32**−**41** use alternative nonoxidizable CH_2R side chains: benzylamino (**32**−**37**), alkyl (**38**), and aminoalkyl (**39**, **40**). Several of the compounds showed significant IVTIs

(e.g., **38**, IVTI = 16), but none were superior to the 1′ $NH(CH_2)_5Me$ subclass. Finally, analogues bearing the electron-withdrawing 1′SO_2NHR group (compounds **42**−**44**) were not effective.

Because of the interesting activities of the subsets of compounds bearing 1′-$N(R)(CH_2)_5Me$ (**13**−**17**, **22**−**25**) and 1′-$N(alkyl)_2$ (**20**, **26**−**31**) side chains, these were also evaluated against *L. donovani*, *T. cruzi*, and *T. brucei* (Table 2). There are considerable physical differences between these test systems. *T. brucei* is comprised of extracellular trypomastigotes,[17] which are likely to be more accessible than the intracellular amastigotes of *L. donovani* and *T. cruzi*, which are in mouse peritoneal macrophages (fully differentiated, nondividing cells). In the macrophage systems, the *L. donovani* amastigotes are in acidic phagolysosomal compartments,[18] whereas the *T. cruzi* amastigotes are in the cytoplasm.[19] Poor cell uptake is therefore likely to be a factor for those compounds which show preferential activity toward *T. brucei* compared with the macrophage-incorporated parasites. However, unlike the *L. major* data, no consistent structure−activity relationships could be discerned in these systems for the compounds of Table 2.

Conclusions

Overall, the present study has confirmed our earlier conclusions[4] that lipophilic electron-donating groups at the 1′-position of 9-anilinoacridines provide analogues (e.g., **13**) with the largest IVTI for activity against *L. major*. However, the present results do not consistently support the utility of 2′-substituents in improving the therapeutic index by lowering mammalian cell toxicity. Our earlier study[4] suggested that 3,6-diNH_2 substitution of the acridine ring abolished antileishmanial activity, and this effect was also confirmed (compounds **33**, **37**, and **43**), despite the fact that such substitution greatly improves potency against malaria parasites.[8] In contrast, the present results consistently indicate that the related 3,6-diNMe_2 substitution pattern is favorable, with the three most potent compounds (**2**, **17**, and **25**) possessing this moiety. However, the SAR patterns observed in *L. major* do not carry over to the other parasites studied.

Experimental Section

Chemistry. Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined using an Electrothermal Model 9200 digital melting point apparatus and are as read. NMR spectra were measured on Bruker DRX-400 or AM-200 spectrometers (Me_4Si). For clarity, aniline protons are designated with primes (e.g., H-2′, H-3′). Mass spectra were recorded on a VG 7070 spectrometer at nominal 5000 resolution. Column chromatography used Merck silica gel, 20−40 mesh.

Preparation of Nitroanilines. *N*-Hexyl-*N*-methyl-4-nitroaniline (49). Method of Scheme 2. Crude hexanoyl chloride (4.4 g, 0.033 mol) (prepared by heating hexanoic acid in $SOCl_2$ under reflux for 1 h and removing excess reagent under reduced pressure) was added to a solution of *N*-methyl-4-nitroaniline (**46**) (5 g, 0.033 mol) in THF (20 mL). The mixture was heated under reflux for 2 h, solvents were removed under reduced pressure, and the residue was partitioned between water and EtOAc. Workup of the organic layer and chromatography of the residue on silica gel, eluting with a gradient of hexane/CH_2Cl_2, gave *N*-methyl-*N*-(4-nitrophenyl)-hexanamide (**48**) (7 g, 85%): mp 86−89 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.0 Hz, 3 H, CH_3), 1.21−1.29 (m, 4 H, 2 CH_2), 1.62 (quintet, J = 7.4 Hz, 2 H, CH_2), 2.20 (t, J = 7.5 Hz, 2 H, CH_2), 3.45 (s, 3 H, NCH_3), 7.41 (d, J = 9.0 Hz, 2 H, H-2,6), 8.30 (d, J = 9.0 Hz, 2 H, H-3,5). Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

A solution of **48** (5 g, 20 mmol) in THF (50 mL) was treated with $Me_2S{\cdot}BH_3$ complex (4 mL, 40 mmol) and heated under reflux for 1 h. Solvent was removed under reduced pressure, and the residue was triturated with water (150 mL). The resulting solid was filtered, washed with water, and recrystallized from aqueous EtOH to give **49** (4 g, 85%): mp 65−67 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.8 Hz, 3 H, CH_3), 1.30−1.37 (m, 6 H, 3 CH_2), 1.62 (quintet, J = 7.7 Hz, 2 H, CH_2), 3.07 (s, 3 H, NCH_3), 3.41 (t, J = 7.6 Hz, 2 H, CH_2), 6.58 (d, J = 9.5 Hz, 2 H, H-2,6), 8.11 (d, J = 9.5 Hz, 2 H, H-3,5). Anal. ($C_{13}H_{20}N_2O_2$) C, H, N.

***N*-Hexyl-*N*-methyl-2-methoxy-4-nitroaniline (51).** Similar reaction of hexanoyl chloride and 2-methoxy-*N*-methyl-4-nitroaniline, followed by chromatography on alumina (elution with a gradient of hexane/CH_2Cl_2), gave *N*-(2-methoxy-4-nitrophenyl)-*N*-methylhexanamide (**50**) (84%): mp 86−89 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 6.7 Hz, 3 H, CH_3), 1.19 (m, 4 H, 2 CH_2), 1.56 (quintet, J = 7.2 Hz, 2 H, CH_2), 1.97 (br s, 2 H, CH_2), 3.18 (s, 3 H, NCH_3), 3.95 (s, 3 H, OCH_3), 7.32 (d, J = 8.6 Hz, 1 H, H-6), 7.82 (d, J = 2.4 Hz, 1 H, H-3), 7.84 (dd, J = 8.9, 2.3 Hz, 1 H, H-5). Anal. ($C_{14}H_{20}N_2O_4$) C, H, N.

Reduction of **50** with $Me_2S{\cdot}BH_3$ as above gave **51** (96%) as an oil, which was used directly: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3 H, CH_3), 1.25−1.32 (m, 6 H, 3 CH_2), 1.58 (quintet, J = 7.4 Hz, 2 H, CH_2), 2.95 (s, 3 H, NCH_3), 3.32 (t, J = 7.7 Hz, 2 H, CH_2), 3.92 (s, 3 H, OCH_3), 6.74 (d, J = 8.7 Hz, 1 H, H-6), 7.68 (d, J = 2.5 Hz, 1 H, H-3), 7.84 (dd, J = 8.9, 2.55 Hz, 1 H, H-5).

***N*-Ethyl-2-methoxy-*N*-methyl-4-nitroaniline (53).** Similar reduction of 2-methoxy-*N*-methyl-4-nitroacetanilide[20] (**52**) with $Me_2S{\cdot}BH_3$ as above gave **53** (50%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3 H, CH_3), 2.93 (s, 3 H, NCH_3), 3.93 (s, 3 H, OCH_3), 6.77 (d, J = 9.0 Hz, 1 H, H-6), 7.69 (d, J = 2.5 Hz, 1 H, H-3), 7.85 (dd, J = 8.9, 2.5 Hz, 1 H, H-5). Anal. ($C_{10}H_{14}N_2O_3$) C, H, N.

***N*,*N*-Diethyl-3-(2-methoxy-4-nitrophenyl)propylamine (56). Method of Scheme 4**. A solution of 2′-chloro-2-methoxy-4-nitroacetanilide[21] (**54**) (6 g, 24.5 mmol) and diethylamine (25 mL) in ethanol (50 mL) was heated under reflux for 72 h. Volatiles were removed under reduced pressure, and the residue was triturated with water (150 mL). The resulting precipitate was collected by filtration, washed with water, and recrystallized from aqueous EtOH to give 2′-(*N*,*N*-diethylamino)-2-methoxy-4-nitroacetanilide (**55**) (5.6 g, 81%): mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.15 Hz, 6 H, 2 CH_3), 2.66 (q, J = 7.1 Hz, 4 H, 2 CH_2), 3.21 (s, 2 H, CH_2CO), 4.01 (s, 3 H, OCH_3), 7.76 (d, J = 2.5 Hz, 1 H, H-3), 7.92 (dd, J = 8.95, 2.4 Hz, 1 H, H-5), 8.60 (d, J = 8.95 Hz, 1 H, H-6), 10.29 (s, 1 H, NH). Anal. ($C_{13}H_{19}N_3O_4$) C, H, N.

Reduction of **55** with $Me_2S{\cdot}BH_3$ complex as in Scheme 2 (reflux for 15 h) gave *N*-[2-(diethylamino)ethyl]-2-methoxy-4-nitroaniline (**56**), purified by chromatography on silica gel (eluting with a gradient of hexane/CH_2Cl_2 containing a few drops of MeOH) to give an oil (2.3 g, 48%): ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 7.15 Hz, 6 H, 2 CH_3), 2.58 (q, J = 7.1 Hz, 2 H, CH_2), 2.74 (t, J = 6.15 Hz, 2 H, CH_2), 3.24 (q, J = 5.8 Hz, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 5.68 (br s, 1 H, NH), 6.46 (d, J = 8.9 Hz, 1 H, H-6), 7.61 (d, J = 2.4 Hz, 1 H, H-3), 7.90 (dd, J = 8.8, 2.4 Hz, 1 H, H-5). Anal. ($C_{13}H_{21}N_3O_3$) C, H, N.

***N*-[3-(Diethylamino)propyl]-4-nitrobenzene (58).** Reaction of 3-(4-nitrophenyl)propanoyl chloride and diethylamine in EtOH under reflux for 1 h gave *N*,*N*-diethyl-3-(4-nitrophenyl)propanamide (**57**) (3.2 g, 75%): mp (aqueous EtOH) 87−88 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (q, J = 7.0 Hz, 6 H, 2 CH_3), 2.64 (t, J = 7.5 Hz, 2 H, CH_2CO), 3.10 (t, J = 7.5 Hz, 2 H, PhCH_2), 3.26 (q, J = 7.2 Hz, 2 H, CH_2), 3.38 (q, J = 7.1 Hz, 2 H, CH_2), 7.40 (d, J = 8.8 Hz, 2 H, H-2,6), 8.14 (d, J = 8.7 Hz, 2 H, H-3,5). Anal. ($C_{13}H_{20}N_2O_2$) C, H, N.

Reduction of **57** with $Me_2S{\cdot}BH_3$ as above (18 h reflux) gave **58** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.3 Hz, 6 H, 2 CH_3), 2.04−2.13 (m, 2 H, CH_2), 2.66−2.87 (m, 8 H, 4 CH_2), 7.37 (d, J = 8.7 Hz, 2 H, H-2,6), 8.17 (d, J = 8.8 Hz, 2 H, H-3,5).

***N*-Methyl-2-isopropoxy-4-nitroaniline (61). Method of Scheme 5**. Excess formaldehyde (20 mL) was added slowly to a solution of 2-isopropoxy-4-nitroaniline[11] (**59**) (7 g, 0.036 mol) and benzotriazole (6 g) in EtOH (100 mL).[22] The mixture was stirred at 20 °C for 3 h, and the resulting precipitate was filtered, washed with ethanol, and dried to give 1-[[*N*-(2-isopropoxy-4-nitrophenyl)amino]methyl]benzotriazole (**60**) (9.5 g, 93%): mp (aqueous EtOH) 163−167 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J = 6.0 Hz, 6 H, 2 CH_3), 4.67 (hept, J = 6.0 Hz, 1 H, OCH), 6.05 (t, J = 6.7 Hz, 1 H, NH), 6.18 (d, J = 7.0 Hz, 2 H, CH_2), 7.09 (d, J = 8.9 Hz, 1 H, H-6), 7.40 (t, J = 7.8 Hz, 1 H, H-5), 7.52 (t, J = 7.6 Hz, 1 H, H-6), 7.63 (s, 1 H, H-3′), 7.83 (dd, J = 9.0, 2.2 Hz, 1 H, H-5′), 8.06 (d, J = 8.35 Hz, 1 H, H-7). Anal. ($C_{10}H_{17}N_5O_3$) C, H.

A mixture of **60** (9 g, 0.032 mol) and $NaBH_4$ (4 g, excess) in 1,4-dioxane (100 mL) was heated under reflux for 3 h, then evaporated to dryness, diluted with water (150 mL), and extracted with EtOAc. The organic layer was washed with dilute NaOH (3 × 100 mL), dried (Na_2SO_4), and worked up. Chromatography of the residue on alumina, eluting with a gradient of hexane/CH_2Cl_2, gave **61** (4 g, 60%): mp (aqueous EtOH) 68−69 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J = 6.0 Hz, 6 H, 2 CH_3), 2.96 (d, J = 5.3 Hz, 3 H, NCH_3), 4.68 (hept, J = 6.1 Hz, 1 H, OCH), 5.06 (br s, 1 H, NH), 6.47 (d, J = 8.9 Hz, 1 H, H-6), 7.61 (d, J = 2.4 Hz, 1 H, H-3), 7.90 (dd, J = 8.85, 2.4 Hz, 1 H, H-5). Anal. ($C_{10}H_{14}N_2O_3$) C, H, N.

7-(4-Nitrophenyl)heptane (65). Method of Scheme 6. 7-Phenylheptane[23] (**58**) (prepared by Wolf−Kisher reduction of 7-phenylheptan-7-one (**62**)) (2.2 g, 12.5 mmol) was nitrated with fuming HNO_3 (*d* 1.54; 15 mL) at 20 °C for 24 h. The mixture was poured into ice water (200 mL) and extracted with EtOAc (3 × 75 mL). Evaporation of solvent gave a mixture (3 g) which was separated on radial TLC (Chromatatron; silica gel) in a gradient of hexane/CH_2Cl_2. The less polar band yielded 7-(2-nitrophenyl)heptane (**64**) (100 mg) as an oil, which was not further characterized: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3 H, CH_3), 1.26−1.41 (m, 8 H, 4 CH_2), 1.63 (quintet, J = 7.6 Hz, 2 H, CH_2), 2.87 (t, J = 7.9 Hz, 2 H, PhCH_2), 7.30−7.35 (m, 2 H, ArH), 7.50 (dt, J = 7.9, 1.25 Hz, 1 H, ArH), 7.86 (dd, J = 8.1, 1.2 Hz, 1 H, H-3).

The more polar band yielded **65** (150 mg) as an oil (lit.[24] oil): ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.24−1.34 (m, 8 H, 4 CH_2), 1.64 (quintet, J = 7.5 Hz, 2 H, CH_2), 2.71 (t, J = 7.7 Hz, 2 H, PhCH_2), 7.32 (d, J = 8.7 Hz, 2 H, H-2,6), 8.14 (d, J = 8.75 Hz, 2 H, H-3,5). A further 600 mg of material was recovered as a mixture.

***N*,*N*-Dipentyl-4-nitroaniline (68). Method of Scheme 7**. A solution of 1-fluoro-4-nitrobenzene (**66**) (5 g) and *N*,*N*-dipentylamine (15 mL) in EtOH (50 mL) was heated under reflux for 48 h; then excess solvent was removed under reduced pressure. The residue was triturated with water and concentrated HCl, and the resulting semisolid was filtered off and dissolved in EtOAc. The aqueous filtrate was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Chromatography of the resulting crude product on silica gel in CH_2Cl_2/hexane (3:7) gave **68** (7.8 g, 79%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 6.7 Hz, 6 H, 2 CH_3), 1.29−1.40 (m, 8 H, 4 CH_2), 1.59−1.65 (m, 4 H, 2 CH_2), 3.35 (t, J = 7.7 Hz, 4 H, 2 CH_2), 6.54 (d, J = 9.5 Hz, 2 H, H-2,6), 8.09 (d, J = 9.5 Hz, 2 H, H-3,5); HRMS (DEI) M^+ 278.1995, $C_{16}H_{26}N_2O_2$ requires M^+ 278.1994.

***N*,*N*-Dihexyl-4-nitroaniline (69).** Similar reaction of **66** with *N*,*N*-dihexylamine gave **69** (19% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.89−0.93 (m, 6 H, 2 CH_3), 1.33−1.36 (m, 12 H, 6 CH_2), 1.58−1.63 (m, 4 H, 2 CH_2), 3.34 (t, J = 7.8 Hz, 4 H, 2 CH_2), 6.54 (d, J = 9.5 Hz, 2 H, H-2,6), 8.09 (d, J = 9.5 Hz, 2 H, H-3,5). Anal. ($C_{18}H_{30}N_2O_2$) C, H, N.

***N*-[3-(Diethylamino)propyl]-4-nitroaniline (70).** Similar reaction of **66** with 3-(diethylamino)propylamine gave **70** (37%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J = 7.1 Hz, 6 H, 2 CH_3), 1.80 (quintet, J = 6.0 Hz, 2 H, CH_2), 2.64 (m, 6 H, 3 CH_2), 3.28 (q, J = 5.6 Hz, 2 H, CH_2), 6.45 (d, J = 9.3 Hz, 2 H, H-2,6), 8.05 (d, J = 9.2 Hz, 2 H, H-3,5). Anal. ($C_{13}H_{21}N_3O_2 \cdot 0.5H_2O$) C, H, N.

***N*-Pentyl-4-nitrobenzylamine (71).** 4-Nitrobenzyl chloride (**67**) (10 g, 0.063 mol) and dimethylamine (50 mL of 40% solution in water) in EtOH (100 mL) were heated under reflux for 1 h, cooled, and poured into water (250 mL). Extraction with EtOAc gave **71** (59%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.1 Hz, 3 H, CH_3), 1.31−1.34 (m, 4 H, 2 CH_2), 1.46−1.52 (m, 2 H, CH_2), 3.89 (s, 2 H, PhCH_2), 7.51 (d, J = 8.4 Hz, 2 H, H-2,6), 8.15 (d, J = 8.5 Hz, 2 H, H-3,5). Anal. ($C_{12}H_{18}N_2O_2$) C, H, N.

***N*-Pyrrolidinyl-4-nitrobenzylamine (72).** Similar reaction of **67** and pyrrolidine gave **72** (84%) as an oil (lit.[25] oil): ^{1}H NMR ($CDCl_3$) δ 1.77−1.84 (m, 4 H, 2 CH_2), 2.49−2.55 (m, 4 H, 2 CH_2), 3.71 (s, 2 H, PhCH_2), 7.51 (d, J = 8.4 Hz, 2 H, H-2,6), 8.17 (d, J = 8.6 Hz, 2 H, H-3,5).

Preparation of 9-[[3-Methoxy-4-(*N*-methylamino)phenyl]amino]acridine (9). Example of the General Method of Scheme 1. *N*-Methyl-4-nitroaniline (1.9 g, 12.5 mmol) was hydrogenated (MeOH/Pt/C) and filtered directly into a solution of 9-chloroacridine (2.14 g, 0.01 mol) in MeOH (200 mL). Two drops of concentrated HCl was added, and the mixture was stirred for 30 min at room temperature. EtOAc (200 mL) was added, and the mixture was concentrated by evaporation until crystals separated. The mixture was then cooled, and the product was filtered and recrystallized from MeOH/EtOAc to give **9** (3.26 g, 84%): mp 232 °C dec; ^{1}H NMR (D_2O) δ 3.12 (s, 3 H, NMe), 3.83 (s, 3 H, OMe), 6.98 (s, 1 H, H-3′), 6.99 (dd, J = 8.5, 2.1 Hz, 1 H, H-5′), 7.47 (t, J = 7.8 Hz, ArH), 7.76 (d, J = 8.7 Hz, 2 H, H-4,5), 7.92 (d, J = 8.5 Hz, 2 H, H-1,8), 7.99 (t, J = 7.6 Hz, 2 H, ArH). Anal. ($C_{21}H_{19}N_3O \cdot 2HCl$) C, H, N, Cl.

9-[[3-Isopropoxy-4-(*N*-methylamino)phenyl]amino]acridine (10): from reduced **61** and 9-chloroacridine, (75%); mp (EtOAc/MeOH) >200 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.19 (d, J = 7.0 Hz, 6 H, 2 CH_3), 2.79 (s, 3 H, NMe), 4.42 (sept, J = 6.0 Hz, 1 H, CH), 5.26 (s, 1 H, NH), 6.57 (d, J = 8.3 Hz, 1 H, H-6) 6.91−6.95 (m, 2 H, H-3′,5′), 7.37 (t, J = 7.6 Hz, 2 H, ArH), 7.92 (t, J = 7.6 Hz, 2 H, ArH), 8.06 (d, J = 8.5 Hz, 2 H, H-4,5), 8.29 (br s, 2 H, H-1,8) 11.76 (br s, 1 H, NH). Anal. ($C_{23}H_{23}N_3O \cdot 2HCl \cdot 0.25H_2O$) C, H, N, Cl.

9-[[4-(*N*-Hexylamino)-3-methoxyphenyl]amino]acridine (14): from reduced *N*-hexyl-3-methoxy-4-nitroaniline and 9-chloroacridine (80%); mp (MeOH/EtOAc) 222−225 °C; ^{1}H NMR (CD_3OD) δ 0.93 (t, J = 7.0 Hz, 3 H, CH_3), 1.35−1.49 (m, 6 H, 3 CH_2), 1.68 (quintet, J = 7.3 Hz, 2 H, CH_2), 3.20 (t, J = 7.1 Hz, 2 H, NCH_2), 3.78 (s, 3 H, OCH_3), 6.68 (d, J = 8.2 Hz, 1 H, H-6′), 6.88−6.92 (m, 2 H, H-3′,5′), 7.39 (t, J = 7.6 Hz, 2 H, H-3,6), 7.85 (dd, J = 8.55, 0.73 Hz, 2 H, H-4,5), 7.93 (dd, J = 7.7, 1.2 Hz, 2 H, H-2,7), 8.21 (d, J = 8.6 Hz, 2 H, H-1,8). Anal. ($C_{26}H_{29}N_3O \cdot HCl \cdot 0.5H_2O$) C, H, N, Cl.

9-[[4-(*N*-Hexylamino)phenyl]amino]-6-chloro-2-methoxyacridine (15): from reduced *N*-hexyl-4-nitroaniline and 6,9-dichloro-2-methoxyacridine (96%); mp (MeOH/EtOAc) 258 °C dec; ^{1}H NMR ($(CD_3)_2SO$) δ 0.89 (t, J = 6.6 Hz, 3 H, CH_3), 1.32 (m, 6 H, 3 CH_2), 1.61 (m, 2 H, CH_2), 3.11 (t, J = 7.1 Hz, 2 H, CH_2), 3.73 (s, 3 H, OCH_3), 6.94 (d, J = 9.15 Hz, 2 H, ArH), 7.27 (d, J = 8.6 Hz, 2 H, ArH), 7.42 (dd, J = 9.3, 1.45 Hz, 1 H, ArH), 7.70 (m, 2 H, ArH), 8.00−8.16 (m, 3 H, ArH), 11.40 (s, 1 H, NH). Anal. ($C_{26}H_{28}ClN_3O \cdot 2HCl$) C, H, N, Cl.

9-[[4-(*N*-Hexylamino)-3-methoxyphenyl]amino]-6-chloro-2-methoxyacridine (16): from reduced *N*-hexyl-3-methoxy-4-nitroaniline and 6,9-dichloro-2-methoxyacridine (80%); mp (MeOH/EtOAc) 250−253 °C dec; ^{1}H NMR ($(CD_3)_2SO$) δ 0.88 (t, J = 6.7 Hz, 3 H, CH_3), 1.29−1.35 (m, 6 H, 3 CH_2), 1.60 (quintet, J = 7.1 Hz, 2 H, CH_2), 3.15 (t, J = 7.3 Hz, 2 H, CH_2), 3.74 (s, 3 H, OCH_3), 6.96 (d, J = 7.2 Hz, 2 H, Ar), 7.06 (s, 1 H, Ar), 7.41 (d, J = 9.4 Hz, 1 H, Ar), 7.72 (dd, J = 9.3, 2.4 Hz, 1 H, Ar), 7.78 (br s, 1 H, Ar), 8.04 (d, J = 9.3 Hz, 1 H, Ar), 8.12 (s, 2 H, Ar), 11.44 (s, 1 H, NH), 14.98 (br s, 1 H, NH). Anal. ($C_{27}H_{30}ClN_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

9-[[4-[[3-(Diethylamino)propyl]amino]phenyl]amino]acridine (18): from reduced **20** and 9-chloroacridine (65%); mp (MeOH/EtOAc) 256−259 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.24 (t, J = 7.2 Hz, 6 H, 2 CH_3), 1.96−2.00 (m, 2 H, CH_2), 3.07−3.26 (m, 8 H, 4 CH_2) 6.72 (d, J = 8.7 Hz, 2 H, H-2′,6′), 7.15 (d, J = 8.6 Hz, 2 H, H-3′,5′), 7.36 (t, J = 7.55 Hz, 2 H, H-3,6), 7.90 (t, J = 7.6 Hz, 2 H, H-2,2′), 8.00 (d, J = 8.4 Hz, 2 H, H-4,5), 8.25 (br s, 2 H, H-1,8), 10.60 (br s 1 H, NH). Anal. ($C_{26}H_{30}N_4 \cdot 2HCl \cdot H_2O$) C, H, N.

9-[[4-[[2-(Diethylamino)ethyl]amino]-3-methoxyphenyl]-amino]acridine (19): from reduced **56** and 9-chloroacridine (87%); mp (MeOH/EtOAc) 248 °C dec; ^{1}H NMR (D_2O) δ 1.46 (t, J = 7.2 Hz, 6 H, 2 CH_3), 3.48 (q, J = 7.2 Hz, 4 H, 2 CH_2-CH_3), 3.57 (t, J = 5.9 Hz, 2 H, CH_2), 3.77 (s, 5 H, OCH_3, CH_2N), 6.68 (s, 1 H, H-3′), 6.78 (d, J = 8.2 Hz, 1 H, H-5′or H-6′), 6.89 (d, J = 8.3 Hz, 1 H, H-5′ or H-6′), 7.28 (t, J = 7.7 Hz, 2 H, H-3,6), 7.61 (d, J = 8.3 Hz, 2 H, H-4,5), 7.72 (d, J = 8.6 Hz, 2 H, H-1,8), 7.87 (t, J = 7.6 Hz, 2 H, H-2,7). Anal. ($C_{26}H_{30}N_4O$·2HCl·2.5H_2O) C, H, N.

9-[[3-Methoxy-4-(*N*-ethyl-*N*-methylamino)phenyl]amino]acridine (21): from reduced **53** and 9-chloroacridine (75%); mp (MeOH/EtOAc) 218−222 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.16 (t, J = 7.1 Hz, 3 H, CH_3), 2.50 (s, 3 H, CH_3), 3.13 (br s, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 7.13 (d, J = 7.1 Hz, 1 H, H-6′), 7.36 (br s, 1 H, H-3′), 7.45 (t, J = 7.6 Hz, 2 H, H-3,6), 7.85 (br s, 1 H, H-5), 8.04 (t, J = 7.6 Hz, 2 H, H-2,7), 8.19 (d, J = 8.2 Hz, 2 H, H-4,5), 8.32 (d, J = 8.7 Hz, 2 H, H-1,8), 11.77 (br s, 1 H, NH), 12.13 (br s, 1 H, NH), 15.23 (br s, 1 H, NH). Anal. ($C_{23}H_{23}N_3O$·2HCl·H_2O) C, H, N, Cl.

9-[[4-(*N*-Hexyl-*N*-methylamino)phenyl]amino]acridine (22): from reduced **49** and 9-chloroacridine (80%); mp (MeOH/EtOAc) 214−216 °C; ^{1}H NMR (CD_3OD) δ 0.87 (t, J = 6.8 Hz, CH_3), 1.29 (m, 6 H, 3 CH_2), 1.53 (m, 2 H, CH_2), 3.49 (m, 2 H, CH_2), 7.02 (br s, 2 H, H-4,5), 7.33 (d, J = 8.4 Hz, 2 H, H-3′,5′), 7.41 (t, J = 7.6 Hz, 2 H, H-2,7), 7.97 (t, J = 7.5 Hz, 2 H, H-3,6), 8.04 (d, J = 8.4 Hz, 2 H, H-2′,6′), 8.26 (d, J = 8.4 Hz, 2 H, H-1,8), 11.49 (s, 1 H, NH), 14.42 (s, 1 H, NH). Anal. ($C_{26}H_{29}N_3$·2HCl·0.5H_2O) C, H, N, Cl.

9-[[4-(*N*-Hexyl-*N*-methylamino)-3-methoxyphenyl]amino]acridine (23): from reduced **51** and 9-chloroacridine (81%); mp (MeOH/EtOAc) 197−200 °C; ^{1}H NMR (CD_3OD) δ 0.91 (t, J = 6.8 Hz, 3 H, CH_3), 1.33 (m, 6 H, 3 CH_2), 1.57 (m, 2 H, CH_2), 3.02 (s, 3 H, CH_3), 3.30 (m, 4 H, 2 CH_2), 3.84 (s, 3 H, OCH_3), 7.04 (dd, J = 8.5, 2.3 Hz, 1 H, H-5′), 7.15 (d, J = 2.3 Hz, 1 H, H-3′), 7.46 (t, J = 7.7 Hz, 2 H, ArH), 7.94−8.02 (m, 4 H, ArH), 8.23 (d, J = 8.8 Hz, 2 H, H-1,8). Anal. ($C_{27}H_{31}N_3O$·2HCl) C, H, N.

9-[[4-(*N*-Hexyl-*N*-methylamino)phenyl]amino]-6-chloro-2-methoxyacridine (24): from reduced **49** and 6,9-dichloro-2-methoxyacridine (72%); mp (MeOH/EtOAc) 223.5−225.5 °C; ^{1}H NMR (CD_3OD) δ 0.92 (t, J = 6.3 Hz, 3 H, CH_3), 1.35 (m, 6 H, 3 CH_2), 1.60 (m, 2 H, CH_2), 3.10 (s, 3 H, CH_3), 3.48 (t, J = 7.6 Hz, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 7.10 (br s, 2 H, H-2′,6′), 7.35 (d, J = 8.8 Hz, 2 H, H-3′,5′), 7.39 (d, J = 9.4 Hz, 1 H, H-3), 7.57 (br s, 1 H, H-4), 7.66 (dd, J = 9.4, 2.6 Hz, 1 H, H-7), 7.81 (d, J = 9.3 Hz, 1 H, H-5), 7.89 (d, J = 1.9 Hz, 1 H, H-1), 1.19 (d, J = 9.4 Hz, 1 H, H-8). Anal. ($C_{27}H_{29}N_3ClO$·2HCl) C, H, N.

9-[[4-(*N*,*N*-Dipropylamino)phenyl]amino]acridine (28): from reduced *N*,*N*-dipropyl-4-nitroaniline and 9-chloroacridine (94%); mp (MeOH/EtOAc) 232−237 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 0.91 (t, J = 7.3 Hz, 6 H, 2 CH_3), 1.58 (sextet, J = 7.35 Hz, 4 H, 2 CH_2), 3.39 (m, 4 H, 2 CH_2), 6.75 (d, J = 9.0 Hz, 2 H, H-3′,5′) 7.22 (d, J = 8.9 Hz, 2 H, H-2′6′), 7.39 (t, J = 7.4 Hz, 2 H, H-2,7), 7.95 (m, 4 H, H-3,4,5,6), 8.28 (d, J = 8.65 Hz, 2 H, H-1,8). Anal. ($C_{25}H_{27}N_3$·HCl·0.5H_2O) C, H, N, Cl.

9-[[4-(*N*,*N*-Dibutylamino)phenyl]amino]acridine (29): from reduced *N*,*N*-dibutyl-4-nitroaniline and 9-chloroacridine (97%); mp (MeOH/EtOAc) 220−224 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 0.93 (t, J = 7.2 Hz, 6 H, 2 CH_3), 1.33 (sextet, J = 7.2 Hz, 4 H, 2 CH_2), 1.54 (quintet, J = 7.6 Hz, 4 H, 2 CH_2), 3.33 (t, J = 7.2 Hz, 4 H, 2 CH_2), 6.75 (d, J = 8.9 Hz, 2 H, H-3′,5′), 7.23 (d, J = 8.8 Hz, 2 H, H-4,5), 7.38 (t, J = 7.3 Hz, H-2,7), 7.90 (m, 4 H, H-3,6,2′,6′), 8.26 (d, J = 8.7 Hz, 2 H, H-1,8), 11.41 (br s, 1 H, NH). Anal. ($C_{27}H_{31}N_3$·HCl·1.5H_2O) C, H, N.

9-[[4-(*N*,*N*-Dipentylamino)phenyl]amino]acridine (30): from reduced **68** and 9-chloroacridine (96%); mp (MeOH/EtOAc) 222−224 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 0.89 (t, J = 6.6 Hz, 6 H, 2 CH_3), 1.29−1.33 (m, 8 H, 4 CH_2), 1.50−1.62 (m, 4 H, 2 CH_2), 3.36 (m, 4 H, 2 CH_2), 6.76 (d, J = 9.0 Hz, 2 H, H-2′,6′), 7.22 (d, J = 8.8 Hz, 2 H, H-3′,5′), 7.38 (t, J = 7.3 Hz, 2 H, ArH), 7.89−8.01 (m, 4 H, ArH), 8.26 (d, J = 8.6 Hz, 2 H, H-1,8). Anal. ($C_{29}H_{35}N_3$·HCl) C, H, N, Cl.

9-[[4-(*N*,*N*-Dihexylamino)phenyl]amino]acridine (31): from reduced **69** and 9-chloroacridine (76%); mp (MeOH/EtOAc) 194−196 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 0.88 (t, J = 4.7 Hz, 6 H, 2 CH_3), 1.31 (m, 12 H, 2 $(CH_2)_3$), 1.31 (m, 4 H, 2 CH_2), 3.32 (t, J = 7.5 Hz, 4 H, 2 CH_2), 6.75 (d, J = 9.0 Hz, 2 H, H-4′,5), 7.20 (d, J = 8.9 Hz, 2 H, H-3′,5′), 7.37 (t, J = 7.5 Hz, 2 H, H-2,7), 7.95 (m, 4 H, H-3,6,2′,6′), 8.25 (br s, 2 H, H-1,8). Anal. ($C_{31}H_{39}N_3$·HCl·1.5H_2O) C, H, N, Cl.

9-[[4-[(*N*-Pentylamino)methyl]phenyl]amino]-acridine (35): from reduced **71** and 9-chloroacridine (45%); mp (MeOH/EtOAc) 244−247 °C; ^{1}H NMR (CD_3OD) δ 0.97 (t, J = 7.0 Hz, 3 H, CH_3), 1.40−1.44 (m, 4 H, 2 CH_2), 1.75−1.84 (m, 2 H, CH_2), 3.12 (t, J = 8.1 Hz, 2 H, CH_2), 4.31 (s, 2 H, CH_2), 7.44−7.48 (m, 2 H, Ar), 7.52 (d, J = 8.5 Hz, 2 H, H-3′,5′), 7.70 (d, J = 8.5 Hz, 2 H, H-2′,6′), 7.98−8.04 (m, 2 H, ArH), 8.23 (d, J = 8.7 Hz, ArH). Anal. ($C_{25}H_{27}N_3$·2HCl·H_2O) C, H, N, Cl.

9-[[4-(*N*-Pyrrolidinomethyl)phenyl]amino]acridine (36): from reduced **72** and 9-chloroacridine (81%); mp (MeOH/EtOAc) 269−270 °C; ^{1}H NMR (D_2O) δ 2.11 (m, 2 H, CH_2), 2.28 (m, 2 H, CH_2), 3.31 (m, 2 H, CH_2), 3.64 (m, 2 H, CH_2), 4.51 (s, 2H, CH_2), 7.34 (d, J = 8.2 Hz, 2 H, H-3′,5′), 7.45 (t, J = 7.8 Hz, 2 H, H-3,6), 7.64 (d, J = 8.2 Hz, 2 H, H-2′,6′), 7.70 (d, J = 8.7 Hz, 2 H, H-4,5), 7.82 (d, J = 8.8 Hz, 2 H, H-1,8), 7.99 (t, J = 7.7 Hz, 2 H, H-2,7). Anal. ($C_{24}H_{23}N_3$·2HCl·0.5H_2O) C, H, N, Cl.

9-[(4-Hexylphenyl)amino]acridine (38): from reduced **65** and 9-chloroacridine (75%); mp (MeOH/EtOAc) 229−234 °C; ^{1}H NMR (CD_3OD) δ 0.91 (t, J = 6.9 Hz, 3 H, CH_3), 1.28−1.40 (m, 8 H, 4 CH_2), 1.70 (quintet, J = 7.4 Hz, 2 H, CH_2), 2.73 (t, J = 7.6 Hz, 2 H, CH_2), 7.33−7.43 (m, 6 H, ArH), 7.90−7.99 (m, 4 H, ArH), 8.17 (d, J = 8.95 Hz, 2 H, ArH). Anal. ($C_{26}H_{28}N_2$·HCl) C, H, N, Cl.

9-[[4-[(*N*,*N*-Diethylamino)propyl]phenyl]amino]-acridine (39): from reduced **58** and 9-chloroacridine (35%); mp (MeOH/EtOAc) >200 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.22 (t, J = 7.2 Hz, 6 H, 2 CH_3), 2.04 (m, 2 H, CH_2), 2.75 (t, J = 7.5 Hz, 2 H, CH_2), 3.02 (m, 2 H, CH_2), 3.10 (m, 4 H, 2 CH_2), 7.34−7.39 (m, 6 H, ArH), 7.95 (t, J = 8.0 Hz, 2 H, ArH), 8.09 (d, J = 8.5 Hz, 2 H, ArH), 8.24 (d, J = 8.8 Hz, 2 H, ArH), 8.74 (s, 1 H, NH). Anal. ($C_{26}H_{29}N_3$·2HCl·0.5H_2O) C, H, N, Cl.

9-[[4-(Hexyloxy)phenyl]amino]acridine (41): from reduced *N*-(hexyloxy)-4-nitrobenzene and 9-chloroacridine (86%); mp (MeOH/EtOAc) 248−251 °C; ^{1}H NMR (CD_3OD) δ 0.95 (t, J = 7.1 Hz, 3 H, CH_3), 1.35−1.45 (m, 4 H, 2 CH_2), 1.49−1.56 (m, 2 H, CH_2), 1.83 (quintet, J = 7.0 Hz, 2 H, CH_2), 4.06 (t, J = 6.4 Hz, 2 H, OCH_2), 7.08 (d, J = 8.9 Hz, 2 H, H-2′,6′), 7.36 (d, J = 8.9 Hz, H-3′,5′), 7.42 (dt, J = 7.8, 1.15 Hz, 2 H, H-2,7), 7.89 (d, J = 8.5 Hz, 2 H, H-4,5), 7.96 (dt, J = 7.7, 1.1 Hz, 2 H, H-3,6), 8.17 (d, J = 8.8 Hz, 2 H, H-1,8). Anal. ($C_{25}H_{26}N_2O$·HCl) C, H, N, Cl.

9-[3-(2-Aminopyridyl)]acridine (7). Method of Scheme 1. *N*-Acetoxy-2-amino-5-nitropyridine (1.96 g, 10.8 mmol) was hydrogenated over Pd/C in MeOH (40 mL), and the solution was filtered directly into a solution of 9-chloroacridine (2.01 g, 10 mmol) in MeOH (30 mL). After 15 h at room temperature, the crude product was precipitated by the addition of EtOAc, then dissolved in 2 N ethanolic HCl, and heated under reflux for 1 h. The cooled mixture was diluted with EtOAc, and the product was recrystallized from MeOH/EtOAc to give **7** as the dihydrochloride salt (0.7 g, 22%): mp 260−268 °C; ^{1}H NMR (D_2O) δ 7.12 (d, J = 9.5 Hz, 1 H, H-5′), 7.57 (t, J = 7.8 Hz, 2 H, H-3,6), 7.65 (d, J = 9.7 Hz, 1 H, H-6′), 7.72 (d, J = 8.4 Hz, 2 H, H-4,5), 7.93 (s, 1 H, H-2′), 7.98 (d, J = 8.8 Hz, 2 H, H-1,8), 8.03 (t, J = 7.7 Hz, 2 H, H-2,7). Anal. ($C_{18}H_{14}N_4$·2HCl·H_2O) C, H, N, Cl.

3,6-Bis(dimethylamino)-9-[[4-(*N*-hexyl-*N*-methylamino)-phenyl]amino]acridine (25). Method of Scheme 2. 3,6-Bis(dimethylamino)-9-(methylthio)acridine[10] (**45**) (0.5 g, 1.6 mmol) and phenol (1.9 g) were heated at 100 °C for 15 min. *N*-Hexyl-*N*-methyl-4-nitroaniline (**49**) (307 mg, 1.6 mmol) was hydrogenated (MeOH/Pt/C) and filtered into the above mixture, which was then stirred at 100 °C for 2 h while the MeOH was allowed to evaporate. The mixture was then cooled to room temperature, Me_2CO (75 mL) and concentrated HCl (8 mL) were added, the mixture was stirred for 2 h, and the product was then precipitated by addition of EtOAc. The resulting gummy material was recrystallized twice from

MeOH/EtOAc to give **25** (516 mg, 63%): mp 238 °C dec; ^{1}H NMR ($(CD_3)_2SO$) δ 0.90 (br s, 3 H, CH_3), 1.31 (m, 6 H, 3 CH_2), 1.56 (br s, 2 H, CH_2), 3.17 (s, 12 H, 2 $N(CH_3)_2$), 3.29 (s, 3 H, NCH_3), 3.58 (br s, 2 H, CH_2), 6.65 (s, 2 H, H-4,5), 6.95 (d, J = 8.7 Hz, 2 H, H-2,7), 7.28 (d, J = 7.8 Hz, 2 H, H-3′,5′), 7.61 (d, J = 7.8 Hz, H-2′,6′), 7.82 (d, J = 9.3 Hz, 2 H, H-1,8); HRMS (DEI) M^+ 469.3209, $C_{30}H_{39}N_5$ requires M^+ 469.3205.

3,6-Bis(dimethylamino)-9-[[4-(*N*-hexylamino)phenyl]-amino]acridine (17). Method of Scheme 2. Similar reaction of **45** with freshly hydrogenated *N*-hexyl-4-nitroaniline gave **17** (76%) as the hydrochloride salt: mp (MeOH/EtOAc) 258 °C dec; ^{1}H NMR ($(CD_3)_2SO$) δ 0.89 (t, J = 6.6 Hz, 3 H, CH_3), 1.33 (m, 6 H, 3 CH_2), 1.60 (m, 2 H, CH_2), 3.05 (s, 12 H, 2 $N(CH_3)_2$), 3.36 (m, 2 H, CH_2), 6.56 (d, J = 2.2 Hz, H-4,5), 6.73 (d, J = 7.9 Hz, 2 H, H-1,8), 6.87 (dd, J = 9.7, 2.2 Hz, 2 H, H-3,6), 6.95 (s, 1 H, NH), 7.06 (d, J = 8.6 Hz, 2 H, H-2′,6′), 7.21 (s, 1 H, NH), 7.88 (d, J = 8.7 Hz, 2 H, H-3′,5′), 10.10 (s, 1 H, NH), 12.6 (s, 1 H, NH); HRMS (DEI) M^+ 455.3048, $C_{29}H_{37}N_5$ requires M^+ 455.3049.

Mammalian Cell Inhibition Assay. These were carried out using the human Jurkat leukemia cell line, as described previously.[7] The IC_{50} values (μM) recorded in Table 1 are the concentration of drug which reduced cell growth to 50% of that of untreated controls, following a 72 h exposure. Cells were counted with an improved Neubauer hemocytometer.

***In Vitro* Antiparasitic Testing**. Drugs were tested as their hydrochloride salts (prepared by recrystallization of the free bases fromn MeOH/EtOAc/HCl) and were prepared as 10 mM stock solutions in 50% aqueous EtOH or 50% aqueous DMSO and stored in the dark at −20 °C. Immediately before testing, aliquots of stock solutions were diluted to 4 mM with 50% aqueous EtOH. Further dilutions were in *N*-(hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid (HEPES)-buffered Dulbecco's medium, supplemented with 10% fetal bovine serum.

L. major: The assays were carried out as previously described[4,12] and were performed in triplicate. Briefly, macrophages from CBA/H mice were infected *in vitro* with *L. major* promastigotes at a parasite to macrophage ratio of 5:1. After incubation at 37 °C for 18−20 h, the infected macrophages (average infection rate 80%) were treated with drug at 37 °C for 48 h. Drugs were tested at about 3-fold dilutions over a range of final concentrations from 0.03 to 10 μM; the exact range was determined by pilot experiments but always included at least four concentrations. At the end of the incubation period, cultures were rinsed to remove excess drug, and the macrophages were lyzed (SDS) to release surviving parasites. These were then incubated in supplemented cultures at 26 °C for 24−48 h to allow transformation to the promastigote form and then treated with 0.5 mCi (2.0 Ci/mmol) of [^{3}H]TdR. The parasites were harvested 24 h later, and the percent of intracellular parasite killingwas calculated by comparing the level of [^{3}H]TdR incorporation with that in control cultures containing only the same volume of EtOH. IC_{50} values were determined from the best-fit straight line from log/linear plots.

L. donovani: Amastigotes (strain MHOM/ET/67/L82) derived from the spleen of a golden hamster (Wright's strain)[18] were used to infect mouse peritoneal macrophages from CD1 (Charles River Ltd.) mice at a parasite/macrophage ratio of 5:1. Infected macrophages were maintained in RPMI1640 medium in Labtek 8 chamber slides at 37 °C in a 50% CO_2/air mixture for 24 h prior to the addition of drugs. Cultures were maintained in the presence of drug at a range of concentrations (3-fold serial dilutions from 30 μM) at 37 °C for 7 days. Activity was scored as percent macrophages cleared of amastigotes in treated cultures. Dose−response curves were analyzed by linear regression to obtain an ED_{50} value. Sodium stibogluconate was used as the positive control (ED_{50} = 4.1 μg/mL Sb(V); MW not known).

T. cruzi: Trypomastigotes (strain MHOM/BR/00/Y) derived from rat myoblast cultures[19] were used to infect mouse peritoneal macrophages isolated from CD1 mice at a parasite/macrophage ratio of 5:1. Infected cultures were maintained in the presence of drug in a 3-fold dilution series for 3 days. Activity was determined from the percent infected macrophages in treated compared with untreated cultures, and dose−response curves were analyzed by linear regression to obtain an ED_{50} value. Nifurtimox was used as the positive control (ED_{50} = 2.7 μM).

T. brucei: Bloodstream trypomastigotes (S427) were maintained in HMI-9 medium containing 10% heat-inactivated calf serum at 37 °C in a 50% CO_2/air mixture.[17] Parasites were incubated with medium containing drug in a 3-fold dilution series for 48 h. Drug activity was determined from the number (determined using a Coulter Counter ZM), and dose−response curves were analyzed by linear regression to obtain an ED_{50} value. Pentamidine was used as the positive control (ED_{50} = 0.008 μM).

Acknowledgment. This investigation received financial support from the Health Research Council of New Zealand (S.A.G., D.P.F., R.K.R., W.A.D.) and from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) (V.Y., D.S., S.L.C.).

References

(1) Olliaro, P.; Bryceson, A. D. M. Practical progress and new drugs for changing patterns of leishmaniasis. *Parasitol. Today* **1993**, *9*, 323−328.
(2) Segovia, M.; Navarro, A.; Artero, M.; Martin-Luemgo, F. Activity of ofloxacin against *Leishmania* amastigotes. Presented at the XIth International Conference on Infectious Parasitic Diseases, 1988; Abstract 266.
(3) Croft, S. L.; Hogg, J. Limited activity of bacterial DNA topoisomerase II inhibitors against *Leishmania donovani* and *Trypanosoma cruzi* amastigotes *in vitro*. *Trans. R. Soc. Trop. Med. Hyg.* **1988**, *82*, 856.
(4) Mauel, J.; Denny, W. A.; Gamage, S. A.; Ransijn, A.; Wojcik, S.; Figgitt, D.; Ralph, R. K. 9-Anilinoacridines as potential antileishmanial agents. *Antimicrob. Agents Chemother.* **1993**, *37*, 991−996.
(5) Baguley, B. C.; Holdaway, K. M.; Fray, L. M. Design of DNA intercalators to overcome topoisomerase II-mediated multidrug resistance. *J. Natl. Cancer Inst.* **1990**, *82*, 398−402.
(6) Figgitt, D.; Denny, W. A.; Chavalitshewinkoon, P.; Wilairat, P.; Ralph, R. K. *In vitro* study of anticancer acridines as potential antitrypanosomal and antimalarial agents. *Antimicrob. Agents Chemother.* **1992**, *36*, 1644−1647.
(7) Chavalitshewinkoon, P.; Wilairat, P.; Gamage, S. A.; Denny, W. A.; Figgitt, D.; Ralph, R. K. Structure-activity relationships and modes of action of 9-anilinoacridines against chloroquine-resistant *Plasmodium falciparum in vitro*. *Antimicrob. Agents Chemother.* **1993**, *37*, 403−406.
(8) Gamage, S. A.; Tepsiri, N.; Wilairat, P.; Wojcik, S. J.; Figgitt, D. P.; Ralph, R. K.; Denny, W. A. Synthesis and *in vitro* evaluation of 9-anilino-3,6-diaminoacridines active against a multi-drug-resistant strain of the malaria parasite *Plasmodium falciparum*. *J. Med. Chem.* **1994**, *37*, 1486−1494.
(9) Denny, W. A.; Atwell, G. J.; Cain, B. F.; Leo, A.; Panthananickal, A.; Hansch, C. Potential Antitumor Agents. Part 36. Quantitative relationships between antitumor potency, toxicity and structure for the general class of 9-anilinoacridine antitumor agents. *J. Med. Chem.* **1982**, *25*, 276−315.
(10) Elslager, E. F. 9-Substituted 3,6-bis(dimethylamino)acridines. *J. Org. Chem.* **1962**, *27*, 4346−4349.
(11) Divakar, K. J.; Gaikwad, B. V.; Tampal, N. F.; Rajappa, S. Quinoneimine route to benzimidazol-2-ylcarbamates. Part 3. Effect of extension of conjugation on the quinone imine. *J. Chem. Res. (M)* **1986**, 1687−1697.
(12) Mauel, J. Intracellular parasite killing induced by electron carriers. I. Effect of electron carriers on intracellular carriers on *Leishmania* sp in macrophages from different genetic backgrounds. *Mol. Biochem. Parasitol.* **1984**, *13*, 83−96.
(13) Hansch, C.; Leo, A. J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience: New York, 1979.
(14) Zwelling, L. A.; Mitchell, M.; Satitpunwaycha, P.; Mayes, J.; Altschuler, E.; Hinds, M.; Baguley, B. C. The relative activity of structural analogs of amsacrine against human leukemia cell lines containing amsacrine-sensitive or resistant forms of topoisomerase II: the use of computer simulations in new drug development. *Cancer Res.* **1992**, *52*, 209−217.
(15) Lee, H. H.; Palmer, B. D.; Denny, W. A. Reactivity of quinoneimine and quinonediimine oxidation products of the antitumor drug amsacrine and related compounds to nucleophiles. *J. Org. Chem.* **1988**, *53*, 6042−6047.

(16) Shoemaker, D. D.; Cysyk, R. L.; Gormly, P. E.; De Souza, J. J. V.; Malspeis, L. Metabolism of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide by rat liver microsomes. *Cancer Res*. **1984**, *44*, 1939−1945.
(17) Hirumi, H.; Hirumi, K. Continuous cultivation of *Trypanosoma brucei* bloodstream forms in a medium containing a low concentration of serum protein without feeder cell layers. *J. Parasitol*. **1989**, *75*, 985−989.
(18) Neal, R. A.; Croft, S. L. An in vitro system for determining the activity of compounds against the intracellular amastigote form of *Leishmania donovani*. *J. Antimicrob. Chemother*. **1984**, *14*, 463−475.
(19) Schmatz, D. M.; Murray, P. K. *Trypanosoma cruzi*: selective isolation of pure trypomastigotes from cultured muscle cells. *J. Parasitol*. **1981**, *67*, 517−521.
(20) Ingold, C. K.; Ingold, E. H. The nature of the alternating effect in carbon chains. Part V. A discussion of aromatic substitution with special reference to the respective roles of polar and nonpolar dissociation; and a further study of the relative directing efficiencies of oxygen and nitrogen. *J. Chem. Soc*. **1926**, 1310−1328.
(21) Prinz, W.; Kyle, A.; Levy, P. R. A novel synthetic route to oximinoacet-2-anisidides and their conversion into 3-hydroxyanthranilic acids via 7-methoxyisatins. *J. Chem. Res. (M)* **1978**, 1347−1370.
(22) Katritzky, A. R.; Fan, W.-Q.; Akutagawa, K.; Wang, J. Carbon dioxide: a reagent for the simultaneous protection of nucleophilic centers and the activation of alternative locations to electrophilic attack. 16. A novel synthetic method for the side-chain functionalization of N-methyl-o-toluidine and for the preparation of 2-substituted N-methylindoles. *Heterocycles* **1990**, *30*, 407−414.
(23) Zeman, A.; Heusinger, H. Intramolecular energy transfer in γ-irradiated alkylbenzenes. *J. Phys. Chem*. **1966**, *70*, 3374−3376.
(24) Ito, K.; Komori, A.; Ogawa, M. Utilization of long-chain alkylanilines in azoic dyes. *Technol. Rep. Kansai Univ*. **1963**, *5*, 31−34; *Chem. Abstr*. **1963**, *61*, 16191d.
(25) Schlinck, J. Zur Kenntniss des Pyrrolidins. (Studies on pyrrolidines.) *Chem. Ber*. **1899**, *32*, 947−959.
(26) Palmer, B. D.; Lee, H. H.; Johnson, P. I.; Baguley, B. C.; Wickham, G.; Wakelin, L. P. G.; McFadyen, W. D.; Denny, W. A. DNA-directed alkylating agents. 2. Synthesis and biological activity of platinum complexes linked to 9-anilinoacridine. *J. Med. Chem*. **1990**, *33*, 3008−3014.

JM970232H