2,4-Diamino-6,7-dimethoxyquinazolines. 2. 2-(4-Carbamoylpiperidino) Derivatives as α_1-Adrenoceptor Antagonists and Antihypertensive Agents

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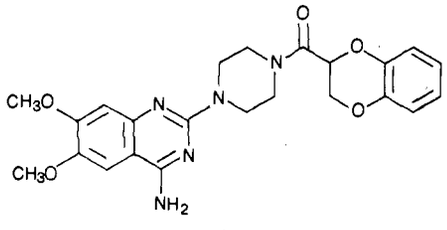
A series of 4-amino-2-(4-carbamoylpiperidino)-6,7-dimethoxyquinazolines (**2**) were synthesized and evaluated for α-adrenoceptor affinity and antihypertensive activity. These compounds displayed high binding affinity (K_i, 10^{-9}–10^{-10} M) and selectivity for α_1-adrenoceptors in vitro, and **12**, **14**, **21**–**26**, and **29** showed similar potency to prazosin. Compounds **26** and **28** were also shown to be competitive antagonists of the postjunctional, vasoconstrictor action of norepinephrine with no significant activity at prejunctional α_2-sites. The high binding affinity for series **2** is rationalized in terms of enhanced basicity of the quinazoline nucleus (pK_a's: **12**, 7.38; **26**, 7.53; prazosin, 6.8) and hydrophobic interactions of the carbamoyl substituents. Molecular mechanics calculations and computer-assisted superimposition suggest that the quinazoline 2-substituents in prazosin and **2** occupy the α_1-adrenoceptor site in different manners. Antihypertensive activity was evaluated after oral administration (5 mg/kg) to spontaneously hypertensive rats, and **11**, **15**, **21**, **22**, and **26** displayed sustained prazosin-like efficacy at the 6-h time point. The high α_1-adrenoceptor affinity demonstrated by series **2** in vitro suggests that these marked, and prolonged, falls in blood pressure result from selective blockade of the α_1-mediated vasoconstrictor effects of norepinephrine.

Recently, the synthesis and pharmacological properties of various 4-amino-2-[4-(1,4-benzodioxan-2-yl-carbonyl)-piperazin-1-yl]-6,7-dimethoxyquinazoline derivatives were described.[1] These compounds are selective α_1-adrenoceptor antagonists and potent antihypertensive agents, and doxazosin (**1**) is currently in late-stage phase III clinical trials.[2] As part of a general program to define structure–activity relationships (SARs) with respect to the role of the quinazoline 2-substituent, the preparation and biological profiles of a series of 2-(4-carbamoylpiperidines), **2**, are now reported. In these compounds, the relatively



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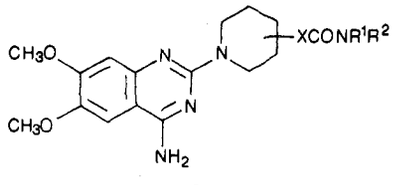

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rigid carboxamide moiety common to doxazosin and prazosin is replaced by an isomeric system (**2**, X = direct bond) in which the carbonyl function can adopt a wider range of spatial orientations. Moreover, by variation of the linking unit X, the optimum location of the carbonyl group relative to the piperidine ring can be established. Finally, modification of the carboxamide substituents (**2**, R_1, R_2) allows the steric requirements of the α_1-adrenoceptor to be probed in quite different regions from those accessible to doxazosin and prazosin. The objectives of these studies were to identify novel, selective α_1-adrenoceptor antagonists with prolonged duration of antihypertensive activity after oral administration.[3]

Chemistry. All compounds for pharmacological testing were prepared by either of the three approaches shown in Scheme I.[5] In route A, a 3- or 4-piperidinecarboxamide was reacted with 4-amino-2-chloro-6,7-dimethoxyquinazoline (**3**) in butanol under reflux, and the products **10**, **12**, **13**, **16**–**19**, **21**–**23**, **26**, and **30** were isolated directly. Alternatively, a 4-amino-6,7-dimethoxy-2-piperidinoquinazoline carboxylic acid derivative, **4**, was condensed with an appropriate amine in the presence of dicyclohexylcarbodiimide and *N*-hydroxysuccinimide (route B; **15**, **27**) or carbonyldiimidazole (route C; **11**, **14**, **20**, **24**, **25**, **28**, **29**). Final compounds were generally characterized as hydrochloride salts, although several proved to be hygroscopic as confirmed by elemental analysis (Table I).

Most of the intermediate piperidinecarboxamides, **5**, employed in route A were prepared by reduction of the corresponding pyridine derivatives **6** (route D, Scheme II) or by reaction of 1-[(phenylmethoxy)carbonyl]-4-piperidinecarbonyl chloride (**7**) with an appropriate amine followed by reductive (H_2/Pd) or acidic (HBr) cleavage of the protecting group (route E, Scheme II). Finally, alkylation of the sodium salt of 1-(phenylmethyl)-4-hydroxypiperidine (**8**) with chloroacetic acid followed by reaction of the acid chloride with butylamine and subsequent deprotection provided the (4-piperidinyloxy)acetamide derivative **9** (route F, Scheme III).

Results and Discussion

SARs for in Vitro α-Adrenoceptor Affinity. Table II summarizes the effects of variation of the piperidinecarboxamide moiety in **2** on α_1-adrenoceptor binding affinity. The primary carboxamide **10** displayed activity in the nanomolar range, but potency could be enhanced further by both alkyl (**12**, **15**) and cycloalkyl (**14**) substituents. Introduction of oxygen functionality into the alkyl chain (**16**, **17**) or elaboration to the tertiary amides **18** and **20** was tolerated, but provided no increase in binding affinity. Movement of the carboxamide function to the 3-position was detrimental, producing a 13-fold (cf. **12**, **13**) or 100-fold (cf. **18**, **19**) decrease in potency. Incorporation of an aromatic moiety into the carboxamide unit proved to be particularly beneficial (**21**–**25**), and the phenylethyl derivative **24** was approximately twice as potent as prazosin. Moreover, the 16-fold difference in

(1) Campbell, S. F.; Davey, M. J.; Hardstone, D. J.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49.
(2) Campbell, S. F.; Davey, M. J. *Drug Design and Delivery* **1986**, *1*, 83.
(3) A recent report[4] on related quinazoline derivatives provided limited in vivo data and no information on SARs for α_1-adrenoceptor affinity.
(4) Honkanen, E.; Pippuri, A.; Kairisalo, P.; Nore, P.; Karppanen, H.; Paakkari, I. *J. Med. Chem.* **1983**, *26*, 1433.
(5) Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. UK Patent 2,021,108B.

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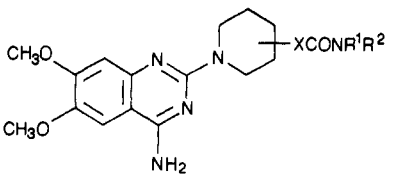
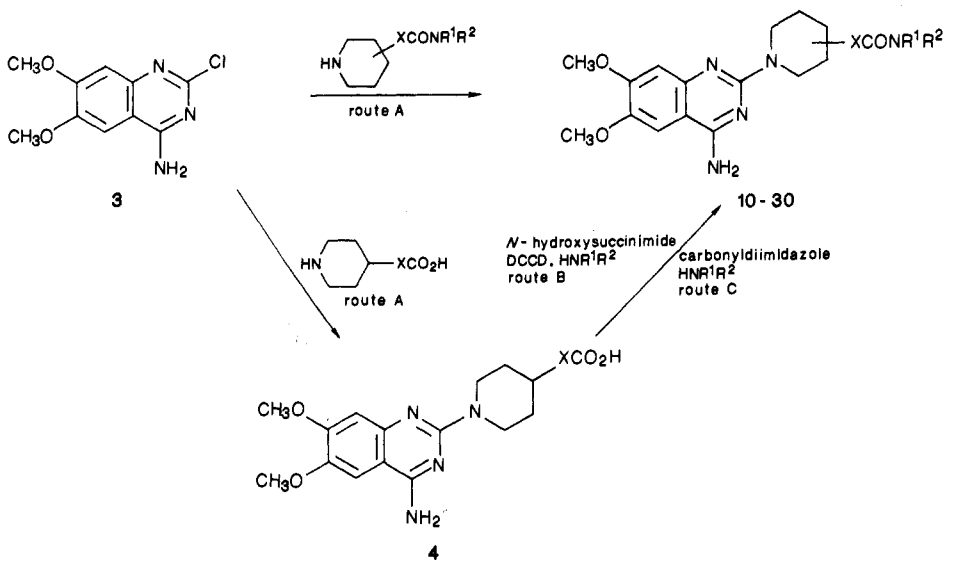
Table I. Synthetic Routes and Physical Data for Variation of Groups X, R^1, and R^2



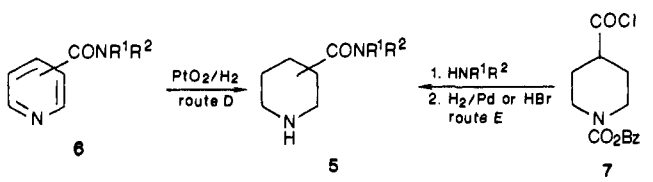
no.	X	piperidine substituent	R^1, R^2	route	mp, °C	formula	analysis
10		4	H, H	A	270–271	$C_{16}H_{21}N_5O_3$·HCl	C, H, N
11		4	H, C_2H_5	C	287–288	$C_{18}H_{25}N_5O_3$·HCl·0.5H_2O	C, H, N
12		4	H, C_4H_9	A	263–264	$C_{20}H_{29}N_5O_3$·HCl	C, H, N
13		3	H, *n*-C_4H_9	A	239–240	$C_{20}H_{29}N_5O_3$·HCl·0.5H_2O	C, H, N
14		4	H, c-C_5H_9	C	263–264	$C_{21}H_{29}N_5O_3$·HCl·H_2O	C, H, N
15		4	H, CH_2-c-C_3H_5	B	270–272	$C_{20}H_{27}N_5O_3$·HCl·0.5H_2O	C, H, N
16		4	H, $(CH_2)_2OH$[a]	A	279–281	$C_{18}H_{25}N_5O_4$·HCl	C, H
17		4	H, $(CH_2)_2OCH_3$	A	276–277	$C_{19}H_{27}N_5O_4$·HCl	C, H, N
18		4	C_2H_5, C_2H_5	A	283–284	$C_{20}H_{29}N_5O_3$·HCl·0.5H_2O	C, H, N
19		3	C_2H_5, C_2H_5	A	282	$C_{20}H_{29}N_5O_3$·HCl	C, H, N
20		4	$(CH_2CH_2)_2O$	C	>300	$C_{20}H_{27}N_5O_4$·HCl	C, H, N
21		4	H, C_6H_5	A	263–266	$C_{22}H_{25}N_5O_3$·HCl	C, H, N
22		4	H, $CH_2C_6H_5$	A	263–264	$C_{23}H_{27}N_5O_3$·HCl	C, H, N
23		4	CH_3, $CH_2C_6H_5$	A	209–211	$C_{24}H_{29}N_5O_3$·HCl·H_2O	C, H, N
24		4	H, $(CH_2)_2C_6H_5$	C	284–285	$C_{24}H_{29}N_5O_3$·HCl	C, H, N
25		4	H, $(CH_2)_2OC_6H_5$	C	210–212	$C_{24}H_{29}N_5O_4$	C, H, N
26	CH_2	4	H, C_3H_7	A	248–250	$C_{20}H_{29}N_5O_3$·HCl	C, H, N
27	CH_2	4	H, *n*-C_4H_9	B	238–239	$C_{21}H_{31}N_5O_3$·HCl·0.5H_2O	C, H, N
28	CH_2	4	H, CH_2-c-C_3H_5	C	247–249	$C_{21}H_{29}N_5O_3$·HCl·0.5H_2O	C, H, N
29	$(CH_2)_2$	4	H, *n*-C_4H_9	C	219–220	$C_{22}H_{33}N_5O_3$·HCl	C, H, N
30	OCH_2	4	H, *n*-C_4H_9	A	232–234	$C_{21}H_{31}N_5O_4$·HCl	C, H, N

[a] N: calcd, 17.0; found, 17.6.

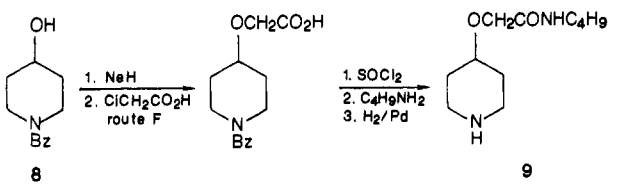
Scheme I



Scheme II



Scheme III



activity between **11** and **24** corresponds to a 1.68 kcal/mol increase in binding energy, which may support a specific hydrophobic interaction between the aromatic ring and the receptor protein.[6] Separation of the carboxamide moiety from the piperidine ring by alkyl or alkoxyalkyl bridges of varying lengths (**26–30**) had only minor influence on α_1-adrenoceptor activity.

Some of the quinazoline derivatives in Table II also displayed affinity for α_2-adrenoceptor binding sites, but at a dose level (10^{-6} M) some 1000–10 000-fold higher than those required for α_1-adrenoceptor activity. Thus, these compounds still display overwhelming α_1/α_2-selectivity ratios, similar to prazosin, and such weak α_2-receptor

(6) For a review on hydrophobic interactions, see: Fersht, A. *Enzyme Structure and Mechanism*; W. H. Freeman: 1985; p 299.

Table II. Binding and Antihypertensive Activities for 4-Amino-2-(4-carbamoyl)piperidino-6,7-dimethoxyquinazoline Derivatives

	α-receptor binding affinity		% reduction in SHR blood pressure[d] (dose, 5 mg/kg, po)	
compd	α_1[a]	α_2[b]	1 h	6 h
10	1.46 ± 0.49	55.6 ± 4.2	10	4
11	1.64 ± 0.25	NA	15	30
12	0.67 ± 0.20	62.7 ± 3.9	18	18
13	8.25 ± 1.81	NA	3	9
14	0.63 ± 0.05	NA	11	13
15	0.90 ± 0.06	NA	13	24
16	1.73 ± 0.42	NA	3	5[e]
17	1.13 ± 0.21	NA	3	19
18	1.11 ± 0.49	NA	20	23
19	116.73 ± 49.81	NA	16	16[e]
20	1.14 ± 0.37	NA	12	17
21	0.47 ± 0.18	NA	12	25
22	0.22 ± 0.03	71.4 ± 3.5	15	25
23	0.20 ± 0.09	68.1 ± 2.6	25	16
24	0.10 ± 0.04	62.1 ± 1.6	17	21
25	0.42 ± 0.05	56.0 ± 1.3	7	10
26	0.65 ± 0.33	54.8 ± 2.4	25	29
27	1.40 ± 0.34	53.9 ± 2.1	9	12
28	1.08 ± 0.27	53.3 ± 1.9	15	18
29	0.47 ± 0.25	64.7 ± 3.7	6	9
30	0.79 ± 0.19	61.3 ± 3.0	14	12
prazosin	0.19 ± 0.02	4830 ± 1280[c]	33	29

[a] K_i (nM) for displacement of [^{3}H]prazosin. [b] Percentage displacement of [^{3}H]clonidine at 10^{-6} M; NA indicates less than 50%. [c] K_i (nM). [d] Falls in blood pressure below 10% are not significant. [e] 4-h time point.

Table III. Functional α-Antagonist Activity for **26**, **28**, and Prazosin against Norepinephrine in the Rabbit Aorta and Rabbit Pulmonary Artery[7,8]

compound	pA_2 (slope)	EC_{40}[b] (post)	EC_{40}[b] (pre)
26	7.42[a] (0.80)	18[c]	NA[e]
28	7.25[a] (0.80)	97[c]	NA[e]
prazosin	8.0[a] (0.80)	4.5[d]	1300

[a] $n = 4$. [b] EC_{40} (pre) is defined as the concentration (nM) of the compound producing a 40% increase in [^{3}H] overflow and EC_{40} (post) as the concentration (nM) producing a 40% reduction in contractile response. [c] $n = 2$. [d] $n = 6$. [e] NA indicates no activity at 10^{-5} M.

binding affinity would be of little pharmacological significance (vide infra).

Functional α-antagonist activity against norepinephrine was determined for selected compounds from Table II in the rabbit aorta and rabbit pulmonary artery.[7,8] Like prazosin, **26** and **28** proved to be competitive antagonists of the postjunctional, α_1-mediated vasoconstrictor action of norepinephrine (Table III). Potency differences were roughly those expected from α_1-binding studies, although the EC_{40} (post) for **28** was perhaps threefold higher than anticipated. Interestingly, neither **26** nor **28** showed any activity at the prejunctional α_2-sites which modulate transmitter release,[9] despite displaying weak α_2-binding affinity.

Thus, the quinazoline derivatives in Table II display high affinity and selectivity for α_1-adrenoceptors, and several compounds (**12**, **14**, **21–26**, **29**) show similar potency to prazosin. These results, and the functional data in Table III, confirm that compounds of general structure **2**

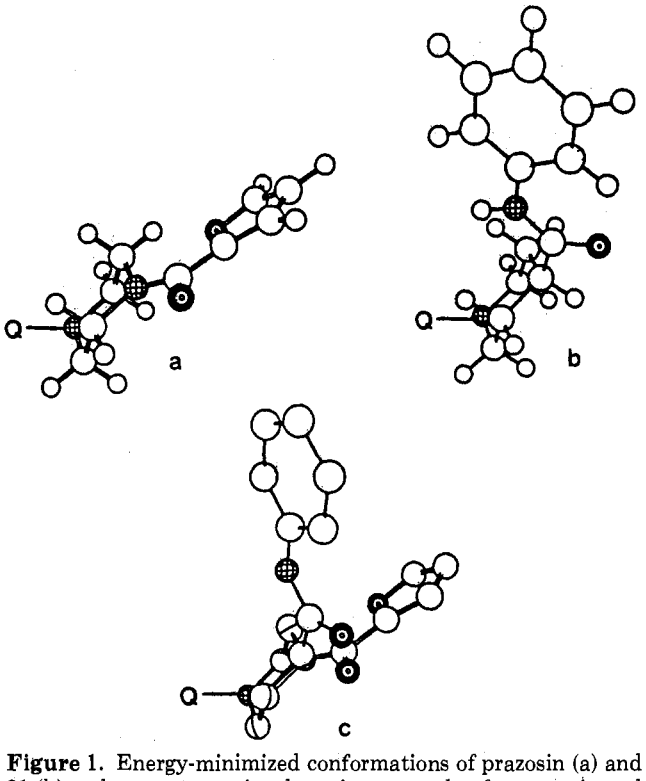
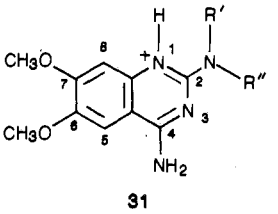


Figure 1. Energy-minimized conformations of prazosin (a) and **21** (b) and computer-assisted maximum overlap for prazosin and **21** (c, hydrogen atoms ommitted); Q = 4-amino-6,7-dimethoxyquinazolin-2-yl.

compete effectively with either prazosin or norepinephrine at the α_1-adrenoceptor. Previously,[1,10,11] it was suggested that the key pharmacophore for initial α_1-receptor recognition by 2,4-diamino-6,7-dimethoxyquinazoline derivatives was the N-1 protonated species **31**, but that modification



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of the 2-substituent (NR'R") could also have an important influence on both in vitro and in vivo activity. For series **2**, there is an overall increase in basicity compared to that of prazosin (pK_a's: **12**, 7.38; **26**, 7.53; prazosin, 6.8) and a greater proportion of the protonated species **31** will be present at physiological pH (**12**, 47%; **26**, 56%; prazosin, 25%). A priori, enhanced α_1-adrenoceptor binding affinity would therefore be expected, but the role of the various carboxamide moieties in **2** must also be taken into account. X-ray studies[1,12] show that the tertiary carboxamide function common to prazosin and doxazosin is essentially planar (Figure 1a) and the calculated[13] rotational barrier (ca. 22 kcal/mol) implies substantial rigidity. No x-ray

(7) Su, C.; Bevan, J. A. *J. Pharmacol. Exp. Ther.* **1970**, *172*, 62.
(8) Starke, K.; Endo, T.; Taube, H. D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1975**, *291*, 55.
(9) Langer, S. Z. *Pharmacol. Rev.* **1981**, *32*, 337.
(10) Campbell, S. F. *X-ray Crystallography and Drug Action* Horn, A. S., De Ranter, C. J., Eds.; Clarendon: Oxford, 1984; p 347.
(11) Campbell, S. F. *Second SCI-RSC Medicinal Chemistry Symposium*; Emmett, J. C., Ed.; Royal Society of Chemistry: 1984, p 18.
(12) J. Bordner, unpublished results.
(13) All calculations were carried out under appropriate CHEMLAB routines. Rigid rotations were performed; no relaxation of bond lengths or angles was attempted.

data appear to be available for 4-carbamoylpiperidine derivatives, but molecular mechanics calculations[13] show that the carbonyl function prefers to be orthogonal to the ring (Figure 1b),[14] although the barrier to free rotation is relatively low (<3.6 kcal/mol). Even so, orientation of this carbonyl function into a prazosin-like location is not possible, and computer-assisted superimposition shows that at closest approach[15] the two oxygen atoms are still 0.9 Å apart, with the carbonyl π systems almost perpendicular to each other (Figure 1c). It therefore appears unlikely that these carbonyl groups play identical roles on the receptor, and, indeed, the similar α_1-adrenoceptor binding affinities displayed by **12**, **27**, **29**, and **30** imply that the location of the latter carbonyl function is of only minor importance for series **2**. Thus, enhanced basicity of the quinazoline nucleus and hydrophobic interactions of the carboxamide substituents (R^1 R^2) appear to dominate, as for example in **21–25**. A major contribution to binding energy presumably derives from the entropy gain as water molecules are driven from the receptor site.[16] The carboxamido substituent in **2** may therefore occupy a relatively open area on the α_1-adrenoceptor, although the reduced binding affinity displayed by the 3-piperidinecarboxamides (**13**,[17] **19**) suggests marked regio and steric constraints.

SARs for in Vivo Antihypertensive Activity. The compounds listed in Table I were tested for antihypertensive activity after oral administration (5 mg/kg) to spontaneously hypertensive rats (SHR) (Table II). Results are expressed as percentage reductions in blood pressure after 1 and 6 h so that both efficacy and duration of action can be compared. Despite high α_1-adrenoceptor affinity in vitro, the primary carboxamide **10** was only poorly active in vivo, possibly due to rapid metabolic degradation to the corresponding carboxylic acid. However, N-alkylation led to a marked improvement in antihypertensive efficacy, and several compounds (**11**, **15**, **21**, **22**, **24**) displayed substantial activity (>20%) at the 6-h time point. Disubstituted derivatives **18** and **20** also displayed a favorable profile although the N-methylated derivative **23** showed a shorter duration of action than **22**. Movement of the carboxamide function to the piperidine 3-position (**13**, **19**) proved to be detrimental, in agreement with reduced α_1-adrenoceptor binding affinity. However, incorporation of a methylene bridge between the piperidine ring and the amide moiety (**26**) was particularly beneficial for both efficacy and duration of action although, unexpectedly, this profile was not maintained in the higher homologue **27**. Insertion of an ethylene or methyleneoxy linkage (**29**, **30**) was not advantageous.

These results demonstrate that various 2-[4-(*N*-substituted-carbamoyl)piperidino]quinazoline derivatives **2** possess marked antihypertensive activity in SHR after oral administration and in particular, **11**, **15**, **21**, **22**, and **26** display sustained, prazosin-like efficacy at the 6-h time point. The high α_1-adrenoceptor affinity demonstrated by this quinazoline series in vitro suggests that these marked, and prolonged, falls in blood pressure result from selective blockade of the α_1-mediated vasoconstrictor effects of norepinephrine.[18]

(14) Compound **21** was selected for the closest structural similarity to prazosin.
(15) Rotation of 45° about the carbonyl–piperidine linkage. This conformation is 2.4 kcal/mol above the global minimum (b).
(16) Andrews, P. *Trends Pharmacol. Sci.* **1986**, *7*, 148.
(17) pK_a, 7.25; 41% protonated at physiological pH.
(18) A similar mechanism has been demonstrated for prazosin[19] and doxazosin in man.[20]

Experimental Section

Chemistry. Melting points are determined in a Büchi apparatus in glass capillary tubes and are uncorrected. Spectroscopic data for all compounds were recorded on Perkin-Elmer 257 (IR), AEI MS12 or VG 7070F (MS), Perkin-Elmer R12B, Varian XL100, 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-[4-(*N*-butylcarbamoyl)piperidino]quinazoline Hydrochloride (12). 4-Amino-2-chloro-6,7-dimethoxyquinazoline (1.2 g, 5.0 mmol), 4-(*N*-butylcarbamoyl)piperidine (1.01 g, 5.5 mmol), and triethylamine (2.52 g, 25 mmol) in butanol (105 mL) were heated under reflux for 24 h. The mixture was cooled, the solvent evaporated, and the residue shaken with chloroform and water. The solid product was collected and recrystallized from ethanol to give 4-amino-6,7-dimethoxy-2-[4-(*N*-butylcarbamoyl)-piperidino]quinazoline hydrochloride (0.57 g, 27%), mp 263–264 °C. Anal. ($C_{20}H_{29}N_5O_3$·HCl) C, H, N.

4-Amino-2-(4-carboxypiperidino)-6,7-dimethoxyquinazoline monohydrate [mp 295 °C; anal. ($C_{16}H_{20}N_4O_4$·H_2O) C, H, N], 4-amino-2-[4-(carboxymethyl)piperidino]-6,7-dimethoxyquinazoline hydrochloride [mp 250–252 °C; anal. ($C_{17}H_{22}N_4O_4$·HCl) C, H, N], and 4-amino-2-[4-(2-carboxyethyl)piperidino]-6,7-dimethoxyquinazoline hydrochloride [mp 238–241 °C; anal. ($C_{18}H_{24}N_4O_4$·HCl) C, H, N] were prepared by the general method of route A. In the latter case, the initial reaction product was the butyl ester, which furnished the parent carboxylic acid after base (NaOH/MeOH) hydrolysis.

Route B. 4-Amino-6,7-dimethoxy-2-[4-[*N*-(cyclopropylmethyl)carbamoyl]piperidino]quinazoline Hydrochloride Hemihydrate (15). 4-Amino-6,7-dimethoxy-2-(4-carboxypiperidino)quinazoline (2.3 g, 6.9 mmol), *N*-hydroxysuccinimide (0.80 g, 6.9 mmol), and DCCD (1.4 g, 6.8 mmol) were stirred in DMF (50 mL) at 80 °C for 2 h, and then cyclopropylmethylamine (0.4 g, 5.6 mmol) was added. The mixture was stirred at 60 °C for 5 h and then poured into HCl (2 N, 100 mL) and chloroform (100 mL). The acidic layer was separated, basified with NaOH (5 N), and then extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated, and the residue was treated with ethereal HCl. The solid product (1.5 g, 50% crude yield) was collected and then recrystallized from ethyl acetate/methanol to give 4-amino-6,7-dimethoxy-2-[4-[*N*-(cyclopropylmethyl)carbamoyl]piperidino]quinazoline hydrochloride hemihydrate, mp 270–272 °C. Anal. ($C_{20}H_{27}N_5O_3$·HCl·0.5H_2O) C, H, N.

Route C. 4-Amino-6,7-dimethoxy-2-[4-[*N*-(2-phenylethyl)carbamoyl]piperidino]quinazoline Hydrochloride (24). *N,N*-Carbonyldiimidazole (2.0 g, 12 mmol) was added to a stirred solution of 4-amino-2-(4-carboxypiperidino)-6,7-dimethoxyquinazoline (2.0 g, 6.0 mmol) in DMF (100 mL) at 70 °C in the presence of 3A molecular sieves. The solution was stirred at 70 °C for 2 h, and then 2-phenylethylamine (1.0 g, 8.2 mmol) was added and the reaction maintained at 70 °C for 3 h. After cooling, the molecular sieves were collected and washed with chloroform, and then the combined organic phase was washed with water, dried (Na_2SO_4), and evaporated. The residue was taken up in the minimum volume of chloroform and treated with ethereal HCl, and the solid was collected and recrystallized from 2-propanol/methanol to give 4-amino-6,7-dimethoxy-2-[4-[*N*-(2-phenylethyl)carbamoyl]piperidino]quinazoline hydrochloride (0.81 g, 28%), mp 284–285 °C. Anal. ($C_{24}H_{29}N_5O_3$·HCl) C, H, N.

Route D. *N*-Butyl-4-piperidinecarboxamide. Isonicotinoyl chloride (100.0 g, 0.71 mol) was added over 1 h to a stirred solution of butylamine (51.6 g, 0.71 mol) in toluene (600 mL) at 0 °C. The mixture was allowed to stand overnight and heated on a steam bath for 0.5 h, and then water was added. The aqueous phase was separated, the pH adjusted to 12 (NaOH), and then the aqueous phase extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue (36

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g) was dissolved in acetic acid (400 mL) and hydrogenated at 50 psi/30 °C by using Adams' catalyst. The catalyst was removed, the filtrate evaporated, and the residue basified to about pH 12 (Na_2CO_3) and then extracted with chloroform. The combined organic extracts were dried (Na_2SO_4) and evaporated to leave *N*-butyl-4-piperidinecarboxamide (18.7 g, 14%), mp 75–79 °C. A sample of the product was converted to the oxalate salt, which was recrystallized from 2-propanol/ethyl acetate, mp 143–144 °C. Anal. ($C_{10}H_{20}N_2O \cdot C_2H_2O_4$) C, H, N. *N*-Butyl-3-piperidinecarboxamide [oxalate salt, mp 145–146 °C; anal. ($C_{10}H_{20}N_2O \cdot C_2H_2O_4$) C, H, N] and *N*-phenyl-4-piperidinecarboxamide [hydrochloride salt, mp 231–233 °C; anal. ($C_{12}H_{16}N_2O \cdot HCl$) C, H, N] were prepared by hydrogenation of *N*-butylnicotinamide and *N*-phenyl-4-pyridinecarboxamide by the method above.

***N*-Propyl-4-piperidineacetamide.** Methyl 4-pyridineacetate (10 g), propylamine (21.5 g), and 3A molecular sieves were heated at 100 °C for 48 h in a stainless steel bomb. Excess amine and molecular sieves were removed, and the crude product in glacial acetic acid (100 mL) was hydrogenated over Adams' catalyst at 30 °C/50 psi. The reaction was filtered and evaporated and the residue basified ($NaHCO_3$ solution) and extracted with ethyl acetate (100 mL). The extract was dried ($MgSO_4$) and evaporated to leave *N*-propyl-4-piperidineacetamide as a crude oil, which was characterized spectroscopically.

Route E. *N*-Methyl-*N*-(phenylmethyl)-4-piperidinecarboxamide. A solution of 1-[(phenylmethoxy)carbonyl]-4-piperidinecarbonyl chloride (7.5 g) in toluene (50 mL) was added dropwise to a cooled (ice/water) solution of *N*-methylbenzylamine (10.0 g) in toluene (100 mL). After the addition was complete, the solution was stirred at room temperature for 7 h and then allowed to stand at room temperature overnight. The mixture was washed with water, dried (Na_2SO_4), and evaporated. A cooled (ice/water), stirred solution of the residue (7.19 g) in acetic acid (25 mL) was slowly treated with a saturated solution of HBr in acetic acid (50 mL) and then the mixture stirred at 0 °C for 1 h and at room temperature for a further 3 h. Ether (250 mL) was added, the mixture evaporated, and the residue basified (Na_2CO_3), extracted with chloroform, dried ($MgSO_4$), and evaporated. The residue was taken up in chloroform and treated with ethereal HCl to give *N*-methyl-*N*-(phenylmethyl)-4-piperidinecarboxamide hydrochloride, mp 175–176 °C. Anal. ($C_{14}H_{20}N_2O \cdot HCl$) C, H, N.

***N*-(2-Methoxyethyl)-4-piperidinecarboxamide.** *N*-(2-Methoxyethyl)-1-[(phenylmethoxy)carbonyl]-4-piperidinecarboxamide (5.76 g) [mp 85–86 °C; Anal. ($C_{17}H_{24}N_2O_4$) C, H, N], prepared as above but with chloroform as solvent, was hydrogenated over 5% Pd/C at 50 psi/50 °C. The catalyst was removed and the filtrate evaporated to leave 4-[*N*-(2-methoxyethyl)carbamoyl]piperidine as an oil, which was characterized spectroscopically. *N*-(2-Hydroxyethyl)-4-piperidinecarboxamide was prepared and characterized similarly.

Route F. *N*-Butyl(4-piperidinyloxy)acetamide Hydrochloride. (a) 1-(Phenylmethyl)-4-hydroxypiperidine (10 g, 52 mmol) in dry DMF (50 mL) was added dropwise to a stirred suspension of NaH (5 g, 50% dispersion in mineral oil) in dry DMF (50 mL) at 20 °C under an atmosphere of nitrogen. The suspension was stirred at 20 °C for 4 h, and then chloroacetic acid (4.95 g, 52 mmol) in DMF (50 mL) was added slowly in two equal portions with a 2-h interval between. The resulting thick slurry was stirred at 20 °C for 24 h, 2-propanol (75 mL) added, and the mixture acidified to pH 6 (2 N HCl) and then concentrated. The aqueous residue was adjusted to pH 10 (NaOH) and extracted with chloroform (3 × 100 mL) and then the aqueous layer acidified to pH 3 (2 N HCl) and extracted with chloroform (3 × 100 mL). The residual aqueous phase was concentrated to half-volume and filtered and the filtrate evaporated to give [[1-(phenylmethyl)-4-piperidinyl]oxy]acetic acid hydrochloride (3 g, 20%), characterized by NMR.

(b) A solution of [[1-(phenylmethyl)-4-piperidinyl]oxy]acetyl chloride [prepared from the corresponding acid hydrochloride salt (7.0 g, 24 mmol) with thionyl chloride] in chloroform (50 mL) was added dropwise to a stirred solution of *n*-butylamine (3.70 g, 50 mmol) in chloroform (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and then left at room temperature overnight. The chloroform solution was washed with water (3 × 50 mL), sodium hydroxide solution (2 N, 3 × 50 mL), and HCl solution (2 N, 3 × 50 mL). The combined acidic extracts were basified to pH 12 and extracted with chloroform (3 × 100 mL), and then the organic extracts were dried (Na_2SO_4) and evaporated. The residue was taken up in ether and then treated with ethereal HCl to give *N*-butyl[[1-(phenylmethyl)-4-piperidinyl]oxy]acetamide hydrochloride (3.5 g, 42%), characterized by NMR.

(c) The above product (3.0 g, 8.8 mmol) in ethanol (100 mL) was hydrogenated over 5% Pd/C at 50 psi/50 °C, then the catalyst removed, and the filtrate evaporated. The residue was triturated with ether and *N*-butyl(4-piperidinyloxy)acetamide hydrochloride (1.7 g, 77%) collected. A sample was recrystallized from 2-propanol/diethyl ether and then ethyl acetate, mp 145–146 °C. Anal. ($C_{11}H_{22}N_2O_2 \cdot HCl$) C, H, N.

Biology. Experimental details for evaluation of binding, functional, and antihypertensive activities have been detailed previously.[1]

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Synthesis of a Series of Compounds Related to Betaxolol, a New β_1-Adrenoceptor Antagonist with a Pharmacological and Pharmacokinetic Profile Optimized for the Treatment of Chronic Cardiovascular Diseases

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A series of para-substituted phenoxypropanolamines has been synthesized and tested for β-adrenoceptor blocking activity. Some derivatives (**8**, 11, **12**, **20**, **21**) exhibited greater in vitro potency than the reference drugs metoprolol and propranolol. This series, in contrast to propranolol but similar to metoprolol, possesses cardioselectivity. The 3-[*p*-[(cycloalkylmethoxy)ethyl]phenoxy]-1-substituted-amino-2-propanol derivatives **8** (cyclopropylmethoxyethyl: betaxolol) and 11 (cyclobutylmethoxyethyl) produced antihypertensive effects in spontaneously hypertensive rats. Betaxolol (Kerlon, **8**) was found to exhibit an appropriate preclinical pharmacological and human pharmacokinetic profile (elevated oral bioavailability and prolonged plasma half-life) for the treatment of chronic cardiovascular diseases such as hypertension and angina.

Certain chronic cardiovascular diseases such as hypertension and angina are treated efficaciously with β-adrenoceptor antagonists. Within this therapeutic class there are drugs that have variable degrees of potency associated with ancillary properties such as membrane stabilizing activity, relative selectivity toward the β_1-adrenoceptor

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