where $\sigma(F_o^2) = [\sigma^2(I) + (0.02|F_o|^2)^2]^{1/2}$, and were reset to $0.3\sigma(F_o^2)$. All data were used in the subsequent analysis and refinements.

Three standard reflections measured every 2 h of X-ray exposure time showed no decline in intensity. Corrections for Lorentz and polarization factors were applied and, in addition, data were correted for absorption by using the semiemprical ψ-scan technique.[25] A single ψ-scan was employed, consisting of 36 measurements of a standard reflection in 10-deg steps of ϕ with the crystal in an approximate equiinclination setting.

Struture Solution and Refinement. The structure was solved by direct methods by employing MULTAN78.[26] Starting sets based on 264 reflections with $E > 1.2$ were subjected to tangent refinement. An E map calculated from the set of phases with the highest combined figure of merit yielded all non-hydrogen atoms. The positions of all hydrogen atoms were then obtained from subsequent least-squares refinements and difference Fourier maps, employing only the low-angle data [$(\sin\theta)/\lambda < 0.4$ Å^{-1}].

The structure was refined by using full-matrix least-squares techniques. The function minimized was $\sum w(\Delta F)^2$ where $\Delta F = |F_o| - |F_c|$. Weights $w = 1/\sigma_{new}^2$ were used where $\sigma_{new}^2 = [\sigma^2 + 0.5A|F_o|^2 + 0.5B[(\sin\theta)/\lambda]^2]^{1/2}$ and $\sigma = \sigma(F_o^2)/2|F_o|$. Values of A and B were obtained by a least-squares minimization of the function $|\Delta F|^2 - \sigma_{new}^2$ for 20 separate segments in $|F_o|$ and $(\sin\theta)/\lambda$. Non-hydrogen atoms were refined anisotropically, the y coordinate of the sulfur atom remaining fixed. Positional parameters of all hydrogen atoms were refined with isotropic temperature factors.

Early refinements and difference maps indicated unambiguously that HO3′ was disordered over two sites. Occupanices were refined and then fixed at 0.6 and 0.4 with thermal parameters fixed at $B = 10$. This provided good convergence of the positional parameters at both sites. Refinement of the position of HO2′ was complicated by proximity to the sulfur atom density. Good convergence was obtained by fixing the thermal parameter of this proton as well.

Final refinements included a type I isotropic extinction correction and utilized all data. These converged to the values of $R = \sum|\Delta F|/\sum|F_o| = 0.052$ and $R_w = [\sum w(\Delta F)^2/\sum w|F_o|^2]^{1/2} = 0.051$ for 1122 observations m and 203 variables n. The discrepancy factor $S = [\sum w(\Delta F)^2/(m-n)]^{1/2} = 1.24$. The largest final parameter shift observed was 0.05σ. Atomic scattering factors for the non-hydrogen atoms and anomalous dispersion corrections for the sulfur atom were from ref 27. Scattering factors for the hydrogen atoms were those of Stewart et al.[28] The DNA system of programs[29] was used throughout. Final fractional atomic coordinates and thermal parameters are deposited.

Acknowledgment. This work was supported in part by Grant IN-18 awarded by the American Cancer Society and by a grant from the James P. Wilmot Foundation. The authors thank Dr. Helen M. Berman for the use of her diffraction facilities and Drs. Kathy Webster and Richard F. Borch for helpful discussions.

Registry No. Tiazofurin, 60084-10-8; aratiazofurin, 92952-33-5.

Supplementary Material Available: Tables of fractional atomic coordinates and thermal parameters, select bond lengths, angles and torsion angles, and hydrogen bond distances and angles (3 pages); table of observed and calculated structure factors (6 pages). Ordering information is given on any current masthead page.

(25) North, A.; Phillips D.; Mathews, F. *Acta Crystallogr., Sect. A: Cryst. Phys. Diffr., Theor. Gen. Crystallogr.* 1968, *A24*, 351–359.
(26) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. MULTAN78; University of York, England, and University of Louvian, Belgium, 1978.
(27) *International Tables for X-ray Crystallography*, 3rd ed.; Kynoch: Birmingham, England, 1974; Vol. IV, pp 99 and 149.
(28) Stewart, R.; Davidson, E.; Simpson, W. *J. Phys. Chem.* **1965**, *42*, 3175–3187.
(29) Takusagawa, F. *Crystallographic Computing System: DNA*; The Institute for Cancer Research: Fox Chase, PA , 1981.

2,4-Diamino-6,7-dimethoxyquinoline Derivatives as α_1-Adrenoceptor Antagonists and Antihypertensive Agents

Simon F. Campbell,* J. David Hardstone, and Michael J. Palmer

Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, United Kingdom. *Received June 17, 1987*

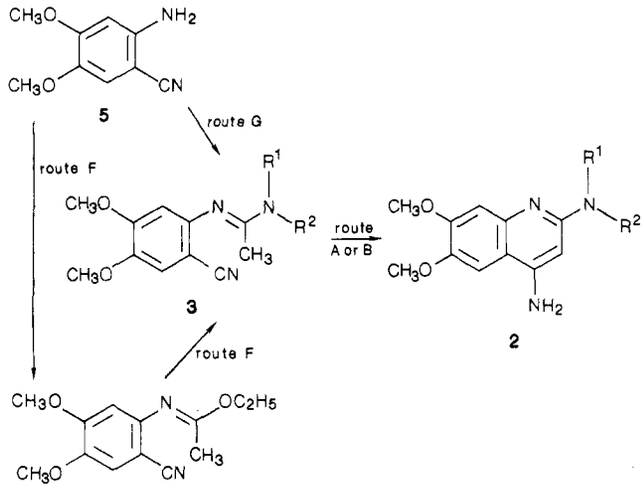
A series of 2,4-diamino-6,7-dimethoxyquinoline derivaties (**2**), prepared by LDA- or $ZnCl_2$-mediated intramolecular cyclization of an *N*-[1-(dialkylamino)ethylidene]-2-cyano-4,5-dimethoxyaniline (**3**), was evaluated for α-adrenoceptor affinity and antihypertensive activity. Most compounds displayed high in vitro binding affinities (K_i's, 10^{-10} M) for α_1-adrenoceptors with α_1-/α_2-selectivity ratios of at least 10 000. 4-Amino-2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinoline (**14**) proved to be the most potent member ($K_i = 1.4 \times 10^{-10}$ M) of series **2**, and displayed no activity at α_2-adrenoceptor binding sites at concentrations up to 10^{-6} M. In the rabbit pulmonary artery, **14** was a highly potent ($pA_2 = 9.76 \pm 0.26$) competitive antagonist of the α_1-mediated vasoconstrictor action of noradrenaline and was some 20 times more active than prazosin. pK_a measurements confirmed that, at physiological pH, N-1 protonation of series **2** would efficiently provide **1b**, a key pharmacophore for α_1-adrenoceptor recognition. Antihypertensive activity for series **2** was evaluated after oral administration (3 mg/kg) to spontaneously hypertensive rats (SHR) and falls in blood pressure were determined at 1 and 4.5 h. Various quinoline derivatives (**2**) proved to be effective antihypertensive agents in SHR, with both efficacy and duration of action at least equivalent to prazosin, and **14** displayed the most favorable overall profile. These observations are consistent with the high affinity and selectivity displayed by series **2** for postjunctional α_1-adrenoceptors.

Previous reports from these laboratories have presented detailed structure–activity relationships (SAR) with respect to α_1-adrenoceptor affinity and antihypertensive activity for various series of 2,4-diamino-6,7-dimethoxyquinazoline derivatives.[1-3] In these studies, attention was concentrated on modification of the quinazoline 2-substituent in order to optimize both in vitro and in vivo performance, and as a result, doxazosin was selected for clinical evaluation.[4] This compound is a potent, highly

(1) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49.
(2) Alabaster, V. A.; Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 999.
(3) Campbell, S. F.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 1794.

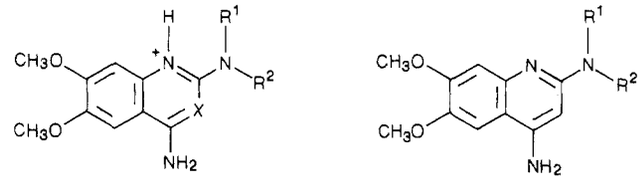
0022-2623/88/1831-1031$01.50/0

Scheme I[a]



[a] Route A: LDA/THF. Route B: $ZnCl_2$/DMA, reflux. Route F: (a) $CH_3C(OC_2H_5)_3$, H^+, 150 °C; (b) HNR^1R^2, H^+, 150 °C. Route G: $CH_3CONR^1R^2/POCl_3/CHCl_3$.

selective α_1-adrenoceptor antagonist which provides 24-h control of blood pressure in man after single daily administration.[5] In order to rationalize the exceptional α_1-adrenoceptor affinity displayed by doxazosin, prazosin, and related derivatives, it was proposed that the 2,4-diamino-6,7-dimethoxyquinazoline nucleus acted as a conformationally restricted, bioisosteric replacement for norepinephrine. A second key feature of this model was the suggestion that the N-1 protonated quinazoline (**1a**)

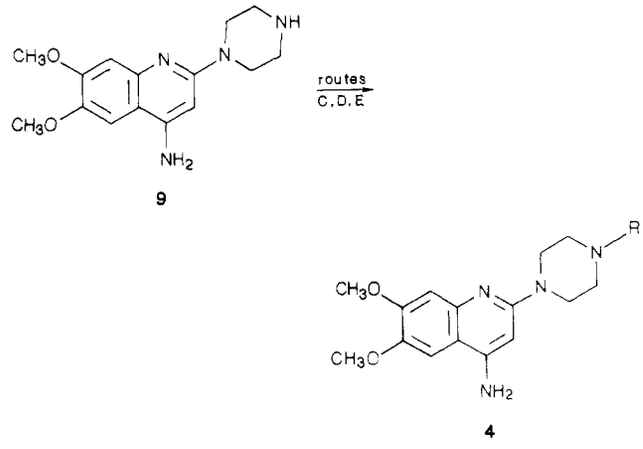


was exquisitely suited for effective charge-reinforced hydrogen bonding with a carboxylate counterion in the ground-state conformation of the α_1-adrenoceptor.[1,6,7] In order to substantiate these proposals, the quinazoline nucleus has now been replaced by isosteric heteroaromatic systems that allow critical assessment of the contribution of N-1 protonation to α_1-adrenoceptor binding interactions. In this paper, the synthesis and biological profile of a series of 2,4-diamino-6,7-dimethoxyquinoline derivatives (**2**) is presented while an accompanying paper deals with the corresponding isoquinoline analogues.[8]

Chemistry

In contrast to the quinazoline series, few diaminoquinolines of type **2** have been documented, and indeed, no convenient syntheses were available at the start of this program. For example, in our hands, selective aminolysis of various 2,4-dihalo-6,7-dimethoxyquinolines was unproductive since unduly harsh conditions were required and regiocontrol was poor.[9,10] An alternative strategy was therefore developed in which the quinoline ring system was constructed via a novel intramolecular cyclization of an acetamidine derivative **3**[11,12] (Scheme I). Ring closure can be initiated under basic (route A, **7**–**10**) or Lewis acid (route B, **11**) conditions and proceeds in high yield for both cases. Formation of the quinoline ring system was apparent from the NMR spectrum by the appearance of a new singlet at 6.0–6.2 ppm (C_3-H) with no sign of the amidine CH_3 (1.9–2.0 ppm) characteristic of starting material. No other products were detected besides **2**, since alternative, N-induced ring closure, to a quinazoline nucleus is not possible.[12] However, cyclization of **3** proceeded poorly when the NR^1R^2 moiety provided alternative sites for proton abstraction or Lewis acid coordination. For these cases, reaction of **9**, prepared via route A or by debenzylation of **11**, with an acid chloride (route C, **12**–**15**), an isocyanate (route D, 16–18), or a 2-chloropyrimidine (route E, **19**–**21**) provided the functionalized piperazines **4** (Scheme II).

Scheme II[a]



[a] Route C: R^3COCl. Route D: R^4NCO. Route E: Het-Cl.

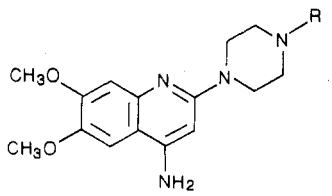
The intermediate acetamidines **3** were prepared by treatment of **5** with triethyl orthoformate to provide **6** followed by reaction with a secondary amine (route F). Alternatively, reaction of **5** with an imidinium chloride, conveniently synthesized by brief treatment of an N,N-disubstituted acetamide with phosphorus oxychloride, gave **3** directly (route G). For the preparation of **25**, treatment of 1-acetyl-4-(trifluoroacetyl)piperazine with phosphorus oxychloride gave only the acetimidinium intermediate and no reaction at the alternative, more electron deficient, carbonyl center was observed.

Results and Discussion

SAR for in Vitro α_1-Adrenoceptor Affinity. In Table III, in vitro binding data for various 2,4-diamino-6,7-dimethoxyquinoline derivatives at α_1- and α_2-adrenoceptors are presented. Moderate α_1-affinity (10^{-8} M) was displayed by the parent 2-dimethylamino derivative **7** (**2**, R^1,R^2 = CH_3), and activity was enhanced some 4-fold with

(4) Campbell, S. F.; Davey, M. J. *Drug Design Delivery* **1986**, *1*, 83.
(5) Torvik, D.; Madsbu, H.-P. *Br. J. Clin. Pharmacol.* **1986**, *21*, 69S.
(6) Campbell, S. F. *X-Ray Crystallography and Drug Action*; Horn, A. S., De Ranter, C. J., Eds.; Clarendon: Oxford, 1984; p 347.
(7) Campbell, S. F. *Second SCI-RSC Medicinal Chemistry Symposium*: Emmett, J. C., Ed.; Royal Society of Chemistry: Letchworth, 1984; p 18.
(8) Bordner, J. Campbell, S. F.; Palmer, M. J.; Tute, M. S. *J. Med. Chem.*, following paper in this issue.
(9) Den Hertog, H. J.; Buurman, D. J. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 841.
(10) Van der Lans, H. N. M.; den Hertog, H. J.; van Veldhuizen, A. *Tetrahedron Lett.* **1971**, 1875.
(11) Campbell, S. F.; Hardstone, J. D. Eur. Pat. Appl. 0100200, 1984.
(12) Campbell, S. F.; Hardstone, J. D.; Palmer, M. J. *Tetrahedron Lett.* **1984**, *25*, 4813.

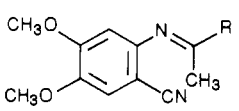
Table I. Synthetic Routes and Physical Data for Variation of the Piperazine Substituent



no.	R	route	mp, °C	yield, %	formula	anal.
9	H	A	260	54	$C_{15}H_{20}N_4O_2 \cdot 2HCl \cdot H_2O$	C, H, N
10	C_6H_5	A	288–290	27	$C_{21}H_{24}N_4O_2 \cdot 2HCl \cdot 0.5H_2O$	C, H, N
11	$CH_2C_6H_5$	B	260–263	51	$C_{22}H_{26}N_4O_2 \cdot 2HCl \cdot 1.5H_2O$	C, H,[a] N
12	$COCH_3$	C	215–220	32	$C_{17}H_{22}N_4O_3 \cdot HCl \cdot 1.5H_2O$	C, H, N
13	COC_6H_5	C	301	46	$C_{22}H_{24}N_4O_3 \cdot HCl \cdot 0.5H_2O$	C, H, N
14	CO-2-furyl	C	270	26	$C_{20}H_{22}N_4O_4 \cdot HCl \cdot 0.25H_2O$	C, H, N
15	CO-2-(1,4-benzodioxanyl)	C	201	16	$C_{24}H_{26}N_4O_5 \cdot HCl \cdot H_2O$	C, H, N
16	$CONHC_3H_7$	D	200 dec	26	$C_{19}H_{27}N_5O_3 \cdot HCl \cdot 0.5H_2O$	C,[b] H, N
17	$CONHCH_2CH{=}CH_2$	D	178–181 dec	50	$C_{19}H_{25}N_5O_3 \cdot H_2O$	C, H, N
18	$CONHC_6H_5$	D	235	19	$C_{22}H_{25}N_5O_3 \cdot 2HCl$	C, H, N
19	4-methylpyrimidin-2-yl	E	282–283	35	$C_{20}H_{24}N_6O_2 \cdot 2HCl \cdot CH_3OH$	C, H, N
20	4-ethoxypyrimidin-2-yl	E	267–269	55	$C_{21}H_{26}N_6O_3 \cdot HCL \cdot 2H_2O$	C,[c] H,[d] N
21	4-dimethylaminopyrimidin-2-yl	E	260–263	9	$C_{21}H_{27}N_7O_2 \cdot 2HCl \cdot 2H_2O$	C, H,[e] N

[a] H: calcd, 6.5; found, 5.9. [b] C: calcd, 54.5; found, 54.0. [c] C: calcd, 52.2; found, 51.7 [d] H: calcd, 6.5; found, 5.8. [e] H: calcd, 6.4; found, 5.8.

Table II. Physical Data for Amidine Derivatives Prepared by Route G



no.	R	mp, °C	yield, %	formula	anal.
22	$N(CH_3)_2$	94–96	80	$C_{13}H_{17}N_3O_2$	C, H, N
23	$N(CH_2)_5$[a]	oil	63	$C_{16}H_{21}N_3O_2$	
24	$N(CH_2CH_2)_2NC_6H_5$	108–109	68	$C_{21}H_{24}N_4O_2$	C, H, N
25	$N(CH_2CH_2)_2NCOCF_3$	136–138	75	$C_{17}H_{19}N_4O_3F_3$	C, H, N

[a] Characterized spectroscopically.

Table III. Binding and Antihypertensive Activities for 2,4-Diamino-6,7-dimethoxyquinoline Derivatives

	α-receptor binding affinity[a]		% reduction in SHR (n = 5) blood pressure,[e] dose: 3 mg/kg, po	
no.	α_1[b]	α_2[c]	1 h	4.5 h
7	11.37 ± 2.0	NA	12	11
8	2.93 ± 0.05	NA	6	6
9	30.06 ± 7.14	NA	11	14
10	1.72 ± 0.11	51.6 ± 5.3	8	24
11	NT	NT	8	10
12	1.17 ± 0.77	NA	4	7
13	0.49 ± 0.22	NA	19	19
14	0.14 ± 0.07	NA	32	25
15	0.81 ± 0.36	NA	6	13
16	0.44 ± 0.08	NA	3	8
17	0.29 ± 0.10	NA	15	17
18	0.34 ± 0.16	66.0 ± 2.7	20	25
19	0.63 ± 0.24	NA	10	8
20	0.42 ± 0.06	NA	19	22
21	0.46 ± 0.13	55.3 ± 2.2	16	19
prazosin	0.19 ± 0.02	4830 ± 1280[d]	24	15

[a] Rat brain homogenate preparation, all results are the means ± SEM of at least three experiments performed in triplicate. [b] K_i (nM) for displacement of [^{3}H]prazosin. [c] Percentage displacement of [^{3}H]clonidine at 10^{-6} M; NA indicates less than 50%; NT, not tested. [d] K_i (nM). [e] Falls in blood pressure below 10% are not physiologically significant.

the cyclized analogue **8** (**2**, $R^1,R^2 = (CH_2)_5$) although incorporation of an additional basic center (**9**) was detrimental. N-Phenylation (**10**) or N-acetylation (**12**) returned affinity into the nanomolar range, and further increases in activity could be achieved by introduction of aroyl (**13**) or heteroaroyl functions (**14**, **15**). Incorporation of a ureido system (**16**–**18**) or a substituted pyrimidine moiety also preserved affinity in the prazosin range. Compounds **18** and **21** showed very modest ability in displacing [^{3}H]clonidine from α_2-binding sites, but even so, the overall α_1–α_2-selectivity ratios for this quinoline series (**2**) are at least 10 000 and may even be greater.

Comparison of the binding data in Table III with results from previous SAR studies[1-3] shows that, in general, the 2,4-diamino-6,7-dimethoxyquinolines (**2**) display similarly high affinity and selectivity for α_1-adrenoceptors to their quinazoline counterparts. Thus, these quinoline and quinazoline systems appear to be recognized in a uniform fashion at the α_1-adrenoceptor with N-1 presumably playing a common role for both nucleii. Indeed, the poor α_1-adrenoceptor affinity displayed by a representative series of 1,3-diaminoisoquinoline derivatives confirms that isosteric relocation of the ring nitrogen atom is unacceptable.[8] Diaminoquinolines are more basic (vide infra) than the corresponding quinazoline analogues,[13] and protonation on N-1 will also be favored at physiological pH. Thus, the exceptional α_1-adrenoceptor affinity and selectivity displayed by both series are consistent with the proposal that the pharmacophores **1a** and **1b** are exquisitely suited to the receptor ground-state conformation.

At physiological pH, **14** (pK_a, 8.18 ± 0.03) will exist mainly (86%) as the N-1 protonated form whereas for prazosin (pK_a = 6.84 ± 0.04), approximately 20% protonation will occur. Thus **14** might be expected to display higher affinity than prazosin for α_1-adrenoceptors, and the data in Table III may support a trend in the expected direction. In addition, functional assays show that **14** is a highly potent (pA_2, 9.76 ± 0.26) competitive antagonist of the α_1-mediated vasoconstrictor action of norepinephrine[15] and is approximately 20 times more active

(13) For example, the pK_a's for 2,4-diaminoquinazoline and 2,4-diaminoquinoline are 7.96 and 9.40, respectively.[14]

(14) *Dissociation Constants of Organic Bases in Aqueous Solution*; Perrin, D. D., Ed.; Butterworth: Boston, 1965, 1972.

(15) Rabbit pulmonary artery.[3] Slopes: **14**, 1.20 ± 0.15 (n = 3); prazosin, 1.14 ± 0.31 (n = 4).

than prazosin ($pA_2 = 8.37 \pm 0.24$). The enhanced basicity of **14** may therefore be more important in functional, rather than binding, experiments where occupation of the α_1-adenoceptor active site requires efficient displacement of the norepinephrine cation.[16]

In conclusion, these SAR studies are consistent with the proposal that 2,4-diamino-6,7-dimethoxyquinazoline and -quinoline derivatives act as conformationally restricted bioisosteres of noradrenaline and that α_1-adrenoceptor recognition is additionally dependent on N-1 protonation.

SAR for in Vivo Antihypertensive Activity. All of the compounds in Table I and **7** and **8** were evaluated for antihypertensive activity after oral administration (3 mg/kg) to spontaneously hypertensive rats (SHR). Results for these compounds (Table III) are not strictly comparable with data previously reported for various quinazoline derivatives[1-3] because of differences in strain of rat employed, dosing regimens and time course of experiments. However, results obtained with prazosin under this revised protocol are included for reference. Moderate antihypertensive actvity was displayed by the simpler members of the series **7–9**, whereas N-phenylation (**10**) or N-acylation (**13, 14**) produced a marked improvement in both efficacy and duration of action. In particular, **14** displayed a superior overall profile to prazosin whereas **15** unexpectedly proved inferior to doxazosin (results not shown). However, while these single-dose experiments are useful for initial compound ranking, a more definite conclusion can only be reached following comparative dose–response studies. The propylurea (**16**) proved to be poorly active, but introduction of an alkenyl (**17**) or aryl (**18**) π-system substantially enhanced antihypertensive activity at both time points. Finally, the alkylpyrimidine derivative **19** had moderate effects on rat blood pressure, but both efficacy and duration of action were markedly improved in the ethoxy (**20**) and dimethylamino (**21**) analogues.

In summary, the results in Table III confirm that various 2,4-diamino-6,7-dimethoxyquinoline derivatives (**2**) are effective antihypertensive agents in spontaneously hypertensive rats, with efficacy and duration of action at least equivalent to prazosin. These observations are consistent with the high affinity and selectivity displayed by series **2** for postjunctional α_1-adrenoceptors.

Experimental Section

Chemistry. Melting points were determined in a Büchi apratus in glass capillary tubes and are uncorrected. Spectroscopic data for all compounds were recorded on Perkin-Elmer 257 (IR), AEI MS12 or VH 7070F (MS), Perkin-Elmer R12B, Varian XL 100, and Nicolet QE300 (NMR) instruments and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

Route A. 4-Amino-6,7-dimethoxy-2-piperidinoquinoline Hydrochloride Hemihydrate (8). *N*-(1-Piperidinoethylidene)-2-cyano-4,5-dimethoxyaniline (**23**, 0.65 g, 2.26 mmol) in THF (15 mL) was added dropwise to a stirred solution of LDA (2.6 mmol) [from *n*-BuLi in hexane (1.65 M, 1.58 mL) and diisopropylamine (0.26 g) in THF (10 mL) at −70 °C]. The resulting solution was stirred at −70 °C for 0.5 h and then allowed to attain room temperature overnight. The mixture was quenched with water (10 mL) and extracted with methylene chloride (3 × 20 mL), and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated. A sample (0.53 g) of the residue (0.65 g) was dissolved in methylene chloride/ethanol and treated with ethereal HCl. The product was collected and washed with ether to give 4-amino-6,7-dimethoxy-2-piperidinoquinoline hydrochloride hemihydrate (0.60 g, 98%): mp 279–280 °C; ^{1}H NMR (DMSO-d_6) δ 1.62 (6 H, s), 3.57 (4 H, s), 3.83 (3 H, s), 3.84 (3 H, s), 6.06 (1 H, s), 7.61 (2 H, s), 7.84 (2 H, br s). Anal. ($C_{16}H_{21}N_3O_2 \cdot HCl \cdot 0.5H_2O$) C, H, N.

4-Amino-6,7-dimethoxy-2-(dimethylamino)quinoline hydrochloride hemihydrate (**7**) (76%) was prepared by the same method: mp 294–295 °C; ^{1}H NMR (DMSO-d_6) δ 3.16 (6 H, s), 3.83 (3 H, s), 3.85 (3 H, s), 5.88 (1 H, s), 7.60 (2 H, s), 7.75 (2 H, br s). Anal. ($C_{13}H_{17}N_3O_2 \cdot HCl \cdot 0.5H_2O$) C, H, N.

Route B. 4-Amino-6,7-dimethoxy-2-(4-benzylpiperazin-1-yl)quinoline Dihydrochloride Sesquihydrate (11). *N*-[1-(4-Benzylpiperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline (**26**, 13.5 g, 26 mmol) and zinc chloride (4.86 g, 36 mmol) in *N*,*N*-dimethylacetamide (90 mL) were stirred under reflux for 2.5 h; further zinc chloride (0.50 g, 0.20 g) was added after 0.5 and 1.5 h, respectively. The mixture was cooled and treated with ether (700 mL, 2 × 100 mL), and the supernatant was discarded each time. The residual tar was then treated with NaOH solution (2 N, 100 mL) and dichloromethane (100 mL) and the mixture was stirred at room temperature for 0.1 h. The organic layer was separated, the aqueous phase was extracted with dichloromethane, and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue (13.0 g) was purified by chromatography on silica gel (250 g), eluting with chloroform/methanol (100:0 → 88:12). A sample of the pure product (6.95 g, 51%) was taken up in ethanol, treated with ethereal HCl, and evaporated. The residue was recrystallized from methanol to give 4-amino-6,7-dimethoxy-2-(4-benzylpiperazin-1-yl)quinoline dihydrochloride sesquihydrate: mp 260–263 °C; ^{1}H NMR (TFA-*d*) δ 4.0 (8 h, br s), 4.1 (6 H, s), 4.5 (2 H, s), 7.3 (1 H, s), 7.4 (1 H, s), 7.5 (5 H, s). Anal. ($C_{22}H_{26}N_4O_2 \cdot 2HCl \cdot 1.5H_2O$) C, N; H: calcd, 6.5; found, 5.9.

Debenzylation (H_2/Pd/C) of the above product (6.2 g, 13 mmol) in ethanol (300 mL) at 50 psi/50 °C followed by standard workup procedure gave **9** (2.42 g, 65%), identical with the product from route A: ^{1}H NMR (DMSO-d_6) δ 3.25 (4 H, m), 3.85 (10 H, m), 6.06 (1 H, s), 7.64 (2 H, s), 8.02 (2 H, br s), 9.47 (2 H, br s).

Route C. 4-Amino-2-(4-benzoylpiperazin-1-yl)-6,7-dimethoxyquinoline Hydrochloride Hemihydrate (13). A solution of benzoyl chloride (0.16 g, 1.15 mmol) in chloroform (5 mL) was added dropwise to a stirred solution of 4-amino-6,7-dimethoxy-2-piperazin-1-yl quinoline (**9**, 0.30 g, 1.04 mmol) in chloroform (25 mL) with triethylamine (0.21 g) at 10–15 °C. The reaction was stirred at 10–15 °C for 0.5 h and then allowed to attain room temperature and stirred overnight. Na_2CO_3 solution 10%, 10 mL) was then added at 10–15 °C, and the organic layer was separated. The aqueous phase was extracted with chloroform (2 × 30 mL), and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on silica gel (20 g) by eluting with chloroform/methanol; (100:0 → 94:6). The pure product was taken up in chloroform, treated with ethereal HCl, and evaporated. The residue was recrystallized from methanol to give 4-amino-2-(4-benzoylpiperazin-1-yl)-6,7-dimethoxyquinoline hydrochloride hemihydrate (254 mg, 46%): mp 301 °C; ^{1}H NMR (DMSO-d_6) δ 3.65 (8 H, br s), 3.84 (3 H, s), 3.86 (3 H, s), 6.01 (1 H, s), 7.46 (6 H, m), 7.61 (1 H, s), 7.90 (2 H, br s). Anal. ($C_{22}H_{24}N_4O_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

Route D. 4-Amino-6,7-dimethoxy-2-[4-(*N*-3-propenylcarbamoyl)piperazin-1-yl]quinoline Hydrate (17). 3-Propenyl isocyanate (0.065 g, 0.77 mmol) in chloroform (5 mL) was added dropwise to a stirred solution of 4-amino-6,7-dimethoxy-2-piperazin-1-ylquinoline (**9**, 0.20 g, 0.7 mmol) in chloroform (20 mL) with triethylamine (0.14 g) at 10 °C. The reaction mixture was allowed to attain room temperature and stirred for 2 h. Na_2CO_3 solution (10% 10 mL) was then added, and the chloroform layer was separated. The aqueous phase was extracted with chloroform, and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel (25 g), eluting with methylene chloride/methanol (100:0 → 88:12). The product was recrystallized from ethyl acetate/hexane to give 4-amino-6,7-dimethoxy-2-[4-(*N*-3-propenylcarbamoyl)piperazin-1-yl]quinoline hydrate (0.135 g, 50%): mp 177–181 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.43 (8 H, m), 3.68 (2 H, s), 3.81 (3 H, s), 3.82 (3 H, s), 5.06 (2 H, m), 5.82 (1 H, m), 6.05 (1 H, s), 6.53 (2 H, br s), 6.75 (1 H, br t), 6.97 (1 H, s), 7.36 (1 H, s). Anal. ($C_{19}H_{25}N_5O_3 \cdot H_2O$) C, H, N.

(16) Norepinephrine: pK_a, 9.6, approximately 95% protonated at physiological pH.

Route E. 4-Amino-6,7-dimethoxy-2-[4-(4-ethoxypyrimidin-2-yl)piperazin-1-yl]quinoline Hydrochloride Dihydrate (20). 4-Amino-6,7-dimethoxy-2-piperazin-1-ylquinoline (**9**, 0.2 g, 0.7 mmol) and 2-chloro-4-ethoxypyrimidine (0.125 g, 0.78 mmol) in 1-butanol (20 mL) were stirred under reflux for 18 h. The reaction mixture was allowed to cool and the resulting precipitate was collected and washed with ether. The solid was recrystallized from ethanol to give 4-amino-6,7-dimethoxy-2-[4-(4-ethoxypyrimidin-2-yl)piperazin-1-yl]quinoline hydrochloride dihydrate (0.185 g, 55%): mp 267–269 °C; ^{1}H NMR (DMSO-d_6) δ 1.31 (3 H, t), 3.68 (4 H, m), 3.84 (3 H, s), 3.87 (3 H, s), 3.91 (4 H, m), 4.35 (2 H, q), 6.5 (1 H, s), 6.13 (1 H, d), 7.48 (1 H, s), 7.61 (1 H, s), 7.91 (2 H, br s), 8.11 (1 H, d). Anal. ($C_{21}H_{26}N_6O_3$·HCl·2H_2O) N; C: calcd, 52.2; found, 51.7; H: calcd, 6.5; found, 5.8.

Route F. *N*-[1-(4-Benzylpiperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline Dihydrochloride Hydrate (26). (a) 2-Cyano-4,5-dimethoxyaniline[17] (20 g, 112 mmol), a trace of the corresponding HCl salt (0.20 g), and triethyl orthoacetate (35.4 g, 218 mmol) were stirred at 150 °C for 1 h with removal of ethanol by distillation. The mixture was then evaporated, and the crude residue of ethyl *N*-(2-cyano-4,5-dimethoxyphenyl)acetimidate (27.95 g, 100%) was used directly.

(b) The crude product from above (26.9 g, 108 mmol), *N*-benzylpiperazine (21 g, 119 mmol), and *p*-toluenesulfonic acid (0.10 g) were stirred together at 150 °C for 2 h under a slight pressure reduction. On cooling, the residue was taken up in dichloromethane and extracted with dilute HCl (2 N, 2 × 200 mL). The acid layer was adjusted to pH 4 (5 N, NaOH) and extracted with methylene chloride (2 × 200 mL), and the extracts were discarded. The aqueous phase was basified to pH 9 and extracted with methylene chloride (3 × 200 mL), and the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on silica gel (400 g) eluting with dichloromethane/methanol (100:0 → 98:2). A sample of the product (11.68 g, 28%) was taken up in ethyl acetate/methanol and treated with ethereal HCl, and the pecipitate was triturated with ether to give *N*-[1-(4-benzylpiperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline dihydrochloride hydrate, mp 181–182 °C. Anal. ($C_{22}H_{26}N_4O_2$·2HCl·H_2O) C, H, N.

Route G. *N*-[1-(Dimethylamino)ethylidene]-2-cyano-4,5-dimethoxyaniline (22). Phosphorus oxychloride (1.0 mL) was added to a stirred solution of *N,N*-dimethylacetamide (2.62 g, 30 mmol) in chloroform (10 mL) at room temperature. The mixture was stirred for 0.1 h, 2-cyano-4,5-dimethoxyaniline (1.78 g, 10 mmol) added, and the reaction mixture was stirred under reflux for 4 h. The mixture was cooled, poured into ice, and extracted with chloroform, and the organic phase was discarded. The aqueous phase was basified (NaOH) and extracted with chloroform, and the combined extracts washed with water, dried (Na_2SO_4), and evaporated. A sample of the oily residue (2.0 g, 80%) was recrystallized from diisopropyl ether to give *N*-[1-(dimethylamino)ethylidene]-2-cyano-4,5-dimethoxyaniline: mp 94–96 °C; ^{1}H NMR (DMSO-d_6) δ 1.85 (3 H, s), 2.98 (6 H, s), 3.70 (3 H, s), 3.74 (3 H, s), 6.33 (1 H, s), 7.07 (1 H, s). Anal. ($C_{13}H_{17}N_3O_2$) C, H, N.

***N*-[1-(Piperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline (27).** A solution of *N*-[1-[4-(trifluoroacetyl)piperazin-1-yl]ethylidene]-2-cyano-4,5-dimethoxyaniline (**25**, 29.5 g, 76.7 mmol) in methanol (400 mL) and sodium hydroxide (2 N, 100 mL) was stirred at room temperature for 3 h. The mixture was then evaporated, the residue was taken up in chloroform (350 mL), and the organic solution was washed with water and dried (Na_2SO_4). Evaporation provided a crude residue of *N*-[1-(piperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline (23 g, 100%), which was characterized spectroscopically and was used without further purification.

2-Chloro-4-ethoxypyrimidine, mp 36–37 °C, was prepared by reaction of 2,4-dichloropyrimidine with sodium ethoxide.[18] Anal. (C_6H_7Cl·N_2O) C, H, N.

pKa values were determined in aqueous solution by spectrometry.

Biology. Radioligand Binding.[19,20] Rat brain membranes were prepared by homogenizing fresh rat brain (minus cerebellum) in ice-cold 50 mM Tris·HCl buffer, pH 7.6, with a Brinkman polytron (setting 6 for 10 s). The resultant homogenate was centrifuged twice at 48000*g* for 0.16 h at 5 °C. The final pellet was resuspended in a small volume of ice-cold buffer and stored at −70 °C for up to 4 weeks. The frozen membrane preparation was thawed and diluted to give a 1 mg/mL protein concentration immediately before use.

Standard displacement assays were run with either 0.7 nM [^{3}H]clonidine (sp act. 27.2 Ci/mmol) or 0.15 nM [^{3}H]prazosin (sp act. 80–88 Ci/mmol). Triplicate assay tubes contained ^{3}H-labeled ligand, various concentrations of the compound being investigated, and 800 μL of tissue homogenate to give a final volume of 1 mL. The reaction was initiated by the addition of tissue and continued for 30 min (clonidine) and 20 min (prazosin) at 25 °C. The reaction was terminated by rapid filtration through Whatman GF/B glass fiber filters under vacuum. Filters were washed with 3 × 5-mL aliquots of ice-cold buffer and dried under vacuum. The entrapped radioactivity was counted in a liquid scintillation counter (L.K.B. counting efficiency 40%) after the addition of 6 mL of Instagel. Specific binding was defined as the difference between sample with and without 10 μM phentolamine for both assays. Data from binding assays were plotted as log concentration vs percent inhibition and analyzed by computerized curve-fitting techniques. The IC_{50} values obtained were used to calculate apparent inhibition constants from the following equation:

$$K_i = IC_{50}/(1 + [C]/K_D)$$

where [C] is the concentration of ligand used and K_D is its receptor dissociation constant (K_D values for prazosin and clonidine are 0.2 and 3 nM, respectively). All results are the mean ± SEM of at least three separate experiments performed in triplicate. Binding data were fitted to a single-site model and all pseudo Hill coefficients were near unity.

Antihypertensive Activity. Compounds were administered orally (3 mg/kg) by gavage to groups of five spontaneously hypertensive Okamoto rats. Recordings of systolic blood pressure and heart rates were obtained by using an inflatable tail cuff and a variable capacitance transducer connected to an oscilloscope. To permit accurate detection of the pulse in the tail artery, the rats were placed in a warm box at 33 °C for 20–30 min prior to blood pressure measurements. Blood pressure and heart rate were recorded predose, then at 1, 2, and 4.5 h following oral administration, but only results at 1 and 4.5 h are reported in Table III. When saline solution was administered to a group of control rats (n = 10), blood pressure fell by 7 ± 2% over the 6-h period.

Acknowledgment. We gratefully thank Drs. V. A. Alabaster and P. J. Bungay for biological results, D. J. Greenan for pK_a data, and K. A. Bevan for technical assistance.

(17) McKee, R. L.; McKee, M. K.; Bost, R. W. *J. Am. Chem. Soc.* **1946**, *68*, 1902.
(18) Kenner, G. W.; Reese, C. B.; Todd, A. R. *J. Chem. Soc.* **1955**, 855.
(19) Greengrass, P.; Bemner, R. *Eur. J. Pharmacol.* **1979**, *55*, 323.
(20) Greenberg, D. A.; U'Prichard, D. C.; Snyder, S. H. *Life Sci.* **1976**, *19*, 69.