Structure–Activity Relationships in Prazosin-Related Compounds. 2.[1] Role of the Piperazine Ring on α-Blocking Activity[2]

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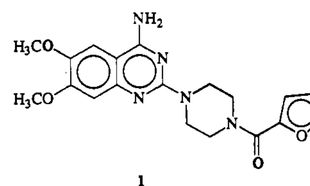
Several prazosin-related compounds have been synthesized and evaluated for their blocking activity toward α-adrenoreceptors. The structural modification performed on the prazosin structure included the replacement of the piperazine ring with 2,3-dialkylpiperazine or 1,2-cyclohexanediamine moieties to characterize a lipophilic binding pocket in the α_1-adrenoreceptor surface. Cyclohexanediamine derivatives **3–6** were almost devoid of potency and selectivity, whereas dialkylpiperazine compounds **7–14** showed high affinity and selectivity toward α_1-adrenoreceptors. The cis derivative **13** (cyclazosin) was the most potent and selective with an α_1/α_2 selectivity ratio value of 7800. The particular trend of antagonist activity within cis/trans stereoisomeric compounds not only supports the presence of a lipophilic binding area on α_1-adrenoreceptor surface but also suggests that the lipophilic pocket is endowed with a well-defined size and spatial orientation. The most active compound of the series, **13**, was tested also in vivo for antihypertensive activity on spontaneously hypertensive rats. It showed an interesting long-lasting hypotensive effect, very similar to that of doxazosin, which was statistically significant 12 h after oral administration.

Introduction

Prazosin (**1**) is a selective α_1-adrenoreceptor antagonist widely used not only as a pharmacological tool for α-adrenoreceptor subtypes characterization but also as an effective agent in the management of hypertension. Its antihypertensive activity depends on a peripheral vasodilatation mediated by a postjunctional α_1-adrenoreceptor blockade. Moreover, given its high α_1-selectivity, prazosin lacks side effects such as tachycardia and hyperreninemia, which are connected with a presynaptic α_2-adrenolytic action.[3–6] In addition, in contrast to certain β-adrenoreceptor antagonists, prazosin improves the plasma lipid profile. It reduces total cholesterol, triglycerides, and the LDL + VLDL cholesterol fraction and improves the HDL cholesterol and the HDL/total cholesterol ratio,[5,7–9] reducing the risk of coronary heart disease. For this reason, prazosin (**1**) represents a valid lead compound to explore α_1-adrenoreceptor binding site topography as a tool in developing new antihypertensive agents.

Recently, we have started a research study to determine the importance of the piperazine ring of prazosin in drug–receptor interaction processes. With this end in view, the piperazine moiety was replaced by an α,ω-alkanediamine chain,[10] and it was found that the piperazine ring may not be essential for activity at α_1-adrenoreceptors. Furthermore, it was observed that activity and selectivity depend on the length of alkane chain and N-methylation of both the amide and the 2-amino functions.[10] Compound **2**, bearing a 1,6-hexanediamine moiety, was the most active of the series, being more potent than prazosin (**1**) in both in vivo and in vitro assays. From these results we advanced the hypothesis that the α_1-adrenoreceptor incorporates a lipophilic area, located between the binding sites for the quinazoline and the furan rings of prazosin, which is able to accommodate optimally a 1,6-disubstituted hexane moiety.[10] However, compound **2** gives only limited information on the size and possible stereochemical requirements of this lipophilic area because its polymethylene chain is very flexible and can assume many conformations. A useful approach when searching for clues about binding site topography is to study conformationally constrained analogs of a lead compound. Following this reasoning we designed a series of compounds in which the polymethylene chain of **2** is incorporated partially or totally into a constrained structure. This structural modification would afford compounds in which the alkane moiety is forced to assume a definite arrangement while keeping quinazoline and furan rings in a position likely similar to that of prazosin, hopefully to give information on the size and the spatial orientation of the lipophilic pocket.



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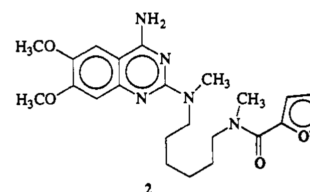

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Here we report the synthesis and α-adrenoreceptor blocking activity of 1,2-cyclohexanediamines **3–6**, mono- and disubstituted piperazines **7–12**, and decahydroquinoxalines **13** (cyclazosin) and **14**.

Chemistry

The structures of the compounds used in the present study are given in Table I. These were synthesized by

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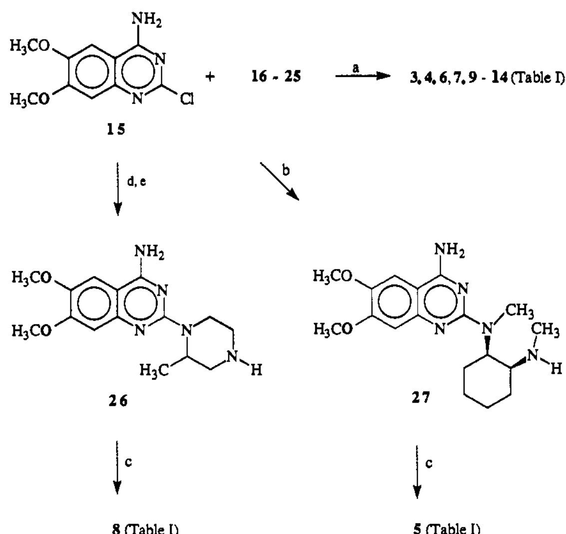
Scheme I[a]



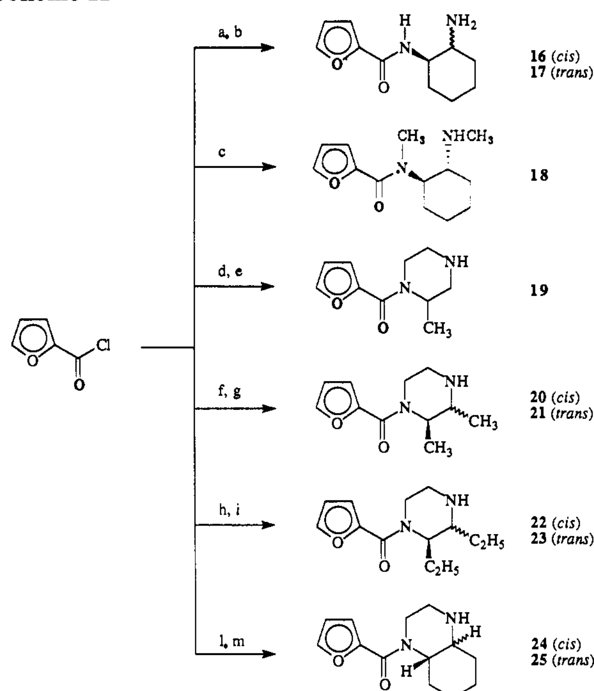
[a] (a) Isoamyl alcohol, reflux; (b) *cis-N,N'*-dimethylcyclohexane-1,2-diamine, isoamyl alcohol, reflux; (c) 2-furoyl chloride, chloroform; (d) 3-methylpiperazine-1-carboxylic acid ethyl ester, isoamyl alcohol, reflux; (e) 30% NaOH, ethanol, reflux.

standard procedures and characterized by ^{1}H NMR and elemental analysis. With the exception of compounds **5** and **8**, all others were obtained by reaction of **15**[11] with amides **16–25** of various cyclic or acyclic diamines (Scheme I). The intermediate amides **16–18** and **20–25** were prepared, following a slightly modified procedure already reported,[11] by acylation of the appropriate diamine with 2-furoyl chloride, whereas **19** was obtained by furoylation of 3-methylpiperazine-1-carboxylic acid *tert*-butyl ester, followed by removal of the protecting group in acidic medium (Scheme II).

Reaction of **15** with *cis-N,N'*-dimethylcyclohexane-1,2-diamine gave **27**, which was allowed to react with 2-furoyl chloride to afford **5**. Compound **8** was prepared by reaction of **15** with 3-methylpiperazine-1-carboxylic acid ethyl ester,[12] followed by N-decarbethoxylation to **26** which was acylated with 2-furoyl chloride (Scheme I).

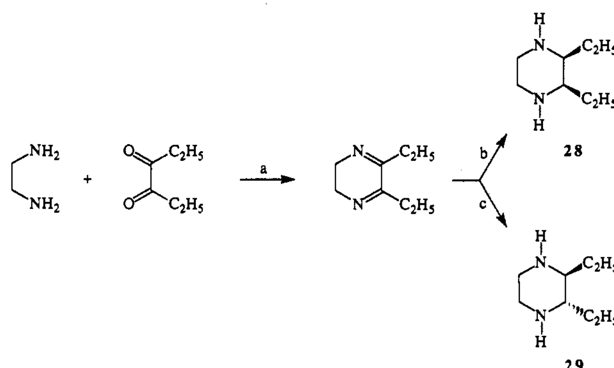
The starting diamines *cis*-cyclohexane-1,2-diamine,[13] *cis*-[14] and *trans-N,N'*-dimethylcyclohexane-1,2-diamine,[15] *cis*- and *trans*-decahydroquinoxaline,[16,17] and *cis*- and *trans*-2,3-dimethylpiperazine[18] were prepared following known procedures whereas *trans*-cyclohexane-1,2-diamine and 2-methylpiperazine were commercially available. Although *cis*- and *trans*-diethylpiperazine (**28** and **29**) have already been described,[19] they were prepared following an adapted procedure for the synthesis of the corresponding methyl analogs.[18] Thus reduction of 2,3-diethyl-5,6-dihydropyrazines[20] with lithium aluminium hydride gave only the cis isomer **28**, whereas with sodium and ethanol it afforded mainly the trans isomer **29** (trans/cis ratio = 1.75 by GC) (Scheme III). Owing to the difficulty to obtain stereoisomerically pure **29** even by chromatographic methods, a particular procedure was adopted for the purification of **29**. A cis/trans mixture was allowed to react with 2-furoyl chloride to give a mixture of *cis/trans*-mono- and difurylcarboxamides. Due to a higher acylation rate of the cis isomer **28**, as revealed by TLC and GC analysis, a moderate amount of pure trans isomer **29** was easily separated from the other products of the reaction mixture. The two isomers **28** and **29** were characterized by TLC, GC, ^{1}H NMR, and elemental analysis of the corresponding hydrochloride salts. ^{1}H NMR spectroscopy

Scheme II[a]



[a] (a) *cis*-Cyclohexane-1,2-diamine; (b) *trans*-cyclohexane-1,2-diamine; (c) *trans-N,N'*-dimethylcyclohexane-1,2-diamine; (d) 3-methylpiperazine-1-carboxylic acid *tert*-butyl ester; (e) 0.5 N HCl/EtOH; (f) *cis*-2,3-dimethylpiperazine; (g) *trans*-2,3-dimethylpiperazine; (h) *cis*-2,3-diethylpiperazine; (i) *trans*-2,3-diethylpiperazine; (l) *cis*-decahydroquinoxaline; (m) *trans*-decahydroquinoxaline.

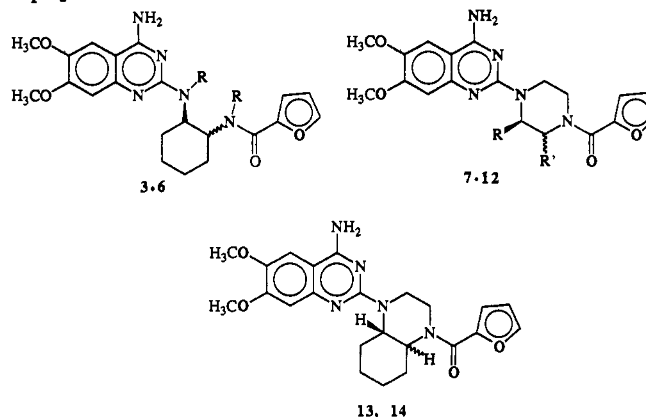
Scheme III[a]



[a] (a) Ethyl ether, reflux; (b) lithium aluminium hydride, ethyl ether; (c) Na/EtOH, reflux.

was used to assign the geometrical configuration of **28** and **29** by measuring their spectra at low temperatures. As already suggested for 2,3-dimethylpiperazines,[21] it was assumed that the trans isomer **29** would not change its equatorial–equatorial conformation into an energetically less favorable axial–axial conformation, whereas the cis isomer **28** could show interchangeable axial–equatorial and equatorial–axial orientations at room temperature. Consequently, ^{1}H NMR analysis should reveal a more complex signal pattern for the trans isomer with respect to the cis one. Furthermore, the trans isomer should not show any significant signal pattern changes going from room temperature to −80 °C, whereas the cis isomer might present considerable changes in its spectrum upon cooling. The ^{1}H NMR spectra of **28** and **29** were as expected: that of the trans isomer **29** did not change significantly upon cooling, except for a slight broadening of the signals likely due to lowering of resolving power by frosting. In contrast, the ^{1}H NMR spectrum of the cis isomer **28** showed an

Table I. α_1- and α_2-Adrenoreceptor pA_2 Values in the Isolated Rat Vas Deferens[a]



no.	stereoisomer	R	R′	α_1 pA_2 against norepinephrine	α_2 pA_2 against clonidine	α_1/α_2[b] selectivity ratio
1				8.54 ± 0.05	5.43 ± 0.13	1300
2				8.93 ± 0.04	6.84 ± 0.06	120
3	*cis*	H		5.74 ± 0.04	5.96 ± 0.11[c]	0.6
4	*trans*	H		6.07 ± 0.03	5.04 ± 0.08[c]	11
5	*cis*	CH_3		5.80 ± 0.10	5.41 ± 0.19[c]	2.5
6	*trans*	CH_3		5.64 ± 0.03	5.54 ± 0.04[c]	1.2
7		H	CH_3	8.61 ± 0.04	5.28 ± 0.09	2100
8		CH_3	H	8.13 ± 0.02	5.94 ± 0.04	150
9	*cis*	CH_3	CH_3	8.75 ± 0.08	6.41 ± 0.04	220
10	*trans*	CH_3	CH_3	7.12 ± 0.05	4.86 ± 0.40[c]	180
11	*cis*	C_2H_5	C_2H_5	8.55 ± 0.06	5.91 ± 0.02	440
12	*trans*	C_2H_5	C_2H_5	7.09 ± 0.01	5.05 ± 0.01	110
13	*cis*			8.97 ± 0.02	5.08 ± 0.10[c]	7800
14	*trans*			7.57 ± 0.03	5.15 ± 0.04	260

[a] pA_2 values ± SEM were calculated according to the method of Arunlakshana and Schild[24] unless otherwise specified, constraining the slope to −1.[34] pA_2 is defined as the negative logarithm to the base 10 of that dose of antagonist that requires a doubling of the agonist dose to compensate for the action of the antagonist. [b] The α_1/α_2 selectivity ratio is the antilog of the difference between pA_2 values at α_1- and α_2-adrenoreceptors. [c] Calculated according to the method of van Rossum[25] since it was not possible to investigate three different concentrations owing to the inhibition of twitch responses of electrically stimulated tissue at concentrations ≥100 μM.

extensive modification with broadening of the signals of multiplets at δ 1.45–1.60 and 2.63–2.95, corresponding to CH_2CH_3 and piperazine ring, respectively. These changes, due to overlapping of contemporaneous axial and equatorial orientations of protons of the diethylpiperazine moiety, were observed also for all other multiplets (δ 1.18–1.33, CH_2CH_3 and 0.87, CH_2CH_3) on going to lower temperatures.

Pharmacology

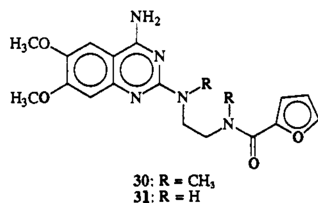
The pharmacological profile of compounds **3–14** was evaluated at α_1- and α_2-adrenoreceptors on isolated rat vas deferens tissues.[22,23] To allow comparison of the results, we used the same techniques and statistical evaluation of the bioassays as for other prazosin-related compounds.[10] Prazosin (**1**) and **2** were used as the standard compounds. α_1-Adrenoreceptor blocking activity was assessed by antagonism of (−)-norepinephrine-induced contractions of the epididymal portion, while α_2-adrenoreceptor-blocking activity was determined by antagonism of the clonidine-induced depression of the twitch responses of the field-stimulated prostatic portion of rat vas deferens. The potency of the drugs was expressed as pA_2 values, calculated according to the method of Arunlakshana and Schild.[24] However, compounds **3–6**, **10**, and **13** were evaluated at only two concentrations when determining α_2-adrenoreceptor blocking activity because of their low affinity for this receptor. In these cases, pA_2 values were calculated according to the method of van Rossum.[25]

The most potent and selective compound of the series, **13**, was examined in vivo and its antihypertensive activity as well as its effect on heart rate were compared to those of prazosin and doxazosin. After intragastric administration, the effects of **13** on blood pressure and heart rate were continuously monitored in freely-moving spontaneously hypertensive rats (SHR) for 30 h after dosing, following a previously described standard protocol.[26] Experimental data were expressed as mean ± SEM and subjected to statistical analysis performed by means of paired Student's *t*-test. Statistical significance was set at $p < 0.05$.

Results and Discussion

The pharmacological results at α_1- and α_2-adrenoreceptors of compounds **3–14** are reported in Table I together with those of the standard compounds prazosin (**1**) and **2** for comparison. All compounds were competitive antagonists as revealed by the slope of the Schild plots, which were not significantly different from unity.

Our study began with the synthesis and evaluation of α-adrenoreceptor blocking activity of the two isomers **5** and **6**, since these are cyclic analogs of **2**. Furthermore, they have lipophilic properties similar to those of **2**. Both **5** and **6** were found to be very weak α_1-adrenoreceptor antagonists as revealed by their pA_2 values, which were 3 orders of magnitude lower than those of either prazosin or **2**. These results are surprising only apparently if one compares the biological profile of **5** and **6** with that of the related ethane chain-bearing compound **30** (pA_2 α_1 = 7.18 ± 0.21).[27] The low affinity of **30**, compared to prazosin, was explained by way of steric hindrance between the two *N*-methyl groups that would force the molecule to assume a conformation different from that adopted by prazosin. This hypothesis was supported by the finding that the



N,N'-desmethyl analog **31**, in which the steric hindrance was diminished by replacing the two methyl groups with two hydrogen atoms, was significantly more potent (pA_2 α_1 = 8.81)[27] than **30**, and as active as prazosin. A similar structural modification was performed on **5** and **6**, affording the corresponding desmethyl analogs **3** and **4**, respectively. In this case, however, the affinity for α_1-adrenoreceptors was not improved since the two pairs of compound were almost equiactive. This clearly indicates that the presence of a cyclohexane moiety, contrary to a linear alkane chain as in **2** and **31**, is highly detrimental for the affinity toward α_1-adrenoreceptors by way of a possible alteration of the distance between quinazoline and furan rings that would prevent an optimal interaction with the receptor. Furthermore, a cis or trans relationship between the two substituents in **3**–**6** does not seem to play a role.

Considering the above results, our attention was focused on studying new substituted piperazine-bearing compounds hopefully able to keep the spatial arrangement of prazosin. Following this reasoning, we designed *cis*- and *trans*-decahydroquinoxaline analogs (**13** and **14**) of prazosin that are closely related to both prazosin and **2**, as they bear a piperazine nucleus as in prazosin and the cyclohexane-constrained hexamethylene chain of **2**. Isomers **13** and **14** proved effective α_1-adrenoreceptor antagonists. Both isomers were very weak α_2-adrenoreceptor antagonists whereas the cis isomer **13** was more than 1 order of magnitude more potent than the trans isomer **14** at α_1-adrenoreceptors. More importantly, a comparison between the open-chain analog **2** and the *cis*-decahydroquinoxaline derivative **13** reveals that the incorporation of a linear hexamethylene chain into a constrained structure such as a decahydroquinoxaline ring slightly increases the affinity for α_1-adrenoreceptors while markedly decreasing the affinity for α_2-adrenoreceptors by almost 2 orders of magnitude, as revealed by pA_2 values (Table I). Interestingly, both isomers **13** and **14** were less potent than prazosin at α_2-adrenoreceptors, whereas the cis isomer **13** was significantly more potent than prazosin at α_1-adrenoreceptors. This finding clearly indicates that the incorporation of the hexamethylene chain of **2** into a decahydroquinoxaline ring is highly detrimental toward α_2-adrenoreceptors either in a cis or in a trans relationship whereas the affinity for α_1-adrenoreceptors is negatively affected, compared to that of both prazosin and **2**, only for a trans relationship. As a consequence, the cis isomer cyclazosin (**13**) proved not only more potent but also more selective than prazosin, as revealed by their pA_2 values (8.97 ± 0.02 vs 8.54 ± 0.05) and α_1/α_2 selectivity ratios (7800 vs 1300). Evidently the stereochemical relationship of the decahydroquinoxaline ring plays an important role in drug–receptor interaction.

To determine the role of the cyclohexane ring of the decahydroquinoxaline moiety, we synthesized compounds **7**–**12** in which the cyclohexane nucleus was replaced by alkyl/hydrogen groups at the 2 and 3 positions of the piperazine ring. Opening of the cyclohexane ring of **13** and **14** afforded the corresponding diethyl analogs **11** and **12**. These compounds were potent α_1-adrenoreceptor antagonists and weak α_2-adrenoreceptor antagonists like the corresponding cyclic analogs **13** and **14**. Again the cis isomer **11** was significantly more potent than the trans isomer **12** toward α_1-adrenoreceptors and almost as active as **13**. However, its selectivity was significantly lower than that of **13** owing to a substantial increase in the affinity for α_2-adrenoreceptors. Replacing the two ethyl with two methyl groups, affording **9** and **10**, did not modify the pharmacological profile at α-adrenoreceptors. Thus replacing the cyclohexane ring of **13** or **14** with ethyl or methyl functions does not markedly alter the affinity for α_1-adrenoreceptors, whereas it significantly affects the affinity for α_2-adrenoreceptors. The overall result of this structural manipulation was a significant decrease in selectivity for cis isomers (compare **9** and **11** to **13**). Evidently a trans relationship is always detrimental for α_2-affinity whereas a cis one gives rise to an increase in α_2-affinity going from a cyclohexane (**13**) to a diethyl (**11**) or a dimethyl moiety (**9**), likely due to a decrease in steric hindrance.

To verify the importance of the two methyl groups of **9** in the interaction process with α-adrenoreceptor subtypes, they were replaced alternatively by a hydrogen atom, affording **7** and **8**. A close inspection of the results reveals that the methyl function at the position 2 or 3 of the piperazine ring plays an important role in both affinity and selectivity for α-adrenoreceptors. The 2-methyl derivative **7** was as active as prazosin at both α_1- and α_2-adrenoreceptors, whereas the 3-methyl analog **8** was significantly less potent at α_1-adrenoreceptors and significantly more potent at α_2-adrenoreceptors. Interestingly, the 2-methyl derivative **7** displayed a biological profile comparable to that of the most potent and selective compound of the series, **13**. Evidently a substituent at position 2 of the piperazine ring is detrimental for the affinity toward α_2-adrenoreceptors, while affinity for α_1-adrenoreceptors is not affected compared to **9**.

It would be very interesting to determine the biological activity of the enantiomers of **7** and **13**. Unfortunately, preliminary attempts to obtain these were unsuccessful for both compounds.

Cyclazosin (**13**) was evaluated in vivo, in comparison with prazosin and doxazosin, in freely-moving SHR, at the dose of 5 mg/kg. Blood pressure and heart rate were continuously monitored for 30 h after dosing and the results are shown in Figure 1.

As expected, prazosin and doxazosin, at 5 mg/kg, gave a marked hypotensive effect with a similar blood pressure drop, and were statistically indistinguishable from each other in the first 12 h after administration. At 24 h, however, the effect of prazosin was still statistically significant ($p < 0.01$), while in doxazosin-treated rats blood pressure was back to control level. At the same dose, cyclazosin (**13**) produced a marked drop in mean blood pressure which remained statistically significant up to 12 h after administration. Its effect was similar and not significantly different from that evoked by doxazosin, but significantly less than that of prazosin at 12 and 24 h after administration. Concerning the effect on heart rate, cyclazosin, like prazosin and doxazosin, caused no significant change in respect to control rats.

Conclusion

We demonstrated that insertion of the alkane chain of **2** into a decahydroquinoxaline nucleus, affording **13**,

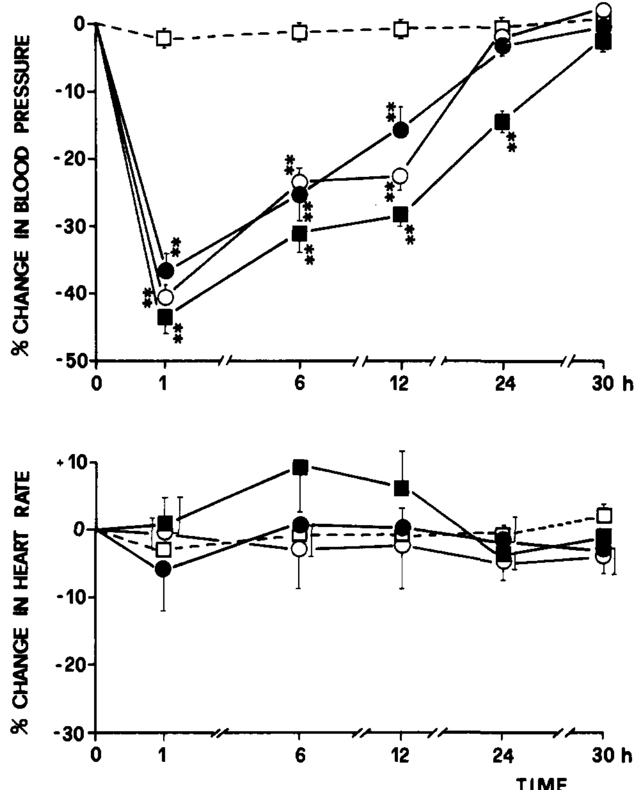


Figure 1. Changes in blood pressure (upper panel) and in heart rate (lower panel) in SHR following intragastric administration of isotonic saline (□) or of 5 mg/kg of prazosin (■), doxazosin (○), and **13** (●). Each point is the mean ± SEM of five subjects (isotonic saline and **13**) or of four subjects (prazosin and doxazosin). Difference from controls: $^{**}p < 0.01$; where not indicated, the difference from controls was not statistically significant.

increases selectivity and affinity for α_1-adrenoreceptors. The high selectivity of **13** could be the result of an unfavorable binding of the *cis*-decahydroquinoxaline ring with α_2-adrenoreceptors, presumably by way of a steric hindrance, while that moiety would interact optimally at the α_1-site, where it produces an increase in affinity. These results suggest also that the selectivity for α_1-adrenoreceptors is strictly related to the presence of a piperazine ring, especially when its flexibility is further reduced by incorporation into a *cis*-decahydroquinoxaline moiety. Thus the hypothesis that the α_1-adrenoreceptor incorporates a lipophilic area,[10] located between the binding sites for quinazoline and furan moieties of prazosin, has been further supported by the present investigation. Furthermore, that lipophilic site appears to have a well-defined spatial orientation since cis isomers (**9**, **11** and **13**) were significantly more potent than the corresponding trans isomers.

The quinoxalinyl derivative cyclazosin (**13**) proved not only a potent and selective α_1-adrenoreceptor antagonist in vitro assays but also an effective antihypertensive agent in the rat. Its duration of action was statistically significant 12 h after administration like doxazosin, although it remained slightly less potent than prazosin. However, given the importance of metabolism and kinetics on the hypotensive effect of prazosin and doxazosin,[28,29] which are markedly dependent on species,[30] it would be interesting to evaluate these parameters as well as the time course of antihypertensive activity of **13** in man.

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Büchi SMP-20 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian VXR 300 instruments, respectively. Although the IR spectra data are not included (because of the lack of unusual features), they were obtained for all compounds reported and were consistent with the assigned structures. The elemental compositions of the compounds agreed to within ±0.4% of the calculated value. Mass spectra were performed with a Hewlett-Packard instrument consisting of a Model 5890 A for the separation section and a Model 5971 A for the mass section. Analytical GC analyses were performed with a Carlo Erba Fractovap 4160 instrument; capillary column, OV_1 duran glass, 25 × 0.3 mm; film thickness, 0.40–0.45 μm; injector temperature, 300 °C; detector flame ionization, 300 °C; carrier, nitrogen at 3 mL/min; column temperature, 65 °C; program, 3 min at 65 °C and then from 65 to 300 °C at 15 °C/min and held. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040–0.063 mm, Merck) by flash chromatography. R_f values were determined with silica gel TLC plates (Kieselgel 60 F_{254}, 0.25-mm layer thickness, Merck). The composition and volumetric ratio of eluting mixtures were A, petroleum ether–ethyl acetate–methanol–28% ammonia (8:6:2:0.2); B, petroleum ether–ethyl acetate–methanol–28% ammonia (3:7:4:0.6); C, methanol–14% ammonia (18.8:1.2); D, petroleum ether–chloroform–methanol–28% ammonia (7.5:12.5:4.0:0.25); E, petroleum ether–ethyl acetate–methanol–28% ammonia (8:6:1.5:0.1); F, cyclohexane–ethyl acetate–methanol (7:7:2); G, cyclohexane–ethyl acetate–chloroform–methanol (2:7:3:3); H, cyclohexane–ethyl acetate–methanol (7:7:2), I, cyclohexane–ethyl acetate–methanol (7:7:1.5); L, cyclohexane–ethyl acetate–methanol (7:7:1); M, ethyl acetate–methanol (8:3); N, petroleum ether–ethyl acetate–methanol–28% ammonia (10:4:3:0.1); O, petroleum ether–ethyl acetate–methanol–28% ammonia (10:4:1.5:0.1); P, petroleum ether–ethyl acetate–methanol–28% ammonia (3:7:3:0.3); Q, petroleum ether–chloroform–methanol–28% ammonia (7.5:12.5:5.0:0.25); R, petroleum ether–chloroform–methanol–28% ammonia (7.5:12.5:2.5:0.25). Petroleum ether refers to the fraction with a boiling point of 40–60 °C. The term "dried" refers to the use of anhydrous sodium sulfate. Compounds were named following IUPAC rules as applied by AUTONOM, PC software for generating systematic names in organic chemistry (Beilstein-Institut and Springer-Verlag).

***cis*-2,3-Diethylpiperazine (28).** A solution of 2,3-diethyl-5,6-dihydropyrazine (16.4 g, 118 mmol) in dry Et_2O (80 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (7.2 g, 189 mmol) in dry Et_2O (420 mL) under N_2. Stirring was continued for 2 h at room temperature, for 30 min under reflux, and for another 72 h at room temperature. Excess $LiAlH_4$ was carefully destroyed in aqueous basic medium, the inorganic salt being filtered off, and the solution was washed with Et_2O. The ethereal extracts were dried and evaporated to yield an oil that was purified by column chromatography. Eluting with mixture B gave 11.8 g (70%) of **28** as an oil: R_f 0.29 (mixture C); GC t_r 8.63 min; bp_{18} 94–97 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 8 Hz, 6, 2 CH_3), 1.18–1.33 (m, 2, CH_3CH_2), 1.45–1.60 (m, 2, CH_3CH_2), 1.75 (br s, 2, 2 NH, exchangeable with D_2O), 2.63–2.71 (m, 4, H-2, H-3, H-4, and H-5), 2.80–2.95 (m, 2, H-4 and H-5). ^1H NMR experiments at variable temperature from 25 to −60 °C in $CDCl_3$ showed broadening of signals relative first to multiplets at δ 1.45–1.60 and 2.63–2.95 and then to multiplets at δ 1.18–1.33 and 0.87. Dihydrochloride salt: mp 238–241 °C (EtOH). Anal. ($C_8H_{20}Cl_2N_2$) C, H, N.

***trans*-2,3-Diethylpiperazine (29).** Sodium (78.8 g) was added portionwise over 48 h to a mechanically stirred solution of 2,3-diethyl-5,6-dihydropyrazine (29.6 g, 0.21 mol) in absolute EtOH (1 L) under reflux and N_2. Refluxing was continued for an additional 12 h then H_2O (450 mL) was added dropwise while EtOH was distilled away. The aqueous mixture was extracted with Et_2O; the ethereal solution was dried and evaporated to give a red oil that was purified by column chromatography. Eluting with mixture B gave a few milligrams of **29** as a solid: mp 98–100 °C; R_f 0.36 (mixture C); GC t_r 8.32 min; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 8 Hz, 6, 2CH_3), 1.22–1.38 (m, 2, CH_3CH_2), 1.62–1.75 (m, 2, CH_3CH_2), 2.22–2.31 (m, 2, H-2 and H-3), 2.68–

2.80 (m, 2, H-4 and H-5), 2.85–2.98 (m, 2, H-4 and H-5), 3.25 (br s, 2, 2 NH, exchangeable with D_2O). ^1H NMR experiments at variable temperature from 25 to −60 °C in $CDCl_3$ did not reveal any change. Dihydrochloride salt: mp >260 °C (MeOH). Anal. ($C_8H_{20}Cl_2N_2$) C, H, N.

The major fraction from the above column was a mixture of the two isomers **28** and **29** (trans/cis ratio 1.75), as shown by TLC and GC analysis. Pure **29** was obtained by the following procedure. Hydrobromic acid (48%) (1.85 g, 22.8 mmol) was added dropwise to a stirred solution of the above cis/trans mixture (9.1 g, 64 mmol) in EtOH (54 mL) and H_2O (6 mL) at 40–45 °C. The resulting solution was treated with 2-furoyl chloride (2.97 g, 22.8 mmol) over 15 min, stirred at 80 °C for 96 h and then concentrated at reduced pressure. After dilution with water and extraction with chloroform, the aqueous layer was made alkaline with 10% NaOH and extracted with chloroform. Removal of dried solvents gave 3.44 g (11%) of **29** as free base.

General Procedure for the Synthesis of Amides 16–18 and 20–25. Hydrobromic acid (48%) (1.44 g, 17.8 mmol) was added dropwise to a stirred solution of the appropriate diamine (25 mmol) (*cis*- or *trans*-2,3-diethylpiperazine, *trans*- or *cis*-decahydroquinoxaline[16,17]) in EtOH (26 mL) and H_2O (4 mL) at 40–45 °C. The resulting solution was treated dropwise with 2-furoyl chloride (1.16 g, 8.9 mmol) over 15 min, stirred at 80 °C for 3 h and then concentrated at reduced pressure, diluted with water, and extracted with chloroform. Removal of dried solvents gave a residue that was purified by column chromatography. Eluting with mixture A gave the desired compound (**22**, **23**, **24**, or **25**) as a solid. Compounds **22** and **23** were obtained in 80% and 15% yield, respectively, whereas the yield of **24** and **25** ranged within 30–50%.

Compounds **16–18**, **20**, and **21** were obtained in 30–50% yields starting from the appropriate diamine (*cis*- or *trans*-cyclohexane-1,2-diamine, *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine, *cis*- or *trans*-2,3-dimethylpiperazine) and 2-furoyl chloride following a slightly modified procedure. After the workup and extraction with chloroform in acidic medium to remove nonbasic materials, the reaction mixture was cooled, made strongly basic with NaOH pellets, and finally extracted with chloroform. Removal of dried solvent gave a residue that was purified as above to afford the desired compound.

Furan-2-carboxylic acid *cis*-2-aminocyclohexylamide (16): oil; R_f 0.33; GC t_r 16.15 min; ^1H NMR ($CDCl_3$) δ 1.35–1.80 (m, 8, 2 H-3, 2 H-4, 2 H-5, and 2 H-6 of cyclohexane), 2.27 (br s, 2, 2 NH, exchangeable with D_2O), 3.08–3.16 (m, 1, H-2 of cyclohexane), 4.03–4.12 (m, 1, H-1 of cyclohexane), 6.46 (m, 1, H-4 of furan), 6.98–7.06 (m, 1, CONH, exchangeable with D_2O), 7.06 (m, 1, H-3 of furan), 7.42 (m, 1, H-5 of furan).

Furan-2-carboxylic acid *trans*-2-aminocyclohexylamide (17): R_f 0.25; GC t_r 16.06 min; mp 98–101 °C; ^1H NMR ($CDCl_3$) δ 1.00–1.43 (m, 4, 2 H-4 and 2 H-5 of cyclohexane), 1.60 (br s, 2, 2 NH, exchangeable with D_2O), 1.66–2.10 (m, 4, 2 H-3 and 2 H-6 of cyclohexane), 2.40–2.53 (m, 1, H-2 of cyclohexane), 3.60–3.76 (m, 1, H-1 of cyclohexane), 6.20–6.38 (m, 1, CONH, exchangeable with D_2O), 6.49 (m, 1, H-4 of furan), 7.11 (m, 1, H-3 of furan), 7.42 (m, 1, H-5 of furan). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

Furan-2-carboxylic acid methyl-*trans*-2-(methylamino)-cyclohexylamide (18): oil; R_f 0.27, GC t_r 16.39 min; ^1H NMR ($CDCl_3$) δ 0.73–2.29 (m, 9, 2 H-3, 2 H-4, 2 H-5, and 2 H-6 of cyclohexane, and NH, exchangeable with D_2O), 2.39 (s, 3, CH_3-NH), 2.40–2.73 (m, 1, H-2 of cyclohexane), 3.07 (br s, 1, CH_3-NCO), 3.79–4.49 (m, 1, H-1 of cyclohexane), 6.46 (m, 1, H-4 of furan), 7.03 (m, 1, H-3 of furan), 7.49 (m, 1, H-5 of furan).

Furan-2-yl(*cis*-2,3-dimethylpiperazin-1-yl)methanone (20): R_f 0.26; GC t_r 14.69 min; mp 60–62 °C; ^1H NMR ($CDCl_3$) δ 1.04 (d, J = 6.6 Hz, 3, CH_3CHNH), 1.15–1.26 (m, 3, CH_3CHN), 1.54 (br s, 1, NH, exchangeable with D_2O), 2.85 (dt, J = 3.3 Hz, J' = 12 Hz, 1, H-5 of piperazine), 2.94–3.08 (m, 2, H-3 and H-5 of piperazine), 3.20–3.42 (m, 1, H-6 of piperazine), 4.07–4.71 (m, 2, H-2 and H-6 of piperazine), 6.48 (m, 1, H-4 of furan), 6.95 (m, 1, H-3 of furan), 7.47 (m, 1, H-5 of furan). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

Furan-2-yl(*trans*-2,3-dimethylpiperazin-1-yl)methanone (21): R_f 0.22; GC t_r 14.51 min; mp 77–79 °C; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.8 Hz, 3, CH_3CHNH), 1.42 (d, 6.8 Hz, 3, CH_3CHN), 2.80–2.87 (m, 1, H-5 of piperazine), 2.90 (br s, 1, NH, exchangeable with D_2O), 2.96 (dq, J = 2.2 Hz, J' = 6.8 Hz, 1, H-3 of piperazine), 3.10–3.30 (m, 2, H-5 and H-6 of piperazine), 4.24–432 (m, 1, H-6 of piperazine), 4.37 (dq, J = 2.2 and 6.8 Hz, 1, H-2 of piperazine), 6.46 (m, 1, H-4 of furan), 6.97 (m, 1, H-3 of furan), 7.46 (m, 1, H-5 of furan). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

Furan-2-yl(*cis*-2,3-diethylpiperazin-1-yl)methanone (22): R_f 0.40; GC: t_r 15.68 min; mp 42–44 °C; ^1H NMR ($CDCl_3$, 50 °C) δ 0.84 (br t, J = 7.3 Hz, 3, CH_3), 0.94 (t, J = 7.3 Hz, 3, CH_3), 1.30–1.55 (m, 3, CH_3CH_2CHNH (2) and CH_3CH_2CHNCO (1)), 1.78 (br s, 1, NH, exchangeable with D_2O), 1.82–1.95 (m, 1, CH_3CH_2CHNCO), 2.70–2.80 (m, 1, H-3 of piperazine), 2.80–3.40 (m, 3, 2 H-5 and H-6 of piperazine), 4.00–4.70 (br m, 2, H-2 and H-6 of piperazine), 6.43 (m, 1, H-4 of furan), 6.91 (m, 1, H-3 of furan), 7.43 (m, 1, H-5 of furan). Anal. ($C_{13}H_{20}N_2O_2$) C, H, N.

Furan-2-yl(*trans*-2,3-diethylpiperazin-1-yl)methanone (23): R_f 0.42; GC t_r 15.49 min; mp 129 °C dec; ^1H NMR ($CDCl_3$, 50 °C) δ 0.90 (t, J = 7.2 Hz, 3, CH_3), 0.93 (t, J = 7.2 Hz, 3, CH_3), 1.52–1.85 (m, 3, CH_3CH_2CHNH (2) and CH_3CH_2CHNCO (1)), 1.95–2.10 (m, 1, CH_3CH_2CHNCO), 2.62–2.67 (m, 1, H-3 of piperazine), 2.68–2.74 (m, 1, H-5 of piperazine), 2.96–3.07 (m, 1, H-5 of piperazine), 3.17 (br m, 1, H-6 of piperazine), 4.25 (br m, 2, H-2 and H-6 of piperazine), 6.48 (m, 1, H-4 of furan), 6.95 (m, 1, H-3 of furan), 7.45 (m, 1, H-5 of furan). Anal. ($C_{13}H_{20}N_2O_2$) C, H, N.

Furan-2-yl(*cis*-octahydroquinoxalin-1-yl)methanone (24): R_f 0.36; GC t_r 17.69 min; mp 178 °C dec; ^1H NMR ($CDCl_3$) δ 1.20–1.90 (m, 8, 2 H-5, 2 H-6, 2 H-7, and 2 H-8 of quinoxaline), 2.00–2.35 (m, 1, H-3 of quinoxaline), 2.75 (br s, 1, NH, exchangeable with D_2O), 2.80–3.20 (m, 3, H-2, H-3, and H-4a of quinoxaline), 4.10–4.60 (m, 2, H-2 and H-8a of quinoxaline), 6.51 (m, 1, H-4 of furan), 6.95 (m, 1, H-3 of furan), 7.50 (m, 1, H-5 of furan). Anal. ($C_{13}H_{18}N_2O_2 \cdot 0.25H_2O$) C, H, N.

Furan-2-yl(*trans*-octahydroquinoxalin-1-yl)methanone (25): R_f 0.25; GC t_r 17.57 min; mp 121–124 °C; ^1H NMR ($CDCl_3$) δ 1.20–1.85 (m, 6, 2 H-5, 2 H-6, and 2 H-7 of quinoxaline), 1.90–2.05 (m, 1, H-8 of quinoxaline), 2.20–2.35 (m, 1, H-8 of quinoxaline), 2.45 (br s, 1, NH, exchangeable with D_2O), 2.81–3.34 (m, 3, H-2, H-3, and H-4a of quinoxaline), 3.50–3.75 (m, 2, H-2 and H-3 of quinoxaline), 3.90–4.05 (m, 1, H-8a of quinoxaline), 6.45 (m, 1, H-4 of furan), 7.00 (m, 1, H-3 of furan), 7.45 (m, 1, H-5 of furan). Anal. ($C_{13}H_{18}N_2O_2$) C, H, N.

Furan-2-yl(2-methylpiperazin-1-yl)methanone (19). A solution of BOC-ON (4.1 g, 16.6 mmol) in $CHCl_3$ (30 mL) was added dropwise over 30 min to a stirred mixture of 2-methylpiperazine (10 g, 99.8 mmol) and triethylamine (2.52 g, 24.9 mmol) in $CHCl_3$ (60 mL). After stirring for 15 h, the mixture was washed with H_2O. Removal of dried solvents gave a residue that was purified by column chromatography. Eluting with mixture N afforded 3 g (90%, based on BOC-ON) of **3-methylpiperazine-1-carboxylic acid *tert*-butyl ester** as an oil: R_f 0.33; ^1H NMR ($CDCl_3$) δ 1.04 (d, J = 5.5 Hz, 3, CH_3), 1.47 (s, 9, $(CH_3)_3C$), 1.72 (br s, 1, NH, exchangeable with D_2O), 2.25–2.49 (m, 1, H-2), 2.64–2.85 (m, 3, H-3 and 2 H-5), 2.87–3.00 (m, 1, H-6), 3.78–4.50 (m, 2, H-2 and H-6); MS m/z 200 $[M]^+$.

2-Furoyl chloride (0.65 g, 5 mmol) in $CHCl_3$ (30 mL) was slowly added to a stirred solution of 3-methylpiperazine-1-carboxylic acid *tert*-butyl ester (1 g, 5 mmol) and triethylamine (0.5 g, 5 mmol) in $CHCl_3$ (75 mL). After stirring at room temperature for 48 h, the solvent was evaporated and the residue purified by column chromatography. Eluting with mixture O afforded **4-(furan-2-ylcarbonyl)-3-methylpiperazine-1-carboxylic acid *tert*-butyl ester** in quantitative yield: mp 65–67 °C; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 7.5 Hz, 3, CH_3), 1.42 (s, 9, $(CH_3)_3C$), 2.77–3.15 (m, 2, H-5 and H-6 of piperazine), 3.17–3.40 (m, 1, H-2 of piperazine), 3.77–4.23 (m, 2, H-2 and H-6 of piperazine), 4.24–4.40 (m, 1, H-5 of piperazine), 4.64–4.80 (m, 1, H-3 of piperazine), 6.47 (m, 1, H-4 of furan), 6.97 (m, 1, H-3 of furan), 7.47 (m, 1, H-5 of furan); MS m/z 294 $[M]^+$. Anal. ($C_{15}H_{22}N_2O_4$) C, H, N.

A 2.5 N solution of HCl/EtOH (20 mL) was added to 4-(furan-2-ylcarbonyl)-3-methylpiperazine-1-carboxylic acid *tert*-butyl ester (0.5 g, 1.7 mmol), the resulting mixture was stirred at room temperature for 48 h. The solvent was evaporated and 1 N NaOH was added to the residue that was extracted with $CHCl_3$. Removal of dried solvents afforded a residue that was purified by column chromatography. Eluting with mixture A gave 0.3 g (91%) of **19** as an oil: R_f 0.18; ^1H NMR ($CDCl_3$) δ 1.40 (d, J = 6.7 Hz, 3, CH_3),

1.69 (br s, 1, NH, exchangeable with D_2O), 2.71–2.91 (m, 2, H-3 and H-5 of piperazine), 2.93–3.10 (m, 2, H-3 and H-5 of piperazine), 3.14–3.32 (m, 1, H-6 of piperazine), 4.22–4.37 (m, 1, H-6 of piperazine), 4.57–4.73 (m, 1, H-2 of piperazine), 6.47 (m, 1, H-4 of furan), 6.96 (m, 1, H-3 of furan), 7.47 (m, 1, H-5 of furan); MS m/z 194 $[M]^+$.

General Procedure for the Synthesis of 3, 4, 6, 7, and 9–14. A mixture of the appropriate amide (**16–25**) (3.85 mmol) and **15** (0.46 g, 1.92 mmol) in isoamyl alcohol (15 mL) was stirred under reflux for 72 h. The solvent was distilled in vacuo and the residue purified by column chromatography. Eluting with an appropriate mixture gave a solid that was transformed into the hydrochloride salt (**3**, **4**, **6**, **9**, **11**, **12**, or **14**) in 15–30% yields. Compounds **7** and **13** were purified in 78% and 30% yield, respectively, by crystallizing the solid obtained upon cooling the reaction mixture. Compound **10** was purified in 25% yield by crystallizing the residue obtained after removal of the reaction solvent.

Furan-2-carboxylic acid *cis*-2-[(4-amino-6,7-dimethoxyquinazolin-2-yl)amino]cyclohexylamide hydrochloride (3): eluting mixture, E; mp 265–268 °C (MeOH/2-PrOH); ^1H NMR (DMSO-d_6) δ 1.35–1.95 (m, 8, 2 H-3, 2 H-4, 2 H-5, and 2 H-6 of cyclohexane), 3.82 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 4.15–4.45 (m, 2, H-1 and H-2 of cyclohexane), 6.60 (m, 1, H-4 of furan), 6.80 (br s, 1, phenyl), 7.15 (m, 1, H-3 of furan), 7.68 (s, 1, phenyl), 7.78 (m, 1, H-5 of furan), 7.93 (br s, 2, NH, exchangeable, and NHCO, slowly exchangeable with D_2O), 8.57 (br s, 1, NH, exchangeable with D_2O), 8.80 (br s, 1, NH, exchangeable with D_2O), 12.30 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{21}H_{26}ClN_5O_4 \cdot 0.5H_2O$) C, H, N.

Furan-2-carboxylic acid *trans*-2-[(4-amino-6,7-dimethoxyquinazolin-2-yl)amino]cyclohexylamide hydrochloride (4): eluting mixture, E; mp 259–261 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.20–2.20 (m, 8, 2 H-3, 2 H-4, 2 H-5, and 2 H-6 of cyclohexane), 3.81 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 3.90–4.28 (m, 2, H-1 and H-2 of cyclohexane), 6.52 (m, 1, H-4 of furan), 6.85 (s, br, 1, phenyl), 7.08 (m, 1, H-3 of furan), 7.70 (br s, 2, H of phenyl and H-5 of furan), 8.30 (br s, 2, NH, exchangeable, and NHCO, slowly exchangeable with D_2O), 8.63 (br s, 1, NH, exchangeable with D_2O), 8.95 (br s, 1, NH, exchangeable with D_2O), 12.25 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{21}H_{26}ClN_5O_4 \cdot H_2O$) C, H, N.

Furan-2-carboxylic acid [*trans*-2-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]cyclohexyl]methylamide hydrochloride (6): eluting mixture G; mp >234 °C dec (2-PrOH); ^1H NMR (DMSO-d_6) δ 1.20–1.92 (m, 8, 2 H-3, 2 H-4, 2 H-5, and 2 H-6 of cyclohexane), 2.60–2.85 (m, 3, CH_3-NCO), 3.00 (br s, 3, CH_3N), 3.82 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 4.62–4.84 (m, 1, H-1 of cyclohexane), 4.93–5.10 (m, 1, H-2 of cyclohexane), 6.52 (m, 1, H-4 of furan), 6.83 (m, 1, H-3 of furan), 7.40 (br s, 1, phenyl), 7.70 (m, 1, H-5 of furan), 7.72 (br s, 1, phenyl), 8.62 (br s, 1, NH, exchangeable with D_2O), 8.85 (br s, 1, NH, exchangeable with D_2O), 11.48 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{23}H_{30}ClN_5O_4 \cdot H_2O \cdot C_3H_8O$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-2-methylpiperazin-1-yl]furan-2-ylmethanone hydrochloride (7): mp 273–274 °C (MeOH/2-PrOH); ^1H NMR (DMSO-d_6) δ 1.23 (d, J = 7.4 Hz, 3, CH_3CH), 3.38–3.68 (m, 3, H-3, H-5, and H-6 of piperazine), 3.83 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 4.23–4.38 (m, 1, H-6 of piperazine), 4.40–4.58 (m, 2, H-3 and H-5 of piperazine), 4.60–4.83 (m, 1, H-2 of piperazine), 6.65 (m, 1, H-4 of furan), 7.05 (m, 1, H-3 of furan), 7.49 (br s, 1, phenyl), 7.71 (s, 1, phenyl), 7.88 (m, 1, H-5 of furan), 8.68 (br s, 1, NH, exchangeable with D_2O), 8.89 (br s, 1, NH, exchangeable with D_2O), 12.23 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{20}H_{24}ClN_5O_4 \cdot 0.25H_2O$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*cis*-2,3-dimethylpiperazin-1-yl]furan-2-ylmethanone hydrochloride (9): eluting mixture, F; mp 188 °C dec (2-PrOH); ^1H NMR (DMSO-d_6) δ 1.36 (d, J = 6.2 Hz, 3, CH_3CHN), 1.40 (d, J = 6.2 Hz, 3, CH_3CHNCO), 3.65–3.75 (m, 1, H-5 of piperazine), 3.83 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 3.78–3.90 (m, 1, H-6 of piperazine), 4.05–4.25 (m, 2, H-5 and H-6 of piperazine), 4.57 (quintuplet, $J_{2,3}$ = 6.6 Hz, 1, H-3 of piperazine), 4.90 (quintuplet, $J_{2,3}$ = 6.6 Hz, 1, H-2 of piperazine), 6.65 (m, 1, H-4 of furan), 7.08 (m, 1, H-3 of furan), 7.52 (s, 1, phenyl), 7.66 (s, 1, phenyl), 7.88 (m, 1, H-5 of furan), 8.66 (br s, 1, NH, exchangeable with D_2O), 8.92 (br s, 1, NH, exchangeable with D_2O), 12.06 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{21}H_{26}ClN_5O_4 \cdot 2H_2O$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*trans*-2,3-dimethylpiperazin-1-yl]furan-2-ylmethanone hydrochloride (10): mp 235–238 °C (MeOH); ^1H NMR (DMSO-d_6) δ 1.15–1.42 (m, 6, 2 CH_3CH), 3.85 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 3.72–3.98 (m, 1, H-5 of piperazine), 4.18–4.470 (m, 4, H-3, H-5, and 2 H-6 of piperazine), 4.80–5.00 (m, 1, H-2 of piperazine), 6.68 (m, 1, H-4 of furan), 7.08 (m, 1, H-3 of furan), 7.65 (br s, 1, phenyl), 7.75 (s, 1, phenyl), 7.90 (m, 1, H-5 of furan), 8.70 (br, s, 1, NH, exchangeable with D_2O), 8.95 (br s, 1, NH, exchangeable with D_2O), 12.40 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{21}H_{26}ClN_5O_4 \cdot 0.5H_2O$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*cis*-2,3-diethylpiperazin-1-yl]furan-2-ylmethanone hydrochloride (11): eluting mixture, L; mp 244–247 °C (2-PrOH/Et_2O); ^1H NMR (DMSO-d_6) δ 0.85–0.96 (m, 6, 2 CH_3CH_2), 1.66–2.06 (m, 4, 2 CH_3CH_2), 3.44–3.60 (m, 1, H-5 of piperazine), 3.66–3.80 (m, 1, H-6 of piperazine), 3.83 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 4.00–4.16 (m, 1, H-5 of piperazine), 4.34–4.44 (m, 2, H-3 and H-6 of piperazine), 5.01 (q, $J_{2,3}$ = 7.0 Hz, 1, H-2 of piperazine), 6.65 (m, 1, H-4 of furan), 7.05 (m, 1, H-3 of furan), 7.63 (br s, 1, phenyl), 7.72 (s, 1, phenyl), 7.83 (m, 1, H-5 of furan), 8.62 (br s, 1, NH, exchangeable with D_2O), 8.90 (br s, 1, NH, exchangeable with D_2O), 12.35 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{23}H_{30}ClN_5O_4$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*trans*-2,3-diethylpiperazin-1-yl]furan-2-ylmethanone hydrochloride (12): eluting mixture, I; mp 217–220 °C (2-PrOH/Et_2O); ^1H NMR (DMSO-d_6) δ 0.65–0.94 (m, 6, 2 CH_3CH_2), 1.46–1.88 (m, 4, 2 CH_3CH_2), 2.90–3.60 (m, 2, H-5 and H-6 of piperazine), 3.83 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 4.10–4.70 (m, 3, H-3, H-5, and H-6 of piperazine), 4.75–5.07 (m, 1, H-2 of piperazine), 6.68 (m, 1, H-4 of furan), 7.05 (m, 1, H-3 of furan), 7.74 (s, 2, phenyl), 7.90 (m, 1, H-5 of furan), 8.68 (br s, 1, NH, exchangeable with D_2O), 8.92 (br s, 1, NH, exchangeable with D_2O), 12.40 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{23}H_{30}ClN_5O_4 \cdot 1.5H_2O$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*cis*-octahydroquinoxalin-1-yl]furan-2-ylmethanone hydrochloride (13; cyclazosin): mp 272–274 °C (EtOH); ^1H NMR (DMSO-d_6) δ 1.30–2.40 (m, 8, 2 H-5, 2 H-6, 2 H-7, and 2 H-8 of quinoxaline), 3.84 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.90–4.20 (m, 4, 2 H-2 and 2 H-3 of quinoxaline), 4.45 (q, 1, H-4a of quinoxaline), 4.68 (m, $J_{4a,8a}$ = 4.9 Hz, 1, H-8a of quinoxaline), 6.68 (m, 1, H-4 of furan), 7.12 (m, 1, H-3 of furan), 7.62 (s, 1, phenyl), 7.76 (s, 1, phenyl), 7.90 (m, 1, H-5 of furan), 8.63 (br s, 1, NH, exchangeable with D_2O), 8.91 (br, 1, NH, exchangeable with D_2O), 12.03 (br, 1, NH, exchangeable with D_2O). Anal. ($C_{23}H_{28}ClN_5O_4$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*trans*-octahydroquinoxalin-1-yl]furan-2-ylmethanone hydrochloride (14): eluting mixture, F; mp >275 °C (2-PrOH); ^1H NMR (DMSO-d_6) δ 1.23–2.42 (m, 8, 2 H-5, 2 H-6, 2 H-7, and 2 H-8 of quinoxaline), 3.83 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 3.60–4.00 (m, 4, H-2, 2 H-3 and H-4a of quinoxaline), 4.23–4.38 (m, 1, H-8a of quinoxaline), 4.42–4.60 (m, 1, H-2 of quinoxaline), 6.60 (m, 1, H-4 of furan), 7.00 (m, 1, H-3 of furan), 7.50 (s, 1, phenyl), 7.72 (s, 1, phenyl), 7.83 (m, 1, H-5 of furan), 8.61 (br, s, 1, NH, exchangeable with D_2O), 8.90 (br s, 1, NH, exchangeable with D_2O), 12.03 (br, 1, NH, exchangeable with D_2O). Anal. ($C_{23}H_{28}ClN_5O_4 \cdot 0.5H_2O \cdot 0.5C_3H_8O$) C, H, N.

6,7-Dimethoxy-2-(2-methylpiperazin-1-yl)quinazolin-4-ylamine (26). A mixture of **15** (3.48 g, 14.5 mmol) and 3-methylpiperazine-1-carboxylic acid ethyl ester (5 g, 29.1 mmol) in isoamyl alcohol (100 mL) was stirred under reflux for 72 h. After cooling a white solid was obtained that was recrystallized from 2-PrOH to give **4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-3-methylpiperazine-1-carboxylic acid ethyl ester hydrochloride:** 2.7 g (42%); mp 242–243 °C, ^1H NMR (DMSO-d_6, 80 °C) δ 1.12 (m, 6, CH_3CH_2O and CH_3CH), 3.05–3.43 (m, 3, H-2, H-5, and H-6 of piperazine), 3.83–3.89 (m, 1, H-2 of piperazine), 3.87 (s, 3, OCH_3), 3.91 (s, 3, OCH_3), 3.95–4.06 (m, 1, H-6 of piperazine), 4.08–4.18 (m, 2, CH_3CH_2O), 4.32–4.46 (m, 1,

H-5 of piperazine), 4.78–4.92 (m, 1, H-3 of piperazine), 7.43 (s, 1, phenyl), 7.71 (s, 1, phenyl). Anal. ($C_{18}H_{26}ClN_5O_4{\cdot}2H_2O$) C, H, N.

Thirty percent sodium hydroxide (11.2 g, 84 mmol) was added to a hot solution of the above compound (2.5 g, 5.6 mmol) in EtOH (40 mL), and then the mixture was stirred under reflux for 112 h. After cooling, the mixture was filtered and the solvent evaporated to give a residue that was purified by column chromatography. Eluting with mixture D gave **26** as an oil: 0.4 g (25%); R_f 0.34; ^{1}H NMR (DMSO-d_6) δ 1.40 (d, J = 7.7 Hz, 3, CH_3CH), 2.94–3.60 (m, 5, 2 H-3, 2 H-5, and H-6 of piperazine), 3.85 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 4.63 (m, 1, H-6 of piperazine), 5.08–5.22 (m, 1, H-2 of piperazine), 7.30 (br s, 1, phenyl), 7.68 (s, 1, phenyl). It was used without further purification.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-3-methylpiperazin-1-yl]furan-2-ylmethanone Hydrochloride (8). 2-Furoyl chloride (0.17 g, 1.3 mmol) in dry chloroform (10 mL) was added dropwise over 20 min to a stirred solution of **26** (0.4 g, 1.3 mmol) in chloroform (25 mL). After 24 h the solvent was removed and the residue purified by column chromatography. Eluting with mixture E gave a solid that was transformed into the hydrochloride salt **8**: yield 0.22 g (35%); mp 221–223 °C (2-PrOH); ^{1}H NMR (DMSO-d_6) δ 1.25 (d, J = 6.6 Hz, 3, CH_3CH), 3.25–3.60 (m, 3, H-2, H-5, and H-6 of piperazine), 3.85 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 4.23 (br d, J = 14.5 Hz, 1, H-2 of piperazine), 4.36 (br d, J = 14.5 Hz, 1, H-6 of piperazine), 4.53 (br d, J = 14.5 Hz, 1, H-5 of piperazine), 4.90–5.06 (m, 1, H-3 of piperazine), 6.70 (m, 1, H-4 of furan), 7.10 (m, 1, H-3 of furan), 7.68 (br s, 1, phenyl), 7.77 (s, 1, phenyl), 7.90 (m, 1, H-5 of furan), 8.70 (br s, 1, NH, exchangeable with D_2O), 8.95 (br s, 1, NH, exchangeable with D_2O), 12.42 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{20}H_{24}ClN_5O_4{\cdot}2H_2O$) C, H, N.

6,7-Dimethoxy-N^2-methyl-N^2-[*cis*-2-(methylamino)cyclohexyl]quinazoline-2,4-diamine Hydrochloride (27). A stirred mixture of *cis*-*N*,*N'*-dimethylcyclohexane-1,2-diamine (1.28 g, 9 mmol) and **15** (1.08 g, 4.5 mmol) in isoamyl alcohol (15 mL) was stirred under reflux for 72 h. The solvent was removed and the residue purified by column chromatography. Eluting consecutively with mixtures P and Q gave **27** as a solid: 0.3 g (19%); mp 145–148 °C; MS m/z 345 [M]$^+$; ^{1}H NMR ($CDCl_3$) δ 1.37–2.22 (m, 9, 2 H-3, 2 H-4, 2 H-5, and 2 H-6 of cyclohexane and NH, exchangeable with D_2O), 2.34 (br s, 3, CH_3NH), 3.10–3.20 (m, 1, H-2 of cyclohexane), 3.23 (s, 3, CH_3N), 3.92 (s, 3, OCH_3), 3.98 (s, 3, OCH_3), 4.40–4.70 (m, 1, H-1 of cyclohexane), 5.15 (br s, 2, NH_2, exchangeable with D_2O), 6.80 (s, 1, phenyl), 6.92 (s, 1, phenyl). It was used without further purification.

Furan-2-carboxylic Acid [*cis*-2-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]cyclohexyl]methylamide Hydrochloride (5). 2-Furoyl chloride (0.067 g, 0.49 mmol) in dry chloroform (10 mL) was added dropwise over 15 min to a stirred solution of **27** (0.17 g, 0.049 mmol) in chloroform (15 mL). After stirring for 24 h at room temperature, the solvent was removed and the residue purified by column chromatography. Eluting with mixture R gave a solid that was transformed into the hydrochloride salt **5**: 0.2 g (46%); mp 207–209 °C (2-PrOH/Et_2OH); ^{1}H NMR (DMSO-d_6) δ 1.38–2.20 (m, 8, 2 H-3, 2 H-4, 2 H-5, and 2 H-6 of cyclohexane), 3.00 (s, 3, CH_3N), 3.25 (s, 3, CH_3NCO), 3.83 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 4.58–5.20 (br m, 2, H-1 and H-2 of cyclohexane), 6.32–6.70 (br m, 1, H-4 of furan), 6.72–7.05 (br m, 1, H-3 of furan), 7.45 (br s, 1, phenyl), 7.60–7.82 (m, 2, H-5 of furan and H of phenyl), 8.43 (br s, 1, NH, exchangeable with D_2O), 8.75 (br s, 1, NH, exchangeable with D_2O), 11.48 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{23}H_{30}ClN_5O_4{\cdot}2H_2O{\cdot}{}^1/_3C_3H_8O$) C, H, N.

Biology. Pharmacological experiments were performed in rats. Given the low solubility in the physiological solution, the compounds were dissolved in 10–30% (v/v) MeOH/H_2O or DMSO/H_2O for in vitro experiments and in 2% (v/v) Poliglycoleum/H_2O for in vivo assays. Solutions were made by dissolving the drug in the cosolvent and then adding the proper amount of water.

Functional Antagonism in Isolated Rat Vas Deferens. Male albino rats (175–200 g) were killed by a sharp blow on the head and both vasa deferentia were isolated, freed from adhering connective tissue, and transversely bisected. Prostatic, 12 mm in length, and epididymal portions, 14 mm in length, were prepared and mounted individually in baths of 20-mL working volume containing Krebs solution of the following composition (mM): NaCl (118.4), KCl (4.7), $CaCl_2$ (2.52), $MgSO_4$ (1.2), KH_2PO_4 (1.2), $NaHCO_3$ (25.0), glucose (11.1). $MgSO_4$ concentration was reduced to 0.6 mM when twitch response to field stimulation was studied. The medium was maintained at 37 °C and gassed with 95% O_2–5% CO_2. The loading tension used to assess α_1- or α_2-blocking activities was 0.4 or 0.5–0.8 g, respectively, and contractions were recorded by means of force transducers connected to a two-channel Gemini 7070 polygraph.

Field stimulation of the tissue was carried out by means of two platinum electrodes, placed near the top and bottom of the vas deferens, at 0.1 Hz using square pulses of 3-ms duration at a voltage of 10–35 V. The stimulation voltage was fixed throughout the experiments. Propranolol hydrochloride (1 μM) and cocaine hydrochloride (10 μM) were present in the Krebs solution throughout the experiments outlined below to block β-adrenoreceptors and neuronal uptake mechanisms, respectively.

The α_1-adrenoreceptor blocking activity was determined on the epididymal portion of the vas deferens. The tissues were allowed to equilibrate for at least 1 h before addition of any drug. Norepinephrine dose–response curves were obtained cumulatively, the first one being discarded and the second one taken as control. After incubation with the antagonist for 30 min, a third dose–response curve was obtained. Responses were expressed as a percentage of the maximal response obtained in the control curve. Parallel experiments, in which tissues did not receive any antagonist, were run in order to correct for time-dependent changes in agonist sensitivity.[31] It was generally verified that the third dose–response curve was identical to the second because the change in dose–ratio was less than 2, which usually represents a minimal correction.

The antagonist potency of compounds at α_1-adrenoreceptors was expressed in terms of their dissociation constants.

The α_2-adrenoreceptor blocking activity was assessed on the prostatic portion of the vas deferens by antagonism to clonidine, which inhibits twitch responses of the field-stimulated vas deferens by acting on the α_2-adrenoreceptor.[32,33] The tissues were allowed to equilibrate for at least 1 h before addition of any drug. A first clonidine dose–response curve, taken as control, was obtained cumulatively avoiding the inhibition of more than 90% of twitch responses. Under these conditions it was possible to obtain a second dose–response curve which was not significantly different from the first one. Thus, after incubation with antagonist for 30 min, a second dose–response curve was obtained and dose–ratio (DR) values were determined from the concentration causing 50% inhibition of the twitch response in the absence and presence of antagonist. Parallel experiments, in which tissues did not receive any antagonist, were run in order to correct for time-dependent changes in agonist sensitivity and to determine concentration of agonist causing 100% inhibition of twitch responses. The results are expressed as dissociation constants.

The dissociation constants (pA_2 values, Table I) were determined by Schild plots[24] obtained from the dose ratios at the EC_{50} values of the agonists calculated at three antagonist concentrations. Each concentration was tested five times and Schild plots were constrained to a slope of -1, as required by theory.[34] When applying this method, it was always verified that the experimental data generated a line whose derived slope was not significantly different from unit ($p > 0.05$). Compounds **3–6**, **10**, and **13**, however, were tested at only two concentrations when determining α_2-adrenoreceptor blocking activity because of their low affinity for this receptor. In these cases, pA_2 values were calculated according to the method of van Rossum. Data are presented as the mean $\pm$ SE of n experiments. Differences between mean values were tested for significance by Student's t-test.

Antihypertensive Activity. Compounds were evaluated for their effects on blood pressure and heart rate in conscious male spontaneously hypertensive rats (SHR, 16–22 weeks old, Charles River Laboratories). Indwelling carotid catheters were implanted, under light ether anesthesia, for continuous direct measurement of blood pressure and heart rate in freely-moving rats as previously described.[26] After surgery, rats were housed in individual cages and allowed to recover at least 5 h before dosing. The drugs tested were administered by gavage at the dose of 5 mg/kg in a

volume of 5 mL/kg. Control rats received injection of the employed dissolving vehicle in a volume of 5 mL/kg. Every rat received only one administration of either vehicle or drug. Blood pressure, recorded by the arterial catheter connected to a pressure transducer (Bentley Trantec, Model 800), and heart rate, measured with a 7090 cardiotachographer connected with a two-channel recorder Gemini apparatus (Basile, model 7082), were monitored predose and at 1, 6, 12, 24, and 30 h following oral administration. Data are presented as means ± SEM. Statistical analysis of data was performed by means of split-plot multifactorial analysis of variance (ANOVA), with between-group comparisons for drug treatment and within-group comparisons for time after injection. Planned pairwise comparisons were made by means of Student's *t*-test. Statistical significance was set at $p < 0.05$.

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