2,4-Diamino-6,7-dimethoxyquinazolines. 1. 2-[4-(1,4-Benzodioxan-2-ylcarbonyl)piperazin-1-yl] Derivatives as α_1-Adrenoceptor Antagonists and Antihypertensive Agents

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A series of 4-amino-2-[4-(1,4-benzodioxan-2-ylcarbonyl)piperazin-1-yl]-6,7-dimethoxyquinazoline derivatives was synthesized for evaluation as α-antagonists and antihypertensive agents. Most compounds displayed high (nM) binding affinity for α_1-adrenoceptors with no significant activity at α_2-sites. Selective antagonism of the α_1-mediated vasoconstrictor effects of norepinephrine is also characteristic of the series. Structure–activity relationships for α_1-adrenoceptor affinity are presented, and structural similarity between the 2,4-diamino-6,7-dimethoxyquinazoline nucleus and norepinephrine is established. An α_1-receptor model is presented in which charge-reinforced hydrogen bonding is important for binding of both antagonist and agonist molecules. Antihypertensive activity was evaluated after oral administration (5 mg/kg) to spontaneously hypertensive rats, and several compounds displayed similar efficacy to prazosin when assessed after 6 h. On the basis of α_1-adrenoceptor affinity/selectivity in vitro and duration of antihypertensive action in vivo, compound 1 (doxazosin) was selected for further evaluation and is currently progressing through phase III clinical trials.

Hypertension affects up to one-fifth of the adult population and is an important risk factor for various cardiovascular disorders.[1] Treatment of patients with marked blood pressure elevation has been routine clinical practice for some considerable time, and over the last few years, drug therapy for mild/moderate hypertension has also become more common.[2] Consequently, clinical interest in improved, novel antihypertensive agents has intensified.[3] Satisfactory blood pressure control invariably requires chronic therapy, and drug side effects must be minimal, particularly since most patients are asymptomatic. Furthermore, it is now realized that the major causes of

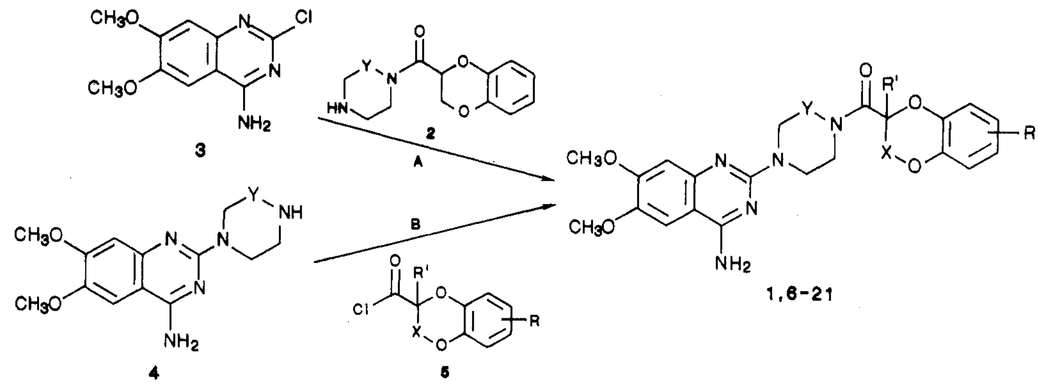
(1) For a review on coronary heart disease, see: *Am. J. Med.* **1984**, *76* (2A).

(2) For the Final Report of the Working Group on Risk and High Blood Pressure: *Hypertension* **1985**, *7*, 641.

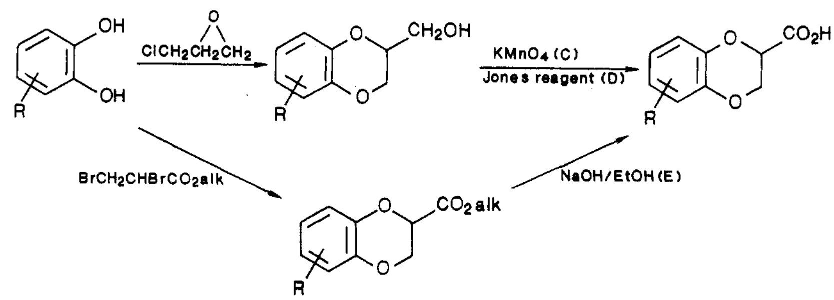
(3) Graham, R. M.; Campbell, W. B. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1981**, *40*, 2291.

0022-2623/87/1830-0049$01.50/0

Scheme I



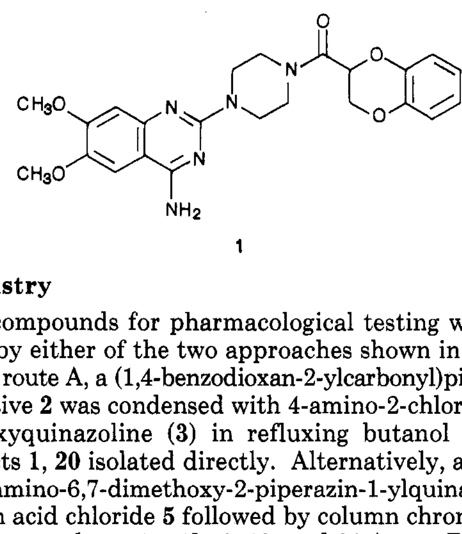
Scheme II



morbidity/mortality for mild/moderate hypertensives derive from atherosclerotic cardiovascular complications,[4] and this has increased awareness that drug therapy should not accentuate the incidence of ischemic heart disease.[5]

Largely for the above reasons, antihypertensive drugs with specific mechanisms of action are increasingly being employed in order to ameliorate selectively particular hemodynamic derangements without affecting normal physiological functions. For example, evidence is accumulating that overactivity of the sympathetic nervous system and abnormal arteriolar tone can be important factors in the development and maintenance of elevated blood pressure.[6,7] For such patients, prazosin, a selective α_1-adrenoceptor antagonist, may provide particularly appropriate therapy by blocking the α_1-mediated, postjunctional, vasoconstrictor effects of norepinephrine without affecting the prejunctional α_2-sites that modulate transmitter release.[8] Unlike earlier, nonselective, α-adrenoceptor blocking agents, prazosin has proved to be a chronically effective antihypertensive agent in animals and man, and causes little change in heart rate.[9] Recent clinical data also show that prazosin produces potentially beneficial effects on plasma lipid profiles,[10] in contrast to diuretics and β-blockers.[5] Indeed, the metabolic consequences of antihypertensive therapy may be important factors in the overall effectiveness of individual drugs in reducing coronary heart disease.

We now report the synthesis and pharmacological properties of a series of 2,4-diamino-6,7-dimethoxyquinazoline derivatives in which a 1,4-benzodioxan moiety replaces the furan ring of prazosin. Our aims were to preserve the α_1-adrenoceptor affinity and selectivity displayed by prazosin in compounds possessing a longer duration of antihypertensive activity that would be suitable for once-daily administration to man. These objectives have now been accomplished with the synthesis of 4-amino-2-[4-(1,4-benzodioxan-2-ylcarbonyl)piperazin-1-yl]-6,7-dimethoxyquinazoline (1, doxazosin), which is in late-stage phase III clinical evaluation.[11]



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Chemistry

All compounds for pharmacological testing were prepared by either of the two approaches shown in Scheme I.[12] In route A, a (1,4-benzodioxan-2-ylcarbonyl)piperazine derivative **2** was condensed with 4-amino-2-chloro-6,7-dimethoxyquinazoline (**3**) in refluxing butanol and the products **1**, **20** isolated directly. Alternatively, acylation of a 4-amino-6,7-dimethoxy-2-piperazin-1-ylquinazoline **4** with an acid chloride **5** followed by column chromatography gave products **1a**, **1b**, **6–19**, and **21** (route B). Final compounds were characterized as acid addition salts, although most proved to be hygroscopic, as shown by elemental analysis (Tables I, II).

The intermediates **2** were prepared by direct reaction of piperazine or homopiperazine with 1,4-benzodioxan-2-carbonyl chloride. Several benzodioxan carboxylic acids (Table III) were prepared (Scheme II) by oxidation of the

(4) Dollery, C. T. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1983**, *42*, 207.
(5) Weinberger, M. H. *Arch. Intern. Med.* **1985**, *145*, 1102.
(6) Bühler, F. R.; Amann, F. W.; Bolli, P.; Hulthēn, L.; Kiowski, W.; Landmann, R.; Burgisser, E. *J. Cardiovasc. Pharmacol.* **1982**, *4*, S134.
(7) Goldstein, D. S. *Hypertension* **1983**, *5*, 86.
(8) Graham, R. M. *Am. J. Cardiol.* **1984**, *53*, 16A.
(9) Stanaszek, W. F.; Kellerman, D.; Brogden, R. N.; Romankiewicz, J. A. *Drugs* **1983**, *25*, 339.
(10) Lowenstein, J. *Am. J. Cardiol.* **1984**, *53*, 21A.
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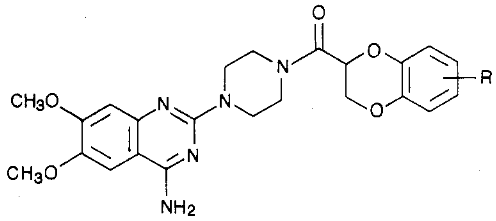
(12) Campbell, S. F., U.K. Patent 2,007,656B.

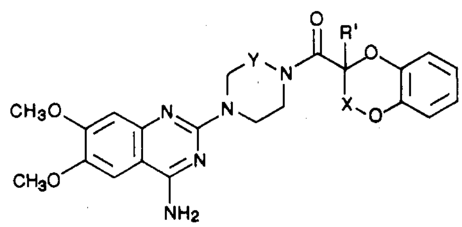
Table I. Synthetic Routes and Physical Data for Variation of the Aromatic Substituent (R)



no.	R	route	mp, °C	formula	anal.
1	H	A	289–290	$C_{23}H_{25}N_5O_5{\cdot}HCl$	C, H, N
1a(−)[a]	H	B	279–280	$C_{23}H_{25}N_5O_5{\cdot}HCl$	C, H, N
1b(+)[b]	H	B	284–286	$C_{23}H_{25}N_5O_5{\cdot}HCl$	C, H, N
6	6-OCH_3[c]	B	220–222	$C_{24}H_{27}N_5O_6{\cdot}HCl{\cdot}H_2O$	H, N
7	8-OCH_3	B	230d	$C_{24}H_{27}N_5O_6{\cdot}HCl{\cdot}H_2O$	C, H, N
8	5/8-CH_3[d]	B	238–240	$C_{24}H_{27}N_5O_5{\cdot}HCl{\cdot}0.5H_2O$	C, H, N
9	8-$CH(CH_3)_2$[e]	B	225–230	$C_{26}H_{31}N_5O_5{\cdot}HCl{\cdot}0.5H_2O$	C, H, N
10	6/7-Cl[f]	B	280–281	$C_{23}H_{24}ClN_5O_5{\cdot}HCl{\cdot}H_2O$	C, H, N
11	6-$COCH_3$	B	272	$C_{25}H_{27}N_5O_6{\cdot}HCl{\cdot}0.5H_2O$	C, H, N
12	7-$COCH_3$	B	230	$C_{25}H_{27}N_5O_6{\cdot}HCl{\cdot}H_2O$	C, H, N
13	6/7-$SO_2N(CH_3)_2$[g]	B	232–234	$C_{25}H_{30}N_6O_7S{\cdot}HCl{\cdot}H_2O$	C, H, N
14	6,7-$(CH_3)_2$	B	286–288	$C_{25}H_{29}N_5O_5{\cdot}HCl{\cdot}0.5H_2O$	C, H, N
15	6,7-Cl_2	B	242–243	$C_{23}H_{23}Cl_2N_5O_5{\cdot}0.5H_2O$	C, H, N

[a] $[\alpha]^{20}_D$ −99.3° (*c* 0.4, DMF). [b] $[\alpha]^{20}_D$ +95° (*c* 0.4, DMF). [c] C: calcd, 53.8; found, 53.3. [d] Mixture of isomers in the ratio 25:75 by 300-MHz NMR. [e] May contain up to 10% of the 5-isomer. [f] 50:50 mixture of 6- and 7-isomers. [g] 6-Isomer expected to predominate from synthetic route.

Table II. Synthetic Routes and Physical Data for Variation of Benzodioxan (R′, X) and Piperazine (Y) Substituents



no.	R′	X	Y	route	mp, °C	formula	anal.
16 (trans)[a]	H	$CH(CH_3)$	CH_2	B	242–243	$C_{24}H_{27}N_5O_5{\cdot}HCl{\cdot}H_2O$	C, H, N
17 (cis)[b]	H	$CH(CH_3)$	CH_2	B	214–215	$C_{24}H_{27}N_5O_5{\cdot}HCl{\cdot}2H_2O$	C, H, N
18	CH_3	CH_2	CH_2	B	234–237	$C_{24}H_{27}N_5O_5{\cdot}HCl{\cdot}H_2O$	C, H, N
19	H	$(CH_2)_2$	CH_2	B	205–207	$C_{24}H_{27}N_5O_5{\cdot}HCl{\cdot}1.5CH_3OH$	C, H, N
20	H	CH_2	$(CH_2)_2$	A	250–251	$C_{24}H_{27}N_5O_5{\cdot}HCl$	C, H, N
21	H	CH_2	$CH(CH_3)$	B	176–179	$C_{24}H_{27}N_5O_5{\cdot}C_2H_2O_4{\cdot}1.5H_2O$	C, H, N

[a] 300-MHz NMR shows 13% of **17**. [b] 300-MHz NMR shows 15% of **16**.

corresponding hydroxymethyl compounds with potassium permanganate (route C) or Jones reagent (route D). Attempted preparation of **26** via the dilithio salt (LDA, −78 °C) of 1,4-benzodioxan-2-carboxylic acid followed by treatment with methyl iodide gave only base-catalyzed fragmentation.[13] Intermediates **27–31** (Table III) were obtained by condensation of an appropriately substituted catechol with an alkyl 2,3-dibromopropionate followed by subsequent base hydrolysis of the intermediate esters (route E, Scheme II). Reaction of catechols with either epichlorohydrin or dihalopropionates proceeds with limited regiocontrol, and product mixtures obtained are usually difficult to separate. However, isomer ratios were established by HPLC and identity confirmed by ^{13}C NMR spectroscopy.

Resolution of 1,4-benzodioxan-2-carboxylic acid was achieved by fractional crystallization of the dehydroabietylamine salt and absolute configurations were assigned by reduction of the *R* enantiomer to (*S*)-2-(hydroxymethyl)-1,4-benzodioxan.[14] No change in optical activity was observed on acid chloride formation ($SOCl_2$) followed by treatment with water, although rotations of the coupled products **1a**, **1b** were opposite to those of the starting benzodioxan carboxylic acids.

Results and Discussion

Structure–Activity Relationships (SARs) for in Vitro α-Adrenoceptor Affinity. Table IV illustrates the effect of substitution in the (1,4-benzodioxan-2-ylcarbonyl)piperazino moiety on α-adrenoceptor affinity, as determined by standard ligand-binding techniques. Most members of the series displayed high (ca. 10^{-9} M) affinity for α_1-receptors and no compounds showed any significant activity (>10^{-6} M) at α_2-sites. Thus, α_1/α_2 selectivity ratios for these quinazoline derivatives are at least a thousand, and are probably much greater. The parent compound **1** was one of the most potent derivatives, and the fivefold lower α_1-affinity compared to that of prazosin may reflect a slightly reduced steric tolerance for the benzodioxan moiety. Both enantiomers **1a** and **1b** showed similar ac-

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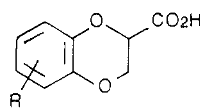
(14) Nelson, W. L.; Wennerstrom, J. E.; Dyer, D. C.; Engel, M. *J. Med. Chem.* **1977**, *20*, 880.

Table III. Synthetic Routes and Physical Data for 1,4-Benzodioxan-2-carboxylic Acids Prepared by Oxidative and Hydrolytic Procedures (Scheme II)



no.	R	route	mp, °C	formula	anal.
22	6-OCH_3	C	120–121	$C_{10}H_{10}O_5$	C, H
23	8-CH_3[a,b]	C	oil	$C_{10}H_{10}O_2$	
24	6/7-$SO_2N(CH_3)_2$[c]	C	156–162	$C_{11}H_{13}NO_6S$	H, N
25	6-$COCH_3$[d]	D	174–175	$C_{11}H_{10}O_5$	H
26	2-CH_3	D	133–134	$C_{10}H_{10}O_4$	C, H
27	6,7-$(CH_3)_2$	E	150–151	$C_{11}H_{12}O_4$	C, H
28	7-$COCH_3$[e,f]	E	167–168	$C_{11}H_{10}O_5$	H
29	8-$CH(CH_3)_2$[g,h]	E	86–88	$C_{12}H_{14}O_4$	C, H
30	6,7-Cl_2[b]	E	155–158	$C_9H_6O_4Cl_2$	
31	6/7-Cl[b]	E	145–146	$C_9H_7O_4Cl$	

[a] Contains ca. 30% of the 5-isomer. [b] Characterized spectroscopically. [c] C: calcd, 46.0; found, 45.5. [d] C: calcd, 59.5; found, 59.0. [e] C: calcd, 59.5; found, 59.0. [f] HPLC shows less than 5% of the 6-isomer. [g] HPLC shows ca. 13% of the 5-isomer. [h] Starting ester (bp 115–120 °C (0.5 mm)) as a mixture of 8- and 5- isomers (70% and 30%, respectively) prepared from 3-isopropylcatechol.

tivity, which does not support a stereoselective interaction with the receptor. Monosubstitution of the aromatic ring of **1** with 8-methoxy (**7**), 8-methyl (**8**), or 7-acetyl (**12**) preserved high α_1-adrenoceptor affinity while there were only small reductions in potency with the 6-methoxy and 6-acetyl isomers (**6**, **11**). Larger substituents (**9**, **13**), or disubstitution (**14**) were also well-tolerated. These results suggested considerable scope for modification of the aromatic moiety but, unexpectedly, the mono- and dichloro derivatives **10**, **15** were some 11-fold less active than **1**. Introduction of a methyl group into the 1,4-benzodioxan system at the 3- (**16**, **17**) or 2-positions (**18**) gave compounds essentially equipotent with **1**. Expansion of the benzodioxan or piperazine rings (**19**, **20**) was also acceptable, but the 3-methylpiperazino derivative (**21**) had slightly reduced activity.

Functional α-antagonist activity was measured in the rabbit pulmonary artery preparation, which allows simultaneous assessment of blockade at post- and prejunctional (α_1 and α_2) adrenoceptors. All of the compounds tested were highly selective (e.g., **1**, >600-fold) antagonists of the α_1-mediated vasoconstrictor effects of norepinephrine and showed no activity (10^{-5} M) at the α_2-sites that modulate transmitter release. Compound **1** displayed high α_1-antagonist activity (10^{-8} M) and competitive blockade of norepinephrine was demonstrated in separate experiments.[11] Some improvement in activity was evident with the enantiomer **1b** and the substituted analogues **6**, **8**, **16**, **17**. Compounds **1b** and **6** showed similar potency to prazosin and, like all compounds tested, displayed increased α_1/α_2-adrenoceptor selectivity. By contrast with binding data, the 8-isopropyl derivative **9** was somewhat less active.

In order to rationalize the exceptional α_1-adrenoceptor affinity and competitive α_1-antagonism displayed by certain 2,4-diamino-6,7-dimethoxyquinazoline derivatives, we visualized these compounds as conformationally restricted analogues of norepinephrine, which would be protonated at physiological pH.[15] X-ray analysis[16] (vide infra) shows that the (diaminodimethoxy)quinazoline nucleus in **32** is planar with O_6–N_2 and O_7–N_2 distances of 7.65 and 7.11 Å, respectively. Molecular mechanics calculations indicate that for the norepinephrine cation (**33**) a coplanar arrangement of the catechol unit, the two-carbon side chain, and nitrogen atom is acceptable[17] with O_4–N and O_3–N separations of 7.82 and 7.49 Å. Computer-simulated superimposition of **32** and **33** (Figure 1) confirms the spatial equivalence of these common molecular features. In addition to structural similarity, protonation of both agonist and antagonist is required for effective receptor binding.[18]

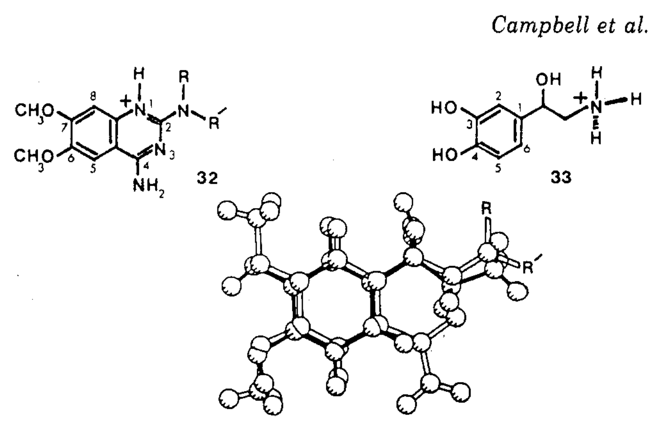


Figure 1. Superimposition of **32** (hollow bonds) and **33** (solid bonds).

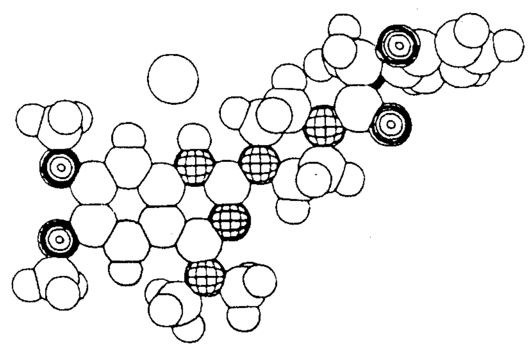


Figure 2. Spacefill representation of X-ray structure for 6,7-dimethoxy-4-(dimethylamino)-2-[4-(1,4-benzodioxan-2-ylcarbonyl)piperazin-1-yl]quinazoline hydrochloride salt (**34**).

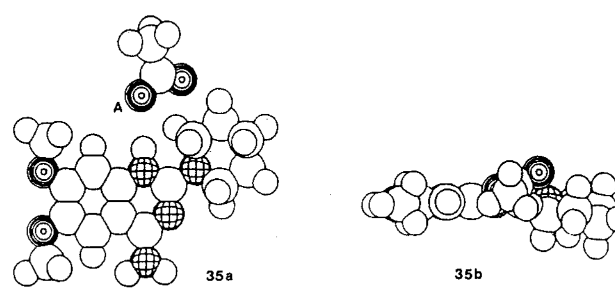


Figure 3. Interaction of N_1-protonated 4-amino-6,7-dimethoxy-2-piperidinoquinazoline (**35**) with a carboxylate counterion, face-on (a) and side view (b) illustrated. Hydrogen-bond data in Table V.

(15) For additional information on these modelling studies: Campbell, S. F. *X-Ray Crystallography and Drug Action*; Horn, A. S., De Ranter, C. J., Eds.; Clarendon: Oxford, 1984; p 347. Campbell, S. F. *Second SCI-RSC Medicinal Chemistry Symposium*; Emmett, J. C., Ed.; Royal Society of Chemistry, 1984; p 18.

(16) X-ray analysis was carried out by Dr. D. J. Williams, Imperial College, London.

(17) This conformation of norepinephrine is less than 2 kcal/mol above the global minimum (phenyl ring rotated through approximately 60°).

(18) Norepinephrine (pK_a = 9.6[19]), prazosin (pK_a = 6.8), and **1** (pK_a = 6.9) are approximately 95%,[20] 25%, and 25% protonated at physiological pH. (pK_a values for prazosin and **1** were determined by spectrometry. A previously reported pK_a of 7.2 for prazosin[15,41] was derived from the pH–solubility profile.) Evidence for the importance of **32** in α_1-adrenoceptor interaction has been presented.[15]

Table IV. Binding (K_i, nM), Functional (EC_{40}, nM), and Antihypertensive Activities for 4-Amino-2-[4-(1,4-benzodioxan-2-ylcarbonyl)piperazin-1-yl]-6,7-dimethoxyquinazoline Derivatives

no.	α-receptor binding affinity: K_i, nM		α-antagonist act. (rabbit pulmonary artery): EC_{40}, nM		% reduction in SHR blood pressure[c] (dose, 5 mg/kg po)	
	1	2[a]	post	pre[b]	1 h	6 h
1	1.1 ± 0.1	NA	50 ± 17	>3 × 10^{-5}	23	27
1a	2.2 ± 0.5	NA	40	NA	12	24
1b	2.6 ± 0.1	NA	7	NA	27	24
6	5.6 ± 0.9	NA	10	NA	34	23
7	2.4 ± 0.3	NA	NT		14	13
8	3.7 ± 1.2	NA	26	NA	16	22
9	6.7 ± 1.7	NA	130	NA	6	3
10	12.6 ± 3.1	NA	NT		27	23
11	6.4 ± 1.6	NA	NT		26	24
12	3.0 ± 0.6	NA	NT		19	24
13	6.5 ± 1.5	NA	NT		10	8
14	7.8 ± 1.8	NA	NT		14	20
15	13.3 ± 0.5	NA	NT		6	9
16	2.1 ± 0.4	NA	13	NA	21	21
17	0.7 ± 0.8	NA	27	NA	23	25
18	1.5 ± 0.1	NA	NT		8	9
19	3.8 ± 1.4	NA	NT		21	16
20	1.6 ± 0.3	NA	NT		22	12
21	6.5 ± 1.5	NA	NT		18	13
prazosin	0.19 ± 0.02	4830 ± 1280	4.5 ± 1.2	1300	33	29

[a] NA indicates no displacement of [^{3}H]clonidine at 10^{-6} M. [b] NA indicates no activity at 10^{-5} M. NT, not tested. [c] Falls in blood pressure below 10% are not significant.

Table V. Major Hydrogen-Bonding Contacts (H···A, ≤2.5 Å, DHA >110°) for 35–37

no.	D–H···A	H···A, Å	∠DHA, deg
35	N_1–H···O_A	2.5	168
36	O–H···O_A	1.9	160
37	O–H···O_A	1.8	170
	N–H_1···O_A	1.7	164
	N–H_1···O_B	2.1	115

INDO calculations indicate that **32** is preferred over the N_3 alternative, whereas protonation of the exocyclic nitrogen atoms is even less favored.[21,22] N_1 protonation is also observed in the crystal structure of **34** (pK_a = 7.1) (Figure 2), the 4-dimethylamino analogue of compound **1**. Thus, despite the ability to occupy similar spatial regions, the different electronic characteristics of the 2-nitrogen atom in **32** and the basic center of **33** are inconsistent with common receptor roles. However, charge delocalization in **32** and **33** is extensive, suggesting that the formal positive centers would be of limited importance for direct receptor interactions.[25] Instead, charge-reinforced hydrogen bonding, involving an anionic site on the receptor, would be expected to play a more dominant role. As a model, interaction of **32** (–NRR′ = piperidino) with a coplanar acetate ion[27] was evaluated[29] and the energy-min-

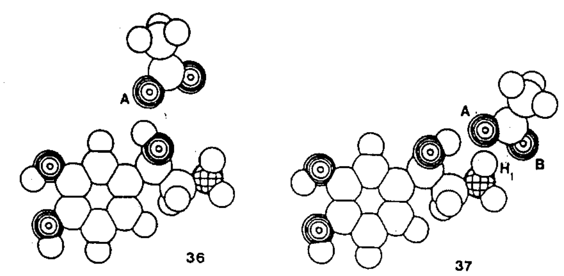


Figure 4. Interaction of noradrenaline cation (**33**) with a carboxylate counterion, α_1-adrenoceptor ground state (**36**), activated state (**37**). Hydrogen-bond data in Table V.

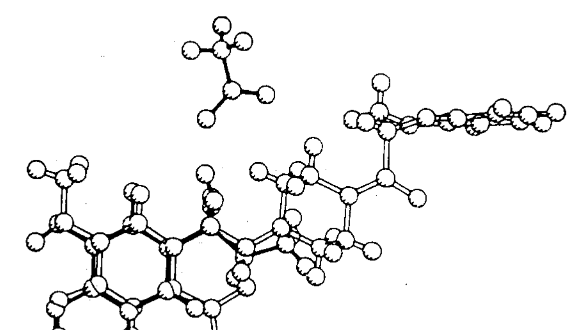


Figure 5. Superimposition of **1** (hollow bonds) and **33** (solid bonds) and interaction with a carboxylate counterion (solid bonds) in the α_1-adrenoceptor ground state location.

(19) Mack, F.; Bönisch, H. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *310*, 1.
(20) Ganellin, C. R. *J. Med. Chem.* **1977**, *20*, 579.
(21) Similar conclusions have been reached for quinazoline dihydrofolate reductase inhibitors: Crippen, G. M. *J. Med. Chem.* **1979**, *22*, 988.
(22) N_1 protonation[23] and quaternization[24] of 2,4-diaminopyrimidines have been reported.
(23) Griffiths, D. V.; Swetnam, S. P. *J. Chem. Soc., Chem. Commun.* **1981**, 1224.
(24) Brown, D. J.; Teitei, T. *J. Chem. Soc.* **1965**, 755.
(25) For protonated amines, positive charge is distributed over the four substituent groups.[26] Calculations show the nitrogen atom in **33** to be essentially neutral with 0.21, 0.22, and 0.23 unit of positive charge on the attached hydrogen atoms. In **32**, the charge on the N_1-hydrogen is 0.16 unit.
(26) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311.
(27) An acetate was chosen as salt bridges involving aspartate or glutamate residues with similar protonated heterocycles have been observed, for example, on dihydrofolate reductase.[15,28]
(28) Matthews, D. A.; Bolin, J. T.; Burridge, J. M.; Filman, D. J.; Volz, K. W.; Kaufman, B. T.; Beddell, C. R.; Champness, J. N.; Stammers, D. K.; Kraut, J. *J. Biol. Chem.* **1985**, *260*, 381.

imized arrangement 35[30] was found to be preferred (Figure 3).[31] We next assumed that these diaminodimethoxyquinazoline antagonists bound only to the ground state of the α_1-adrenoceptor and that, in addition to the carboxylate counterion, fixed recognition sites for the vicinal oxygen atoms and the hydrophobic aromatic ring also existed. As complex 35 is a minimum-enthalpy arrangement, any conformational reorganization essential for receptor activation would not be favored. Norepinephrine must also interact, at least initially, with the receptor ground state, and if the catechol moiety occupies the same area as the dimethoxybenzene unit in 35, only the benzylic hydroxyl function[32] can bind to the carboxylate ion (36) (Figure 4).[31] However, charge-reinforced hydrogen bonding can be optimized (Table V) by migration (ca. 4 Å) of the counterion to generate the minimum-energy, coplanar arrangement 37[33] (Figure 4).[31] The rearrangement of 36 to 37 may represent the receptor transition from ground to activated state, and the decrease in enthalpy could offset the entropy loss associated with the conformational change in the protein structure. Indeed, it has recently been shown that interaction of norepinephrine with α_1-adrenoceptors is enthalpy driven and that entropy also decreases.[35] Thus, while the quinazoline nucleus of antagonists such as 1 and norepinephrine may occupy the α_1-receptor ground state in a similar manner (Figure 5), subsequent events have little in common.[36] In summary, we propose that the 2,4-diamino-6,7-dimethoxyquinazoline system exhibits a high degree of structural complementarity for the α_1-adrenoceptor[38] and acts as a conformationally restricted substitute for norepinephrine. N_1 protonation is exquisitely suited for recognition by the carboxylate counterion in the ground state with additional affinity generated by hydrophobic attraction and the entropy gain associated with release of water.[39] In this model, the quinazoline 2-substituent could occupy a relatively open area on the receptor, which may close on agonist-induced activation, and the present study shows that quite large moieties are well-tolerated (Table IV).

Finally, the overwhelming α_1-selectivity of compound 1 and related analogues can be rationalized if the carboxylate counterion in the α_2-adrenoceptor is located perpendicular to, not coplanar with, the aromatic rings in 35–37. This geometry can be accomodated by flexible molecules such as norepinephrine or an orthogonally arranged α_2-agonist like clonidine, but not by the rigid, coplanar quinazoline nucleus.[40]

SARs for in Vivo Antihypertensive Activity. All of the compounds in Table IV were tested for antihypertensive activity in spontaneously hypertensive rats (SHR) after oral administration (5 mg/kg). Percentage reduction in blood pressure after 1 and 6 h are presented in order to compare both efficacy and duration of action. Several members of the series, 1, 1a, 1b, 6, 10, 11, 12, and 17, proved to be potent, long-acting antihypertensive agents in the rat with activity at the 6 h time point similar to prazosin. In agreement with functional α_1-antagonist data, 9 was only poorly effective, although similar results with 13, 15, and 18 were less expected. Duration of action and efficacy were moderate for 19–21. These results show that 1 and several related derivatives have a long duration of antihypertensive action in SHR after oral administration and that modification of the benzodioxanoylpiperazino substituent influences in vivo performance.

On the basis of the data in Table IV and synthetic accessibility, compound 1 (UK-33,274, doxazosin) was selected for detailed pharmacological profiling. Thus, 1 is a potent, highly selective competitive α_1-antagonist that lowers blood pressure in SHR and hypertensive dogs after acute or chronic administration and has a prolonged duration of action. Moreover, 24-h control of blood pressure in dogs is achieved after single daily dosing (0.5 mg/kg, po) and an extended plasma half-life for 1 (4.7 h) over prazosin (2.8 h) is consistent with this improved duration of antihypertensive activity.[41] Compound 1 is currently in late-stage phase III clinical evaluation where once-daily dosing has been shown to provide effective antihypertensive therapy.[11]

Experimental Section

Chemistry. Melting points were 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 XL 100, and Nicolet QE300 (NMR) instruments and were consistent with assigned structures. ^{13}C NMR spectra were determined on a Varian XL 100 instrument. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values. HPLC analyses were carried out on a Spectra Physics 3,500 cs machine; column 1 ft × 0.25 in. o.d. Bondapak C-18; eluant, CH_3CN/0.15 M potassium hydrogen phosphate buffer; flow rate, 0.6–14 mL/min; pressure, 600–780 psi.

Route A. 4-Amino-2-[4-(1,4-benzodioxan-2-ylcarbonyl)-piperazin-1-yl]-6,7-dimethoxyquinazoline Hydrochloride (1).[42] 4-Amino-2-chloro-6,7-dimethoxyquinazoline (140 g, 0.58 mol) and *N*-(1,4-benzodioxan-2-ylcarbonyl)piperazine (150 g, 0.60 mol) were stirred together under reflux in 1-butanol (2 L) for 3.5 h. The mixture was then cooled to 80 °C, and the solid product was collected, washed with cold 1-butanol (2 × 250 mL), and dried. The crude mixture was dissolved in hot (80 °C) dimethyl formamide (530 mL) and water (130 mL), filtered, concentrated in vacuo to about 300 mL, and then cooled, and ether (1.8 L) was added. The solid so obtained was washed with ether and was dried to yield 1 (251 g, 88%), mp 289–290 °C. Anal. ($C_{23}H_{25}N_5O_5 \cdot HCl$) C, H, N.

(29) Molecular mechanics simulation of nonbonded forces (van der Waals and Coulombic) was used to identify favorable binding positions and then full relaxation energy minimization was initiated to determine preferred geometries of interaction. Final binding energies (enthalpies of interaction) were calculated by INDO.
(30) The piperidino derivative 35 was chosen as a convenient, steric equivalent to 1 and related derivatives for assessing N_1-hydrogen–carboxylate interactions.
(31) Enthalpies of interaction for 35, 36, and 37 are −72.2, −74.5, and −155.9 kcal/mol, respectively. These binding energies should be treated qualitatively not quantitatively.
(32) The charge on the hydroxyl hydrogen (0.18 unit) is similar to the N_1-hydrogen (0.16 unit) in 35.
(33) Similar hydrogen-bonding arrangements involving the benzylic hydroxyl function, ammonium head, and a counterion are observed in crystal structures of norepinephrine salts.[34]
(34) Norepinephrine hydrochloride: Carlström, D.; Bergin, R. *Acta Crystallogr.* **1967**, *23*, 313. Ephedrine monohydrogen phosphate: Hearn, R. A.; Freeman, G. R.; Bugg, C. E. *J. Am. Chem. Soc.* **1973**, *95*, 7150.
(35) Raffa, R. B.; Aceto, J. F.; Tallarida, R. J. *J. Pharmacol. Exp. Ther.* **1985**, *235*, 596.
(36) Agonist binding to β-receptors is also enthalpy driven and entropy decreases. For β-antagonists, the major contribution to binding affinity derives from the entropy increase associated with release of water.[37]
(37) Weiland, G. A.; Minneman, K. P.; Molinoff, P. B. *Mol. Pharmacol.* **1980**, *18*, 341.
(38) To our knowledge, prazosin, 1, and related quinazoline derivatives do not interact with any other receptors at relevant dose levels.
(39) A K_i value of 1×10^{-9} M for 1 corresponds to a binding free energy of 12.26 kcal/mol at 25 °C.
(40) Campbell, S. F.; Tute, M. S., unpublished results.
(41) Campbell, S. F. *Drug Design Delivery* **1986**, *1*, 83.
(42) We thank Dr. I. C. Appleby for these experimental details.

Route B. 4-Amino-2-[4-(6-methoxy-1,4-benzodioxan-2-ylcarbonyl)piperazinyl]-6,7-dimethoxyquinazoline Hydrochloride Hydrate (6). A solution of 6-methoxy-1,4-benzodioxan-2-carbonyl chloride (2.17 g, 9.5 mmol) in dichloromethane (25 mL) was added dropwise to a stirred suspension of 4-amino-6,7-dimethoxy-2-piperazin-1-ylquinazoline (2.48 g, 8.6 mmol) in dichloromethane (50 mL) at room temperature. The mixture was then stirred at room temperature for 4 h and filtered, and the solid was suspended in aqueous potassium carbonate and was extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to leave a solid residue (4.15 g), which was chromatographed on silica gel (160 g). Elution with chloroform and then with chloroform–methanol (97.5:2.5) followed by evaporation of solvent yielded a product which was dissolved in ethyl acetate–methanol and treated with ethereal hydrogen chloride. Addition of further ether followed by cooling yielded a solid which was recrystallized from methanol to give 6 (0.95 g, 21%), mp 220–222 °C. Anal. ($C_{24}H_{27}N_5O_6{\cdot}HCl{\cdot}H_2O$) H, N; C: calcd, 53.8; found, 53.3.

Route C. 6-Methoxy-1,4-benzodioxan-2-carboxylic Acid (22). Potassium permanganate (5.02 g, 31.8 mmol) was added in four portions to a stirred suspension of 2-(hydroxymethyl)-6-methoxy-1,4-benzodioxan[43] (4.52 g, 23.0 mmol) in potassium hydroxide solution (1.47 g, in 42 mL water) at 5 °C. During addition, the reaction temperature was maintained between 5 and 15 °C, and then the mixture was stirred for a further 4 h at room temperature and set aside overnight. Manganese dioxide was removed by filtration, the solid was washed with water, and the combined aqueous phases were acidified (pH 1) with concentrated HCl and then extracted with chloroform. The combined extracts were washed with sodium hydroxide solution (5 N, 2 × 40 mL), and then the basic phase was washed with chloroform, cooled, acidified (pH 1) with concentrated HCl and reextracted with chloroform. This latter chloroform solution was washed with water, dried (Na_2SO_4), and evaporated to leave 6-methoxy-1,4-benzodioxan-2-carboxylic acid (2.33 g, 48%). A sample was recrystallized from water, mp 120–121 °C. Anal. ($C_{10}H_{10}O_5$) C, H.

Route D. 6-Acetyl-1,4-benzodioxan-2-carboxylic Acid (25). Jones reagent (11.6 mL) was added dropwise to a stirred solution of 6-acetyl-2-(hydroxymethyl)-1,4-benzodioxan[44] (4.0 g, 19.2 mmol) in acetone at 10–15 °C. The reaction was stirred at room temperature for 18 h and then was diluted with 2-propanol/water/chloroform, and the organic layer was separated and evaporated. The residue was taken up in chloroform and was extracted with saturated sodium bicarbonate solution (2 × 30 mL), and the basic phase was washed with chloroform, cooled, and then acidified (pH 1) with concentrated HCl. The acidic solution was extracted with chloroform, and the combined extracts were washed with brine, dried (Na_2SO_4) and then evaporated to give 6-acetyl-1,4-benzodioxan-2-carboxylic acid (1.56 g, 37%), mp 159–162 °C. A sample was recrystallized from ethanol/ethyl acetate, mp 174–175 °C. Anal. ($C_{11}H_{10}O_5$) H; C: calcd, 59.5; found, 59.0.

Route E. 6,7-Dimethyl-1,4-benzodioxan-2-carboxylic Acid (27). (a) To a stirred solution of 4,5-dimethylcatechol (7.0 g, 50.7 mmol) in dry acetone (45 mL) heated under reflux was added potassium carbonate (5 g) followed by ethyl dibromoproprionate (3.5 g, 13.6 mmol) dropwise. The addition procedure was repeated three more times over 1.25 h, and then the reaction mixture was stirred under reflux for a further 3.75 h. After the mixture was cooled, it was filtered, the solids were washed with acetone, and then the combined filtrates were evaporated. Water (35 mL) was added to the residue, and the resulting solid collected, washed with petroleum, and then taken up in ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated to give ethyl 6,7-dimethyl-1,4-benzodioxan-2-carboxylate (10.17 g, 85%), mp 70–71 °C. Anal. ($C_{13}H_{16}O_4$) C, H. (b) Hydrolysis of the above ester (5.0 g) with sodium hydroxide (13 mL) in ethanol (125 mL) gave **27** (4.04 g, 92%). A sample was recrystallized from water, mp 150–151 °C. Anal. ($C_{11}H_{12}O_4$) C, H.

6- and 7-Acetyl-1,4-benzodioxan-2-carboxylic Acid. A mixture (2:1 by ^{13}C NMR spectroscopy) of methyl 6/7-acetyl-1,4-benzodioxan-2-carboxylate (mp 68–80 °C) was prepared as in (a). Anal. ($C_{12}H_{12}O_5$) C, H. Hydrolysis of the product (7.0 g) followed by recrystallization from ethyl acetate/methanol gave **28** (see Table IV). The acidic aqueous phase from the hydrolysis reaction was evaporated, the residue was extracted with methanol, and the combined extracts were evaporated. Recrystallization of the product (5.5 g) from ethyl acetate/methanol gave 6-acetyl-1,4-benzodioxan-2-carboxylic acid (**25**), which was identical with a sample prepared previously (Table III). HPLC indicated only a single isomer.

6/7-[(*N*,*N*-Dimethylamino)sulfonyl]-1,4-benzodioxan-2-carboxylic Acid (24). (a) Phosphorus pentachloride (378 g, 1.8 mol) was added dropwise to a stirred solution of the pyridinium salt of 3,4-diacetoxybenzenesulfonic acid (302.5 g, 1.1 mol) in chloroform (1 L) at 0 °C at such a rate that the reaction temperature did not exceed 15 °C. After addition, the mixture was stirred at room temperature overnight and filtered, the chloroform solution was evaporated, and the residual oil was poured into ice–water. The aqueous phase was extracted with chloroform, and the combined extracts were dried (Na_2SO_4) and evaporated to leave a semisolid, which was recrystallized from carbon tetrachloride. This product (26.7 g) was treated with aqueous dimethylamine (265 mL, 15%) at 20 °C, and the reaction mixture was left at room temperature overnight and then evaporated. The residue was diluted with acetone (250 mL) and decanted, the solution was evaporated, and the residual oil was stirred with an equal volume of sodium hydroxide solution at room temperature for 2 h. The solution was acidified (concentrated HCl), and the resulting solid was collected and then crystallized from water to give *N*,*N*-dimethyl-3,4-dihydroxybenzenesulfonamide, mp 142 °C.

(b) A solution of sodium hydroxide (0.61 g) in water (5 mL) was added dropwise to a stirred suspension of the above product (3.0 g,13.8 mmol) and epichlorohydrin (1.43 mL, 18.3 mmol) in water (15 mL), and then the reaction mixture was heated at 80 °C for 1.5 h. After cooling, the reaction mixture was extracted with dichloromethane, and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated to leave 6/7-[(*N*,*N*-dimethylamino)sulfonyl]-2-(hydroxymethyl)-1,4-benzodioxan (2.84 g, 75%) as an oil, which was characterized spectroscopically.

(c) Oxidation of the above product (route C) gave **24** (Table III).

8-Methoxy-1,4-benzodioxan-2-carboxylic Acid. 8-Methoxy-1,4-benzodioxan-2-carboxamide (2.41 g, 11.5 mmol) in 50% HCl (35 mL) was stirred at 100 °C for 1 h. The resulting solution was cooled, diluted with water (200 mL), and extracted with chloroform (3 × 100 mL), and the combined extracts were dried ($MgSO_4$) and then evaporated. The residue (1.8 g) was recrystallized frm water, mp 75–78 °C, followed by ethyl acetate/hexane to give the title compound, mp 131–132 °C. Anal. ($C_{10}H_{10}O_5$) C, H. 5-Methoxy-1,4-benzodioxan-2-carboxylic acid, mp 139–141 °C, was prepared from the corresponding 5-carboxamide. Anal. ($C_{10}H_{10}O_5$) C, H.

(*R*)-(+)-1,4-Benzodioxan-2-carboxylic Acid. 1,4-Benzodioxan-2-carboxylic acid (21.6 g) and (+)-dehydroabietylamine (34.26 g) were mixed together in hot ethanol (95%, 1 L), and then the mixture was allowed to stand at room temperature for 24 h. The precipitate (20 g) was collected, and the filtrate was concentrated (600 mL) and left for 48 h when further solid product (4.0 g) was formed. The combined solids (24.0 g, mp 229–230 °C) were repeatedly crystallized from ethanol/methanol to constant melting point (229–230 °C). The mother liquors from the last two recrystallizations were combined and reduced in volume, and the solid product (5.6 g) was collected. This salt was converted to the free carboxylic acid (5.5 g), $[\alpha]^{20}_D$ +60.1° (*c* 1, $CHCl_3$), and then recrystallized twice from toluene to give (*R*)-(+)-1,4-benzodioxan-2-carboxylic acid (0.23 g), mp 98–99 °C, $[\alpha]^{20}_D$ +62.1° (*c* 1, $CHCl_3$). Anal. ($C_9H_8O_4$) C, H.

A sample of this acid in tetrahydrofuran was reduced with LAH to give (*S*)-(−)-2-(hydroxymethyl)-1,4-benzodioxan,[14] mp 69–71 °C, $[\alpha]^{20}_D$ −34.7° (*c* 0.1, EtOH).

(*S*)-(−)-1,4-Benzodioxan-2-carboxylic Acid. The initial mother liquors (600 mL) from above were evaporated, and the oily residue was taken up in acetone (250 mL) and then set aside until crystallization was complete. The solid product (10.0 g) was

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crystallized from acetone and then the salt (6.0 g) converted to the corresponding carboxylic acid. The crude product was chromatographed on silica with chloroform as eluant and the product was recrystallized from toluene to give (*S*)-(−)-1,4-benzodioxan-2-carboxylic acid (0.09 g), mp 98–99 °C, $[\alpha]^{20}_D$ −66.1° (*c* 1, $CHCl_3$). Anal. ($C_9H_8O_4$) C, H.

4-Amino-6,7-dimethoxy-2-(3-methylpiperazin-1-yl)-quinazoline Hemihydrate. 4-Amino-2-chloro-6,7-dimethoxy-quinazoline (8.05 g, 33.6 mmol) and 2-methylpiperazine (10 g, 100 mmol) were heated under reflux in butanol for 15 h. The reaction was evaporated, and the residue was taken up in chloroform (200 mL), washed with water (4 × 50 mL), dried ($MgSO_4$), and evaporated. The residual oil (13 g) was recrystallized from 2-propanol to give 4-amino-6,7-dimethoxy-2-(3-methylpiperazin-1-yl)quinazoline hemihydrate (3.0 g, 29%), mp 185–187 °C. Anal. ($C_{15}H_{21}N_5O_2{\cdot}0{\cdot}5H_20$) C, H, N.

1-(1,4-Benzodioxan-2-ylcarbonyl)piperazine Hydrochloride.[42] A solution of 1,4-benzodioxan-2-carbonyl chloride (16.53 g, 83 mmol) in ethyl acetate (33 mL) was added dropwise over 0.5 h to a stirred solution of piperazine (21.53 g, 250 mmol) in methanol (54 mL), water (33 mL), and concentrated HCl (21.9 mL, 250 mmol) at 20–25 °C. The reaction was stirred for a further 0.5 h and extracted with dichloromethane (2 × 54 mL), the extracts were washed with water (2 × 22 mL), and then the combined aqueous phases were adjusted to pH 8 with 0.880 ammonia (27.6 mL). The mixture was extracted with dichloromethane (1 × 100 mL, 2 × 55 mL), the combined extracts were washed with water (3 × 25 mL) and then concentrated (100 mL), and the residual solvent removed by azeotroping with methanol. The solution (100 mL) was cooled to 5 °C, treated with concentrated HCl (7.3 mL), and stored at −12 °C overnight, and then 1-(1,4-benzodioxan-2-ylcarbonyl)piperazine hydrochloride (16.08 g, 68%), mp 262–263 °C, was collected. Anal. ($C_{13}H_{16}N_2O_3{\cdot}HCl$) C, H, N.

1-(1,4-Benzodioxan-2-ylcarbonyl)homopiperazine hydrochloride, mp 189 °C, was prepared similarly. Anal. ($C_{14}H_{18}N_2O_3{\cdot}HCl$) C, H, N.

Biology. Radioligand Binding.[45,46] 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 throught 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 samples 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:

$$K_i = \frac{IC_{50}}{1 + [C]/K_D}$$

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.

Functional Antagonism.[47,48] The affinity of compounds for prejunctional (α_2) and postjunctional (α_1) adrenoceptor sites was measured with use of Krebs superfused rabbit pulmonary artery preparations labeled with [^{3}H]norepinephrine. Stimulation of sympathetic nerve endings was elicited by transmural electrical stimulation (3 Hz for 0.05 h). Tension changes were measured by an isometric transducer and afforded an estimation of postjunctional activity. ^{3}H overflow, measured by liquid scintillation counting methods, permitted an estimation of prejunctional action. Percent antagonism of the prejunctional (overflow) and postjunctional (tension) changes were plotted against concentration of compound and EC_{40} values were derived from the graph. EC_{40}-pre is defined as the concentration of compound producing a 40% increase in ^{3}H-overflow and EC_{40}-post as the concentration producing a 40% reduction in contractile response. Results in Table IV are averaged from two separate experiments except for 1 and prazosin ($n = 6$).

Antihypertensive Activity. Compounds were administered orally (5 mg/kg) by gavage to groups of six spontaneously hypertensive rats. Recordings of systolic blood pressures 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, 4, and 6 h following oral administration, but only results at 1 and 6 h are reported in Table IV. When saline solution was administered to a group of control rats ($n = 10$), blood pressure fell by 7 ± 2% over the 6-h period. All animals used in these studies had starting systolic pressures in excess of 175 mmHg.

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Registry No. 1, 70918-01-3; 1 (free base), 74191-85-8; **1a**, 77173-63-8; **1a** (free base), 70918-17-1; **1b**, 70918-18-2; **1b** (free base), 104874-86-4; **2** (Y = CH_2), 70918-00-2; **2** (Y = CH_2)·HCl, 70918-74-0; **2** (Y = $(CH_2)_2$)·HCl, 70918-55-7; **3**, 23680-84-4; **4** (Y = CH_2), 60547-97-9; **4** (Y = CH(CH3)), 70918-67-1; **5** (R = R^1 = H, X = CH_2), 3663-81-8; *cis*-**5** (R = R^1 = H, X = CH(CH_3)), 77156-56-0; *trans*-**5** (R = R^1 = H, X = CH(CH_3)), 77156-55-9; **5** (R = R^1 = H, X = $(CH_2)_2$), 77156-62-8; **5** (R = H, R^1 = CH_3, X = CH_2), 22735-16-6; **5** (R = 6-MeO, R^1 = H, X = CH_2), 70918-06-8; **6**, 70918-07-9; **6** (free base), 104808-22-2; **7**, 70918-13-7; **7** (free base), 104808-23-3; **8** (R = 5-CH_3), 70918-73-9; **8** (R = 5-CH_3) (free base), 104808-24-4; **8** (R = 8-CH_3), 70918-08-0; **8** (R = 8-CH_3) (free base), 104808-25-5; **9**, 70918-10-4; **9** (free base), 104808-26-6; **10** (R = 6-Cl), 70918-15-9; **10** (R = 6-Cl) (free base), 104808-27-7; **10** (R = 7-Cl), 70918-14-8; **10** (R = 7-Cl) (free base), 104808-28-8; **11**, 70918-22-8; **11** (free base), 104808-29-9; **12**, 70918-23-9; **12** (free base), 104808-30-2; **13** (R = 6-$SO_2NC(H_3)_2$), 70918-24-0; **13** (R = 6-$SO_2N(CH_3)_2$) (free base), 104808-31-3; **13** (R = 7-$SO_2N(CH_3)_2$), 70918-25-1; **13** (R = 7-$SO_2N(CH_3)_2$) (free base), 104808-32-4; **14**, 70918-11-5; **14** (free base), 104808-33-5; **15**, 70918-16-0; **16**, 70918-19-3; **16** (free base), 104808-34-6; **17**, 70918-20-6; **17** (free base), 104808-35-7; **18**, 70918-21-7; **18** (free base), 104808-36-8; **19**, 70918-26-2; **19** (free base), 104808-37-9; **20**, 70918-05-7; **20** (free base), 104808-38-0; **21**, 104808-20-0; **21** (free base), 70918-27-3; **22**, 70918-36-4; **22** (alcohol), 70918-35-3; (+)-**22** (R = H), 34385-93-8; (*R*)-**22** (R = H), 70918-53-5; (*R*)-**22** (R = H) (dehydroabietylamine salt), 104972-85-2; (*S*)-**22** (R = H), 70918-54-6; (*S*)-**22** (R = H) (dehydroabietylamine salt), 104972-86-3; **22** (R = 5-OMe), 70918-47-7; **22** (R = 5-OMe) (carboxamide), 70918-46-6; **22** (R = 8-OMe), 70918-45-5; **22** (R = 8-OMe) (carboxamide), 70918-44-4; **23** (R = 5-CH_3), 70918-40-0; **23** (R = 5-CH_3) (alcohol), 2164-55-8;

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23 (R = 8-CH_3), 70970-73-9; **23** (R = 8-CH_3) (alcohol), 2164-59-2; **24** (R = 6-$SO_2N(Me)_2$), 70918-64-8; **24** (R = 6-$SO_2N(Me)_2$) (alcohol), 70918-62-6; **24** (R = 7-$SO_2N(Me)_2$), 70918-65-9; **24** (R = 7-$SO_2N(Me)_2$) (alcohol), 70918-63-7; **25**, 70918-49-9; **25** (alcohol), 70918-48-8; **25** (methyl ester), 70918-50-2; **26**, 68281-27-6; **26**, 68281-27-6; **26** (alcohol), 16163-83-0; **27**, 70918-42-2; **27** (ethyl ester), 70918-41-1; **28**, 70918-52-4; **28** (methyl ester), 70918-51-3; **29** (R = 5-Pr-i), 70918-38-6; **29** (R = 5-Pr-*i*) (ethyl ester), 104808-40-4; **29** (R = 8-Pr-i), 70918-39-7; **29** (R = 8-Pr-i) (ethyl ester), 104808-39-1; **30**, 70918-43-3; **30** (ethyl ester), 16212-66-1; **31** (R = 6-Cl), 70918-58-0; **31** (R = 6-Cl) (ethyl ester), 51714-18-2; **31** (R = 7-Cl), 16212-69-4; **31** (R = 7-Cl) (ethyl ester), 16212-65-0; **34**, 104808-21-1; $BrCH_2CH(Br)CO_2Et$, 3674-13-3; 4,5-dimethylcatechol, 2785-74-2; 3,4-diacetoxybenzenesulfonic acid pyridinium salt, 70918-60-4; dimethylamine, 124-40-3; *N*,*N*-dimethyl-3,4-dihydroxybenzenesulfonamide, 70918-61-5; epichlorohydrin, 106-89-8; (+)-dehydroabietylamine, 99306-87-3; 2-methyl piperazine, 109-07-9; piperazine, 110-85-0; homopiperazine, 505-66-8; 4-acetylcatechol, 1197-09-7.

Supplementary Material Available: X-ray data are available for 6,7-dimethoxy-4-(dimethylamino)-2-[4-(1,4-benzodioxan-2-ylcarbonyl)piperazin-1-yl]quinazoline hydrochloride (**34**) (4 pages). Ordering information is given on any current masthead page.