Analogues of Prazosin That Bear a Benextramine-Related Polyamine Backbone Exhibit Different Antagonism toward α_1-Adrenoreceptor Subtypes

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Hybrid tetraaamine disulfides **4**−**9** were synthesized by combining the structural features of prazosin (**1**), a competitive α_1-adrenoreceptor antagonist, and benextramine (**2**), an irreversible α_1/α_2-adrenoreceptor antagonist, and their biological profiles at α_1-adrenoreceptor subtypes were assessed by functional experiments in isolated rat vas deferens (α_{1A}), spleen (α_{1B}), and aorta (α_{1D}). To verify the role of the disulfide moiety on the interaction with α_1-adrenoreceptor subtypes, carbon analogues **10**−**15** were included in this study. All quinazolines lacking the disulfide bridge behaved, like **1**, as competitive antagonists, whereas all polyamine disulfides displayed a nonhomogeneous mechanism of inhibition at the three subtypes since they were, like **2**, noncompetitive antagonists at the α_{1A} and α_{1B} subtypes while being, unlike **2**, competitive antagonists at the α_{1D}. In particular, the blocking effects were characterized by a decrease of the maximal response to noradrenaline that was affected only slightly by washings. Probably the α_{1A} and α_{1B} subtypes bear in the binding pocket a suitable thiol function that would suffer an interchange reaction with the disulfide moiety of the antagonist and which is missing, or not accessible, in the α_{1D} subtype. Polyamines **8**, **9**, and **14**, among others, emerged as promising tools for the characterization of α_1-adrenoreceptors, owing to their receptor subtype selectivity. Finally, the effect of nonbasic substituents on the phenyl ring of prazosin analogues **16**−**28** on potency and selectivity for the different subtypes can hardly be rationalized.

Introduction

Current evidence indicates that α_1-adrenoreceptors can be classified into at least three subtypes, that is, α_{1A} (α_{1a}), α_{1B} (α_{1b}), and α_{1D} (α_{1d}), with upper and lower case subscripts being used to designate native or recombinant receptors, respectively.[1−3] The existence of an additional subtype (α_{1L}) displaying a low affinity for prazosin has also been claimed. Although this α_1-adrenoreceptor subtype has not been cloned yet, its characterization may not be difficult since several isolated tissue models have been shown to have α_{1L} characteristics.[4]

The effort to design agents selective for each of the three α_1-adrenoreceptor subtypes has been an active area of research. While α_{1A}-adrenoreceptor antagonists might be useful in the treatment of benign prostatic hyperplasia,[5] a potential therapeutic use for both α_{1B}- and α_{1D}-subtype antagonists remains to be established.

A vast array of structurally unrelated compounds interacts with α_1-adrenoreceptor subtypes, which makes it difficult to determine the structural requirements leading to receptor subtype selectivity.[5] Our research group has long been involved in designing new α_1-adrenoreceptor antagonists that display different antagonism with the goal of developing high-affinity, site-selective ligands for α_1-adrenoreceptor subtypes. For example, we have investigated antagonists structurally related to prazosin (**1**),[6−11] the prototype of quinazoline-bearing compounds, which displays a competitive antagonism, and antagonists structurally related to benextramine (**2**),[12] the prototype of tetraamine disulfides, which inhibits α_1-adrenoreceptors by an irreversible (nonequilibrium in the kinetic sense) mechanism of action.

The observation that modifying both piperazine and furan rings of **1** may afford antagonists[10] that are able to differentiate among α_1-adrenoreceptor subtypes may form the basis to further modify the structure of these analogues, in an attempt to improve the selectivity. It turned out that the piperazine ring of **1** is not essential for activity and can be replaced by an α,ω-alkanediamine.[6,7] The most potent open analogue of **1** was the one bearing a 1,6-disubstituted hexanediamine moiety, and it was suggested that the hexane chain of this compound might contribute to the binding by interacting with a lipophilic site located between the sites where quinazoline and furan rings interact.[6] Since benextramine (**2**)[12] also has a 1,6-hexanediamine residue, separating the inner from the outer nitrogens of the structure allowed us to speculate that this alkane chain might interact with the same lipophilic pocket where prazosin analogues bind. To test this hypothesis we designed hybrid structures by combining the structural features of both prazosin and benextramine.[13] In these compounds, the tetraamine backbone of benextramine was kept constant owing to the observation that the four amine functions have already been shown to be important for α_1-adrenoreceptor blocking activity, whereas the

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terminal benzyl groups of benextramine were replaced with a quinazoline unit of prazosin because this functionality is essential for high affinity toward α_1-adrenoreceptors. Interestingly, all hybrid tetraamine disulfides investigated, unlike benextramine, did not irreversibly inhibit α_1-adrenoreceptors, rather they competitively antagonized agonist-induced responses such as prazosin.[13] This remarkable difference in the observed antagonism of hybrid tetraamine disulfides compared to benextramine stimulated our interest in designing new structures in which the whole structure of both benextramine and prazosin is almost retained.

The design strategy was based on the observation that the replacement of the furan ring of **1** with a phenyl moiety significantly increased the selectivity toward α_1-adrenoreceptors.[10] This finding convinced us to design prazosin analogues bearing a phenyl ring because it offered the possibility to investigate the effect of substituents on both affinity and selectivity. It turned out that the insertion of substituents on the benzene ring affected, according to the type and the position of the substituent, affinity and selectivity for α_1-adrenoreceptor subtypes. Interestingly, the insertion of a 1,6-hexanediamine moiety in the phenyl ring did not cause a decrease in affinity, which allowed us to conclude that the insertion of appropriate substituents in the phenyl ring may form the basis of designing new selective ligands for α_1-adrenoreceptor subtypes. In addition, the fact that a diamine function did not give rise to negative interactions with the receptor clearly indicates that the protonated amines recognize additional sites on the receptor.[10] Thus, the presence of a polyamine backbone might increase the possibility to achieve receptor subtype selectivity.

These observations taken together formed the basis for the synthesis of hybrid tetraamine disulfides **4**−**9**. Furthermore, the corresponding carbon analogues **10**−**15** were included in this study to verify the role, if any, of the disulfide functionality on the interaction with α_1-adrenoreceptor subtypes.

Finally, the presence of a phenyl ring in place of the furan ring of **1** in prazosin analogues afforded the opportunity to further examine the effect of substituents on both potency and selectivity toward α_1-adrenoreceptor subtypes. In the present study, our aim was to determine only whether electronic and/or lipophilic properties of substituents in all positions of the phenyl could exert any favorable effect on selectivity and affinity for α_1-adrenoreceptor subtypes, rather than assess a quantitative relationship. It seemed this could be determined with a few properly chosen substituents, which were selected in such a way as to have σ and π values in a positive or negative direction, in all combinations.[14] Comparison of the activity of these substituted derivatives with either the parent compound **1** or the unsubstituted analogue **16** should reveal the importance, if any, of one or both of these parameters. The compounds used were the CF_3 ($+\pi$, $+\sigma$), Me ($+\pi$, $-\sigma$), CHO ($-\pi$, $+\sigma$), and OMe ($-\pi$, $-\sigma$) derivatives (**17**−**28**).

The design strategy for our compounds is shown in Figure 1.

We describe here the synthesis and the pharmacological profile of hybrid polyamines **4**−**15** and substituted quinazolines **16**−**28** in functional experiments in comparison with prototypes prazosin (**1**), benextramine (**2**), and its carbon analogue **3**.

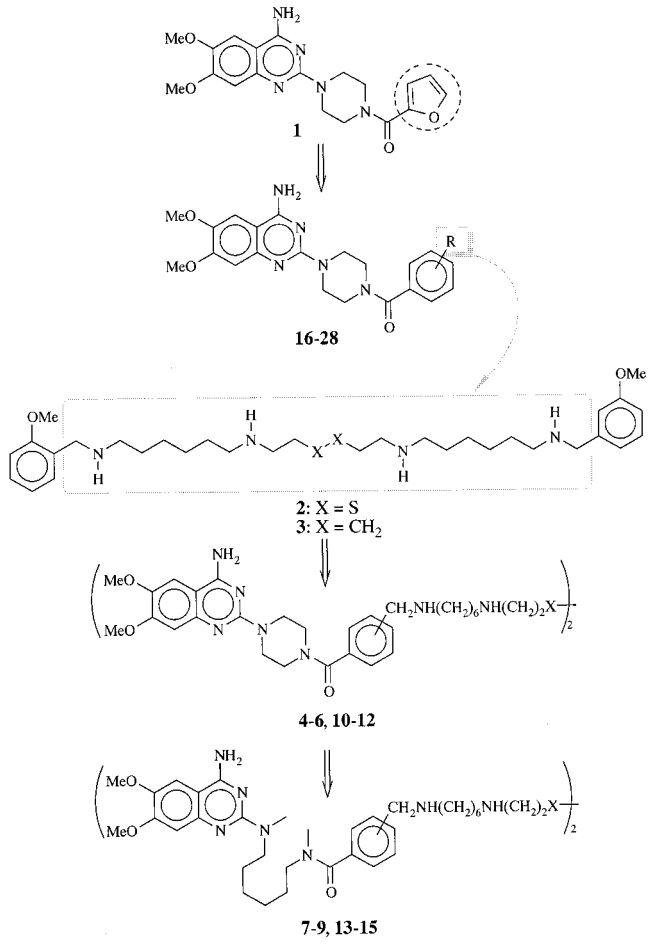
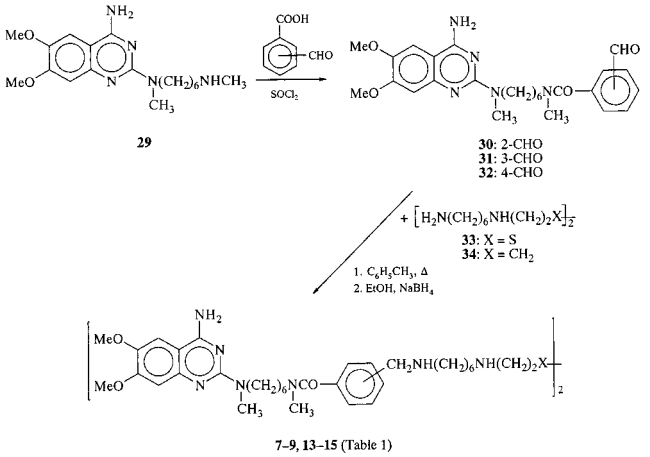


Figure 1. Design strategy for the synthesis of hybrid structures **4**−**15** by inserting the structural features of prazosin (**1**)-related compounds on the terminal nitrogens of the tetraamine backbone of benextramine (**2**) or of its carbon analogue (**3**).

Scheme 1

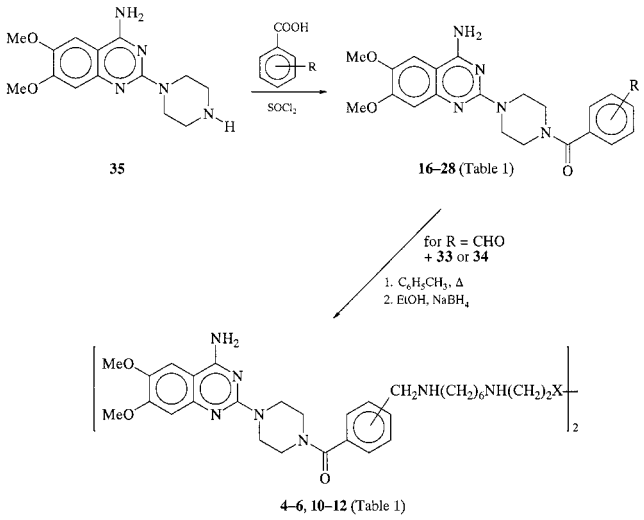


Chemistry

All the compounds were synthesized by standard procedures (Schemes 1 and 2) and were characterized by IR, ^{1}H NMR, mass spectra, and elemental analysis.

Aldehydes **31** and **32** were synthesized by following an adapted procedure described for **30**.[10] Thus, amida-

Scheme 2



tion of **29**[15] with 3-formyl- or 4-formyl-benzoyl chloride, which were generated in situ by treating the corresponding formylbenzoic acid with $SOCl_2$, afforded **31** and **32**, respectively. The condensation of aldehydes **30**−**32** with tetraamine disulfide **33**[16] or its carbon analogue **34**[16] and subsequent reduction of the intermediate Schiff bases afforded polyamine disulfides **7**−**9** and the corresponding carbon analogues **13**−**15** (Scheme 1).

Similarly, compounds **16**−**28** were obtained through amidation of **35**[17] with an appropriate substituted benzoyl chloride. Polyamine disulfides **4**−**6** and the corresponding carbon analogues **10**−**12** were obtained by condensation of aldehydes **17**, **21**, and **25** with **33** or **34** followed by the reduction of the intermediate Schiff bases (Scheme 2).

Biology

The pharmacological profile of prazosin- and benextramine-related compounds **4**−**28** was evaluated at α_1-adrenoreceptor subtypes on different isolated tissues using prazosin (**1**) and benextramine (**2**) together with the carbon analogue **3** of **2** as standard compounds. α_1-Adrenoreceptor subtype blocking activity was assessed by antagonism of (−)-noradrenaline-induced contraction of prostatic vas deferens (α_{1A})[18] or thoracic aorta (α_{1D})[19] and by antagonism of (−)-phenylephrine-induced contraction of spleen (α_{1B}).[20]

The noncompetitive (irreversible) α_1-antagonism was determined after a 30 min incubation followed by 30 min of washings. The decrease in maximum response was expressed as a percentage of the control value and used to estimate the IC_{50} values from graphical plots of percent inhibition vs log molar concentration. The potency of irreversible inhibitors was expressed as pIC_{50} values, whereas the potency of the competitive antagonists was expressed as pK_b values.[21]

Results and Discussion

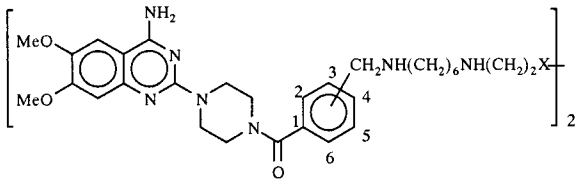
The biological activity, expressed as pK_b or pIC_{50} values, at α_1-adrenoreceptor subtypes of compounds used in the present study is shown in Table 1. To make relevant considerations on structure−activity relationships, prototypes **1** and **2** and the carbon analogue **3** of **2** were included for comparison. All quinazolines lacking the disulfide bridge behaved, like **1**, as competitive antagonists as they did not affect the maximal responses induced by the agonist while causing a parallel shift to the right of the concentration−response curves to the agonist. By contrast, all polyamine disulfides **4**−**9** displayed a nonhomogeneous mechanism of receptor inhibition at the three different α_1-adrenoreceptor subtypes, as they were, like **2**, noncompetitive antagonists at the α_{1A} and α_{1B} subtypes while being, unlike **2**, competitive antagonists at the α_{1D} subtype. It is evident that the presence of the disulfide functionality is necessary, although not always sufficient, for a noncompetitive mechanism of receptor inhibition.

Previously, it has been established that tetraamine disulfide **2** inhibits α_1-adrenoreceptors by way of a disulfide bond formation through an interchange reaction between the disulfide group of **2** and a thiol function of the receptor.[12,16] It is also clear that the disulfide moiety is necessary for a covalent receptor inactivation as revealed by the fact that the carbon analogue **3** of **2** behaved as a competitive antagonist at all α_1-adrenoreceptors. To gain information about the mechanism of inhibition, we compared the blocking effects of the disulfide **8** with those of its corresponding carbon (two methylenes for the disulfide bridge) analogue **14**. It turned out that the inhibition of 0.1 μM **14** against noradrenaline in the prostatic portion of rat vas deferens (α_{1A} subtype) resulted in no decrease of the maximal response with a parallel shift to the right of the concentration−response curves and was recovered completely after 3 h washings, whereas the blocking effects of **8**, which were characterized by a decrease in the maximal response, were affected only slightly by washings (Figure 2). Interestingly, the blocking effects of both **8** and **14** were recovered by the same extent following washings of rat aorta (α_{1D} subtype) (Figure 3), revealing a similar competitive mechanism of receptor inhibition. Taken together these results suggest that polyamine disulfide **8**, like tetraamine disulfide **2**, may inhibit irreversibly α_{1A}- and α_{1B}-adrenoreceptor subtypes. This conclusion may apply also to the other polyamine disulfides **4**−**7** and **9** since their blocking effects were similar to those of **8**.

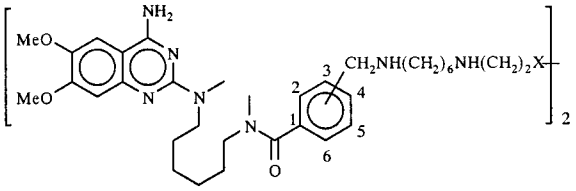
If this assumption were correct, then α_{1A}- and α_{1B}-adrenoreceptors bear in the binding pocket for polyamine disulfides a suitable thiol function that would suffer an interchange reaction with the disulfide moiety of the antagonist leading to receptor inactivation, which is missing in the α_{1D} subtype or that is not accessible to the disulfide group of the antagonist.

By taking as a starting point the tetraamine disulfide **2**, it is possible to observe how affinity and selectivity for α_1-adrenoreceptor subtypes can be markedly affected by replacing the 2-methoxy group by the structural feature of **1** and related open analogues, leading to **4**−**9** as shown in Figure 1. As discussed above, **4**−**9** resulted in noncompetitive antagonists at both α_{1A} and α_{1B} subtypes and competitive antagonists at the α_{1D} type. All these disulfide-bearing compounds were more potent than **2** at the α_{1A} subtype while being more potent (**4**, **7**−**9**) than or as potent as (**5**, **6**) the prototype at the α_{1B} subtype. Interestingly, **8** was 355-fold more potent than **2** at the α_{1A}-adrenoreceptors and also displayed a 38-fold selectivity for the α_{1A} subtype relative to the α_{1B}

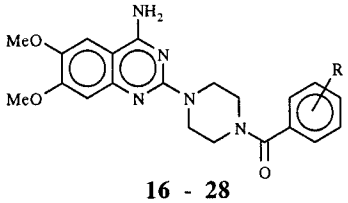
Table 1. Antagonist Affinities, Expressed as pK_b or pIC_{50} Values, of Polyamines **4**−**15** and Substituted Quinazolines **16**−**28** at α_1-Adrenoreceptors on Isolated Tissue from the Rat, Namely, Prostatic Vas Deferens (α_{1A}), Spleen (α_{1B}), and Thoracic Aorta (α_{1D}), in Comparison to Reference Compounds Prazosin (**1**), Benextramine (**2**), and Carbon Analogue (**3**)



4 - 6, 10 - 12



7 - 9, 13 - 15



16 - 28

				pK_b (pIC_{50})[a]		
no.	position	X	R	α_{1A}[b]	α_{1B}	α_{1D}[c]
1				8.99 ± 0.01	8.74 ± 0.01	9.71 ± 0.17
2				(4.79 ± 0.01)	(4.17 ± 0.03)	(5.30 ± 0.01)
3				5.32 ± 0.16	6.01 ± 0.10	6.21 ± 0.13
4	2	S		(5.30 ± 0.01)	(5.29 ± 0.03)	7.57 ± 0.06
5	3	S		(5.41 ± 0.02)	(4.26 ± 0.05)	7.09 ± 0.02
6	4	S		(5.70 ± 0.11)	(4.38 ± 0.06)	7.61 ± 0.14
7	2	S		(5.73 ± 0.01)	(5.73 ± 0.05)	8.05 ± 0.15
8	3	S		(7.34 ± 0.03)	(5.76 ± 0.04)	8.34 ± 0.09
9	4	S		(5.33 ± 0.03)	(5.67 ± 0.01)	8.50 ± 0.14
10	2	CH_2		7.74 ± 0.18	6.80 ± 0.12	7.94 ± 0.22
11	3	CH_2		7.29 ± 0.03	6.50 ± 0.12	7.43 ± 0.14
12	4	CH_2		6.97 ± 0.04	7.16 ± 0.21	7.47 ± 0.13
13	2	CH_2		8.17 ± 0.08	7.22 ± 0.10	8.47 ± 0.13
14	3	CH_2		8.48 ± 0.13	7.41 ± 0.15	9.30 ± 0.21
15	4	CH_2		8.53 ± 0.20	7.56 ± 0.19	7.90 ± 0.14
16			H	7.66 ± 0.23	7.44 ± 0.11	8.86 ± 0.02
17			2-CHO	6.94 ± 0.09	6.50 ± 0.11	7.56 ± 0.03
18			2-Me	6.97 ± 0.13	7.33 ± 0.13	7.99 ± 0.12
19			2-OMe	7.34 ± 0.15	6.77 ± 0.09	7.76 ± 0.17
20			2-CF_3	6.43 ± 0.11	6.55 ± 0.16	8.31 ± 0.04
21			3-CHO	7.79 ± 0.06	6.92 ± 0.15	8.07 ± 0.23
22			3-Me	8.49 ± 0.14	8.12 ± 0.15	9.12 ± 0.12
23			3-OMe	7.87 ± 0.23	7.84 ± 0.05	7.46 ± 0.04
24			3-CF_3	7.49 ± 0.10	7.16 ± 0.21	8.38 ± 0.13
25			4-CHO	7.59 ± 0.07	6.95 ± 0.10	8.38 ± 0.13
26			4-Me	7.96 ± 0.11	7.67 ± 0.02	8.91 ± 0.19
27			4-OMe	8.46 ± 0.10	7.74 ± 0.11	8.98 ± 0.17
28			4-CF_3	7.43 ± 0.14	7.45 ± 0.21	8.31 ± 0.06

[a] Apparent pK_b values ± SE were calculated according to Arunlakshana and Schild[21] with the following equation: $pK_b = -\log K_b = \log(DR - 1) - \log [B]$. The log(DR − 1) was calculated from two to three different antagonist concentrations, which were tested four times. Dose−ratio (DR) values represent the ratio of the potency of the agonist (EC_{50}) in the presence of the antagonist and in its absence. pIC_{50} values ± SE, expressing noncompetitive (irreversible) blockade, are defined as the concentrations producing 50% inhibition of the maximal response to agonist. [b] It was reported that the rat vas deferens may also have α_{1L} pharmacology.[22] [c] The rat aorta appears to have primarily α_{1D} pharmacology. However, it may contain multiple α_1-adrenoreceptors.[23]

type. This peculiarity emerging at α_{1A} and α_{1B} subtypes, taken together with the competitive antagonism at α_{1D}-adrenoreceptors, might have relevance. It is clear that the competitive blocking effects at the latter receptor subtype can be reversed by washings, which makes **8** an interesting tool for characterizing the α_{1A}-adrenoreceptor subtype. Furthermore, **8** may also be important for investigating α_{1D}-adrenoreceptors owing to its higher potency toward this subtype relative to both α_{1A} and α_{1B}.

A comparison between **4**−**6** and the corresponding open analogues **7**−**9** reveals that replacing the piperazine ring with a 1,6-diaminohexane moiety caused a significant increase in potency at all α_1-adrenoreceptor subtypes, the only exception being that **9** was slightly less potent than **6** at α_{1A}-adrenoreceptors. Clearly, a more flexible spacer between quinazoline and benzene rings allows the open analogues to better interact with their binding site. The same trend was observed for the potency displayed by the carbon analogues **10**−**15**. Open analogues **13**−**15** were always more potent than the corresponding piperazine analogues **10**−**12** at the three α_1-adrenoreceptor subtypes. Again, a comparison between the carbon analogue **3** of **2** and the prazosin-related polyamines **10**−**15** reveals that replacing the 2-methoxy group of **3** with the quinazolinyl moiety of **1** resulted in a significant increase in potency at α_1-adrenoreceptor subtypes. Thus, these results confirm

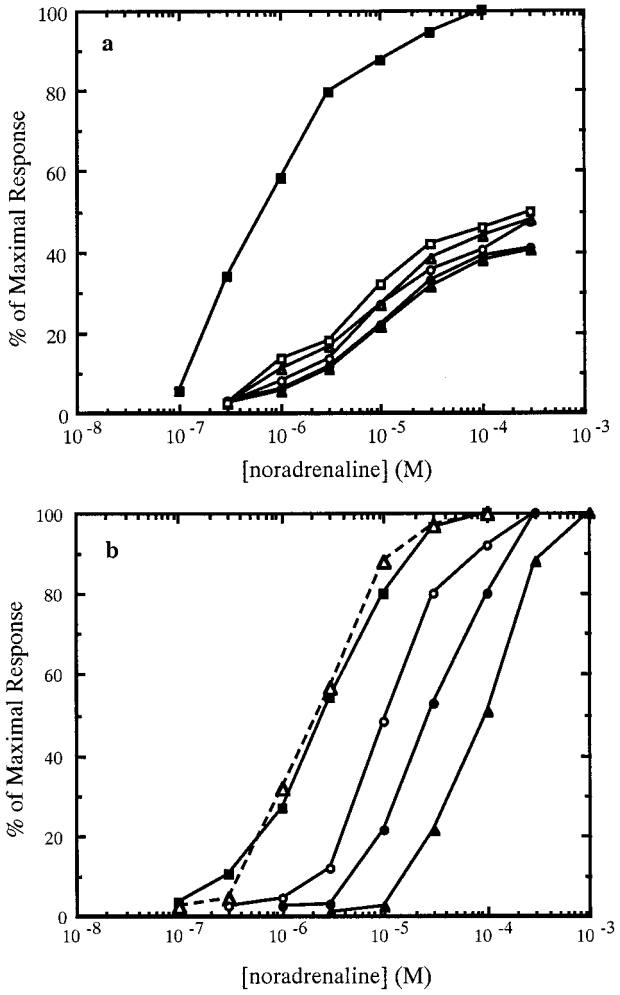


Figure 2. Effect of polyamine **8** (a) and **14** (b) on rat vas deferens α_{1A}-adrenoreceptors. Concentration−response curves for noradrenaline were obtained before (■) and after exposure to 0.1 μM **8** or **14** for 30 min (▲), and after exposure to 0.1 μM **8** or **14** for 30 min followed by 30 (●), 60 (○), 120 (△), and 180 min (□) washings. Each point is the mean of at least four independent observations. The SEMs were less than 10% and are not shown.

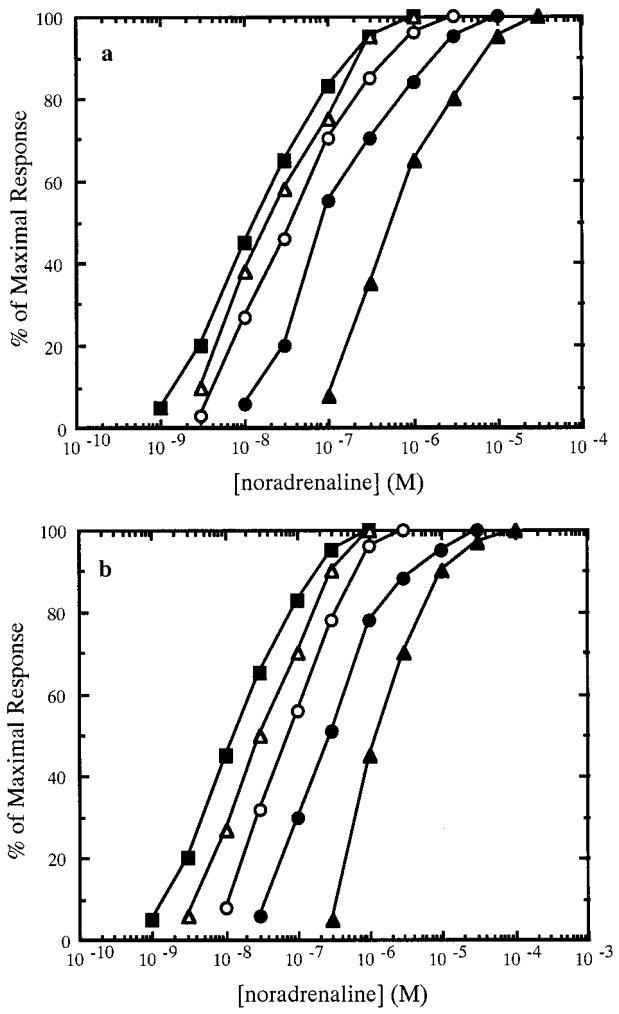


Figure 3. Effect of polyamine **8** (a) and **14** (b) on rat aorta α_{1D}-adrenoreceptors. Concentration−response curves for noradrenaline were obtained before (■) and after exposure to 0.1 μM **8** or 30 nM **14** for 30 min (▲), and after exposure to 0.1 μM **8** or 30 nM **14** for 30 min followed by 60 (●), 120 (○), and 180 min (△) washings. Each point is the mean of at least four independent observations. The SEMs were less than 10% and are not shown.

and extend the view that the inclusion of a polyamine backbone on the benzene ring of prazosin-related compounds may not produce negative interactions with the receptor and can lead to selectivity. In particular, polyamine **14** showed an interesting selectivity profile, being 7- and 78-fold more potent at α_{1D}-adrenoreceptors than at α_{1A}- and α_{1B}-adrenoreceptors, respectively. However, concerning the selectivity toward α_{1D}-adrenoreceptors, the most promising polyamine appears to be **9**, which turned out to be more potent at this receptor subtype than at both α_{1A} and α_{1B} subtypes.

A further analysis of the results shown in Table 1 reveals that high affinity for both α_{1A}- and α_{1D}-adrenoreceptors is observed when the polyamine chain is inserted at position 3 of the benzene ring as in **8** and **14**, suggesting that at these receptors the polyamine chain can contribute to the binding. This reasoning finds further support by comparing the results observed for the unsubstituted analogue **16**, which is less potent than polyamine **14**. The situation is less clear for the α_{1B} subtype since the inclusion of a polyamine chain at any position of the benzene ring did not markedly affect affinity.

To verify the effect of the nonbasic substituents on the potency for α_1-adrenoreceptor subtypes, we investigated derivatives **16**−**28**. Clearly, the insertion of a substituent on the benzene ring of **16** affected the affinity and, as a consequence, the selectivity for α_1-adrenoreceptor subtypes differently, according to the substituent type and position. Any substituent investigated at position 2 (**17**−**20**) gave a decrease in potency in comparison with **16** for all α_1-adrenoreceptor subtypes, revealing that a substituent in this position is not tolerated by way of a possible steric hindrance with the receptor. However, derivatives **17**−**20** retained a selectivity profile similar to that of **16**. In particular, the 2-trifluoromethyl substituted derivative **20** was markedly selective, being 76- and 58-fold more potent at α_{1D}-adrenoreceptors than at the α_{1A} and α_{1B} subtypes, respectively. The insertion of the same substituents at position 3 of the benzene ring of **16**, affording **21**−**24**, produced different results. The selectivity profile was similar, albeit different from a quantitative point of view, to that displayed by **16**, the only exception being the 3-methoxy derivative **23** that turned out to be

slightly more potent at both α_{1A}- and α_{1B}-adrenoreceptors than at α_{1D}-adrenoreceptors. However, these compounds were as active as or even more potent than **16** at α_{1A}-adrenoreceptors, whereas the situation at the other receptor subtypes was more complex. At the α_{1B}-adrenoreceptors, **22** and **23** were more potent whereas **21** and **24** were less potent than **16**, suggesting perhaps that an electron-donating group might increase the binding with the receptor. On the other hand, at α_{1D}-adrenoreceptors all 3-substituted derivatives were significantly less potent than **16**, the only important exception being the 3-methyl derivative **22**, which turned out to be more potent than not only prototype **16** but also **21**, **23**, and **24**, pointing to a possible positive effect of both electronic and lipophilic properties of a methyl substituent. Compound **26** was slightly more potent than **16** at the α_{1A} and α_{1B} subtypes but equipotent at the α_{1D} subtype. Compound **27** was clearly more potent than **16** at the α_{1A} subtype, slightly more potent at the α_{1B} subtype, and practically equipotent at the α_{1D} subtype. This suggests that an electron-releasing substituent at position 4 of the benzene ring may not be detrimental to affinity. However, **25** and **28**, although bearing electron-attracting substituents, were only slightly less potent than the unsubstituted prototype **16**.

In conclusion, the effects of nonbasic substituents on the phenyl ring of **16**, affording **17**−**28**, on potency, and on selectivity for α_1-adrenoreceptors can be hardly rationalized on a firm basis with our series of compounds. On the other hand, the inclusion of a tetraamine backbone into prazosin-related compounds afforded a series of polyamines that displayed an intriguing antagonism, which was different, according to the type and position of the tetraamine chain in the phenyl ring, for α_1-adrenoreceptor subtypes. In particular, polyamines **8**, **9**, and **14**, among others, emerged as promising tools for the characterization of α_1-adrenoreceptor subtypes, owing to their receptor subtype selectivity. Moreover, several compounds, like **13**, **14**, and **21**, may be prototypes for the design of competitive α_{1A}/α_{1D}-antagonists, a selectivity profile postulated to be of utility in benign prostatic hyperplasia due to actions on both prostate and bladder.[5]

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Büchi SMP-20 apparatus and are uncorrected. IR, MALDI-TOF-MS, and ^{1}H NMR spectra were recorded on Perkin-Elmer 297, Bruker Biflex III, and Varian VXR 300 instruments, respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and spin multiplicities are given as s (singlet), br s (broad singlet), d (doublet), t (triplet), or m (multiplet). 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. When the elemental analysis is not included, crude compounds were used in the next step without further purification. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040−0.063 mm, Merck) by flash chromatography. Compounds were named following IUPAC rules as applied by ACD/NAME, a PC integrated software package for systematic naming in organic chemistry (Advanced Chemistry Development Inc.).

***N*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]hexyl}-3-formyl-*N*-methylbenzamide (31).** This compound was synthesized following an adapted procedure described for the synthesis of the analogue **30**.[10] A solution of 3-formylbenzoic acid (0.15 g, 1 mmol) and $SOCl_2$ (0.73 mL, 10 mmol) in toluene (10 mL) was refluxed for 1 h. Removal of the solvent under reduced pressure afforded crude 3-formylbenzoyl chloride in a quantitative yield. A solution of this chloride (0.168 g, 1 mmol) in dioxane (5 mL) was added dropwise to a solution of **29**[15] (0.35 g, 1 mmol) and triethylamine (0.14 mL, 1 mmol) in dioxane (10 mL). After the mixture was stirred at room temperature for 24 h, the solvent was removed under reduced pressure to give a residue that was purified by chromatography. Eluting with methylene chloride−petroleum ether−ethanol−aqueous 30% ammonia (8:2:0.5:0.05) afforded 0.37 g (77% yield) of **31**: mp (hydrochloride) 251 °C; ^{1}H NMR ($CDCl_3$) δ 1.10−1.82 (m, 8), 2.82−3.31 (m, 7), 3.45−3.78 (m, 3), 3.90 (s, 3), 3.95 (s, 3), 5.21 (br s, 2, exchangeable with D_2O), 6.81 (s, 1), 6.95−7.02 (m, 1), 7.51−7.73 (m, 2), 7.89 (s, 2), 10.01 (s, 1).

***N*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]hexyl}-4-formyl-*N*-methylbenzamide (32).** It was synthesized from 4-formylbenzoic acid and **29**[15] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.5:0.5:0.04) afforded **31**: 71% yield; mp (hydrochloride) 221 °C; ^{1}H NMR ($CDCl_3$) δ 1.34−1.86 (m, 8), 2.89−3.21 (m, 7), 3.51−3.70 (m, 3), 3.91 (s, 3), 3.97 (s, 3), 5.21 (br s, 2, exchangeable with D_2O), 6.80 (s, 1), 6.85−7.01 (m, 1), 7.51 (d, 2), 7.90 (d, 2), 10.04 (s, 1).

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(phenyl)methanone Hydrochloride (16). It was synthesized from benzoyl chloride and **35**[17] following the procedure described for **31** and purified by crystallization: 64% yield; mp 278 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 3.41−3.70 (m, 4), 3.71−3.85 (m, 4), 3.92 (s, 3), 3.97 (s, 3), 5.23 (br s, 2, exchangeable with D_2O), 6.83 (s, 1), 6.94 (s, 1), 7.31−7.50 (m, 5). Anal. ($C_{21}H_{24}ClN_5O_3$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(2-formylphenyl)methanone Oxalate (17). It was synthesized from 2-formylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.5:0.5:0.04) afforded, in 64% yield, **17** as the free base, which was transformed into the oxalate salt: mp 240 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 3.23 (t, 2), 3.71−3.79 (m, 2), 3.80−4.01 (m, 4), 3.88 (s, 3), 3.93 (s, 3), 5.42 (br s, 2, exchangeable with D_2O), 6.87 (s, 1), 6.89 (s, 1), 7.37−7.41 (m, 1), 7.45−7.71 (m, 2), 7.89−7.97 (m, 1), 10.05 (s, 1). Anal. ($C_{24}H_{25}N_5O_8$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(2-methylphenyl)methanone Hydrochloride (18). It was synthesized from 2-methylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.6:0.4:0.04) afforded, in 80% yield, **18** as the free base, which was transformed into the hydrochloride salt: mp 290 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 2.27 (s, 3), 3.22−3.38 (m, 2), 3.62−3.80 (m, 2), 3.81−4.02 (m, 4), 3.89 (s, 3), 3.93 (s, 3), 5.22 (br s, 2, exchangeable with D_2O), 6.81 (s, 1), 6.91 (s, 1), 7.18−7.32 (m, 4). Anal. ($C_{22}H_{26}ClN_5O_3$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(2-methoxyphenyl)methanone Hydrochloride (19). It was synthesized from 2-methoxybenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.6:0.4:0.04) afforded, in 78% yield, **19** as the free base, which was transformed into the hydrochloride salt: mp 270 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 3.22−3.39 (m, 2), 3.78−3.99 (m, 6), 3.82 (s, 3), 3.92 (s, 3), 3.94 (s, 3), 5.22 (br s, 2, exchangeable with D_2O), 6.82−7.05 (m, 4), 7.27−7.42 (m, 2). Anal. ($C_{22}H_{26}ClN_5O_4$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(2-trifluoromethylphenyl)methanone Hydrochloride (20). It was synthesized from 2-trifluoromethylbenzoic acid and **35**[17]

following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.7:0.3:0.03) afforded in 71% yield **20** as the free base, which was transformed into the hydrochloride salt: mp 280 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 3.23 (t, 2), 3.63−3.74 (m, 2), 3.80−4.01 (m, 4), 3.87 (s, 3), 3.93 (s, 3), 5.34 (br s, 2, exchangeable with D_2O), 6.85 (s, 1), 6.89 (s, 1), 7.31−7.36 (m, 1), 7.57 (m, 2), 7.69−7.79 (m, 1). Anal. ($C_{22}H_{23}ClF_3N_5O_3$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(3-formylphenyl)methanone Hydrochloride (21). It was synthesized from 3-formylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−petroleum ether−ethanol−aqueous 30% ammonia (8:1.6:0.4:0.035) afforded in 60% yield **21** as the free base, which was transformed into the hydrochloride salt: the mp was indefinite, fusion started at 135 °C but was not complete up to 300 °C: ^{1}H NMR (D_2O) δ 3.42−3.82 (m, 8), 3.64 (s, 3), 3,72 (s, 3), 6.51 (s, 1), 6.86 (s, 1), 7.45−7.99 (m, 4), 9.79 (s, 1). Anal. ($C_{22}H_{24}ClN_5O_4$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(3-methylphenyl)methanone Hydrochloride (22). It was synthesized from 3-methylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.6:0.4:0.04) afforded, in 71% yield, **22** as the free base, which was transformed into the hydrochloride salt: mp 190−192 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 2.32 (s, 3), 3.33−3.51 (m, 2), 3.62−3.82 (m, 6), 3.83 (s, 3), 3.87 (s, 3), 5.35 (br s, 2, exchangeable with D_2O), 6.82 (s, 1), 6.84 (s, 1), 7.08−7.31 (m, 4). Anal. ($C_{22}H_{26}ClN_5O_3$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(3-methoxyphenyl)methanone Hydrochloride (23). It was synthesized from 3-methoxybenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.6:0.4:0.04) afforded, in 85% yield, **23** as the free base, which was transformed into the hydrochloride salt: mp 250 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 3.37−3.63 (m, 2), 3.69−4.08 (m, 6), 3.69 (s, 3), 3.81 (s, 3), 3.91 (s, 3), 5.23 (br s, 2, exchangeable with D_2O), 6.67−6.99 (m, 5), 7.19−7.27 (m, 1). Anal. ($C_{22}H_{26}ClN_5O_4$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(3-trifluoromethylphenyl)methanone Hydrochloride (24). It was synthesized from 3-trifluoromethylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.7:0.3:0.03) afforded, in 56% yield, **24** as the free base, which was transformed into the hydrochloride salt: mp 275 °C (from EtOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 3.45−3.61 (m, 2), 3.68−4.01 (m, 6), 3.79 (s, 3), 3.85 (s, 3), 7.41 (s, 1), 7.63−7.90 (m, 5), 8.61 (br s, 1, exchangeable with D_2O), 8.82 (br s, 1, exchangeable with D_2O), 12.10 (br s, 1, exchangeable with D_2O). Anal. ($C_{22}H_{23}ClF_3N_5O_3$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(4-formylphenyl)methanone Hydrochloride (25). It was synthesized from 4-formylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.7:0.3:0.03) afforded, in 77% yield, **25** as the free base, which was transformed into the hydrochloride salt: mp 250 °C (from EtOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 3.40−3.61 (m, 2), 3.62−4.10 (m, 6), 3,79 (s, 3), 3.81 (s, 3), 7.45 (s, 3), 7.60−7.78 (m, 2), 7.96−8.02 (m, 1), 8.33 (br s, 1, exchangeable with D_2O), 8.42 (br s, 1, exchangeable with D_2O), 10.06 (s, 1), 12.15 (br s, 1, exchangeable with D_2O). Anal. ($C_{22}H_{24}ClN_5O_4$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(4-methylphenyl)methanone Hydrochloride (26). It was synthesized from 4-methylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.7:0.3:0.03) afforded, in 74% yield, **26** as the free base, which was transformed into the hydrochloride salt: mp 280 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 2.37 (s, 3), 3.42−3.64 (m, 2), 3.71−3.99 (m, 6), 3.83 (s, 3), 3.89 (s, 3), 5.32 (br s, 2, exchangeable with D_2O), 6.83 (s, 1), 6.91 (s, 1), 7.28 (dd, 4). Anal. ($C_{22}H_{26}ClN_5O_3$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(4-methoxyphenyl)methanone Hydrochloride (27). It was synthesized from 4-methoxybenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.7:0.3:0.03) afforded, in 77% yield, **27** as the free base, which was transformed into the hydrochloride salt: mp 230 °C (from EtOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 3.23−3.45 (m, 4), 3.46−3.71 (m, 4), 3.77 (s, 3), 3.81 (s, 3), 3.86 (s, 3), 6.97−7.10 (m, 2), 7.35−7.42 (m, 2), 7.43 (s, 1), 7.68 (s, 1), 8.63 (br s, 1, exchangeable with D_2O), 8.62 (br s, 1, exchangeable with D_2O), 12. 10 (br s, 1, exchangeable with D_2O). Anal. ($C_{22}H_{26}ClN_5O_4$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(4-trifluoromethylphenyl)methanone Hydrochloride (28). It was synthesized from 4-trifluoromethylbenzoic acid and **35**[17] following the procedure described for **31** and purified by chromatography. Eluting with methylene chloride−methanol−aqueous 30% ammonia (9.7:0.3:0.03) afforded, in 74% yield, **28** as the free base, which was transformed into the hydrochloride salt: mp 240 °C (from EtOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 3.40−3.61 (m, 2), 3.71−4.07 (m, 6), 3.81 (s, 3), 3.90 (s, 3), 7.42 (s, 1), 7.63−7.79 (m, 3), 7.80−7.91 (m, 2), 8.67 (br s, 1, exchangeable with D_2O), 8.90 (br s, 1, exchangeable with D_2O), 12.20 (br s, 1, exchangeable with D_2O). Anal. ($C_{22}H_{23}ClF_3N_5O_3$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-{2-[({6-[(2-{[2-({6-[(2-{[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-piperazino]carbonyl}benzyl)amino]hexyl}amino)ethyl]-disulfanyl}ethyl)amino]hexyl}amino)methyl]phenyl}methanone Hexahydrochloride (4). A solution of **17** (0.2 g, 0.42 mmol) and **33**[16] (50 mg, 0.14 mmol) in toluene (10 mL) was refluxed and the water formed continuously removed for 8 h. The cooled mixture was filtered and the filtrate evaporated to give the corresponding Schiff base that was dissolved in ethanol (15 mL) and treated with $NaBH_4$ (11 mg, 0.30 mmol). After the mixture was stirred at room temperature overnight, removal of dried solvents gave an oil that was purified by chromatography. Eluting with methylene chloride−methanol−30% ammonia (8.5:1.5:0.15) afforded, in 38% yield, **4** as the free base that was converted into the hexahydrochloride salt: mp 253 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.17−1.49 (m, 16), 2.40 (br s, 4, exchangeable with D_2O), 2.45−2.59 (m, 8), 2.71−2.82 (m, 4), 2.83−2.94 (m, 4), 3.2−3.39 (m, 4), 3.68−3.98 (m, 12), 3.67 (s, 4), 3.86 (s, 6), 3.92 (s, 6), 5.42 (br s, 4, exchangeable with D_2O), 6.86 (s, 4), 7.15−7.41 (m, 8). MALDI-MS calcd for $C_{60}H_{85}N_{14}O_6S_2$ 1161.62 $(M + H)^+$, found 1161.75. Anal. ($C_{60}H_{90}Cl_6N_{14}O_6S_2$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-{3-[({6-[(2-{[2-({6-[(3-{[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-piperazino]carbonyl}benzyl)amino]hexyl}amino)ethyl]-disulfanyl}ethyl)amino]hexyl}amino)methyl]phenyl}methanone Hexahydrochloride (5). It was synthesized from **21** and **33**[16] following the procedure described for **4** and purified by chromatography. Eluting with methylene chloride−ethanol−30% ammonia (8.5:1.5:0.15) afforded, in 32% yield, **5** as the free base that was converted into the hexahydrochloride salt: mp 252 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.10−1.75 (m, 16), 2. 10 (br s, 4, exchangeable with D_2O), 2.55−2.69 (m, 8), 2.77−2.98 (m, 8), 3.41−3.62 (m, 4), 3.71−4.09 (m, 12), 3.82 (s, 4), 3.91 (s, 6), 3.96 (s, 6), 5.35 (br s, 4, exchangeable with D_2O), 6.85 (s, 2), 6.91 (s, 2) 7.23−7.50 (m, 8). MALDI-MS calcd for $C_{60}H_{85}N_{14}O_6S_2$ 1161.62 $(M + H)^+$, found 1161.64. Anal. ($C_{60}H_{90}Cl_6N_{14}O_6S_2$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-{4-[({6-[(2-{[2-({6-[(4-{[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-piperazino]carbonyl}benzyl)amino]hexyl}amino)ethyl]-disulfanyl}ethyl) amino]hexyl}amino)methyl]phenyl}methanone Hexahydrochloride (6). It was synthesized from **25** and **33**[16] following the procedure described for **4** and purified

by chromatography. Eluting with methylene chloride−ethanol−30% ammonia (8.5:1.5:0.15) afforded, in 31% yield, **6** as the free base that was converted into the hexahydrochloride salt: mp 250 °C (from EtOH/Et_2O); ^{1}H NMR (CD_3OD) δ 2.01−2.19 (m, 8), 2.31−2.58 (m, 8), 3.61−3.79 (m, 8), 3.82−4.09 (m, 8), 4.10−4.29 (m, 4), 4.46−4.71 (m, 4), 4.62 (s, 12), 4.64−4.81 (m, 8), 4.92 (s, 4), 8.22−8.38 (m, 4), 8.40−8.59 (m, 8), 9.41 (br s, 2, exchangeable with D_2O), 9.72 (br s, 2, exchangeable with D_2O), 10.05 (br s, 4, exchangeable with D_2O), 10.20 (br s, 6, exchangeable with D_2O). MALDI-MS calcd for $C_{60}H_{85}N_{14}O_6S_2$ 1161.62 $(M + H)^+$, found 1161.66. Anal. ($C_{60}H_{90}Cl_6N_{14}O_6S_2$) C, H, N.

***N1*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}-*N1*-methyl-2-{[(6-{[6-({2-[(2-{[6-[(2-{[(6-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}(methyl)amino]carbonyl}benzyl)amino]hexyl}amino)ethyl]disulfanyl}ethyl)amino]hexyl)amino)methyl}benzenamide Hexahydrochloride (7).** It was synthesized from **30** and **33**[16] following the procedure described for **4** and purified by chromatography. Eluting with methylene chloride−ethanol−30% ammonia (8.5:1.5:0.15) afforded 60 mg (34% yield) of **7** as free base, which was converted into the hexahydrochloride salt: mp 199−203 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.01−1.81 (m, 32 + 4 exchangeable with D_2O), 2.41−2.70 (m, 8), 2.7−3.21 (m, 22), 3.49−3.80 (m, 10), 3.88 (s, 6), 3.93 (s, 6), 5.39 (br s, 2, exchangeable with D_2O), 5.55 (br s, 2, exchangeable with D_2O), 6.81−7.01 (m, 4), 7.12−7.43 (m, 8). MALDI-MS calcd for $C_{68}H_{105}N_{14}O_6S_2$ 1277.78 $(M + H)^+$, found 1277.94. Anal. ($C_{68}H_{110}Cl_6N_{14}O_6S_2$) C, H, N.

***N1*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}-*N1*-methyl-3-{[(6-{[6-({2-[(3-{[6-[(2-{[(6-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}(methyl)amino]carbonyl}benzyl)amino]hexyl}amino)ethyl]disulfanyl}ethyl)amino]hexyl)amino)methyl}benzenamide Hexahydrochloride (8).** It was synthesized from **31** and **33**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−methanol−30% ammonia (8.5:1.5:0.15) gave, in 31% yield, **8** as the free base that was converted into the hexahydrochloride salt: mp 229 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.01−1.78 (m, 32), 2.08 (br s, 4, exchangeable with D_2O), 2.24−2.41 (m, 8), 2.71−3.21 (m, 22), 3.41−3.70 (m, 6), 3.75 (s, 4), 3.84 (s, 6), 3.91 (s, 6), 5.41 (br s, 4, exchangeable with D_2O), 6.81−6.95 (m, 4), 7.18−7.38 (m, 8). MALDI-MS calcd for $C_{68}H_{105}N_{14}O_6S_2$ 1277.78 $(M + H)^+$, found 1277.82. Anal. ($C_{68}H_{110}Cl_6N_{14}O_6S_2$) C, H, N.

***N1*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}-*N1*-methyl-4-{[(6-{[6-({2-[(4-{[6-[(2-{[(6-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}(methyl)amino]carbonyl}benzyl)amino]hexyl}amino)ethyl]disulfanyl}ethyl)amino]hexyl)amino)methyl}benzenamide Hexahydrochloride (9).** It was synthesized from **32** and **33**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−ethanol−30% ammonia (8.5:1.5:0.15) gave, in 23% yield, **9** as the free base that was converted into the hexahydrochloride salt: mp 241 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.09−1.73 (m, 32), 2.03 (br s, 4, exchangeable with D_2O), 2.50−2.61 (m, 8), 2.70−3.21 (m, 22), 3.41−3.71 (m, 6), 3.78 (s, 4), 3.88 (s, 6), 3.94 (s, 6), 5.36 (br s, 4, exchangeable with D_2O), 6.83 (s, 2), 6.91 (s, 2), 7.32 (s, 8). MALDI-MS calcd for $C_{68}H_{105}N_{14}O_6S_2$ 1277.78 $(M + H)^+$, found 1277.82. Anal. ($C_{68}H_{110}Cl_6N_{14}O_6S_2$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(2-{[(6-{[6-({6-[(2-{[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazino]carbonyl}benzyl)amino]hexyl}amino)hexyl]amino}hexyl) amino]methyl}phenyl)methanone Hexahydrochloride (10). It was synthesized from **17** and **34**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−ethanol−30% ammonia (7.5:2.5:0.25) afforded, in 60% yield, **10** as the free base that was converted into the hexahydrochloride salt: mp 259 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.20−1.69 (m, 24 + 4 exchangeable with D_2O), 2.54 (t, 4), 2.55−2.64 (m, 8), 3.21−3.39 (m, 4), 3.71−3.99 (m, 12), 3.74 (s, 4), 3.88 (s, 6), 3.92 (s, 6), 5.66 (br s, 4, exchangeable with D_2O), 6.86 (s, 2), 6.98 (s, 2), 7.15−7.21 (m, 8). MALDI-MS calcd for $C_{62}H_{89}N_{14}O_6$ 1125.71 $(M + H)^+$, found 1125.83. Anal. ($C_{62}H_{94}Cl_6N_{14}O_6$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(3-{[(6-{[6-({6-[(3-{[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazino]carbonyl}benzyl)amino]hexyl}amino)hexyl]amino}hexyl) amino]methyl}phenyl)methanone Hexahydrochloride (11). It was synthesized from **21** and **34**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−ethanol−30% ammonia (7.5:2.5:0.25) afforded in 55% yield **11** as the free base that was converted into the hexahydrochloride salt: mp > 300 °C (from EtOH/Et_2O); ^{1}H NMR (D_2O) δ 1.15−1.26 (m, 12), 1.39−1.60 (m, 12), 2.78−2.85 (m, 8), 2.91 (t, 4), 3.43−3.81 (m, 16), 3.64 (s, 6), 3.71 (s, 6), 4.13 (s, 4), 6.55 (s, 2), 6.84 (s, 2), 7.39−7.55 (m, 8). MALDI-MS calcd for $C_{62}H_{89}N_{14}O_6$ 1125.71 $(M + H)^+$, found 1125.71. Anal. ($C_{62}H_{94}Cl_6N_{14}O_6$) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazino]-(4-{[(6-{[6-({6-[(4-{[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-piperazino]carbonyl}benzyl)amino]hexyl}amino)hexyl]-amino}hexyl)amino]methyl}phenyl)methanone Hexahydrochloride (12). It was synthesized from **25** and **34**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−methanol−30% ammonia (7.5:2.5:0.25) afforded in 60% yield **12** as the free base that was converted into the hexahydrochloride salt: mp > 300 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.12−1.62 (m, 24 + 4 exchangeable with D_2O) 2.51−2.69 (m, 12), 3.39−3.58 (m, 4), 3.69−3.99 (m, 12), 3.78 (s, 4), 3.87 (s, 6), 3.92 (s, 6), 5.42 (br s, 4, exchangeable with D_2O) 6.82−6.93 (m, 4), 7.38 (s, 8). MALDI-MS calcd for $C_{62}H_{89}N_{14}O_6$ 1125.71 $(M + H)^+$, found 1125.80. Anal. ($C_{62}H_{94}Cl_6N_{14}O_6$) C, H, N.

***N1*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}-*N1*-methyl-2-{[(6-{[6-({6-[(2-{[{6-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}(methyl)amino]carbonyl}benzyl)amino]hexyl}amino)hexyl]amino}hexyl)amino]methyl}benzenamide Hexahydrochloride (13).** It was synthesized from **30** and **34**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−ethanol−30% ammonia (8:2:0.2) afforded, in 43% yield, **13** as the free base that was converted into the hexahydrochloride salt: mp 250−255 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.10−1.71 (m, 40), 2.07 (br s, 4, exchangeable with D_2O), 2.40−2.61 (m, 12), 2.77 (s, 3), 2.90−3.18 (m, 11), 3.44−3.72 (m, 6), 3.69 (s, 4), 3.86 (s, 6), 3.93 (s, 6), 5.29 (br s, 2, exchangeable with D_2O), 5.43 (br s, 2, exchangeable with D_2O), 6.83 (s, 2), 6.85−6.92 (m, 2) 7.09−7.43 (m, 8). MALDI-MS calcd for $C_{70}H_{109}N_{14}O_6$ 1241.87 $(M + H)^+$, found 1241.88. Anal. ($C_{70}H_{114}Cl_6N_{14}O_6$) C, H, N.

***N1*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}-*N1*-methyl-3-{[(6-{[6-({6-[(3-{[{6-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}(methyl)amino]carbonyl}benzyl)amino]hexyl}amino)hexyl]amino}hexyl)amino]methyl}benzenamide Hexahydrochloride (14).** It was synthesized from **31** and **34**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−methanol−30% ammonia (8:2:0.2) afforded, in 42% yield, **14** as the free base that was converted into the hexahydrochloride salt: mp > 300 °C (from EtOH/Et_2O); ^{1}H NMR (free base; $CDCl_3$) δ 1.10−1.71 (m, 40 + 4 exchangeable with D_2O), 2.41−2.71 (m, 12), 2.80−3.31 (m, 14), 3.41−3.72 (m, 6), 3.76 (s, 4), 3.87 (s, 6), 3.93 (s, 6), 5.41 (br s, 4, exchangeable with D_2O), 6.88 (s, 4), 7.19−7.41 (m, 8). MALDI-MS calcd for $C_{70}H_{109}N_{14}O_6$ 1241.87 $(M + H)^+$, found 1242.02. Anal. ($C_{70}H_{114}Cl_6N_{14}O_6$) C, H, N.

***N1*-{6-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}-*N1*-methyl-4-{[(6-{[6-({6-[(4-{[{6-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]hexyl}(methyl)amino]carbonyl}benzyl)amino]hexyl}amino)hexyl]amino}hexyl)amino]methyl}benzenamide Hexahydrochloride (15).** It was synthesized from **32**

and **34**[16] following the procedure described for **4** and purified by chromatography. Eluting with chloroform−methanol−30% ammonia (7.75:2.25:0.25) afforded, in 48% yield, **15** as the free base that was converted into the hexahydrochloride salt: mp 220 °C (from EtOH/Et_2O); ^1H NMR (free base; $CDCl_3$) δ 1.10−1.79 (m, 40 + 4 exchangeable with D_2O),2.45−2.79 (m, 12), 2.80−3.15 (m, 14), 3.21−3.76 (m, 6), 3.77 (s, 4), 3.88 (s, 6), 3.92 (s, 6), 5.58 (br s, 4, exchangeable with D_2O), 6.91−7.02 (m, 4), 7.217.38 (m, 8). MALDI-MS calcd for $C_{70}H_{109}N_{14}O_6$ 1241.87 (M + H)$^+$, found 1241.97. Anal. ($C_{70}H_{114}Cl_6N_{14}O_6$) C, H, N.

Biology. Functional Antagonism in Isolated Tissues. Male Wistar rats (275−300 g) were killed by cervical dislocation, and the organs required were isolated, freed from adhering connective tissue, and set up rapidly under a suitable resting tension in 20 mL organ baths containing physiological salt solution kept at 37 °C and aerated with 5% CO_2−95% O_2 at pH 7.4. Concentration−response curves were constructed by cumulative addition of agonist. The concentration of agonist in the organ bath was increased approximately 3-fold at each step, with each addition being made only after the response to the previous addition had attained a maximal level and remained steady. Contractions were recorded by means of a force displacement transducer connected to the MacLab system PowerLab/800 and to a poligraph channel recorder (Gemini). In addition, parallel experiments in which tissues did not receive any antagonist were run in order to check any variation in sensitivity.

Vas Deferens Prostatic Portion. This tissue was used to assess the antagonism toward α_{1A}-adrenoreceptors.[18] Prostatic portions of 2 cm length were mounted under 0.5 g tension at 37 °C in Tyrode solution of the following composition (mM): NaCl, 130; KCl, 2; $CaCl_2$, 1.8; $MgCl_2$, 0.89; NaH_2PO_4, 0.42; $NaHCO_3$, 25; glucose, 5.6. Cocaine hydrochloride (0.1 μM) was added to the Tyrode to prevent the neuronal uptake of (−)-noradrenaline. The preparations were equilibrated for 60 min with washing every 15 min. After the equilibration period, tissues were primed two times by addition of 10 μM noradrenaline. After another washing and equilibration period of 60 min, a noradrenaline concentration−response curve was constructed (basal response). When measuring the effect of noncompetitive antagonism, the antagonist was allowed to equilibrate with the tissue for 30 min followed by 30 min washing; then a new concentration−response curve to the agonist was obtained. In all other cases, the antagonist was allowed to equilibrate with the tissue for 30 min before constructing a new concentration−response curve to the agonist. (−)-Noradrenaline solutions contained 0.05% $Na_2S_2O_5$ to prevent oxidation.

Spleen. This tissue was used to assess the antagonism toward α_{1B}-adrenoreceptors.[19] The spleen was removed and bisected longitudinally into two strips, which were suspended in tissue baths containing Krebs solution of the following composition (mM): NaCl, 120; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.5; KH_2PO_4, 1.2; $NaHCO_3$, 20; glucose, 11; K_2EDTA, 0.01. Propranolol hydrochloride (4 μM) was added to block β-adrenoreceptors. The spleen strips were placed under 1 g resting tension and equilibrated for 2 h. The cumulative concentration−response curves to phenyelphrine were measured isometrically and obtained at 30 min intervals, the first one being discarded and the second one taken as control. When measuring the effect of noncompetitive antagonism, the antagonist was allowed to equilibrate with the tissue for 30 min followed by 30 min washing; then a new concentration−response curve to the agonist was constructed. In all other cases, the antagonist was allowed to equilibrate with the tissue for 30 min before constructing a new concentration−response curve to the agonist.

Aorta. This tissue was used to assess the antagonism toward α_{1D}-adrenoreceptors.[19] Thoracic aorta was cleaned from extraneous connective tissue and placed in Krebs solution of the following composition (mM): NaCl, 118.4; KCl, 4.7; $CaCl_2$, 1.9; $MgSO_4$, 1.2; NaH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11.7. Cocaine hydrochloride (0.1 μM) and propranolol hydrochloride (4 μM) were added to prevent the neuronal uptake of (−)-noradrenaline and to block β-adrenoreceptors, respectively. Two helicoidal strips (15 mm × 3 mm) were cut from each aorta beginning from the end most proximal to the heart. The endothelium was removed by rubbing with filter paper: the absence of acetylcholine (100 μM)-induced relaxation to preparations contracted with (−)-noradrenaline (1 μM) was taken as an indicator that the vessel was denuded successfully. Vascular strips were then tied with surgical thread and suspended in a jacketed tissue bath containing Tyrode solution. Strip contractions were measured isometrically. After at least a 2 h equilibration period under an optimal tension of 1 g, cumulative (−)-noradrenaline concentration−response curves were recorded at 1 h intervals, the first two being discarded and the third one taken as control. The antagonist was allowed to equilibrate with the tissue for 30 min before the generation of the fourth cumulative concentration−response curve to (−)-noradrenaline. (−)-Noradrenaline solutions contained 0.05% K_2EDTA in 0.9% NaCl to prevent oxidation.

Data Analysis. The affinity constants (pK_b values, Table 1) that were determined according to Arunlakshana and Schild[21] with the equation $pK_b = -\log K_b = \log(DR - 1) - \log [B]$, where DR represents the ratio of the potency of the agonist (EC_{50}) in the presence of the antagonist [B] and in its absence. EC_{50} values were calculated at two or three different antagonist concentrations. Each concentration was tested at least four times. The noncompetitive antagonist potency was expressed by the negative logarithm of concentration that causes 50% inhibition of agonist action (pIC_{50}, Table 1). Data were analyzed by pharmacological computer programs[24] and are presented as the mean ± SE of *n* experiments. Differences between mean values were tested for significance by Student's *t*-test.

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References

(1) (a) Bylund, D. B.; Eikenberg, D. C.; Hieble, J. P.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Molinoff, P. B.; Ruffolo, R. R., Jr.; Trendelenburg, U. IV. International union of pharmacology nomenclature of adrenoceptors. *Pharmacol. Rev.* **1994**, *46*, 121−136. (b) Hieble, J. P.; Bylund, D. B.; Clarke, D. E.; Eikenburg, D. C.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Ruffolo, R. R. International union of pharmacology X. Recommendation for nomenclature of α_1-adrenoceptors: consensus update. *Pharmacol. Rev.* **1995**, *47*, 267−270.

(2) Faure, C.; Pimoule, C.; Arbilla, S.; Langer, S. Z.; Graham, D. Expression of α_1-adrenoceptor subtypes in rat tissues: implications for α_1-adrenoceptor classification. *Eur. J. Pharmacol. (Mol. Pharmacol. Section)* **1994**, *268*, 141−149.

(3) Ford, A. P. D. W.; Williams, T. J.; Blue, D. R.; Clarke, D. E. α_1-Adrenoceptor classification: sharpening Occam's razor. *Trends Pharmacol. Sci.* **1994**, *15*, 167−170.

(4) Testa, R.; Guarneri, L.; Angelico, P.; Poggesi, E.; Taddei, C.; Sironi, G.; Colombo, D.; Sulpizio, A. C.; Naselsky, D. P.; Hieble, J. P.; Leonardi, A. Pharmacological characterization of the uroselective *alpha*-1 antagonist Rec 15/2739 (SB 216469): role of the *alpha*-1L adrenoceptor in tissue selectivity. Part II. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1284−1293.

(5) (a) Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. Pharmacological options in the treatment of benign prostatic hyperplasia. *J. Med. Chem.* **1997**, *40*, 1293−1315. (b) Leonardi, A.; Testa, R.; Motta, G.; De Benedetti, P. G.; Hieble, P.; Giardinà, D. α_1-Adrenoceptors: subtype- and organ-selectivity of different agents. In *Perspective in Receptor Research*; Giardinà, D., Piergentili, A., Pigini, M., Eds.; Elsevier: Amsterdam, 1996; pp 135−152. (c) Ruffolo, R. R., Jr.; Bondinell, W.; Hieble, J. P. α- and β-Adrenoceptors. From the gene to the clinic. 2. Structure−activity relationships and therapeutic applications. *J. Med. Chem.* **1995**, *38*, 3681−3716. (d) Matyus, P.; Horvath, K. α-Adrenergic approach in the medical management of benign prostatic hyperplasia. *Med. Res. Rev.* **1997**, *17*, 523−535. (e) Cooper, K. L.; McKiernan, J. M.; Kaplan, S. A. α-Adrenoceptor antagonists in the treatment of benign prostatic hyperplasia. *Drugs* **1999**, *57*, 9−17. (f) Meyer, M. D.; Altenbach, R. J.; Basha, F. T.; Carroll, W. A.; Condon, S.; Elmore, S. W.; Kerwin, J. F., Jr.; Sippy, K. B.; Tietje, K.; Wendt, M. D.; Hancock, A. A.; Brune, M. E.;

Buckner, S. A.; Drizin, I. Structure−activity studies for a novel series of tricyclic substituted hexahydro[*e*]isoindole α_{1A} adrenoceptor antagonists as potential agents for the symptomatic treatment of benign prostatic hyperplasia (BHP). *J. Med. Chem.* **2000**, *43*, 1586−1603.

(6) Giardinà, D.; Brasili, L.; Gregori, M.; Massi, M.; Picchio, M. T.; Quaglia, W.; Melchiorre, C. Structure−activity relationships among prazosin-related compounds. Effect of piperazine ring replacement by an alkanediamine moiety on α_1-adrenoreceptor blocking activity. *J. Med. Chem.* **1989**, *32*, 50−55.

(7) Giardinà, D.; Gulini, U.; Massi, M.; Piloni, M. G.; Pompei, P.; Rafaiani, G.; Melchiorre, C. Structure−activity relationships in prazosin-related compounds. 2. Role of the piperazine ring on α-blocking activity. *J. Med. Chem.* **1993**, *36*, 690−698.

(8) Giardinà, D.; Crucianelli, M.; Melchiorre, C.; Taddei, C.; Testa, R. Receptor binding profile of cyclazosin, a new α_{1B}-adrenoceptor antagonist. *Eur. J. Pharmacol.* **1995**, *287*, 13−16.

(9) Giardinà, D.; Crucianelli, M.; Romanelli, R.; Leonardi, A.; Poggesi, E.; Melchiorre, C. Synthesis and biological profile of the enantiomers of [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-cis-octahydroquinoxalin-l-yl]furan-2-ylmethanone (cyclazosin), a potent competitive α_{1B}-adrenoceptor antagonist. *J. Med. Chem.* **1996**, *39*, 4602−4607.

(10) Bolognesi, M. L.; Budriesi, R.; Chiarini, A.; Poggesi, E.; Leonardi, A.; Melchiorre, C. Design, synthesis, and biological activity of prazosin-related antagonists. Role of the piperazine and furan units of prazosin on the selectivity for α_1-adrenoreceptor subtypes. *J. Med. Chem.* **1998**, *41*, 4844−4853.

(11) Minarini, A.; Budriesi, R.; Chiarini, A.; Leonardi, A.; Melchiorre, C. Search for α_1-adrenoceptor subtypes selective antagonists: design, synthesis and biological activity of cystazosin, an α_{1D}-adrenoceptor antagonist. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1353−1358.

(12) For a review, see: (a) Melchiorre, C. Tetramine disulfides: a new tool in α-adrenergic pharmacology. *Trends Pharmacol. Sci.* **1981**, *2*, 209−211. (b) Melchiorre, C.; Recanatini, M.; Bolognesi, M. L.; Filippi, P.; Minarini, A. Polyamines: a case of multiple yet specific receptor recognition. *Curr. Top. Med. Chem.* **1993**, *1*, 43−65.

(13) Giardinà, D.; Crucianelli, M.; Gulini, U.; Marucci, G.; Melchiorre, C.; Spampinato, S. Synthesis and α_1-antagonist activity of new prazosin- and benextramine-related tetraamine disulfides. *Eur. J. Med. Chem.* **1997**, *32*, 9−20.

(14) Craig, P. N. Interdependence between physical parameters and selection of substituent groups for correlation studies. *J. Med. Chem.* **1971**, *14*, 680.

(15) Giardinà, D.; Crucianelli, M.; Marucci, G.; Melchiorre, C.; Polidori, C.; Pompei, P.; Massi, M. Pharmacological evaluation of prazosin- and doxazosin-related compounds with modified piperazine ring. *Arzneim.-Forsch./Drug Res.* **1996**, *46* (II), 1054−1059.

(16) Melchiorre, C.; Yong, M. S.; Benfey, B. G.; Belleau, B. Molecular properties of the adrenergic α receptor. 2. Optimum covalent inhibition by two different prototypes of polyamine disulfides. *J. Med. Chem.* **1978**, *21*, 1126−1132.

(17) Althuis, T. H.; Hess, H.-J. Synthesis and identification of the major metabolites of prazosin formed in dog and rat. *J. Med. Chem.* **1977**, *20*, 146−149.

(18) Eltze, M.; Boer, R.; Sanders, K. H.; Kolossa, N. Vasodilatation elicited by 5-HT_{1A} receptor agonist in constant-pressure-perfused rat kidney is mediated by blockade of α_{1A}-adrenoceptors. *Eur. J. Pharmacol.* **1991**, *202*, 33−44.

(19) Ko, F. N.; Guh, J. H.; Yu, S. M.; Wu, Y. C.; Teng, C. M. (−)-Discretamine, a Selective α_{1D}-Adrenoceptor Antagonist, Isolated from *Fissistigma glaucescens*. *Br. J. Pharmacol.* **1995**, *6*, 1174−1180.

(20) Buckner, S. A.; Oheim, K. W.; Morse, P. A.; Knepper S. M.; Hancock A. A. α_1-Adrenoceptor-Induced Contractility in Rat Aorta Is Mediated by The α_{1D} Subtype. *Eur. J. Pharmacol.* **1996**, *297*, 241−248.

(21) Arunlakshana, O.; Schild, H. O. Some quantitative uses of drug antagonists. *Br. J. Pharmacol.* **1959**, *14*, 48−58.

(22) Muramatsu, I.; Takita, M.; Suzuki, F.; Miyamoto, S.; Sakamoto, S.; Ohmura, T. Subtype selectivity of a new α_1-adrenoceptor antagonist, JTH-601: comparison with prazosin. *Eur. J. Pharmacol.* **1996**, *300*, 155−157.

(23) Van der Graaf, P. H.; Shankley, N. P.; Black, J. W. Analysis of the activity of α_1-adrenoceptor antagonists in rat aorta. *Br. J. Pharmacol.* **1996**, *118*, 299−310.

(24) Tallarida, R. J.; Murray, R. B. *Manual of Pharmacological Calculations with Computer Programs, Version 4.2*; Springer-Verlag: New York, 1991.

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