tions are also superimposable on the 2-aminotetralin moieties of low-energy conformations of the potent DA-receptor agonists (6a*R*)-apomorphine and (4a*S*,10b*S*)-*trans*-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline.[29] A similar conclusion was drawn in the report on the DA_1 inactivity of **4a**,[7] and our MMP2 calculations support the suggestion that **4a** is capable of assuming a "DA-active conformation". In order to rationalize the detrimental effect of the C(2)-methyl group, Nichols et al.[7] proposed a DA_1-receptor geometry "that may either be a groove or a slot into which the agonist fits or one where the receptor may fold in on the agonist during the process of receptor activation". In our opinion, the present results and those of Nichols et al.[7] can equally well be explained by assuming that the approach of (2*S*)-**1** and (2*R*)-**3a** (the DA-active enantiomers of **1** and **3**[30]) to the respective DA receptors is from the unsubstituted faces of the tetralin rings.[31]

(29) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.

(30) It has been demonstrated that the 2*R* enantiomer of **3a** is the more potent antipode: McDermed, J. D.; Freeman, H. S. In "Advances in Dopamine Research"; Kohsaka, M.; Shohmori, T.; Tsukada, Y.; Woodruff, G. N., Eds.; Pergamon: Oxford, 1981; p 179.

(31) It has been suggested that the approach of (*R*)-apomorphine to the DA receptor occurs from the corresponding face of the aporphine ring: Camerman, N.; Chan, L. Y. Y.; Camerman, A. *Mol. Pharmacol.* **1979**, *16*, 729.

Experimental Section

The syntheses of compounds **1** and **2** have been previously reported.[3a,5] The structural modelling was performed by use of the interactive computer graphics program MIMIC (methods for interactive modelling in chemistry).[23] Calculations were performed on a VAX 11/780 computer using Allingers MMP2 force field[17] to which had been added parameters for the phenol[18] and amino groups.[19] Computational times ranged from 1 to 30 min/minimization.

^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz or 22.5 MHz on JEOL GX-400 and FX-90Q spectrometers using 0.1 M CD_3OD solutions of the hydrochlorides at 25 °C. Chemical shifts were measured relative to internal tetramethylsilane. Apparent coupling constants were measured from expanded (1-2 Hz/cm) spectra and refined by use of the JEOL FASNO 5 NMR spectrum simulation program. Pulse sequences used for COSY, NOESY (mixing time 0.35 s.), and C-H shift correlation two-dimensional experiments were obtained from the GX-400 software.

Acknowledgment. We thank Dr. Tommy Liljefors and Dr. Robert E. Carter for kindly introducing us to and providing access to the MIMIC program and professor Charles S. Kraihanzel for preliminary molecular mechanics calculations. The financial support from the Swedish Academy of Pharmaceutical sciences, C.D. Carlssons Stiftelse, and IF's Stiftelse is gratefully acknowledged.

Registry No. (*S*)-**1**, 68643-08-3; (*S*-**1**·HCl, 58349-19-2; (*S*)-**2**, 101626-89-5; (*S*)-**2**·HCl, 101626-90-8; **3b**, 67445-12-9; (*S*)-**3c**·HCl, 21880-88-6; **3c**, 21880-87-5; (*S*)-**4c**, 101418-84-2; **5**·HBr, 78943-51-8.

(32) Bucourt, R. *Topics Stereochem.* **1974**, *8*, 159.

Synthesis, Antimalarial Activity, and Quantitative Structure–Activity Relationships of Tebuquine and a Series of Related 5-[(7-Chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1′-biphenyl]-2-ols and N^{ω}-Oxides[1,2]

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Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. *Received June 17, 1985*

A series of 5-[(7-chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1′-biphenyl]-2-ols and N^{ω}-oxides was prepared from the substituted 1-phenyl-2-propanones proceeding through the 5-nitro[1,1′-biphenyl]-2-ols, the corresponding amino, and acetamido derivatives to the *N*-[5-[(alkylamino)methyl]-6-hydroxy[1,1′-biphenyl]-3-yl]acetamides and final condensation with 4,7-dichloroquinoline or the *N*-oxide. In a quantitative structure–activity relationship study first run on 28 and later expanded to 40 substituted phenyl analogues and their N^{ω}-oxides, increasing antimalarial potency vs. *Plasmodium berghei* in mice was found to be correlated with decreasing size ($\sum$MR) and electron donation ($\sum\sigma$) of the phenyl ring substituents. A significant correlation with N^{ω}-oxidation could not be demonstrated. Initial high activity against *P. berghei* infections in mice led to expanded studies that demonstrated in addition excellent activity against resistant strains of parasite, activity in primate models, and pharmacokinetic properties apparently allowing protection against infection for extended periods of time even after oral administration. Such properties encourage the clinical trial of a member of this class in man.

The ability of the malaria parasite to counteract man's efforts at its eradication by modulating its existence in some, still unknown, manner so that it is resistant to most known drugs remains a major problem for the chemotherapist. Our efforts to devise a solution to this problem led us to return to the well-explored 4-aminoquinolines.

The early classic work of Burckhalter[3] and colleagues on the modification of the bialamicol (**1**) structure led to the development of amodiaquine[4] (**2**). Recent efforts[5] on

(1) This is paper 60 of a series on antimalarial drugs. For paper 59, see: Werbel, L. M.; Hung, J.; McNamara, D.; Ortwine, D. F. *Eur. J. Med. Chem.* **1985**, *20*, 363.

(2) This investigation was supported by U.S. Army Medical Research and Development Command Contracts DADA-17-72-C-2077 and DAMD-17-79-C-9115. This is Contribution No. 1765 to the U.S. Drug Development Program.

(3) Burckhalter, J. B.; Tendick, F. H.; Jones, E. M.; Holcomb, W. F.; Rawlins, A. L. *J. Am. Chem. Soc.* **1946**, *68*, 1894.

(4) Burckhalter, J. B.; Tendick, F. H.; Jones, E. M.; Jones, P. A.; Holcomb, W. F.; Rawlins, A. L. *J. Am. Chem. Soc.* **1948**, *70*, 1363.

(5) Colwell, W. T. *Abstracts of Papers*, Antimalarial Drug Development Program, Chemistry Contractors Conference, Washington, DC, June 13, 1973.

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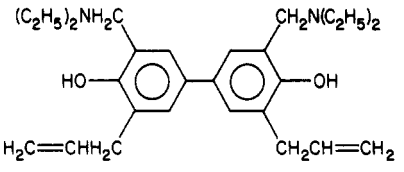
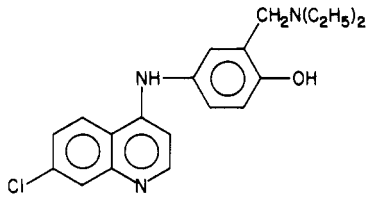
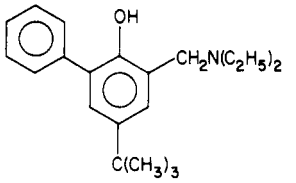


1

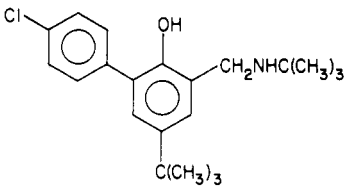


2

modification of the early α-(dialkylamino)-*o*-cresol structure **3** led to improved potency against *Plasmodium berghei* infections in mice and interesting prophylactic effects against *P. cynomolgi* in rhesus monkeys with **4**.



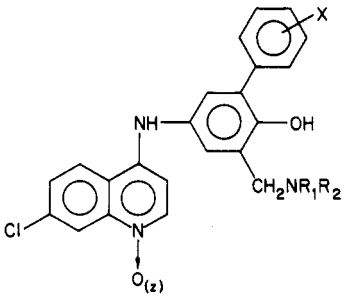
3



4

Amodiaquine has been shown to be somewhat effective against certain chloroquine-resistant strains of *P. falciparum* in vitro[6,7] in owl monkeys,[6] and in man.[6,8] Moreover we have reported[9] that oxidation of the quinoline nitrogen of amodiaquine increased the potency some 3.4 times against *P. berghei* infections in mice.

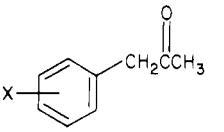
It was thus of interest to examine hybrid structures such as **5**, and in this paper we report the synthesis and biological activity of a series of analogues that has demonstrated outstanding antimalarial activity against both drug-sensitive and -resistant strains as well as an extended duration of activity.



5

(6) Rieckmann, K. H. *J. Am.Med. Assoc.* **1971**, 217, 573.
(7) Fitch, C. D. *Clin. Res.* **1973**, 21, 599.
(8) Hall, A. P.; Segal, H. E.; Pearlman, E. J., Phintuyothin, P. Kosakal, S. *Am. J. Trop. Med. Hyg.* **1975**, 24, 575.
(9) Elslager, E. F.; Gold, E. H., Tendick, F. H.; Werbel, L. M.; Worth, D. F. *J. Heterocycl. Chem.* **1964**, 1, 6.

Table I. Physical Properties of 1-Phenyl-2-propanones **12**



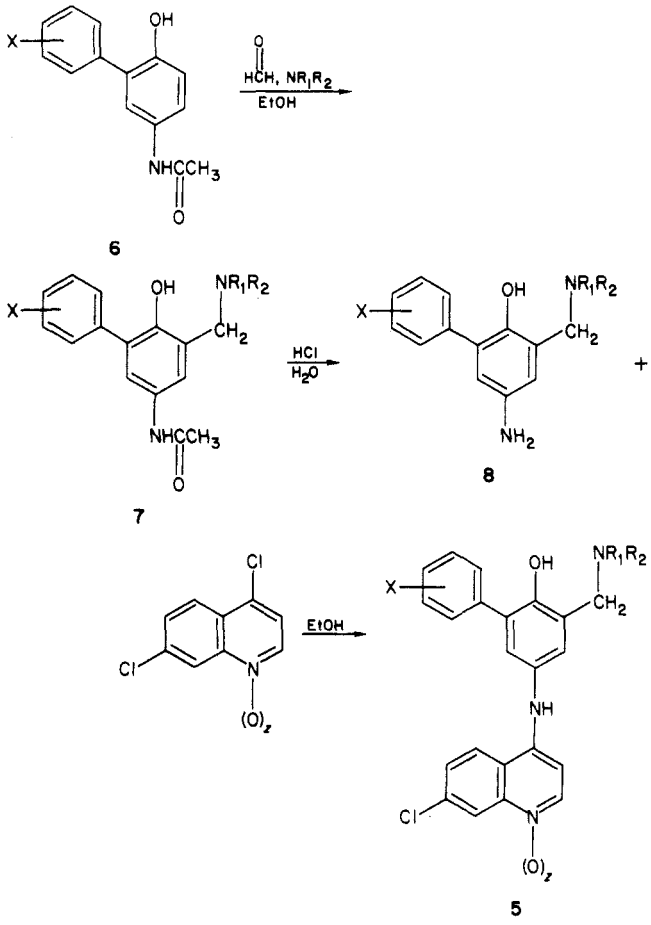
no.	X	bp (mmHg) or mp, °C	% yield[a] (method)	formula
12a	4-Cl	*b*	49[e] (H)	C_9H_9ClO
12b	3,4-Cl_2	*d*	47 (H)	$C_9H_8Cl_2O$
12c	2-CF_3	*c*	17[f] (D)	$C_{10}H_9F_3O$
12d	4-OH	*g*	69 (C)	$C_9H_{10}O_2$
12e	4-$OCH_2OCH_2CH_2OCH_3$		40[h]	$C_{13}H_{18}O_4$
12f	2,3-	*i*	38[j] (H)	$C_{13}H_{12}O$
12g	4-aza	78–80 (0.3)[k]	24 (G)	C_8H_9NO
12h	3-aza	*l*	15[m] (E)	C_8H_9NO
12i	2-aza	*n*	93[o] (F)	C_8H_9NO
12j	4-F	60–65 (0.25)[p]	94 (C)	C_9H_9FO
12k	3-F	65–70 (0.5)[q]	97 (C)	C_9H_9FO
12l	2-F	*r*	96 (C)	C_9H_9FO
12m	2,3-F_2	43–53 (1)	*s* (E)	$C_9H_8F_2O$
12n	2,6-F_2	63–73 (0.1–0.15)	48[t] (E)	$C_9H_8F_2O$
12o	2,3,4,5,6-F_5	42–48 (0.05–0.1)[u]	14[v] (E)	$C_9H_5F_5O$
12p	4-SCH_3	105–115 (0.05–0.30)	24[v] (E)	$C_{10}H_{12}OS$

[a] The analyses were generally not within 0.4% of the calculated values for C, H, N. Compounds were used in subsequent reactions without further purification. Yields are of material of sufficient purity to be used in the next reaction. Yields are calculated from the benzeneacetic acids for methods C and D, the benzaldehydes for method E, the methylpyridines for methods F and G, and the benzeneacetonitriles for method H. [b] Lit.[37] bp 110–112 °C (6 mm). [c] This material was 91% pure by GC analysis. [d] Lit.[37] bp 132–135 °C (1.5 mm). [e] Lit.[37] bp 90–91 °C (2 mm). [f] This material was 96% pure by GC analysis. [g] Lit.[44] bp 168–170 °C (11 mm). [h] This compound was obtained by treating **12d** with (β-methoxyethoxy)methyl chloride (see Experimental Section). [i] Lit.[43] bp 121–126 °C (0.75 mm). [j] This material was 90% pure by GC analysis. [k] Lit.[40] bp 110–115 °C (3–4 mm). [l] Lit.[45] bp 80–81 °C (1 mm). [m] This material was 54% pure by GC analysis. [n] Lit.[39] bp 60–65 °C (0.4 mm). [o] This material was 92% pure by GC analysis. [p] Lit.[35] bp 103 °C (15 mm). [q] Lit.[35] bp 101 °C (13 mm). [r] Lit.[37] bp 83–85 °C (3 mm). [s] It was not appropriate to calculate a yield at this point. 2,3-Difluorobenzaldehyde was prepared from 1,2-difluorobenzene as reported by Roe[46] to give a 51% yield of material, bp 70–110 °C (15 mm) (lit.[46] bp 69–73 °C (15 mm)). GC analysis showed this material to be a 53:43 mixture. This crude 2,3-difluorobenzaldehyde was used to prepare **12m**. GC analysis showed **12m** to be a 55:43 mixture. [t] This material was 98% pure by GC analysis. The starting material 2,6-difluorobenzaldehyde was synthesized from 1,3-difluorobenzene according to Roe et al.[47] [u] Lit.[38] mp 35.5–36.5 °C. [v] This material was 93% pure by GC analysis.

Chemistry. The general route for synthesis of the 5-[(7-chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl]-[1,1′-biphenyl]-2-ols and N^{ω}-oxides (**5**) (Table V) is depicted in Scheme I and is essentially that utilized for the original synthesis of amodiaquine.[4] Thus the *N*-(6-hydroxy[1,1′-biphenyl]-3-yl)acetamides **6a–y** (Table III) were allowed to react with the requisite amine and aqueous formaldehyde in ethanol to give the corresponding *N*-[5-[(alkylamino)methyl]-6-hydroxy[1,1′-biphenyl]-3-yl]-acetamides (**7a–11**, Table IV). Hydrolysis to the free amines (**8**) was achieved upon heating with 6 N HCl. The amines were not purified, and the reaction mixture was simply evaporated in vacuo and the residue was dissolved in ethanol and treated with either 4,7-dichloroquinoline or the *N*-oxide to provide the target compounds **5**.

Preparation of the requisite N-(6-hydroxy[1,1′-biphenyl]-3-yl)acetamides (**6**) provided the most critical challenge, and these were prepared by two routes (Scheme II). Initially, route A was utilized, but when the potential

Scheme I



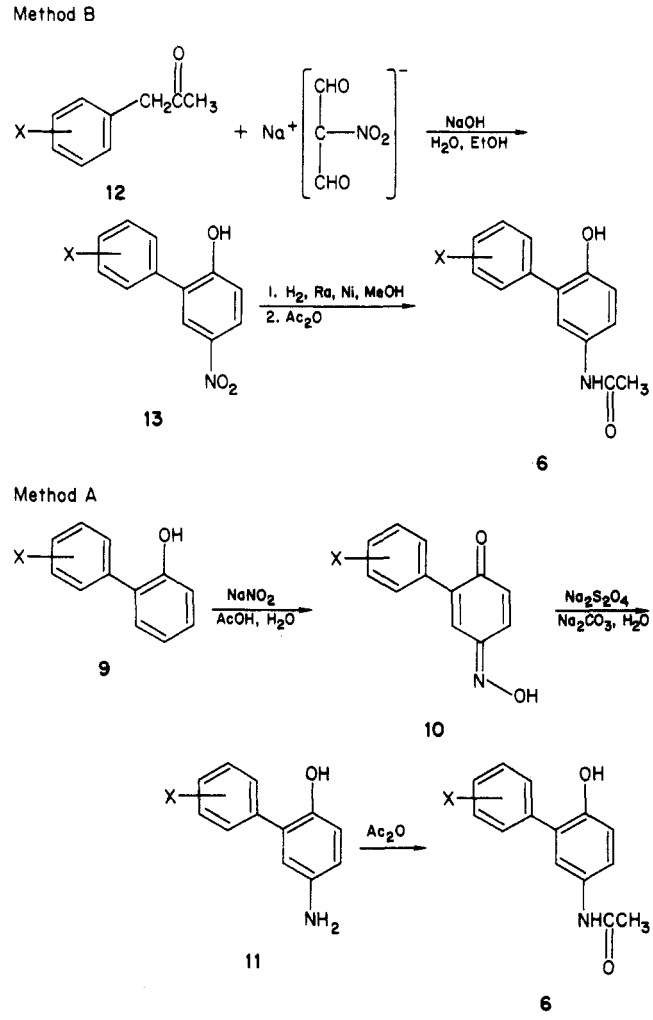
of this series became obvious and it was clear that substantial structure modification would be necessary, route B was developed to avoid the difficulties inherent in the synthesis of [1,1′-biphenyl]-2-ols (**9**). The synthesis of 4′-chloro[1,1′-biphenyl]-2-ol (**9**, X = 4-Cl), for example, involved (Scheme III) the Ullmann reaction between 1-chloro-4-iodobenzene and 1-iodo-2-methoxybenzene to prepare 4′-chloro-2-methoxy[1,1′-biphenyl] followed by HBr hydrolysis to the desired phenol.

Route A then proceeds via nitrosation[10] to the 2-phenyl-2,5-cyclohexadiene-1,4-dione 4-oxime (**10**), which was reduced with sodium dithionite to provide the 5-amino[1,1′-biphenyl]-2-ol (**11**). Conversion to the acetamide **12** was then accomplished with acetic anhydride.

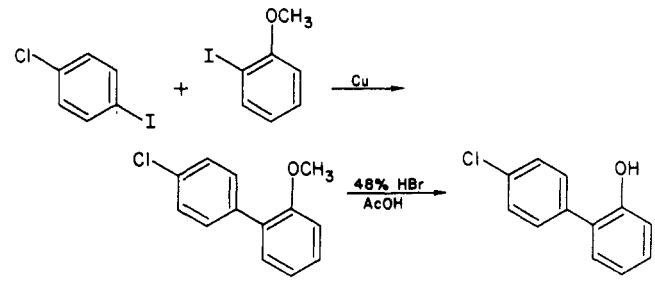
Route B, which was much superior in terms of ease, yield, availability of starting materials, and scope, utilized the unique formation of a multiply substituted aromatic system from aliphatic components reported by Hill and Hale in 1905.[11]

Thus an appropriately substituted 1-phenyl-2-propanone (**12**) was condensed with sodium nitromalonaldehyde hydrate in the presence of NaOH to afford the 5-nitro-[1,1′-biphenyl]-2-ols (**13a–x**, Table II). Catalytic reduction and treatment with acetic anhydride then provided the protected aminophenols (**6**). The required 1-phenyl-2-propanones (**12a–p**, Table I) which were not available commercially were synthesized by one of six routes (Scheme IV). Route selection depended upon both commercial availability of starting materials and literature precedent. Thus **12d** and **12j–l** were obtained by treating the appropriately substituted benzeneacetic acids with

Scheme II. Methods for the Synthesis of *N*-(6-Hydroxy[1,1′-biphenyl]-3-yl)acetamides **6**



Scheme III

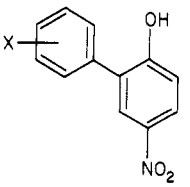


methyllithium (Scheme IVa).[12] Protection of the hydroxyl group in **12d** was achieved with (β-methoxyethoxy)methyl chloride to afford **12e**. Analogue **12c** was prepared by the Dakin–West[13] treatment of 2-(trifluoromethyl)benzeneacetic acid with acetic anhydride in pyridine followed by acid hydrolysis (Scheme IVb).

Alternatively, analogues **12h,m–p** were obtained from the corresponding benzaldehyde by condensation with nitroethane to the 2-nitro-1-propenyl derivatives followed by reduction and hydrolysis with iron in HCl (Scheme IVc).[14] Appropriately substituted benzeneacetonitriles

(10) Borsche, W.; Scholten, B. G. B. *Chem. Ber.* **1917**, 50, 596.
(11) Hill, H. B.; Hale, W. J. *Am. Chem. J.* **1905**, *33*, 1.
(12) For a discussion of addition of organolithium reagents to metal carboxylates, see: Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: New York, 1974; pp 124–128.
(13) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 91, 745, 757.
(14) For precedent, see: Rabjohn, N., Ed. *Organic Syntheses*; Wiley: New York, 1963; Vol. IV, pp 573–576.

Table II. Physical Properties of 5-Nitro[1,1′-biphenyl]-2-ols **13**



no.	X	mp, °C	% yield[a]	recrystn solvent	formula	anal.[b]
13a	4-Cl	161–163	62	toluene	$C_{12}H_8ClNo_3$	
13b	3-Cl	180–182	65	toluene–ethanol	$C_{12}H_8ClNO_3$	C, H, N
13c	2-Cl	155–157	51	toluene	$C_{12}H_8ClNO_3$	C, N[k]
13d	3,4-Cl_2	243–245	85	2-propanol–water	$C_{12}H_7Cl_2NO_3$	C, H, N
13e	4-CF_3	185–188	67	toluene	$C_{13}H_8F_3NO_3$	C, H, N
13f	3-CF_3	185–187	61	toluene–2-propanol	$C_{13}H_8F_3NO_3$	C, H, N
13g	2-CF_3	125–127	54	dichloromethane–hexane	$C_{13}H_8F_3NO_3$	C, H, N
13h	4-OCH_3	127–130	40	toluene	$C_{13}H_{11}NO_4$	C, H, N
13i	2-OCH_3	131–133[l]	54	ethanol–water	$C_{13}H_{11}NO_4$	C, H, N
13j	2,5-$(OCH_3)_2$	108–109	50	benzene–ethyl acetate[c]	$C_{14}H_{13}NO_5$	C, H, N
13k	3,4-$(OCH_3)_2$	194–196	48	toluene	$C_{14}H_{13}NO_5$	C, H, N
13l	4-CH_3	127–129	67	toluene	$C_{13}H_{11}NO_3$	C, H, N
13m	4-$OCH_2OCH_2CH_2OCH_3$	*d*	66	*d*	$C_{16}H_{17}NO_6$	
13n	2,3- 	132–134	48	2-propanol–water; toluene[e]	$C_{16}H_{11}NO_3$	
13o	4-aza	*f*	71	*g*	$C_{11}H_8N_2O_3$	
13p	3-aza	226[h]	9.1[j]	*g*	$C_{11}H_8N_2O_3$	
13q	2-aza	211[h]	56	ethanol[c]	$C_{11}H_8N_2O_3$	
13r	4-F	182–184[h]	80	ether–hexane[e]	$C_{12}H_8FNO_3$	C, H, N
13s	3-F	143–146	64	toluene	$C_{12}H_8FNO_3$	C, H, N
13t	2-F	*f*	62	*g*	$C_{12}H_8FNO_3$	
13u	2,3-F_2	158–160	4.7[i]	toluene	$C_{12}H_7F_2NO_3$	C, H, N
13v	2,6-F_2	186–188	52	toluene	$C_{12}H_7F_2NO_3$	C, H, N
13w	2,3,4,5,6-F_5	200–204	44	toluene	$C_{12}H_4F_5NO_3$	
13x	4-SCH_3	162–165	62	toluene	$C_{13}H_{11}NO_3S$	C, H, N

[a] Yields are of material of sufficient purity to be used in the next reaction and are calculated from the respective **12** except where noted. [b] Analyses are given if obtained. [c] Triturated in the solvent. [d] Chromatography over silica gel with benzene–ethyl acetate (1:1) furnished a low melting solid. [e] Recrystallized with charcoal treatment. [f] No melting point recorded. [g] Obtained as a solid and not purified. [h] Melts with decomposition. [i] From 1,2-difluorobenzene. [j] From 3-pyridinecarboxaldehyde. [k] H: calcd, 3.73; found, 3.22. [l] Lit.[48] mp 133–135 °C.

were the starting materials for **12a,b,f** via base-catalyzed condensation with ethyl acetate followed by acidic hydrolysis and decarboxylation[15] (Scheme IVd). Pyridine analogues **12i** and **12g** were obtained by acylating the corresponding methylpyridine with *N,N*-dimethylacetamide (Scheme IVe)[16] and methyl acetate (Scheme IVf),[17] respectively.

Suppressive Antimalarial Screening in Mice. The 5-[(7-chloro-4-quinolinyl)amino]-3-[(alkylamino)-methyl][1,1′-biphenyl]-2-ols and the N^{ω}-oxides were tested initially against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route.[18,19] These results are summarized in Table VI. The test compounds were dissolved or suspended in peanut oil, and a single dose was administered subcutaneously 72 h after the mice had been infected with *Plasmodium berghei*. In the present study the mean survival time of the control mice (MSTC) was 6.2 days. Extension of the mean survival time of the treated mice (MSTT) is interpreted as evidence of antimalarial activity. An increase of 100% in the MSTT is considered the minimum effective response for activity. Mice that survive 60 days postinfection are termed "cured".

Results and Discussion

Initial mouse test data revealed outstanding activity in this series. Table VII, for example, compares data for amodiaquine (A = H), the current 4-Cl-C_6H_4 analogue (compound **5f**), cycloquine, one of the very few 6-substituted analogues prepared previously (A = CH_2NEt_2), and the 4-(chlorophenyl)-6-(*tert*-butylamino)methyl analogue of **3**. The superiority of the current series as represented by compound **5f** is evident.

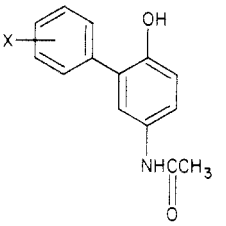
It should be noted that Burckhalter et al.[4] actually prepared the parent unsubstituted analogue of this type (**5**, X = H), but the synthetic methodology of the time did not allow preparation of sufficient material for biological testing. It should also be noted that the structure–activity relationships described in this early work would not have encouraged one to prepare analogues in which a substituent was installed adjacent to the phenolic oxygen.

This lead was then followed up expeditiously, and the antimalarial screening data are summarized in Table VI. Activity was present broadly over a wide range of structural modifications. Thus, 64 of the 65 analogues included showed curative activity at one or more dose levels, and all compounds were well tolerated by the mice.

Variation of the phenyl substituent (X in structure **5**) received a great deal of attention. In order to optimize the phenyl substitution with regard to antimalarial potency, a QSAR study was undertaken on compounds having the general structure **5**, holding R_1 and R_2 fixed as ethyl. Although QSAR analyses have been reported for analogues of chloroquine and amodiaquine,[20] none has considered

(15) For precedent, see: Blatt, A. H., Ed. *Organic Syntheses*; Wiley: New York, 1943; Vol. 2, pp 487, 391.
(16) Cassity, R. P.; Taylor, L. T., Wolfe, J. F. *J. Org. Chem.* **1978**, *43*, 2286.
(17) Osuch, C.; Levine, R. *J. Org. Chem.* **1957**, *22*, 939.
(18) The parenteral antimalarial screening in mice was carried out in the laboratory of Dr. Leo Rane of the University of Miami. Test results were provided through the courtesy of Drs. T. R. Sweeney, E. A. Steck, M. Musallam, and D. Davidson of the Walter Reed Army Institute of Research.
(19) For a description of the test method, see: Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.

Table III. Physical Properties of *N*-[6-Hydroxy[1,1'-biphenyl]-3-yl]acetamides **6**



no.	X	mp,[b] °C	% yield[a] (method)	recrystn solvent	formula	anal.[b]
6a	H	153–155	64 (B)	*c*	$C_{14}H_{13}NO_2$	C, H, N
6b	4-Cl	135	81 (B)	toluene	$C_{14}H_{12}ClNO_2$	C, H, N
6b	4-Cl		*d*, *j* (A)		$C_{14}H_{12}ClNO_2$	
6c	3-Cl	152–154	94 (A)	toluene[e]	$C_{14}H_{12}ClNO_2$	C, H, N
6d	2-Cl	111–117	87 (A)	*f*	$C_{14}H_{12}ClNO_2$	C, H, N, Cl
6e	3,4-Cl_2	187–189	98 (A)	toluene[e]	$C_{14}H_{11}Cl_2NO_2$	C, H, N, Cl
6f	4-CF_3	186–188	78 (A)	toluene–2-propanol	$C_{15}H_{12}F_3NO_2$	C, H, N
6g	3-CF_3	145–147	87 (A)	toluene	$C_{15}H_{12}F_3NO_2$	C, H, N
6h	2-CF_3		*d*, *j* (A)		$C_{15}H_{12}F_3NO_2$	
6i	4-OCH_3	160–162	77 (A)	*g*	$C_{15}H_{15}NO_3$	C, H, N
6j	2-OCH_3	200–202	78 (A)	toluene[c]	$C_{15}H_{15}NO_3 \cdot 0.1H_2O$	C, H, N, H_2O
6k	2,5-$(OCH_3)_2$	193–195	84 (A)	C	$C_{16}H_{17}NO_4$	C, H, N
6l	3,4-$(OCH_3)_2$	175–176	76 (A)	2-propanol[h]	$C_{16}H_{17}NO_4$	C, H, N
6m	4-CH_3	137–139	95 (A)	toluene[e]	$C_{15}H_{15}NO_2$	C, H, N
6n	4-$OCH_2OCH_2CH_2OCH_3$		87[d] (A)		$C_{18}H_{21}NO_5$	
6o	2,3- 	181–183	97 (A)	toluene[e]	$C_{18}H_{15}NO_2 \cdot 0.2C_7H_8$[i]	C, H, N
6p	4-aza		69 (A)	ethanol	$C_{13}H_{12}N_2O_2$	
6q	3-aza	156–160	43 (A)	chloroform[e]	$C_{13}H_{12}N_2O_2$	
6r	2-aza	180	85 (A)	toluene[e]	$C_{13}H_{12}N_2O_2$	C, H, N
6s	4-F		*d*, *j* (A)		$C_{14}H_{12}FNO_2$	
6t	3-F		*d*, *j* (A)		$C_{14}H_{12}FNO_2$	
6u	2-F		95[d] (A)		$C_{14}H_{12}FNO_2$	
6v	2,3-F_2		*d*, *j* (A)		$C_{14}H_{11}F_2NO_2$	
6w	2,6-F_2		*d*, *j* (A)		$C_{14}H_{11}F_2NO_2$	
6x	2,3,4,5,6-F_5		*d*, *j* (A)		$C_{14}H_8F_5NO_2$	
6y	4-SCH_3	145–147	85 (A)	acetonitrile	$C_{15}H_{15}NO_2S$	C, H, N

[a] Yields are of material of sufficient purity to be used in the next reaction. Yields are calculated from the respective **13** for method A and from **11** for method B. [b] Analyses and melting point are given if obtained. [c] Obtained pure from the reaction mixture. [d] The product of this reaction was obtained by evaporating the solvent in vacuo. TLC showed the material to be pure; further purification was not attempted. [e] Triturated in the solvent. [f] The crude product was first chromatographed over silica gel with use of ethyl acetate and then triturated in toluene. [g] The crude product was heated in ethanol containing aqueous sodium hydroxide. The solution was diluted first with acetic acid and then with water to precipitate the pure product. [h] The crude product was first chromatographed over silica gel with dichloromethane, gradually adding methanol to the eluting solvent to a maximum of 7%. [i] The presence of toluene was confirmed in the NMR spectrum. [j] For the purpose of yield calculations in subsequent reactions, the yield of this reaction was assumed to be 100%.

anilino side chain substitution or oxidation of the quinoline nitrogen.

At the time the study was begun, 28 compounds ("initial set", Table VIII) had been tested for antimalarial activity in the initial screen. The logarithm of the molar ED_{30} ($MLOGED_{30}$, Table VIII), the dose that provided a 30-day extension in life span (see Experimental Section), was used as the measure of potency; values ranged from −1.87 to 1.68 with a standard error of 0.28. Parameters used in the correlations included benzene π values (denoted by $\sum\pi_a$, $\sum\pi_a^2$), $\sum\sigma$, $\sum$MR as published by Hansch,[21] summed for the phenyl ring substituents, and the positional-dependent benzene π values (denoted by $\sum\pi_b$, $\sum\pi_b^2$), $\sum F$, and $\sum R$ of Norrington et al.[22] and N_OXIDE, an indicator variable denoting oxidation of the quinoline nitrogen. MR was multiplied by 0.1 to place it on a scale similar to that of the other parameters. Table IX shows the pairwise correlations of all the parameters; values for those parameters appearing in eq 1–7 are given in Table VIII.

Multiple regression analysis using these nine parameters on a 27-compound set (compound **5ss** was excluded) produced eq 1 and 2. Calculated potencies using eq 2 and

$$MLOGED_{30} = 1.37(\pm0.27)\sum MR - 1.81 \quad (1)$$

$$n = 27,\ r^2 = 0.50,\ s = 0.72,\ F = 25.2$$

$$MLOGED_{30} = 1.19(\pm0.20)\sum MR - 1.67(\pm0.36)\sum\sigma - 1.51 \quad (2)$$

$$n = 27,\ r^2 = 0.74,\ s = 0.53,\ F = 34.1$$

residuals appear in Table VIII. Replacing $\sum\sigma$ with $\sum F$ and $\sum R$ generated eq 3, a marginal improvement over eq 2. A statistically significant relationship could also be demonstrated by including $\sum\pi_b$ (eq 4), but little weight is placed on this equation due to the high correlation between $\sum\sigma$ and $\sum\pi_b$ (Table IX). Compound **5ss**, a mar-

$$MLOGED_{30} = 1.39(\pm0.22)\sum MR - 1.43(\pm0.29)\sum F - 1.16(\pm0.42)\sum R - 1.23 \quad (3)$$

$$n = 27,\ r^2 = 0.78,\ s = 0.49,\ F = 27.8$$

(20) (a) Hudson, D. R.; Bass, G. E.; Purcell, W. P. *J. Med. Chem.* **1970**, *13*, 1184. (b) Bass, G. E.; Hudson, D. R.; Parker, J. E.; Purcell, W. P. *J. Med. Chem.* **1971**, *14*, 275. (c) Bass, G. E.; Hudson, D. R.; Parker, J. C.; Purcell, W. P. *Prog. Mol. Subcell. Biol.* **1971**, *2*, 126.
(21) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.
(22) Norrington, F. E.; Hyde, R. M.; Williams, S. G.; Wooton, R. *J. Med. Chem.* **1975**, *18*, 604.

$$\text{MLOGED}_{30} = 0.95(\pm0.22)\sum\text{MR} - 2.94(\pm0.16)\sum\sigma + 0.72(\pm0.32)\sum\pi_b - 1.54 \quad (4)$$

$$n = 27,\ r^2 = 0.79,\ s = 0.49,\ F = 28.2$$

ginally active analogue whose ED_{30} value was the result of a large extrapolation, was excluded from the above correlations. Including it lowered the correlation coefficient but did not significantly alter the coefficients associated with the physicochemical parameters (eq 5).

$$\text{MLOGED}_{30} = 1.08(\pm0.26)\sum\text{MR} - 1.95(\pm0.44)\sum\sigma - 1.32 \quad (5)$$

$$n = 28,\ r^2 = 0.64,\ s = 0.67,\ F = 22.0$$

Equations 2 and 3 show that a relationship exists between overall steric and electronic properties of the substituted phenyl ring and in vivo antimalarial potency, with decreasing size and increasing electron withdrawal properties of the substituents increasing potency. Interestingly, oxidation of the quinoline nitrogen, thought to increase antimalarial potency, failed to appear in any of the equations in a statistically significant manner. Examination of Table VIII reveals three pairs of compounds with the same phenyl substitution (compounds **5nn**, **5oo**, **5pp**, **5qq**, **5cc**, and **5dd**) where the *N*-oxides were more potent than the des-*N*-oxides. For the other 10 pairs, however, the des-*N*-oxide is the more potent. Thus, in general (especially for the more potent compounds), there appears to be a tendency for N-oxidation of the quinoline nitrogen to reduce potency, even though inclusion of the indicator variable in eq 1–5 was not statistically justified (partial *F* test).

With use of these correlations as guidance, an additional 10 analogues ("later set", Table VIII) containing groups predicted by eq 2 to impart high antimalarial potency were prepared. The results on these new compounds are in accord with the QSAR conclusions. They are among the most potent compounds in the series, and although most were predicted to be more potent than found (note the positive residuals on the lower part of Table VIII), the potencies fell within one (compounds **5ggg**, **5hhh**, **5iii**, **5jjj**, **5eee**, and **5bbb**) or two (compounds **5hh**, **5ii**, **5kkk**, **5fff**, **5lll**, and **5mmm**) standard deviations of the predictions from eq 2. The 4-SCH_3 analogues (compounds **5lll** and **5mmm**) were prepared as intermediates for the SO_2CH_3, a group calculated by eq 2 to impart high potency; however, the oxidation to the sulfone was not successful.

Equation 6 shows the correlation when the entire compound set (minus compound **5ss**) was analyzed. Com-

$$\text{MLOGED}_{30} = 0.99(\pm0.16)\sum\text{MR} - 1.35(\pm0.28)\sum\sigma - 1.34 \quad (6)$$

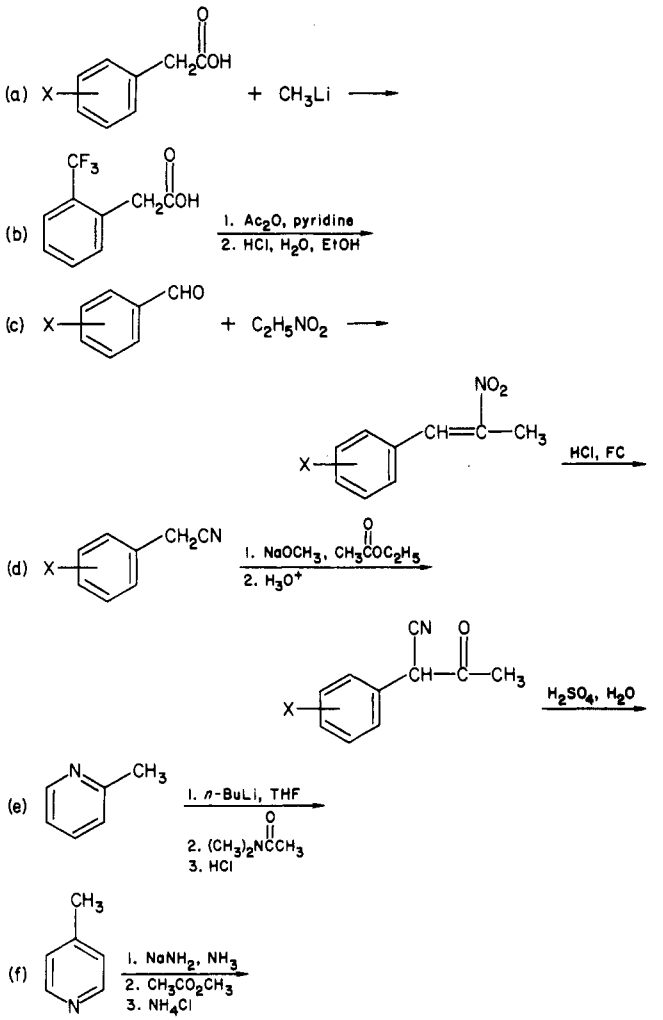
$$n = 39,\ r^2 = 0.70,\ s = 0.50,\ F = 41.8$$

paring eq 2 and 6, note that the signs and the magnitudes of the coefficients and the intercept terms are quite similar, indicating that a stable relationship exists. Once again, the indicator variable denoting oxidation of the quinoline nitrogen failed to be statistically significant, even though the N^{ω}-oxides of the new set were less potent than the corresponding des-N^{ω}-oxides in every case. $\sum\pi_b$ and $\sum\sigma$ remained moderately correlated in the expanded compound set ($r = 0.65$); however, $\sum\pi_b$ was no longer statistically significant in an equation containing $\sum$MR, $\sum\sigma$, and $\sum\pi_b$. Including all the compounds produced eq 7.

$$\text{MLOGED}_{30} = 0.93(\pm0.19)\sum\text{MR} - 1.58(\pm0.34)\sum\sigma - 1.21 \quad (7)$$

$$n = 40,\ r^2 = 0.62,\ s = 0.61,\ F = 30.5$$

Scheme IV



Since preparation of substituents predicted by eq 2 to enhance potency resulted only in a maintenance of high potency, it was felt that further work on phenyl substitution to enhance potency was not warranted. Since small, electron-withdrawing groups are predicted to increase potency, the replacement of the phenyl ring by a pyridyl moiety seemed appropriate, since a 4-pyridyl is considered electronically analogous to a 4-nitrophenyl[23] yet is smaller. A 4-nitrophenyl compound is predicted to be quite potent ($\text{MLOGED}_{30} = -1.66$) by eq 6. Unfortunately, the pyridyl derivatives possessed only moderate potency (Table X). Therefore, work was terminated in this area.

Substantial variation was also introduced into the Mannich side chain (NR_1R_2 structure **5**) and it appeared that reasonable change could be introduced at this position without drastically affecting the biological activity. Thus both NEt_2 (**5l**) and $NHC(CH_3)_3$ (**5g**) exhibited high activity; however, analogues with a smaller (NMe_2, **5l**) or larger (NHadamantyl, **5r**) substituent also retained substantial activity.

Later when interest was focused on compound **5g** as one of the compounds of most potential interest, additional studies were undertaken by Peters and colleagues.[24] These studies with *P. berghei* infections in mice showed that **5g** was active against a highly chloroquine-resistant RC line while cresol **4** was not. Only slightly reduced activity was

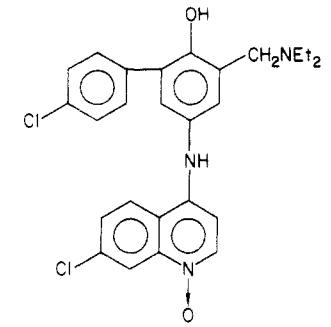
(23) Tomasik, P.; Johnson, C. D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1976; Vol. 20, p 1.

(24) Peters, W.; Robinson, B. L. *Ann. Trop. Med. Parasitol.* **1984**, *78*, 561.

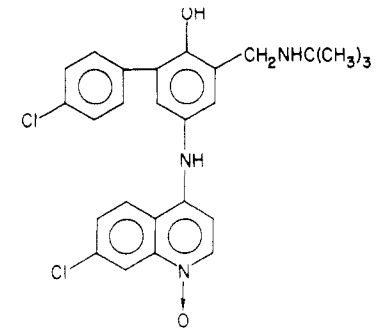
shown against a highly mefloquine-resistant line. Moreover **5g** was at least as active orally as it was subcutaneously. Additional studies to discern details of the mode of action of **5g** and to attempt to predict the clinical utility of the agent against drug-resistant strains suggested[25] that the mode of action of **5g** in vivo differs from that of chloroquine and that it was probable that the drug would be effective against infections due to chloroquine-resistant *P. falciparum*.

Expanded Biological Studies. Studies were initiated by Walter Reed Army Institute of Research to determine whether this structural class possessed other properties that would reinforce their potential as clinical agents in malaria. Initial results of trials against drug-resistant parasites in rodents were encouraging but somewhat puzzling.

Thus, whereas amodiaquine is more than 400-fold cross-resistant with chloroquine and cycloquine is some 120-fold cross-resistant with chloroquine at its SD_{70}, compound **5f** exhibited no cross-resistance with chloroquine or indeed with cycloguanil or pyrimethamine, although some cross-resistance with mefloquine and quinine was evident.



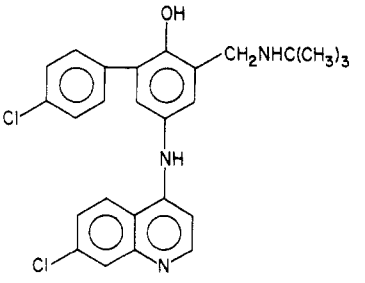
5f



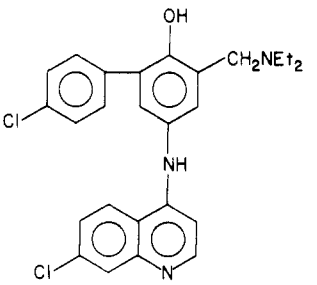
5h

Surprisingly the *tert*-butyl analogue **5h** and the des-*N*-oxide **5g** were cross-resistant to chloroquine and quinine.

Data received from testing in primates[26] were equally reassuring. Thus analogues were examined against three resistant strains of *P. falciparum* in the *Panamanian aotus* monkey: the Vietnam Smith (resistant to maximally tolerated doses of chloroquine, pyrimethamine, and quinine); the Vietnam Oak Knoll (resistant to chloroquine and quinine but sensitive to pyrimethamine), and Uganda Palo Alto (resistant to pyrimethamine and sensitive to chloroquine and quinine). Drugs were adminstered by gastric intubation, once daily, for 3 consecutive days. Compounds **5e–h** all achieved clearance or cure of infections of two chloroquine-resistant strains at doses of 1 or 2 mg/kg.

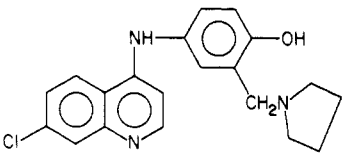


5g



5e

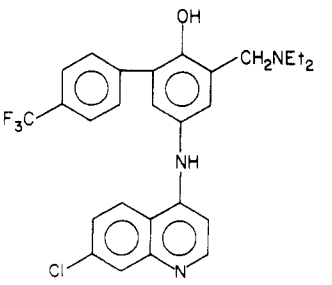
Thus both **5f** and **5h** by this criterion are at least 25 times more active as curative agents than the positive control drug amopyroquine (**15**) with **5g** and **5e** being at least 50



15

times more active relative to parasite clearance. Moreover, against the Oak Knoll strain **5f** and **5h** were 20 times as active as amodiaquine as curative agents and **5g** was 20 times as effective as amodiaquine in terms of its ability to clear parasitemias. In addition, **5g** cleared the parasitemia of the Uganda Palo Alto strain given orally at 1.0 mg/kg.

A further characteristic that appeared to make this class of compounds of interest for clinical evaluation is their apparent ability to protect against infection for extended periods of time even after oral administration. Thus, for example, analogue **5cc** at an oral dose of 64 mg/kg was



5cc

shown to protect mice completely against parasite challenge through 21 days. This might offer clinically the desirable possibility of protection for personnel in an endemic area for 1 month or more.

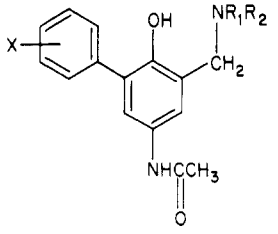
Studies on the pharmacokinetics of **5g** in rodents confirmed that it too has a long biological half-life.[27]

(25) Peters, W.; Irare, D. S.; Ellis, D. C.; Warhurst, D. C.; Robinson, B. L. *Ann Trop. Med. Parasitol.* **1984**, *78*, 567.

(26) Unpublished data of Rossan, R. N. Gorgas Memorial Laboratory, Panama.

(27) Sweeney, T. R.; Davidson, D. E.; Nodiff, E. A.; Saggiomo, A. J.; Lamontagne, M. P. In *Chemotherapy and Immunology in the Control of Malaria, Filariasis, and Leishmaniasis*, Anand, N., Sen, A. B., Eds.; New Delhi: Tata McGraw-Hill, 1983; pp 36–54.

Table IV. Physical Properties of *N*-[5-(Alkylamino)methyl]-6-hydroxy[1,1′-biphenyl]-3-yl]acetamides **7**



no.	X	NR_1R_2	purifn method[a]	% yield[b]	no.	X	NR_1R_2	purifn method[a]	% yield[b]
7a	H	$N(C_2H_5)_2$	*c*	82	**7t**	2-CF_3	$N(C_2H_5)_2$	*e*	*w*
7b	H	$NHC(CH_3)_3$	*d, c*	56	**7u**	4-OCH_3	$N(C_2H_5)_2$	*l*	60[o]
7c	4-Cl	$N(C_2H_5)_2$	*c*	92	**7v**	2-OCH_3	$N(C_2H_5)_2$	*c*	88
7d	4-Cl	$NHC(CH_3)_3$	*d*	84	**7w**	2,5-$(OCH_3)_2$	$N(C_2H_5)_2$	*c*	100
7e	4-Cl	$NHCH(CH_3)(C_2H_5)$	*d*	93	**7x**	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	*e*	97
7f	4-Cl	$NHCH_2CH(CH_3)_2$	*d*	80	**7y**	4-CH_3	$N(C_2H_5)_2$	*d*	87
7g	4-Cl	$N(CH_3)_2$	*e*	98	**7z**	4-OCH_2OCH_2-CH_2OCH_3	$N(C_2H_5)_2$	*p*	80
7h	4-Cl	$N(n\text{-}C_4H_9)_2$	*f*	*w*					
7i	4-Cl	$N(n\text{-}C_3H_7)_2$	*e*	*w*	**7aa**	2,3-	$N(C_2H_5)_2$	*q*	75[r]
7j	4-Cl	NH	*g*	*w*					
7k	4-Cl	NHAdamantyl	*h*	58[i]	**7bb**	4-aza	$N(C_2H_5)_2$	*s*	66
7l	3-Cl	$N(C_2H_5)_2$	*d, c*	74	**7cc**	3-aza	$N(C_2H_5)_2$	*t*	64
7m	2-Cl	$N(C_2H_5)_2$	*c*	80	**7dd**	2-aza	$N(C_2H_5)_2$	*e*	*w*
7n	3,4-Cl_2	$N(C_2H_5)_2$	*c*	75[k]	**7ee**	4-F	$N(C_2H_5)_2$	*u*	70
7o	3,4-Cl_2	N	*c*	79	**7ff**	4-F	$NHC(CH_3)_3$	*e*	*w*
					7gg	3-F	$N(C_2H_5)_2$	*e*	*w*
					7hh	2-F	$N(C_2H_5)_2$	*v*	*w*
7p	3,4-Cl_2	$NHC(CH_3)_3$	*l*	82[m]	**7ii**	2,3-F_2	$N(C_2H_5)_2$	*e*	*w*
7q	4-CF_3	$N(C_2H_5)_2$	*d*	94	**7jj**	2,6-F_2	$N(C_2H_5)_2$	*e*	*w*
7r	4-CF_3	$NHC(CH_3)_3$	*d*	81	**7kk**	2,3,4,5,6-F_5	$N(C_2H_5)_2$	*e*	*w*
7s	3-CF_3	$N(C_2H_5)_2$	*c, l*	70[n]	**7ll**	4-SCH_3	$N(C_2H_5)_2$	*e*	*w*

[a] Compounds **7** were purified by many different methods; these are described in footnotes to this table. Even after purification, most compounds **7** were viscous oils, for which microanalytical values were not obtained. Microanalytical values and melting points are footnoted when obtained. [b] Yields are of material of sufficient purity to be used in the next reaction and are calculated from the appropriate **6**. [c] Chromatographed over alumina using ethyl acetate. [d] The crude product was dissolved in organic solvent and extracted into dilute acid. The aqueous layer was then made basic, and the product was extracted with an organic solvent. The organic extracts were washed with water, dried, and evaporated in vacuo to give the product. [e] Product obtained by concentrating the reaction mixture. [f] Chromatographed over silica gel using chloroform–ethyl acetate (1:1). [g] Chromatographed over silica gel using chloroform–methanol (9:1). [h] Recrystallized from ether–petroleum ether. [i] Mp 136–139 °C. [j] Recrystallized from toluene. [k] Anal. ($C_{19}H_{22}Cl_2N_2O_2 \cdot 0.2C_7H_8$) C, H, Cl; N: calcd, 7.01; found, 7.47. The presence of toluene was substantiated by the NMR spectrum. Mp 75–85 °C. [l] Recrystallized from 2-propanol–water. [m] Anal. ($C_{19}H_{22}Cl_2N_2O_2$) C, H, N. Mp 161–164 °C. [n] Anal. ($C_{20}H_{23}F_3N_2O_2$) C, H, N. Mp 116–119 °C. [o] Anal. ($C_{20}H_{26}N_2O_3$) C, H, N. Mp 118–120 °C. [p] Chromatographed over silica gel using ethyl acetate. [q] Pure product precipitated from the reaction mixture. [r] Anal. ($C_{23}H_{26}N_2O_3$) C, H, N. Mp 153–155 °C. [s] Recrystallized from ethyl acetate–ether. [t] Chromatographed over silica gel using acetonitrile–0.2 M NH_4Cl (20:1), followed by acetonitrile–methanol (10:1). [u] Chromatographed over silica gel using ethyl acetate–methanol (20:1). [v] Chromatographed over silica gel using chloroform–methanol (10:1). [w] For the purpose of yield calculation in subsequent reactions, the yield of this reaction was assumed to be 100%.

Conclusions. On the basis of these results, **5g** (tebuquine)[28] has been selected for preclinical toxicology studies prior to evaluation in man.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR 90-MHz spectra were obtained with a Varian EM390 or Bruker B-NC-12 spectrometer. IR spectra were obtained on Digilab DP-1-5 and Beckman IR-9 spectrophotometers. The NMR and IR spectra of all compounds and intermediates were consistent with the assigned structures.

Calculation of ED_{30} Values. A typical dose–response curve for the initial antimalarial screen is shown in Figure 1. Plusses represent survival times of individual mice ("cured" mice were considered to have survived 60 days) and squares denote the mean survival time for each dose. The ED_{30} is the dose that provides a 30-day extension of life span and was obtained by fitting a line to the ascending (linear) portion of the curve (for compound **5hh**, the top two and bottom three dose levels were excluded) and interpolating or extrapolating to a 30-day survival. Note that the mean survival times are plotted for illustrative purposes only; the line was fit to the individual survival times.

The standard deviations of the ED_{30} values were estimated by back-calculation from the 95% confidence limits on the regression line relating survival to log dose.[29] Since the 95% confidence interval represents ca. 2 standard errors, the error was taken as 0.25 the distance between the upper and lower bounds. The average standard deviation for all compounds was then computed as the root mean square of the individual standard deviations.

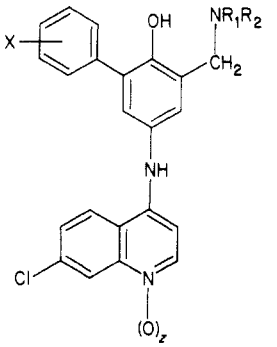
Data Processing. Correlations, regressions, and plots were run on an IBM 3033 machine using the SAS program package.[30] In eq 1–7, the figures in parentheses are the standard errors of the regression coefficients. For a given equation, n is the number of compounds, r is the correlation coefficient, F is a significance test, and s is the standard error.

4′-Chloro-2-methoxy[1,1′-biphenyl]. A mixture of 99.5 g (0.425 mol) of 1-iodo-2-methoxyphenyl, 202 g (0.85 mol) of 1-chloro-4-iodophenyl, and 400 g of copper powder was stirred in an oil bath at 220–240 °C for 6 h, allowed to cool overnight, and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and concentrated to dryness in vacuo. The residue was taken up in 1 L of hot pentane and filtered to remove 30 g of

(28) Tebuquine is the USAN approved name for 4′-chloro-5[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]-methyl][1,1′-biphenyl]-2-ol.

(29) Graybill, F. A. *An Introduction to Linear Statistical Methods*; McGraw-Hill: New York, 1961; Vol. 1, p 125.
(30) SAS Institute, Inc. *SAS User's Guide: Statistics, 1982 Edition*; SAS Institute Inc.: Cary, NC, 1982.

Table V. Physical Properties of 5-[(7-Chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1′-biphenyl]-2-ols and N^{w}-Oxides 5



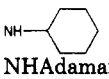
no.	X	NR_1R_2	z	mp, °C	% yield[a]	recrystn solvent	formula	anal.
5a	H	$N(C_2H_5)_2$	0	235–238[b,x]	12	ethanol	$C_{26}H_{26}ClN_3O$	C, H, N
5b	H	$N(C_2H_5)_2$	1	198–200	20	*c*	$C_{26}H_{26}ClN_3O_2 \cdot 0.9H_2O$	C, H, N, Cl, H_2O
5c	H	$NHC(CH_3)_3$	0	139–142[b]	84	2-propanol–dilute NH_4OH	$C_{26}H_{26}ClN_3O \cdot H_2O$	C, H, N, H_2O
5d	H	$NHC(CH_3)_3$	1	190[b]	18	*d*; acetonitrile–2-propanol	$C_{26}H_{26}ClN_3O_2$	C, H, N
5e	4-Cl	$N(C_2H_5)_2$	0	229–232	61	acetonitrile–toluene	$C_{26}H_{25}Cl_2N_3O$	C, H, N, Cl
5f	4-Cl	$N(C_2H_5)_2$	1	210–213[b]	34	*e*; ethanol	$C_{26}H_{25}Cl_2N_3O_2$	C, H, N, Cl
5g	4-Cl	$NHC(CH_3)_3$	0	228[b]	64	acetonitrile	$C_{26}H_{25}Cl_2N_3O$	C, H, N, Cl
5h	4-Cl	$NHC(CH_3)_3$	1	196[b]	28	*c*; acetonitrile–2-propanol	$C_{26}H_{25}Cl_2N_3O_2 \cdot H_2O$	C, H, N, Cl, H_2O
5i	4-Cl	$NHCH(CH_3)(C_2H_5)$	0	285–287[b]	78	*f*	$C_{26}H_{25}Cl_2N_3O \cdot 0.2HCl$	C, H, N, Cl^{-g}
5j	4-Cl	$NHCH(CH_3)(C_2H_5)$	1	193–195[b]	69	*d*; acetonitrile–2-propanol	$C_{26}H_{25}Cl_2N_3O_2 \cdot 0.5H_2O$	C, H, N, Cl, H_2O
5k	4-Cl	$NHCH_2CH(CH_3)_2$	0	277–280[b]	37	*f*	$C_{26}H_{25}Cl_2N_3O \cdot 0.2HCl$	C, H, N, Cl, Cl^-
5l	4-Cl	$N(CH_3)_2$	0	222–226	44	ethanol	$C_{24}H_{21}Cl_2N_3O$	C, H, N
5m	4-Cl	$N(CH_3)_2$	1	160–175[b]	47	2-propanol	$C_{24}H_{21}Cl_2N_3O_2 \cdot 0.3H_2O$	C, H, N, H_2O
5n	4-Cl	$N(n\text{-}C_4H_9)_2$	0	166–170	18	cyclohexane	$C_{30}H_{33}Cl_2N_3O$	C, H, N
5o	4-Cl	$N(n\text{-}C_4H_9)_2$	1	160–166	12	acetonitrile	$C_{30}H_{33}Cl_2N_3O_2 \cdot H_2O$	C, H, N, H_2O
5p	4-Cl	$N(n\text{-}C_3H_7)_2$	0	220–222	43	DMF–methanol	$C_{28}H_{29}Cl_2N_3O$	C, H, N, Cl
5q	4-Cl		0	106–120[b]	9	*i*; cyclohexane	$C_{28}H_{27}Cl_2N_3O \cdot 0.1C_6H_{12}$	C, H, N
5r	4-Cl	NHAdamantyl	0	155–159	58	ethanol	$C_{32}H_{31}Cl_2N_3O \cdot 0.25\text{-}C_2H_5OH \cdot 0.1H_2O$	C, H, N, Cl, H_2O
5s	3-Cl	$N(C_2H_5)_2$	0	238–240[b]	50	2-butanone	$C_{26}H_{25}Cl_2N_3O$	C, H, N, Cl
5t	3-Cl	$N(C_2H_5)_2$	1	224–225[b]	16	methanol	$C_{26}H_{25}Cl_2N_3O_2$	C, H, N, Cl
5u	2-Cl	$N(C_2H_5)_2$	0	231–234[b]	44	toluene	$C_{26}H_{25}Cl_2N_3O$	C, H, N
5v	2-Cl	$N(C_2H_5)_2$	1	223–225[b]	22	*d*; 2-propanol[j]	$C_{26}H_{25}Cl_2N_3O_2$	C, H, N
5w	3,4-Cl_2	$N(C_2H_5)_2$	0	242–244[b]	46	2-propanol–toluene	$C_{26}H_{24}Cl_3N_3O$	C, H, N, Cl
5x	3,4-Cl_2	$N(C_2H_5)_2$	1	186–190[b]	24	*k*	$C_{26}H_{24}Cl_3N_3O_2 \cdot 0.7H_2O$	C, H, N, Cl, H_2O
5y	3,4-Cl_2		0	287–288[b]	81	*f*	$C_{26}H_{22}Cl_3N_3O \cdot 2HCl \cdot 0.1C_2H_5OH$[l]	C, H, N, Cl, Cl^-
5z	3,4-Cl_2		1	245–246[b]	18	*d*; DMF	$C_{26}H_{22}Cl_3N_3O_2 \cdot 0.1C_3H_7NO$[m]	C, H, N, Cl
5aa	3,4-Cl_2	$NHC(CH_3)_3$	0	220–222[b]	26	toluene	$C_{26}H_{24}Cl_3N_3O \cdot 0.4H_2O$	C, H, N, H_2O
5bb	3,4-Cl_2	$NHC(CH_3)_3$	1	200–202[b]	49	*d*	$C_{26}H_{24}Cl_3N_3O_2 \cdot H_2O$	C, H, N, H_2O
5cc	4-CF_3	$N(C_2H_5)_2$	0	227–229[b]	64	acetonitrile	$C_{27}H_{25}ClF_3N_3O$	C, H, N
5dd	4-CF_3	$N(C_2H_5)_2$	1	169–172[b]	52	*d*	$C_{27}H_{25}ClF_3N_3O_2 \cdot H_2O$	C, H, N, H_2O
5ee	4-CF_3	$NHC(CH_3)_3$	0	292–294[b]	91	*f*	$C_{27}H_{25}ClF_3N_3O \cdot 2HCl$	C, H, N, Cl^-
5ff	3-CF_3	$N(C_2H_5)_2$	0	234–236[b]	50	ethanol	$C_{27}H_{25}ClF_3N_3O$	C, H, N
5gg	3-CF_3	$N(C_2H_5)_2$	1	227–229[b]	26	*c*; methanol	$C_{27}H_{25}ClF_3N_3O_2$	C, H, N
5hh	2-CF_3	$N(C_2H_5)_2$	0	210–213	54	dichloromethane–methanol	$C_{27}H_{25}ClF_3N_3O$	C, H, N, Cl, F
5ii	2-CF_3	$N(C_2H_5)_2$	1	205–207	32	*c*; DMF–dichloromethane	$C_{27}H_{25}ClF_3N_3O_2$	C, H, N, Cl, F
5jj	4-OCH_3	$N(C_2H_5)_2$	0	206–209	67	acetonitrile–50% NH_4OH	$C_{27}H_{28}ClN_3O_2$	C, H, N
5kk	4-OCH_3	$N(C_2H_5)_2$	1	200–201[b]	26	*d*; acetonitrile–2-propanol	$C_{27}H_{28}ClN_3O_3$	C, H, N
5ll	2-OCH_3	$N(C_2H_5)_2$	0	130–133[h]	38	2-propanol–water	$C_{27}H_{28}ClN_3O_2 \cdot H_2O$	C, H, N[o]
5mm	2-OCH_3	$N(C_2H_5)_2$	1	220–222[b]	36	*d*	$C_{27}H_{28}ClN_3O_3$	C, H, N
5nn	2,5-$(OCH_3)_2$	$N(C_2H_5)_2$	0	105–112	50	ethanol	$C_{28}H_{30}ClN_3O_3 \cdot 0.3H_2O$	C, H, N, Cl, H_2O
5oo	2,5-$(OCH_3)_2$	$N(C_2H_5)_2$	1	218–220[b]	44	*d*	$C_{28}H_{30}ClN_3O_4$	C, H, N
5pp	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	0	162–165[b]	46	acetonitrile–dilute NH_4OH	$C_{28}H_{30}ClN_3O_3 \cdot 0.5H_2O$	C, H, N, Cl[p]
5qq	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	1	207–210[b]	34	*d*; acetonitrile	$C_{28}H_{30}ClN_3O_4$	C, H, N
5rr	4-CH_3	$N(C_2H_5)_2$	0	238–241[b]	52	2-propanol	$C_{27}H_{28}ClN_3O \cdot 0.1H_2O$	C, H, N, H_2O
5ss	4-CH_3	$N(C_2H_5)_2$	1	170–175[b]	42	*q*	$C_{27}H_{28}ClN_3O_2$	C, H, N, Cl, H_2O
5tt	4-OH[r]	$N(C_2H_5)_2$	0	240–245[b]	30	*s*; water–ethanol	$C_{26}H_{26}ClN_3O_2$	C, H, N
5uu		$N(C_2H_5)_2$	0	219–222[b]	72	acetonitrile–dilute NH_4OH	$C_{30}H_{28}ClN_3O$	C, H, N, Cl
5vv		$N(C_2H_5)_2$	1	233–234[b]	53	*d*	$C_{30}H_{28}ClN_3O$	C, H, N, Cl

Table V (Continued)

no.	X	NR_1R_2	z	mp, °C	% yield[a]	recrystn solvent	formula	anal.
5ww	4-aza	$N(C_2H_5)_2$	0	216–218	30	water–ethanol	$C_{25}H_{25}ClN_4O \cdot 0.3H_2O$	C, H, N, H_2O
5xx	4-aza	$N(C_2H_5)_2$	1	149[b]	18	*u*; water–ethanol	$C_{25}H_{25}ClN_4O_2 \cdot 0.25H_2O$	C, N, H_2O[v]
5yy	3-aza	$N(C_2H_5)_2$	0	219–221	58	dichloromethane–ethyl acetate	$C_{25}H_{25}ClN_4O$	C, H, N, Cl
5zz	2-aza	$N(C_2H_5)_2$	0	90–95	67	*t*	$C_{25}H_{25}ClN_4O \cdot 0.3H_2O$	C, H, N, H_2O
5aaa	2-aza	$N(C_2H_5)_2$	1	160–163[b]	59	acetonitrile[j]	$C_{25}H_{25}ClN_4O_2 \cdot 1.7H_2O$	C, H, N, H_2O
5bbb	4-F	$N(C_2H_5)_2$	0	225–228[b]	57	ethanol[y]	$C_{26}H_{25}ClFN_3O$	H, N[w]
5ccc	4-F	$N(C_2H_5)_2$	1	151–154[b]	28	chloroform–ethyl acetate–triethylamine	$C_{26}H_{25}ClFN_3O_2 \cdot 0.5H_2O$	C, H, N
5ddd	4-F	$NHC(CH_3)_3$	0	>154[b]	73	water–ethanol	$C_{26}H_{25}ClFN_3O \cdot 0.35H_2O$	C, H, N, H_2O
5eee	3-F	$N(C_2H_5)_2$	0	230–232	28	ethanol	$C_{26}H_{25}ClFN_3O$	C, H, N
5fff	3-F	$N(C_2H_5)_2$	1	160–163[b]	29	acetonitrile; ethanol–water	$C_{26}H_{25}ClFN_3O_2 \cdot H_2O$	C, H, N, H_2O
5ggg	2-F	$N(C_2H_5)_2$	0	232–234	15	ethanol	$C_{26}H_{25}ClFN_3O$	C, H, N
5hhh	2-F	$N(C_2H_5)_2$	1	202[b]	15	*t*; ethanol	$C_{26}H_{25}ClFN_3O_2 \cdot 0.8H_2O$	C, H, N, H_2O
5iii	2,3-F_2	$N(C_2H_5)_2$	0	234–235[b]	51	ethanol; acetonitrile	$C_{26}H_{24}ClF_2N_3O$	C, H, N
5jjj	2,6-F_2	$N(C_2H_5)_2$	0	220–222	61	acetonitrile	$C_{26}H_{24}ClF_2N_3O$	C, H, N
5kkk	2,3,4,5,6-F_5	$N(C_2H_5)_2$	0	195–199	78	toluene–cyclohexane	$C_{26}H_{21}ClF_5N_3O \cdot 0.67C_6H_{12}$[h]	C, H, N
5lll	4-SCH_3	$N(C_2H_5)_2$	0	96–109	65	ethanol	$C_{27}H_{28}ClN_3OS$	C, H, N
5mmm	4-SCH_3	$N(C_2H_5)_2$	1	186[b]	26	*t*; ethyl acetate[j]	$C_{27}H_{28}ClN_3O_2S \cdot 0.2H_2O$	C, H, N, H_2O

[a] The yields are of analytical material and are calculated from the appropriate 7. [b] Melts with decomposition. [c] Chromatographed over silica gel with ethyl acetate and gradually increasing amounts of methanol. [d] Chromatographed over silica gel with ethyl acetate–dichloromethane. [e] Chromatographed over silica gel with ethyl acetate–methanol (9:1). [f] Precipitated pure from the reaction mixture. [g] Cl: calcd, 26.30; found, 25.86. [h] The presence of cyclohexane was substantiated by the NMR spectrum. [i] Chromatographed over silica gel using chloroform–methanol (9:1). [j] Triturated in the solvent. [k] Chromatographed over silica gel using ethyl acetate–dichloromethane–methanol (1:1:0.1). [l] The presence of ethanol was substantiated by the NMR spectrum. [m] The presence of DMF was substantiated by the NMR spectrum. [n] Resolidified and remelted[b] at 196–198 °C. [o] H_2O: calcd, 3.75; found, 3.27. [p] H_2O: calcd, 1.80; found, 2.23. [q] Chromatographed over silica gel with dichloromethane and gradually increasing amounts of methanol. [r] The 4′-(methoxyethoxy)methyl protecting group was removed in the course of this reaction. [s] Chromatographed over silica gel using chloroform–methanol (5:1). [t] Chromatographed over silica gel using ethyl acetate–methanol–triethylamine (75:24:1). [u] Chromatographed over silica gel using chloroform–methanol–triethylamine (10:1:1).

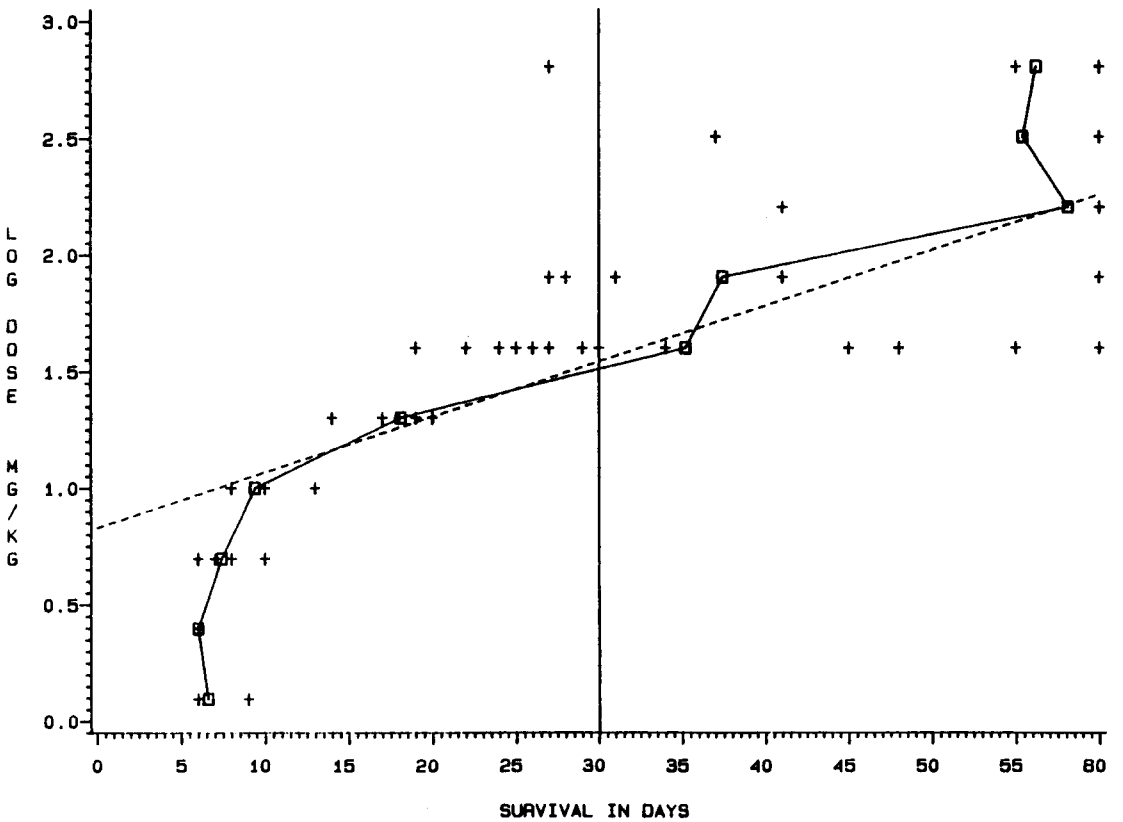
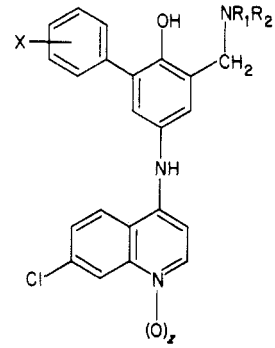


Figure 1. Dose–response curve for compound **5hh**.

insoluble material. The filtrate was filtered twice more to remove an additional 26 g of material and then applied on a column of 800 g of silica gel equilibrated with hexane. The column was first eluted with hexane until the product (R_f 0.3; SiO_2, hexane) began to appear and then with hexane containing 2% ether. The fractions containing the product were combined and evaporated to dryness in vacuo to afford 32.5 g (25%) of the desired compound, mp 49–51 °C. For analysis, a 2-g sample was recrystallized from hexane to give 1.5 g of the title compound, mp 50–52 °C (lit.[31] mp 58 °C). Anal. ($C_{13}H_{11}ClO$) C, H.

Table VI. Parenteral Antimalarial Effects of 5-[(7-Chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1′-biphenyl]-2-ols and N^{10}-Oxides **5** against *Plasmodium berghei* in Mice



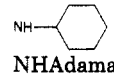
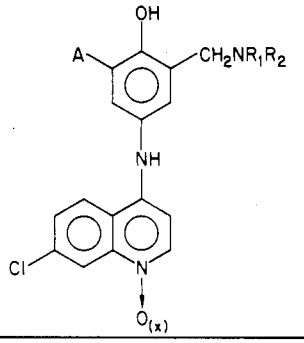
				ΔMST, C after single sc dose, mg/kg[a]									
no.	X	NR_1R_2	z	640	320	160	80	40	20	10	5	2.5	1.25
5a	H	$N(C_2H_5)_2$	0	5C	5C	5C	5C	5C	5C	2C (11.9)	0.7	0.3	0.3
5b	H	$N(C_2H_5)_2$	1	3C (23.9)	3C (24.9)	5C	2C (19.9)	2C (29.6)	1C (17.4)	7.7	5.1	0.3	0.3
5c	H	$NHC(CH_3)_3$	0	1C (13.0)	1C (12.3)	1C (12.8)	1C (27.3)	2C (20.2)	1C (14.8)	29.5	13.7	5.3	0.3
5d	H	$NHC(CH_3)_3$	1	3C (14.0)	3C (14.5)	2C (23.2)	1C (15.5)	1C (21.0)	1C (21.0)	12.5	4.5	−0.1	−0.3
5e	4-Cl	$N(C_2H_5)_2$	0	1C (11.9)	2C (11.2)	4C (11.9)	5C	5C	1C (33.7)	1C (30.2)	20.7	0.1	0.1
5f	4-Cl	$N(C_2H_5)_2$	1	5C	5C	5C	5C	4C (36.9)	3C (20.9)	2C (14.2)	5.7	1.3	0.7
5g	4-Cl	$NHC(CH_3)_3$	0	17.1	1C (16.4)	2C (14.9)	3C (14.9)	4C (19.9)	3C (14.9)	2C (14.9)	1C (11.4)	2.3	0.3
5h	4-Cl	$NHC(CH_3)_3$	1	4C (13.9)	4C (13.9)	3C (13.4)	2C (20.6)	4C (24.9)	4C (28.9)	1C (26.3)	1C (10.3)	0.2	0.0
5i	4-Cl	$NHCH(CH_3)(C_2H_5)$	0	14.2	1C (12.5)	14.2	3C (14.0)	4C (15.0)	3C (21.0)	23.6	11.0	2.0	0.2
5j	4-Cl	$NHCH(CH_3)(C_2H_5)$	1	3C (11.6)	3C (17.1)	4C (14.6)	3C (23.6)	2C (21.3)	3C (22.6)	7.2	3.6	1.6	0.0
5k	4-Cl	$NHCH_2CH(CH_3)_2$	0	13.4	2C (11.3)	2C (4.9)	5C	5C	2C (19.6)	14.8	5.2	2.0	0.8
5l	4-Cl	$N(CH_3)_2$	0	1C (18.7)	1C (14.4)	5C	4C (45.4)	4C (18.8)	3C (36.8)	20.4	14.2	6.0	1.2
5m	4-Cl	$N(CH_3)_2$	1	1C (20.7)	3C (17.9)	5C	3C (21.9)	3C (26.3)	3C (27.8)	1C (17.8)	17.6	5.0	0.0
5n	4-Cl	$N(n\text{-}C_4H_9)_2$	0	3C (34.4)	24.0	17.0	12.6	8.2	4.6	2.0	0.2	0.2	0.4
5o	4-Cl	$N(n\text{-}C_4H_9)_2$	1	1C (31.7)	21.2	12.0	8.0	2.2	3.2	−0.2	0.4	−0.2	0.4
5p	4-Cl	$N(n\text{-}C_3H_7)_2$	0	3C (18.1)	4C (29.6)	2C (26.6)	3C (27.6)	1C (24.4)	11.2	6.8	3.8	0.8	0.4
5q	4-Cl		0	4C (17.6)	4C (−0.4)	4C (20.6)	3C (23.6)	17.9	12.9	4.1	1.5	0.5	0.7
5r	4-Cl	NHAdamantyl	0	2C (19.0)	5C	4C (39.0)	4C (23.0)	18.5	7.5	0.1	−0.3	−0.3	−0.5
5s	3-Cl	$N(C_2H_5)_2$	0	4C (21.9)	5C	4C (31.9)	2C (31.9)	3C (29.4)	1C (22.4)	15.5	3.9	1.3	0.3
5t	3-Cl	$N(C_2H_5)_2$	1	3C (16.4)	4C (21.9)	4C (28.9)	2C (25.6)	2C (25.9)	16.5	9.7	2.1	0.7	0.3
5u	2-Cl	$N(C_2H_5)_2$	0	5C	4C (41.9)	4C (41.9)	5C	5C	2C (17.2)	14.7	4.7	0.3	0.7
5v	2-Cl	$N(C_2H_5)_2$	1	5C	3C (41.9)	3C (33.4)	2C (34.9)	1C (25.8)	19.2	8.0	6.4	−0.2	−0.2
5w	3,4-Cl_2	$N(C_2H_5)_2$	0	3C (10.9)	5C	4C (21.4)	4C (33.4)	3C (23.7)	15.7	0.9	0.1	−0.3	−0.1
5x	3,4-Cl_2	$N(C_2H_5)_2$	1	5C	5C	2C (29.1)	2C (25.7)	1C (21.2)	12.0	5.9	0.7	−0.1	−0.1
5y	3,4-Cl_2		0	3C (33.9)	3C (25.9)	4C (27.4)	1C (30.2)	18.5	8.3	0.1	−0.1	−0.1	−0.1
5z	3,4-Cl_2		1	5C	5C	3C (24.4)	2C (25.4)	10.7	7.9	2.3	0.7	−0.1	−0.1
5aa	3,4-Cl_2	$NHC(CH_3)_3$	0	4C (16.4)	3C (14.4)	4C (13.4)	4C (30.4)	2C (27.4)	1C (10.5)	9.7	6.1	0.1	0.7
5bb	3,4-Cl_2	$NHC(CH_3)_3$	1	2C (38.1)	3C (25.9)	1C (25.9)	1C (23.2)	8.9	5.9	2.9	0.5	−0.1	−0.3
5cc	4-CF_3	$N(C_2H_5)_2$	0	1C (17.0)	10.1	11.9	2C (12.0)	2C (13.0)	2C (19.4)	1C (18.9)	11.0	2.0	0.0
5dd	4-CF_3	$N(C_2H_5)_2$	1	1C (16.5)	2C (12.7)	3C (13.2)	3C (19.7)	2C (28.6)	2C (33.6)	1C (27.9)	13.6	2.6	0.2
5ee	4-CF_3	$NHC(CH_3)_3$	0	3C (11.7)	12.1	9.1	10.7	2C (14.9)	21.2	1C (10.4)	11.8	3.4	0.2
5ff	3-CF_3	$N(C_2H_5)_2$	0	3C (17.9)	3C (21.9)	4C (21.9)	2C (28.2)	3C (31.4)	23.7	1C (15.2)	13.5	9.7	0.5
5gg	3-CF_3	$N(C_2H_5)_2$	1	4C (27.9)	1C (24.9)	21.1	11.7	8.5	5.9	1.1	0.3	−0.1	0.3
5hh	2-CF_3	$N(C_2H_5)_2$	0	4C (20.7)	4C (30.7)	5C	1C (25.5)	1C (18.5)	12.5	3.1	1.1	−0.3	0.3
5ii	2-CF_3	$N(C_2H_5)_2$	1	5C	5C	4C (24.7)	24.7	15.5	7.7	4.1	0.7	0.1	0.5
5jj	4-OCH_3	$N(C_2H_5)_2$	0	5C	3C (28.9)	2C (16.1)	1C (12.4)	7.3	4.3	2.9	1.3	0.1	0.5
5kk	4-OCH_3	$N(C_2H_5)_2$	1	2C (15.0)	1C (8.2)	7.3	9.1	7.3	3.7	1.1	0.1	−0.1	0.1
5ll	2-OCH_3	$N(C_2H_5)_2$	0	5C	2C (37.9)	2C (18.9)	2C (14.9)	9.4	6.2	2.6	0.4	0.2	−0.2
5mm	2-OCH_3	$N(C_2H_5)_2$	1	1C (27.2)	1C (36.2)	2C (8.9)	8.7	6.9	0.7				
5nn	2,5-$(OCH_3)_2$	$N(C_2H_5)_2$	0	8.6	8.8	4.0	3.6	3.8	0.0				
5oo	2,5-$(OCH_3)_2$	$N(C_2H_5)_2$	1	1C (27.1)	7.8	6.0	2.0	2.6	0.6				
5pp	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	0	1C (13.1)	12.0	8.6	5.4	3.8	1.2				
5qq	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	1	2C (11.0)	3C (12.4)	11.4	5.0	5.4	2.4				
5rr	4-CH_3	$N(C_2H_5)_2$	0	20.5	14.5	9.7	6.5	4.5	3.3	1.6	0.4	0.4	0.4
5ss	4-CH_3	$N(C_2H_5)_2$	1	10.5	15.7	5.1	4.3	0.5	1.3				
5tt	4-OH	$N(C_2H_5)_2$	0	1C (4.1)	2C (3.6)	6.8	4.8	0.8	−0.2				
5uu		$N(C_2H_5)_2$	0	2C (8.1)	1C (11.2)	6.6	5.8	2.3	0.3	0.7	−0.3	−0.1	0.1
5vv		$N(C_2H_5)_2$	1	1C (12.9)	1.6	6.4	3.0	0.4	0.0				

Table VI (Continued)

				ΔMST, C after single sc dose, mg/kg[a]									
no.	X	NR_1R_2	z	640	320	160	80	40	20	10	5	2.5	1.25
5ww	4-aza	$N(C_2H_5)_2$	0	2C (25.0)	1C (21.2)	1C (21.7)	1C (11.5)	9.3	5.5	2.1	1.9	0.5	−0.1
5xx	4-aza	$N(C_2H_5)_2$	1	3C (21.9)	2C (12.6)	10.7	8.3	5.7	3.3				
5yy	3-aza	$N(C_2H_5)_2$	0	3C (34.8)	4C (37.8)	4C (18.8)	1C (19.6)	1C (20.3)	1C (13.6)	1C (8.6)	1C (10.6)	5.4	1.8
5zz	2-aza	$N(C_2H_5)_2$	0	3C (25.3)	3C (15.8)	11.2	7.8	3.8	2.6				
5aaa	2-aza	$N(C_2H_5)_2$	1	1C (9.1)	1C (5.1)	3.0	1.0	0.0	0.4				
5bbb	4-F	$N(C_2H_5)_2$	0	14.8		12.8		2C (13.4)					
5ccc	4-F	$N(C_2H_5)_2$	1	15.0	4C (8.6)	5C	4C (23.6)	2C (21.7)	14.1	10.5	5.1	2.1	0.5
5ddd	4-F	$NHC(CH_3)_3$	0	14.4	16.6	1C (11.9)	1C (12.4)	3C (15.2)	1C (18.0)	1C (16.5)	8.9	7.5	1.7
5eee	3-F	$N(C_2H_5)_2$	0	3C (15.8)	1C (13.8)	3C (14.8)	2C (12.8)	3C (25.1)	2C (23.6)	23.2	1C (5.6)	1.8	0.4
5fff	3-F	$N(C_2H_5)_2$	1	1C (14.8)	3C (24.1)	3C (29.6)	2C (22.6)	22.8	27.2		4.5	0.5	−0.1
5ggg	2-F	$N(C_2H_5)_2$	0	5C	5C	2C (33.1)	26.2	1C (18.4)	16.4	12.8	4.4	0.4	0.0
5hhh	2-F	$N(C_2H_5)_2$	1	4C (35.6)	2C (31.9)	3C (20.1)	15.6	1C (17.1)	12.2	6.1	1.5	−0.1	−0.1
5iii	2,3-F_2	$N(C_2H_5)_2$	0	4C (19.8)	4C (19.8)	2C (35.1)	3C (33.3)	3C (39.4)	2C (22.2)	1C (16.7)	13.7	6.7	0.7
5jjj	2,6-F_2	$N(C_2H_5)_2$	0	4C (36.8)	5C	5C	2C (24.1)	1C (16.9)	1C (12.2)	8.3	7.9	2.7	0.1
5kkk	2,3,4,5,6-F_5	$N(C_2H_5)_2$	0	5C	5C	4C (47.0)	5C	4C (20.5)	1C (18.8)	2C (18.8)	12.9	7.9	3.5
5lll	4-SCH_3	$N(C_2H_5)_2$	0	4C (13.6)	2C (25.3)	19.2	10.0	9.1	6.7	1.3	0.5	0.1	0.5
5mmm	4-SCH_3	$N(C_2H_5)_2$	1	2C (27.3)	4C (18.6)	1C (19.9)	1C (9.4)	10.3	6.5	2.1	1.5	0.5	0.1

[a] ΔMST is the change in mean survival time of the treated mice, in days, calculated by subtracting the mean survival time of the control mice (an average of 6.2 days in these experiments) from the mean survival time of the treated mice. In calculating the mean survival time of the treated mice, 60-day survivors are not included. C indicates the number of mice surviving at 60 days postinfection and termed "cured". Each compound was administered as a single sc dose 72-h postinfection. Each entry at each dose represents results with a five-animal group.

Table VII. Comparison of Amodiaquine and Substituted Analogues against Trophozoite-Induced *Plasmodium berghei* in Mice



				ΔMST after single sc dose						
compound	A	NR_1R_2	x	640	320	160	80	40	20	10
amodiaquine	H	$N(Et)_2$	0	5C	5C	5C	2C	11.9	8.3	5.7
amodiaquine *N*-oxide	H	$N(Et)_2$	1	3C	5C	3C				
cycloquine	$(Et)_2NCH_2$	$N(Et)_2$	0	5C	5C	4C	2C	19.1	15.1	11.5
cycloquine *N*-oxide	$(Et)_2NCH_2$	$N(Et)_2$	1	3C	3C	1C	8.5	6.9	3.9	
5f	4-Cl-C_6H_4	$N(Et)_2$	1	5C	5C	5C	5C	4C	3C	2C (14.2)
4[51]	*a*			5C	5C	5C	15.7	12.9	5.1	

[a] 2-(4-Chlorophenyl)-4-*tert*-butyl-6-[(*tert*-butylamino)methyl]phenol (**4**).

4′-Chloro[1,1′-biphenyl]-2-ol (9, X = 4-Cl). A mixture of 31.5 g (0.144 mol) of 4′-chloro-2-methoxy[1,1′-biphenyl] and 126 mL of 48% hydrobromic acid in 600 mL of acetic acid was heated under reflux for 18 h, allowed to cool, poured into 1 L of water, and extracted with ether. The ether extracts were washed with water, dried (Na_2SO_4), and concentrated to dryness in vacuo. The residue was recrystallized from hexane to give 19.2 g (65.3%) of the product, mp 49.5–52 °C (lit.[32] mp 53 °C). Anal. ($C_{12}H_9ClO$) C, H. The filtrate afforded an additional 3.1 g of the product, mp 46–49 °C; total yield, 76%.

2-(4-Chlorophenyl)-2,5-cyclohexadiene-1,4-dione 4-Oxime (10, X = 4-Cl).[33] A solution of 4.08 g (0.020 mol) of 4′-chloro-[1,1′-biphenyl]-2-ol in 63 mL of acetic acid and 40 mL of water was chilled to 5 °C and treated dropwise with a solution of 1.5 g (0.022 mol) of sodium nitrite in 7 mL of water. The mixture was stirred several hours at 5 °C and then filtered. Recrystallization first from 33% acetic acid and then from toluene gave 1.2 g (26%) of the title compound, mp 182–184 °C dec. Anal. ($C_{12}H_8ClNO_2$) C, H, Cl, N.

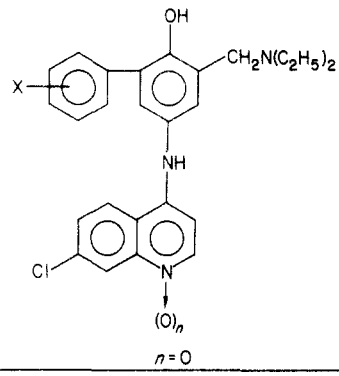
2-Phenyl-2,5-cyclohexadiene-1,4-dione 4-Oxime (10, X = H) was synthesized analogously in 39% yield from [1,1′-biphenyl]-2-ol, mp 174 °C (lit.[34] mp 170–172 °C). Anal. ($C_{12}H_9NO_2$) C, H, N.

5-Amino-4′-chloro[1,1′-biphenyl]-2-ol (11, X = 4-Cl). To a stirred suspension of 7.82 g (0.0335 mol) of 2-(4-chlorophenyl)-2,5-cyclohexadiene-1,4-dione 4-oxime in 170 mL of 1 N sodium carbonate was added in portions 23 g (0.13 mol) of sodium dithionite. The temperature rose from 23 to 35 °C. The reaction mixture was stirred for 5 h, filtered, and washed with water to give 11 g (97%) of the product, mp 185–190 °C. A 0.15-g sample was recrystallized from toluene (charcoal) to give 0.12 g of analytical material, mp 189–191 °C. Anal. ($C_{12}H_{10}ClNO$) C, N; H: calcd, 4.59; found, 5.02.

5-Amino[1,1′-biphenyl]-2-ol (11, X = H) was synthesized analogously from 2-phenyl-2,5-cyclohexadiene-1,4-dione 4-oxime in 82% yield, mp 196–198 °C. Recrystallization of a sample from ethanol (charcoal) gave analytical material, mp 198–199 °C (lit.[35]

(31) Migeta, T.; Morikawa, N.; Simamura, O. *Bull Chem. Soc. Jpn.* **1983**, *980*, 36.
(32) Colbert, J. C.; Lacy, R. M. *J. Am. Chem. Soc.* **1946**, *68*, 200.
(33) This procedure was used by W. Borsche and B. G. B. Scholten (*Chem. Ber.* **1917**, *50*, 596) to nitrosate [1,1′-biphenyl]-2-ol.
(34) Borsche, W. *Ann. Chem.* **1900**, *312*, 211.
(35) Hill, H. B.; Hale, W. J. *Am. Chem. Soc.* **1905**, *33*, 1.

Table VIII. Data Used To Formulate the QSAR



compd	X	N_OXIDE	$\sum\pi_b$[a]	$\sum\sigma$	$\sum F$	$\sum R$	$\sum$MR	ED_{30}, mg/kg	log molar ED_{30}	calcd[b]	residual
initial set											
5a	H	0	0.00	0.00	0.00	0.00	0.10	10.4	−1.62	−1.38	−0.24
5b	H	1	0.00	0.00	0.00	0.00	0.10	26.3	−1.23	−1.38	0.15
5u	2-Cl	0	0.76	0.23	0.86	−0.14	0.60	15.3	−1.48	−1.18	−0.30
5v	2-Cl	1	0.76	0.23	0.86	−0.14	0.60	27.4	−1.24	−1.18	−0.06
5ll	2-OCH_3	0	−0.33	−0.27	0.52	−0.43	0.79	74.0	−0.80	−0.12	−0.68
5mm	2-OCH_3	1	−0.33	−0.27	0.52	−0.43	0.79	170	−0.45	−0.12	−0.33
5uu	2,3-$(CHCH)_2$	0	1.30	0.00	0.20	−0.15	1.75	4200	0.94	0.57	0.37
5vv	2,3-$(CHCH)_2$	1	1.30	0.00	0.20	−0.15	1.75	14400	1.46	0.57	0.89
5nn	2,5-$(OCH_3)_2$	0	−0.21	−0.15	0.93	−0.60	1.57	9160	1.27	0.61	0.66
5oo	2,5-$(OCH_3)_2$	1	−0.21	−0.15	0.93	−0.60	1.57	2450	0.68	0.61	0.07
5ff	3-CF_3	0	1.10	0.43	0.62	0.07	0.50	16.3	−1.48	−1.63	0.15
5gg	3-CF_3	1	1.10	0.43	0.62	0.07	0.50	113	−0.66	−1.63	0.97
5s	3-Cl	0	0.77	0.37	0.68	−0.06	0.60	17.3	−1.43	−1.41	−0.02
5t	3-Cl	1	0.77	0.37	0.68	−0.06	0.60	27.4	−1.24	−1.41	0.17
5pp	3,4-$(OCH_3)_2$	0	0.08	−0.12	0.82	−0.67	1.57	927	0.28	0.56	−0.28
5qq	3,4-$(OCH_3)_2$	1	0.08	−0.12	0.82	−0.67	1.57	204	−0.40	0.56	−0.96
5w	3,4-Cl_2	0	1.25	0.52	1.37	−0.22	1.21	22.7	−1.34	−0.95	−0.39
5x	3,4-Cl_2	1	1.25	0.52	1.37	−0.22	1.21	36.6	−1.15	−0.95	−0.20
5cc	4-CF_3	0	1.04	0.54	0.63	0.19	0.50	9.8	−1.71	−1.81	0.10
5dd	4-CF_3	1	1.04	0.54	0.63	0.19	0.50	7.4	−1.84	−1.81	−0.03
5rr	4-CH_3	0	0.60	−0.17	−0.07	−0.11	0.56	1530	0.54	−0.55	1.09
5ss	4-CH_3	1	0.60	−0.17	−0.07	−0.11	0.56	22100	1.68	−0.55	2.23[c]
5l	4-Cl	0	0.73	0.23	0.69	−0.16	0.60	6.2	−1.87	−1.18	−0.69
5f	4-Cl	1	0.73	0.23	0.69	−0.16	0.60	9.2	−1.72	−1.18	−0.54
5ccc	4-F	1	0.15	0.06	0.71	−0.34	0.09	19.7	−1.37	−1.50	0.13
5jj	4-OCH_3	0	−0.03	−0.27	0.41	−0.50	0.79	112	−0.61	−0.12	−0.49
5kk	4-OCH_3	1	−0.03	−0.27	0.41	−0.50	0.79	423	−0.05	−0.12	0.07
5tt	4-OH	0	−0.61	−0.37	0.49	−0.64	0.28	320	−0.15	−0.55	0.40
later set											
5hh	2-CF_3	0	1.04	0.54	0.79	0.16	0.50	34.7	−1.16	−1.81	0.65[c]
5ii	2-CF_3	1	1.04	0.54	0.79	0.16	0.50	56.1	−0.96	−1.81	0.85[c]
5ggg	2-F	0	0.00	0.06	0.88	−0.29	0.09	26.8	−1.22	−1.50	0.28[c]
5hhh	2-F	1	0.00	0.06	0.88	−0.29	0.09	48.4	−0.98	−1.50	0.52[c]
5iii	2,3-F_2	0	0.22	0.40	1.57	−0.41	0.18	8.7	−1.73	−1.96	0.23[c]
5kkk	2,3,4,5,6-F_5	0	0.59	0.86	3.85	−1.16	0.46	7.4	−1.85	−2.40	0.55[c]
5jjj	2,6-F_2	0	0.00	0.12	1.76	−0.58	0.18	23.7	−1.29	−1.49	0.20[c]
5eee	3-F	0	0.22	0.34	0.69	−0.12	0.09	12.4	−1.56	−1.97	0.41[c]
5fff	3-F	1	0.22	0.34	0.69	−0.12	0.09	33.7	−1.14	−1.97	0.83[c]
5bbb	4-F	0	0.15	0.06	0.71	−0.34	0.09	8.8	−1.71	−1.50	−0.21[c]
5lll	4-SCH_3	0	0.87	0.00	0.33	−0.19	1.38	151	−0.50	0.13	−0.63[c]
5mmm	4-SCH_3	1	0.87	0.00	0.33	−0.19	1.38	158	−0.50	0.13	−0.63[c]

[a] Benzene π values of Norrington et al.[22] [b] Using eq 2. [c] These compounds were not used in the development of eq 2.

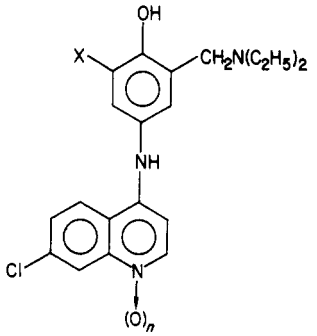
Table IX. Correlation Matrix

	$\sum\pi_a$	$\sum\pi_a^2$	$\sum\pi_b$	$\sum\pi_b^2$	$\sum\sigma$	$\sum F$	$\sum R$	$\sum$MR	N_OXIDE
$\sum\pi_a$	1.00								
$\sum\pi_a^2$	0.86	1.00							
$\sum\pi_b$	0.97	0.81	1.00						
$\sum\pi_b^2$	0.89	0.95	0.88	1.00					
$\sum\sigma$	0.76	0.59	0.80	0.67	1.00				
$\sum F$	0.25	0.31	0.17	0.22	0.46	1.00			
$\sum R$	0.63	0.39	0.71	0.54	0.73	−0.24	1.00		
$\sum$MR	0.22	0.33	0.11	0.25	−0.17	0.32	−0.48	1.00	
N_OXIDE	0.05	−0.02	0.05	−0.02	0.05	0.02	0.04	−0.01	1.00

mp 198–199 °C). Anal. ($C_{12}H_{11}NO$) C, H, N.

Preparation of 1-Phenyl-2-propanones (12) (Table I). 1-(3-Chlorophenyl)-2-propanone, 1-(2-chlorophenyl)-2-propanone, 1-[4-(trifluoromethyl)phenyl]-2-propanone, 1-[3-(trifluoromethyl)phenyl]-2-propanone, 1-(4-methoxyphenyl)-2-propanone, 1-(2-methoxyphenyl)-2-propanone, 1-(2,5-dimethoxyphenyl)-2-

Table X. Potencies of Pyridyl Analogues



compd	X	n	ED_{30}, mg/kg	log molar ED_{30}
5zz	2-pyridyl	0	160	−0.42
5aaa	2-pyridyl	1	550	0.09
5yy	3-pyridyl	0	31	−1.15
5ww	4-pyridyl	0	89	−0.52
5xx	4-pyridyl	1	330	−0.14

propane, 1-(3,4-dimethoxyphenyl)-2-propanone, and 1-(4-methylphenyl)-2-propanone were purchased commercially. Compounds **12a–d** and **12f–p** in Table I were made by one of six different methods (Scheme IV). Compound **12e** was made from **12d** (see below).

1-(4-Fluorophenyl)-2-propanone (12j). Method C (Scheme IV). To a solution of 14 g (0.091 mol) of 4-fluorobenzeneacetic acid in 500 mL of anhydrous ether and 500 mL of anhydrous tetrahydrofuran, cooled to −50 ± 10 °C, was added during 30 min 200 mL (0.30 mol) of a 1.5 M methyllithium/lithium bromide complex in ether, while the temperature was maintained at −50 ± 10 °C. After the addition the cooling bath was removed and the temperature rose to 20 °C. The light yellow solution was heated under reflux for 1 h, cooled, and poured into 1 L of ice–water. The organic layer was removed and the aqueous layer was extracted with ether. The combined, dried ($MgSO_4$) extracts were evaporated in vacuo to give 13 g (94%) of the product as a light yellow oil, bp 60–65 °C (0.25 mm) (lit.[36] bp 103 °C (15 mm)).

Compounds **13k,l,d** in Table I were prepared similarly.

1-[2-(Trifluoromethyl)phenyl]-2-propanone (5c). Method D (Scheme IV). A mixture of 20.4 g (0.1 mol) of 2-(trifluoromethyl)benzeneacetic acid, 40 mL of pyridine, and 100 mL of acetic anhydride was heated under reflux for 4 h. The dark mixture was concentrated in vacuo to give a viscous oil. Distillation gave 4.0 g of a colorless liquid, bp 67–76 °C (3.5 mm). This liquid analyzed roughly for the desired 1-en-2-ol acetate of the title compound. GC analysis showed two major components, 68% and 24%, presumably corresponding to the two geometrical isomers. This material was taken up in 10 mL of ethanol and 2 mL of concentrated hydrochloric acid was added. The resulting solution was heated under reflux for 2 h, cooled, and concentrated in vacuo to give an oil. This was partitioned between 50 mL of water and 50 mL of ether. The ether layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 3.5 g (17%) of a liquid which was 86% pure by GC analysis and displayed an NMR spectrum characteristic of the desired product (lit.[37] bp 90–91 °C (2 mm)).

1-(Pentafluorophenyl)-2-propanone (12o). Method E (Scheme IV). A mixture of 50.0 g (0.255 mol) of pentafluorobenzaldehyde and 5.91 g (0.0767 mol) of ammonium acetate in 152 mL (2.10 mol) of nitroethane was heated under relux for 5 h. The resulting solution was concentrated in vacuo. The residue was dissolved in chloroform and the solution was washed first with water and then with a saturated sodium chloride solution. The solution was dried ($MgSO_4$) and concentrated in vacuo to give 53.0 g (82%) of pentafluoro(2-nitro-1-propenyl)benzene as a yellow oil. This was used as is, without characterization, in the next reaction.

A mixture of 53.0 g (0.209 mol) of pentafluoro(2-nitro-1-propenyl)benzene, 45.1 g (0.809 mol) of 40-mesh iron, and 1.37 g (0.005 mol) of ferric chloride hexahydrate in 100 mL of water was heated to reflux on a steam bath. To the mixture was added 81 mL of concentrated hydrochloric acid in portions during 3 h, and the mixture was then heated for 4 h on a steam bath. The mixture was diluted with water and chloroform, the two-layered mixture was filtered to remove the iron compounds, and the chloroform layer was separated. The aqueous layer was extracted with chloroform, and the combined organic extracts were washed first with water and then with a saturated sodium chloride solution and dried ($MgSO_4$). Concentration of the solution in vacuo gave 43.8 g of a black oil. Distillation gave 7.87 g (13.8% from pentafluorobenzaldehyde) of the product as a yellow oil, bp 42–48 °C (0.05–0.10 mm) (lit.[38] mp 35.5–36.5 °C). GC analysis showed this to be 93% pure.

Compounds **12h,m,n,p** in Table I were prepared similarly with minor variations.

1-(2-Pyridinyl)-2-propanone (12i). Method F (Scheme III). This compound was synthesized from 2-methylpyridine according to Wolfe et al.[39] in 93% yield. It was 92% pure by GC analysis (lit.[39] bp 60–65 °C (0.4 mm)).

1-(4-Pyridinyl)-2-propanone (12g). Method G (Scheme III). To a solution of 23 g (1 mol) of sodium and 500 mg of ferric chloride in 1.25 L of liquid ammonia was added portionwise 93 g (1 mol) of 4-methylpyridine, followed by the rapid addition of 40 g (0.54 mol) of methyl acetate. The suspension was allowed to evaporate with stirring overnight, treated with 1 L of ether, 55 g (1.03 mol) of ammonium chloride, and carefully with 1 L of water. The ether layer was removed, dried ($MgSO_4$), and concentrated in vacuo to provide 93 g of a reddish-brown oil. Fractional distillation of the oil provided 34 g of 4-methylpyridine and 16 g (24%) of the product, bp 78–80 °C (0.3 mm) (lit.[40] bp 110–115 °C (3–4 mm)).

1-(3,4-Dichlorophenyl)-2-propanone (12b). Method H (Scheme III). This compound was synthesized from 3,4-dichlorobenzeneacetonitrile according to Hanson[41] in 47% yield. Compounds **12a,f** were made similarly. Compound **12f** was also made from 1-naphthaleneacetic acid in 89% yield[42] according to Zimmerman and McKelvey.[43]

1-[4-[(2-Methoxyethoxy)methoxy]phenyl]-2-propanone (12e). To a solution of 13.0 g (0.0866 mol) of **12d** in 100 mL of dry DMF was added 2.08 g (0.0866 mol) of sodium hydride (from 4.16 g of a 50% dispersion, washed with hexane), and the solution was heated at 50 °C for several minutes. To the solution was added 10.8 g (0.0866 mol) of (2-methoxyethoxy)methyl chloride in several portions. The solution was heated rapidly to 100 °C, cooled, and evaporated in vacuo to a syrup, which was distributed between ethyl acetate and water. The aqueous layer was reextracted with ethyl acetate, and the combined, dried ($MgSO_4$) organic extracts were evaporated in vacuo to provide the crude product. This material was dissolved in benzene–ethyl acetate (4:1) and chromatographed over 500 g of silica gel with use of the same solvent system to give 8.3 g (40%) of the title compound as a light yellow oil.

Preparation of 5-Nitro[1,1′-biphenyl]-2-ols (13). These compounds were synthesized according to the procedure of Hill and Hale[11] and Anjaneyulu et al.[48] (Scheme II, method A).

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5-Nitro-3'-(trifluoromethyl)[1,1'-biphenyl]-2-ol (13f). To a mixture of 12.5 g (0.080 mol) of sodium nitromalonaldehyde hydrate[49] in 137 mL of water and 50 mL of 10% sodium hydroxide was added 25 g (0.080 mol) of 1-[3-(trifluoromethyl)phenyl]-2-propanone (65% by GC) in 190 mL of ethanol. The mixture was swirled, allowed to stand for 20 h, and concentrated in vacuo to remove the ethanol. The aqueous concentrate was extracted with ether, chilled with ice, and made acidic with 10 N hydrochloric acid. The resulting oil was extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and concentrated to dryness in vacuo. The residue was recrystallized from toluene containing a small amount of 2-propanol to give 4.6 g (20%) of the product, mp 185–187 °C. Anal. ($C_{13}H_8F_3NO_3$) C, H, N. A second crop of 9.1 g (40%), mp 184–187 °C, was obtained by concentrating the filtrate.

The other compounds in Table II were prepared similarly.

Preparation of *N*-(6-Hydroxy[1,1'-biphenyl]-3-yl)acetamides (6). These compounds were made either by a modification of the procedure of Burckhalter et al.[4] (Scheme II, method A) or by method B (Scheme II).

Method A (Scheme II). *N*-[6-Hydroxy-3'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]acetamide (6g). A solution of 13.7 g (0.0485 mol) of **13f** in 200 mL of methanol was hydrogenated over 1.5 g of Raney nickel at an initial pressure of 53 psi at room temperature for 5.6 h and then filtered into a flask containing 5.0 mL (0.053 mol) of acetic anhydride. The mixture was heated on the steam bath for 10 min and then concentrated to dryness in vacuo. Trituration of the residue with toluene followed by recrystallization from the same solvent afforded 12.5 g (87%) of the product, mp 145–147 °C. Anal. ($C_{15}H_{12}F_3NO_2$) C, H, N.

Compounds **6b–f,h–y** in Table III were prepared similarly.

Method B (Scheme II). *N*-(4'-Chloro-6-hydroxy[1,1'-biphenyl]-3-yl)acetamide (6b). A solution of 7.0 g (0.032 mol) of 5-amino-4'-chloro[1,1'-biphenyl]-2-ol and 3.0 mL (3.3 g, 0.032 mol) of acetic anhydride in 400 mL of toluene was treated with charcoal, boiled 1 min, filtered through Celite, and cooled to afford 6.67 g 81.2%) of the product, mp 135–137 °C. A small sample was recrystallized from toluene to give an analytical sample, mp 135 °C. Anal. ($C_{14}H_{12}ClNO_2$) C, H, N.

Compound **6a** in Table III was prepared similarly from 5-amino[1,1'-biphenyl]-2-ol.

Compound **6b** was also made by by reducing **13a**, following by acetylation (method A).

Preparation of *N*-[5-[(Alkylamino)methyl]-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamides (7). These compounds were prepared according to the general procedure of Burckhalter et al.[4] (Scheme I).

***N*-[5-[(Diethylamino)methyl]-6-hydroxy-3'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]acetamide (7s).** A solution of 12.5 g (0.0423 mol) of **6g** in 70 mL of ethanol was treated with a solution of 3.6 mol (0.044 mol) of 37% formaldehyde and 5.0 mL (0.048 mol) of diethylamine in 10 mL of ethanol and heated under reflux for 32 h. After 18 and 25 h of heating, additional amounts of 37% formaldehyde (1.8 mL) and diethylamine (2.5 mL) were added. The reaction mixture was concentrated in vacuo to an oil and taken up in ether, ethyl acetate, and water. The organic layer was separated, washed with water, dried ($MgSO_4$), concentrated to 30 mL, and chromatographed over 500 g of alumina (Alcoa F-20) with ethyl acetate as the eluting solvent. The product-containing eluant (R_f 0.6, alumina–ethyl acetate) was concentrated to dryness in vacuo. The residue was recrystallized from 2-propanol–water to give 8.9 g (55%) of the product, mp 116–119 °C. Anal. ($C_{20}H_{23}F_3N_2O_2$) C, H, N. Dilution of the filtrate with water gave an additional 2.3 g of material, mp 115–118 °C. Total yield, 70%.

The other compounds in Table IV were prepared similarly from the appropriate **6**, amine, and formaldehyde. Many of the compounds **7** were synthesized as above but in a stainless steel bomb at 100 °C, thus considerably shortening reaction times.

Preparation of 5-[(7-Chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1'-biphenyl]-2-ols and N^{ω}-Oxides (5). These compounds were made according to the general procedure of Burckhalter et al.[4] (Scheme I).

5-[(7-Chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]-3'-(trifluoromethyl)[1,1'-biphenyl]-2-ol (5ff). A solution of 1.5 g (0.0040 mol) of **7s** in 9 mL of 6 N hydrochloric acid was heated under reflux for 1 h. The solution was concentrated in vacuo and then coevaporated with ethanol. To a solution of the residual oil in 20 mL of ethanol was added 0.8 g (0.004 mol) of 4,7-dichloroquinoline. The solution was heated under reflux for 1.5 h and poured into cold 5% ammonium hydroxide. The resulting precipitate was collected, washed with water, and recrystallized from ethanol to give 1.0 g (50%) of the product, mp 234–236 °C dec. Anal. ($C_{27}H_{25}ClF_3N_3O$) C, H, N.

5-[(7-Chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]-3'-(trifluoromethyl)[1,1'-biphenyl]-2-ol N^{ω}-Oxide (5gg). A solution of 5.7 g (0.015 mol) of **7s** in 25 mL of 6 N hydrochloric acid was heated under reflux for 1 h. The solution was diluted with ethanol, concentrated under reflux for 1 h. The solution was diluted with ethanol, concentrated under reduced pressure, and then coevporated with ethanol. To a solution of the residue in 30 mL of ethanol was added 3.2 g (0.015 mol) of 4,7-dichloroquinoline 1-oxide.[9] The solution was heated under reflux for 1.5 h and poured into 150 mL of cold 5% ammonium hydroxide. The resulting precipitate was collected and triturated first in 150 mL of methanol and then in 150 mL of ethyl acetate to give a first crop of 2.9 g of the crude product. The methanol and ethyl acetate triturates were combined and chromatographed over 200 g of silica gel, eluting first with ethyl acetate and then with 5%, 10%, and 15% solutions of methanol in ethyl acetate. The eluant containing the product was concentrated to dryness in vacuo to give a second crop of 1.3 g of the crude product. The two crops were combined and recrystallized from methanol to give 2.0 g (26%) of the product, mp 227–229 °C (dec with prior darkening). Anal. ($C_{27}H_{25}ClF_3N_3O_2$) C, H, N.

The other compounds in Table V were prepared similarly from the appropriate **7** and 4,7-dichloroquinoline or 4,7-dichloroquinoline 1-oxide.

Acknowledgment. We are indebted to William M. Pearlman and Donald R. Johnson for performing the hydrogenations and Forrest A. MacKellar and his group for the microanalytical and spectral data. We also thank Dr. W. Ewy for his assistance in calculating the error of the ED_{30} values.

Registry No. **4**, 69121-82-0; **5a**, 101712-65-6; **5b**, 101712-66-7; **5c**, 101712-67-8; **5d**, 101712-68-9; **5e**, 79286-94-5; **5f**, 79286-95-6; **5g**, 74129-03-6; **5h**, 79286-96-7; **5i**, 101712-69-0; **5j**, 79287-10-8; **5k**, 79287-55-1; **5l**, 79287-15-3; **5m**, 79287-16-4; **5n**, 79287-17-5; **5o**, 79287-18-6; **5p**, 79287-14-2; **5q**, 79287-23-3; **5r**, 101712-70-3; **5s**, 79305-46-7; **5t**, 79286-97-8; **5u**, 79286-98-9; **5v**, 79286-99-0; **5w**, 79287-01-7; **5x**, 79287-02-8; **5y**, 101712-71-4; **5z**, 79287-04-0; **5aa**, 79287-05-1; **5bb**, 79287-06-2; **5cc**, 79287-56-2; **5dd**, 79287-58-4; **5ee**, 79287-57-3; **5ff**, 79305-47-8; **5gg**, 79305-48-9; **5hh**, 101712-72-5; **5ii**, 101712-73-6; **5jj**, 79287-07-3; **5kk**, 79287-08-4; **5ll**, 79287-00-6; **5nn**, 101712-74-7; **5oo**, 101712-75-8; **5pp**, 101712-76-9; **5qq**, 101712-77-0; **5rr**, 101712-78-1; **5ss**, 101712-79-2; **5tt**, 79287-20-0; **5uu**, 101712-80-5; **5vv**, 101712-81-6; **5ww**, 101712-82-7; **5xx**, 101712-83-8; **5yy**, 101712-84-9; **5zz**, 101712-85-0; **5aaa**, 101712-86-1; **5bbb**, 79287-19-7; **5ccc**, 79287-21-1; **5ddd**, 79287-22-2; **5eee**, 101712-87-2; **5fff**, 101712-88-3; **5ggg**, 101712-89-4; **5hhh**, 101712-90-7; **5iii**, 101712-91-8; **5jjj**, 101712-92-9; **5kkk**, 101712-93-0; **5lll**, 101712-94-1; **5mmm**, 101712-95-2; **6a**, 29785-41-9; **6b**, 79287-24-4; **6c**, 79287-37-9; **6d**, 79287-39-1; **6e**, 79287-40-4; **6f**, 79305-52-5; **6g**, 79287-38-0; **6h**, 79290-53-2; **6i**, 101712-33-8; **6j**, 101712-34-9; **6k**, 101712-35-0; **6l**, 101712-36-1; **6m**, 101712-37-2; **6n**, 79290-52-1; **6o**, 101712-38-3; **6p**, 101712-39-4; **6q**, 101712-40-7; **6re**, 67274-80-0; **6s**, 79290-51-0; **6t**, 101712-41-8; **6u**, 101712-42-9; **6v**, 101712-43-0; **6w**, 101712-44-1; **6x**, 101712-45-2; **6y**, 101712-46-3; **7a**, 101712-47-4; **7b**, 101712-48-5; **7c**, 79287-25-5; **7d**, 79287-26-6; **7e**, 101712-49-6; **7f**, 79287-28-8; **7g**, 79287-30-2; **7h**, 79287-31-3; **7i**, 79287-29-9; **7j**, 79287-32-4; **7k**, 101712-50-9; **7l**, 79287-33-5; **7m**, 79287-35-7; **7n**, 79305-51-4; **7o**, 79287-50-6; **7p**, 79287-51-7; **7q**,

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Syntheses and in Vitro Evaluation of 4-(2-Aminoethyl)-2(3*H*)-indolones and Related Compounds as Peripheral Prejunctional Dopamine Receptor Agonists

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A series of (β-aminoethyl)indolones and related compounds was synthesized and evaluated in vitro as peripheral prejunctional dopaminergic agonists in the field-stimulated isolated perfused rabbit ear artery. 4-[2-(Di-*n*-propylamino)ethyl]-7-hydroxy-2(3*H*)-indolone (**26**) was the most potent compound (ED_{50} = 2 ± 0.3 nM) tested, while the related secondary amine **24** and the des-OH derivatives **28** and **34** were only slightly less potent. 4-Methoxybenzeneethanamine and 2-methyl-3-nitrophenylacetic acid were employed as starting materials for the synthesis of the 4-(β-aminoethyl)indolones. The ring-opened 3-acylamino analogues **46** and **47** were prepared via nitration of the phenethylamine **43** derived from 4-methoxyphenylacetic acid. The inactive isomeric indolones **38**, **39**, and **41** were derived from 4-nitrobenzeneethanamine and from indolone-6-acetic acid (**13**).

During the past decade, evidence has accumulated to show that there are two distinct dopamine receptors in peripheral tissues. The peripheral postjunctional (D_1) receptor, located primarily in specific vascular beds such as the renal, mesenteric, and coronary arteries, mediates vasodilation.[1] The existence of this receptor was first suggested by in vivo studies showing dopamine-induced increases in renal blood flow in the dog.[2] This vascular D_1 receptor closely resembles the adenylate cyclase linked dopamine receptor found in the central nervous system.[3]

Recently, Langer discovered that activation of a dopaminergic receptor located on sympathetic nerve terminals in the perfused cat spleen would inhibit the release of neurotransmitter evoked by nerve stimulation.[4] Subsequent studies have shown this prejunctional receptor to be present on terminals of many, but not all, sympathetic nerves, and although activation of this dopamine receptor has similar effects to activation of prejunctional α_2-adrenoceptors, these two neuroinhibitory receptors are pharmacologically distinct.[5] The peripheral prejunctional dopamine receptor, designated D_2 by most investigators, is sensitive to dopamine and apomorphine at nanomolar concentrations and appears not to be coupled to adenylate cyclase. Much higher concentrations of dopamine, in the micromolar range, are required to activate D_1 receptors, and apomorphine acts as a weak partial agonist.[4] In addition, D_1 and D_2 receptors can be differentiated with selective antagonists. The *l* enantiomer of sulpiride preferentially blocks the D_2 receptor, and the recently discovered benzazepine derivatives SCH23390[6] and SK&F 83566[7] are highly selective for the D_1 subtype.

Stimulation of peripheral D_2 receptors is likely to be of therapeutic benefit in the treatment of cardiovascular disorders characterized by inappropriately high sympathetic tone. By inhibition of neurotransmitter release from the cardiac sympathetic nerve terminals, a D_2 agonist should attenuate the increase in cardiac work induced by exercise, stress, or any other stimulus that results in increased sympathetic drive. An additional benefit would be expected from concurrent inhibition of transmitter release from vascular sympathetic terminals, which would limit increases in vascular resistance and lower cardiac afterload. These sympathoinhibitory actions should be proportional to the degree of sympathetic activation; therefore a peripheral D_2 agonist should have little effect during intervals of low stress when sympathetic drive is low.

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