Synthesis, Pharmacological Evaluation, and Structure−Activity Relationship and Quantitative Structure−Activity Relationship Studies on Novel Derivatives of 2,4-Diamino-6,7-dimethoxyquinazoline α_1-Adrenoceptor Antagonists

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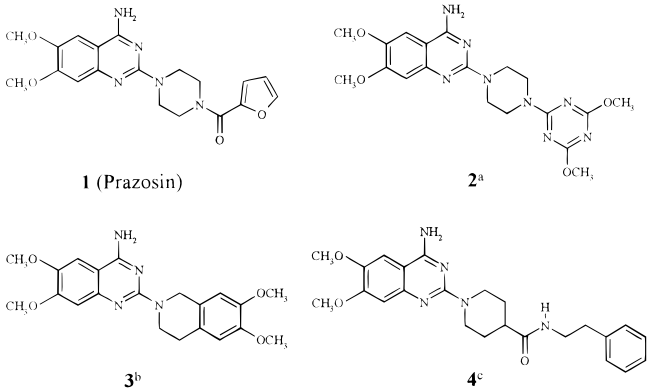
A new series of novel piperazine and non-piperazine derivatives of 2,4-diamino-6,7-dimethoxyquinazoline was synthesized and evaluated for binding affinity toward α_1-adrenergic and other G-protein-coupled aminergic receptors. The α_1-adrenoceptor (AR) subtype selectivity was also investigated for the most interesting compounds. Only compound **16** showed moderate selectivity toward the α_{1b}-AR subtype. Selected compounds were tested in vivo in a dog model indicating activity on blood pressure and on the lower urinary tract. Compound **10** showed in vivo potency close to that of prazosin. Powerful interpretative and predictive theoretical QSAR models have been obtained. The theoretical descriptors employed in the rationalization of the α_1-adrenergic binding affinity depict the key features for receptor binding which can be summarized in an electrostatic interaction between the protonated amine function and a primary nucleophilic site of the receptor, complemented by short-range attractive (polar and dispersive) and repulsive (steric) intermolecular interactions. Moreover, on predictive grounds, the ad hoc derived size and shape QSAR model developed in a previous paper (Rastelli, G.; et al. *J. Mol. Struct.* **1991**, *251*, 307−318) proved to be successful in predicting nanomolar α_1-adrenergic binding affinity for compound **28**.

Introduction

Among the compounds classified as antagonists of the α_1-adrenoceptor,[1−7] the derivatives of 2,4-diamino-6,7-dimethoxyquinazoline proved to be the first to show potent and selective activity.[8] This relevant characteristic granted the synthesis and pharmacological evaluation of a large number of derivatives by different research groups.[9−22] In Chart 1 the structure of the earliest example, prazosin (**1**), is shown, together with those of other very potent α_1-adrenoceptor antagonists (**2**−**4**) of this class.

Recent structure−activity relationship (SAR) studies on the wide-ranging series of 2,4-diamino-6,7-dimethoxyquinazoline[8−23] and -quinoline[24] derivatives have qualitatively rationalized the relevant affinity and selectivity of these compounds for the α_1-adrenoceptor. It has been proposed that the 2,4-diamino-6,7-dimethoxyquinazoline nucleus acts as a conformationally restricted bioisosteric replacement of noradrenaline with the N^1-protonated form being particularly suited for effective charge-reinforced hydrogen bonding with the carboxylate counterion in the ground-state conformation of the α_1-adrenoceptor.[8,9] This is corroborated by the lack of significant affinity and antihypertensive activity of the structurally closely related isoquinolines, where the bioisosteric substitution (C-H instead of N^1) abolishes any biological activity.[14]

Chart 1. 2-(Substituted-amino)-4-amino-6,7-dimethoxyquinazoline α_1-AR Antagonists



[a] See ref 11. [b] See ref 15. [c] See ref 12.

Further support comes from a recent report on molecular modeling and quantitative structure−activity relationship (QSAR) analysis of a heterogeneous series of quinazoline, quinoline and isoquinoline derivatives.[25] The QSAR models obtained in this paper by correlating theoretical molecular descriptors with both the experimental acidity constants and the α_1-adrenoceptor binding affinity data values clearly depicted the fundamental role of the protonated quinazoline nucleus for a productive interaction with the receptor. Furthermore, subsequent studies[26] have pointed out that once the electronic requirements of the common quinazoline moiety are satisfied, the binding affinities are modulated by the molecular shape of the quinazoline 2-substituent, through

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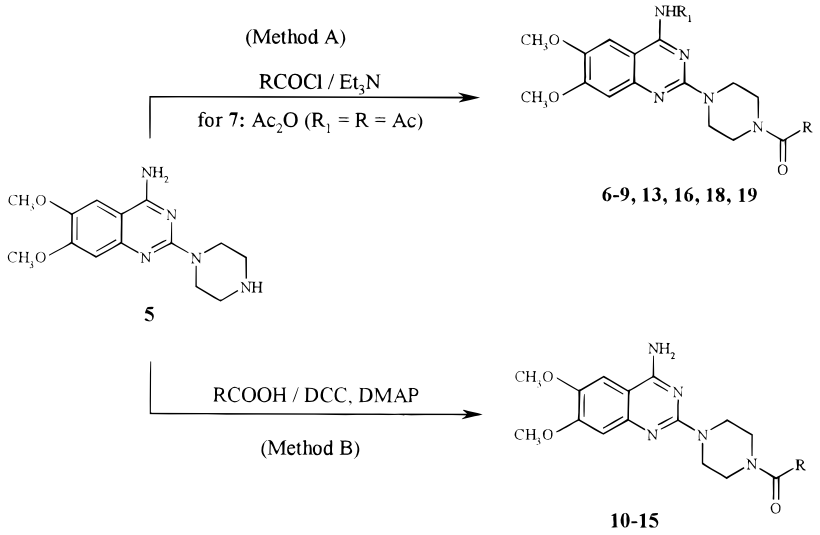
Scheme 1



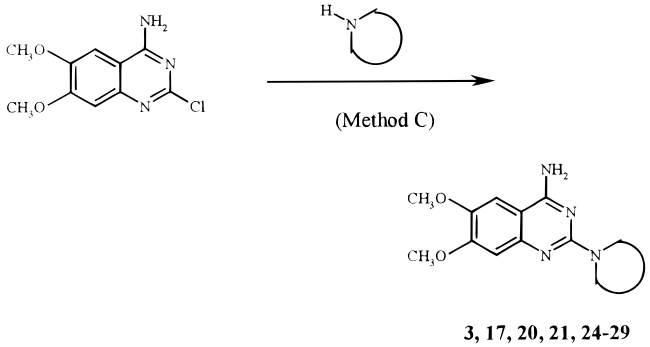
the optimization of both dispersive and steric interactions. In this respect, ad hoc derived size and shape descriptors defined on the ligand bioactive molecular form have proven to be very successful to derive QSAR models for several molecular series of G-protein-coupled receptor ligands.[27−29] These indices describe the size−shape similarity with respect to a reference supermolecule obtained by superposition of the most active and structurally different compounds, better if conformationally constrained. According to the ligand pharmacophore similarity−target receptor complementarity paradigm, the supermolecule represents the overall shape and the conformational flexibility of the receptor binding site.

On these bases, in order to validate the recently proposed theoretical QSAR models, novel piperazine (Table 1) and non-piperazine (Table 2) derivatives of 2,4-diamino-6,7-dimethoxyquinazoline were designed, synthesized, and tested for their binding affinity for the α_1-adrenoceptor in rat cortex. Selectivity toward other G-protein-coupled receptors, namely, α_2, D_2, and 5-HT_{1A} sites, was also investigated. Moreover, the most interesting compounds were submitted to enlarged receptor binding screening on α_1-adrenoceptor subtypes and in vivo tests to evaluate their effects on the lower urinary tract and the cardiovascular system. Finally, theoretical descriptors calculated on a single structure and ad hoc defined size and shape descriptors[30,31] have been employed in order to capture, on a quantitative ground, the molecular features responsible for the observed variation in the α_1-adrenoceptor binding affinity.

Chemistry

The synthesis of 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazolines **6**−**16**, **18**, and **19** is summarized in Scheme 1. The 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline (**5**) was treated with a suitable acyl chloride, in the presence of TEA as proton acceptor in $CHCl_3$ or DMF at room temperature, to afford derivatives **6**, **8**, **9**, **13**, **16**, **18**, and **19** (method A). Using Ac_2O instead of acetyl chloride, without TEA or solvent, the diacetyl derivative **7** was obtained. Compounds **10**−**15** were prepared by an alternative acylation procedure reacting **5** with the appropriate acids in DMF or $CHCl_3$ in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) at room temperature (method B).

Scheme 2

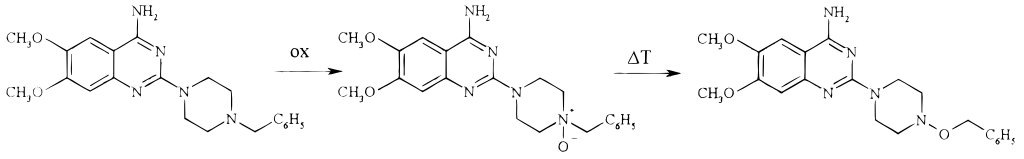


Compounds **3**, **17**, **20**, **21**, and **24**−**29** were synthesized as shown in Scheme 2. 4-Amino-2-chloro-6,7-dimethoxyquinazoline was reacted with a slight excess of the appropriate cyclic or acyclic base in isoamyl alcohol at reflux, optionally in the presence of potassium iodide (method C). The benzyl derivative **20** was oxidized with magnesium monoperoxyphthalate in methanol to afford in high yield the N^4-oxide derivative **22**, which was submitted to Meisenheimer thermal rearrangement conditions and afforded **23** in low yield, as depicted in Scheme 3.

The 2-isopropyl-6-methoxyphenoxy acids **31**, **33**, and **35** were obtained by alkaline hydrolysis of the corresponding ethyl esters **30**, **32**, and **34** (not isolated), which were prepared by O-alkylation of the sodium salt of 2-isopropyl-6-methoxyphenol with the suitable α-bromo esters under phase-transfer conditions at 60−65 °C, as depicted in Scheme 4.

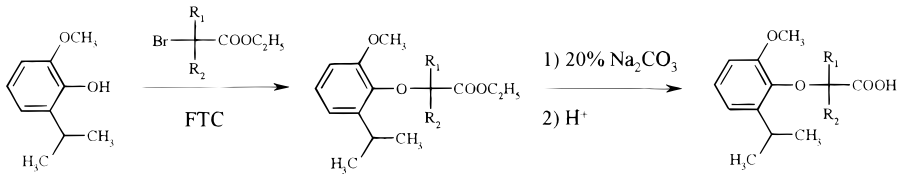
Chloride **36** (Scheme 5) was prepared by chlorination of the corresponding acid with $SOCl_2$ and used to acylate piperazine monohydrobromide in EtOH−THF mixture at reflux temperature to afford the piperazinyl intermediate **37** in moderate yield. In this last step a discrete amount of the bis-acyl derivative was formed and easily separated as an insoluble solid by acid treatment of the reaction mixture. **37** was then used for the synthesis of **17**.

Scheme 3



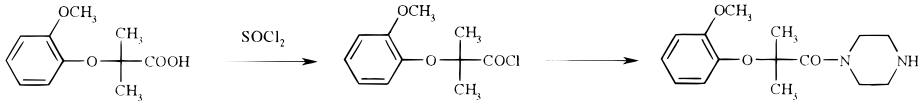
20 **22** **23**

Scheme 4



30	$R_1 = R_2 = H$	**31**
32	$R_1 = H, R_2 = CH_3$	**33**
34	$R_1 = R_2 = CH_3$	**35**

Scheme 5



36 **37**

Results and Discussion

Affinity of all compounds for the α_1-adrenoceptor was determined in rat cortex[32] and was found to be in the nanomolar to micromolar range, as shown in Tables 1 and 2. Affinity for the native α_2,[33] D_2,[34] 5-HT_{1A},[35] and 5-HT_{2A}[36] receptors was also checked. All compounds proved inactive at these sites (IC_{50} > 1000 nM) except compound **14**, showing IC_{50} = 170 nM at the 5-HT_{1A} receptor.

The compounds endowed with high affinity for the native α_1-adrenoceptor were also tested on the three α_1-adrenoceptor subtypes of animal origin expressed in the COS-7 cell line (Table 3). In agreement with the literature, prazosin exhibited high affinity for the three subtypes, with no selectivity. The absence of selectivity was confirmed for all tested compounds, except compound **16**, which exhibited high affinity and moderate selectivity for the α_{1b}-adrenoceptor subtype. Despite its relative absolute value, it is worth noting that selectivity for the α_{1b} subtype of compound **16** could be due to the bulkiness of the aromatic group. Bulkiness, even if in a different position, closer to the protonated N^1 atom of quinazoline, is also a common characteristic of two selective α_{1b}-adrenergic antagonists recentely reported: (+)-cyclazosin ([4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-*cis*-octahydroquinoxalin-1-yl]furan-2-ylmethanone hydrochloride[34]) and (*S*)-4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-*N*-(1,1-dimethylethyl)-1-(2-furoyl)piperazine-2-carboxamide.[37]

On the basis of the overall lack of high subtype selectivity and on the fact that affinity for the native α_1-adrenoceptor shown in Table 1 adequately reflects the data from Table 3, other compounds were not further tested for subtype selectivity. Thus the following comments and QSAR analysis refer to the native α_1-adrenoceptor.

SAR for Native α_1-Adrenoceptor Affinity. 1. *N*-Acylpiperazine Derivatives. Double acylation of piperazine N^4 and 4-NH_2 (**7**) groups led to a loss of affinity for compound **5**, itself showing a low affinity. The absence of affinity in compound **7** can be due to a reduction in basicity of the anilino nitrogen (as shown by the values of the nucleophilic superdelocalizability: $S^L(NH_2)$ = 0.018 eV^{-1} for **5** and 0.011 eV^{-1} for **7**) and/or to violation of the steric requirements of the receptor binding site.

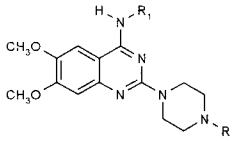
When acylation is limited to the piperazine N^4, a consistent increase of affinity is evident and apparently modulated by the bulkiness of the substituent, the optimum being obtained when planar rings (**1** and **9**) or mono- or disubstituted methylene units are in position α to the carbonyl group. When this methylene unit is trisubstituted, affinity is reduced to a different extent (**8** and **17**) or almost lost (**19**).

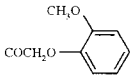
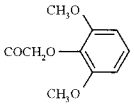
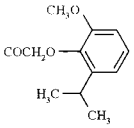
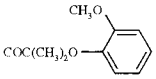
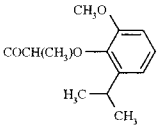
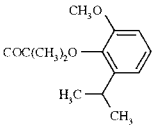
The different nature of the substituents present in compounds with high affinity for this receptor supports the relative tolerance to bulkiness in this portion of the molecules, which is challenged when methyl groups are inserted at the α-carbonyl methylene and an isopropyl group is simultaneously inserted at position 2 (6) of the phenoxy ring (**18** and **19**).

2. Other Piperazines. Alkylation of piperazine N^4 with bulky groups improves affinity (**20** and **21**) also but to a lesser extent than acylation with groups having close steric requirements (**9** and **12**). Affinity is slightly reduced when the benzyl group is replaced by a benzyloxy group (**23**) and is lost when N^4 of compound **20** is transformed into its *N*-oxide derivative. These results suggest that changes in basicity of the piperazine N^4 may play a relevant role in determining affinity for the α_1-adrenoceptor.

In fact, the trend in the electrophilic superdelocalizability on this atom suggests that the most active ligands are less susceptible to an electrophilic attack

Table 1. Derivatives (**5**−**23**) of 2-(1-Piperazinyl)-4-amino-6,7-dimethoxyquinazoline



Compd	R	R_1	Method	Yield (%)	M.p. (°C)	Recryst. solvent	Formula	IC_{50} (nM) α_1[a]
5[b]	H	H	--	75	(281-283)	EtOH 90	$C_{14}H_{19}N_5O_2$ .2HCl .H_2O	340
6	$COCH_3$	H	A	66	244-245	EtOH	$C_{16}H_{21}N_5O_3$ .HCl .2.5H_2O	45
7	$COCH_3$	$COCH_3$	--	62	>270	DMF-EtOH 1:2	$C_{18}H_{23}N_5O_4$	5080
8	$COC(CH_3)_3$	H	A	71	>270	EtOH	$C_{19}H_{27}N_5O_3$ .HCl .0.75H_2O	340
9[c]	COC_6H_5	H			(>275)			4.6
10	$COCH_2COC_6H_5$	H	B	60	214-215	ACN	$C_{23}H_{25}N_5O_4$	7.2
11	$COCH_2CH_2COC_6H_5$	H	B	62	>270	ACN-H_2O 65:35	$C_{24}H_{27}N_5O_4$ .HCl .H_2O	15
12	$COCH(C_6H_5)_2$	H	B	60	282-283	EtOH 90	$C_{28}H_{29}N_5O_3$ .HCl .0.75H_2O	3.2
13	$COCH_2CH(C_6H_5)_2$	H	B	55	239-240	ACN-H_2O 4:1	$C_{29}H_{31}N_5O_3$ .HCl	1.4
14		H	A B	43 61	263-265	DMF-H_2O 1:2	$C_{23}H_{27}N_5O_5$ .HCl	17
15		H	B	21	258-260 dec.	DMF	$C_{24}H_{29}N_5O_6$ .HCl .0.25H_2O	6
16		H	A	45	252-254	EtOH	$C_{26}H_{33}N_5O_5$ .HCl	4
17		H	C	57	288 dec.	EtOH 80	$C_{25}H_{31}N_5O_5$ .HCl	49
18		H	A	58	227-229	EtOH	$C_{27}H_{35}N_5O_5$ .HCl	123
19		H	A	73	263-265	EtOH	$C_{28}H_{37}N_5O_5$ .HCl	1180
20	$CH_2C_6H_5$	H	C	56	265-267	ACN-H_2O 7:3	$C_{21}H_{25}N_5O_2$ .2HCl .0.5H_2O	32
21	$CH(C_6H_5)_2$	H	C	56	273-274	--	$C_{27}H_{29}N_5O_2$ .2HCl .0.5H_2O	40
22	$CH_2C_6H_5$ (N-oxide)	H	--	86	219-221	EtOH +Et_2O	$C_{21}H_{25}N_5O_3$ .2HCl .0.75H_2O	>> 1000
23	$OCH_2C_6H_5$	H	--	11	179-180	ACN	$C_{21}H_{25}N_5O_3$	111
1	2-furoyl	H	--	--	--	--	--	2

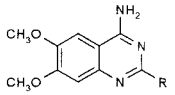
[a] Mean of 2−3 different evaluations. SEM (always less than 15%) was omitted for clarity. [b] See refs 8 and 39. [c] See ref 23.

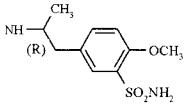
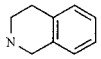
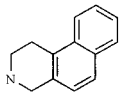
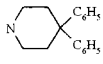
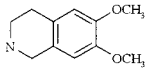
(protonation) to this site: $S^H(N^4) = 8.38 \times 10^{-4}$ and 9.74×10^{-4} eV^{-1} for the PhCO derivative **9** and the $PhCH_2$ analogue **20**, respectively, and 2.61×10^{-3} and 2.65×10^{-3} eV^{-1} for **23** (R = $PhCH_2O$) and **5** (R = H), respectively.

3. Other Amines at Position 2 of the Quinazoline Ring. The attempt to realize a "hybrid" structure bearing the substituted phenylpropylamino chain characteristic of tamsulosin (**26**) gave an inactive compound. Open chain or cyclized amines bearing phenyl groups showed limited affinity (**24**, **25**, and **29**).

On the contrary, compound **28** proved to be a high-affinity ligand for the α_1-AR. It was designed on the basis of the superposition of compound **3** to compound **2** (Figure 1). Its affinity was calculated in advance to be in the nanomolar range by making use of a QSAR model recently published[26] and by comparison of its reactivity determinants ($S^L(N)$ and ΔE_{prot}, Table 4) with

Table 2. 2-(Substituted-amino)-4-amino-6,7-dimethoxyquinazolines **3** and **24**−**29**



Compd	R	Method	Yield (%)	M.p. (°C)	Recryst. solvent	Formula	IC_{50} (nM) α_1[a]
24	$N(CH_3)CH_2C_6H_5$	C	62	261-262	EtOH	$C_{18}H_{20}N_4O_2$ .HCl	70
25	$N(CH_3)CH_2CH_2CH(C_6H_5)_2$	C	29	258-259	EtOH 95	$C_{26}H_{28}N_4O_2$ .HCl	85
26		C	35	234-236	ACN-H_2O 7:1	$C_{20}H_{25}N_5O_5S$ .HCl .0.8H_2O	3140
27[b]		C	(44)	(223-225)	(EtOH 97)	$C_{19}H_{20}N_4O_2$ .HCl .0.5H_2O	4.1
28		C	30	177-180 dec	EtOH	$C_{23}H_{22}N_4O_4$ .0.25 C_2H_5OH	1.6
29		C	61	>290	DMF-H_2O 1:1	$C_{27}H_{28}N_4O_2$ .HCl .0.65H_2O	259
3[c]		C	(73)	(230-232)	(EtOH)	$C_{21}H_{24}N_4O_4$	0.2

[a] Mean of 2−3 different evaluations. SEM (always less than 15%) was omitted for clarity. [b] See ref 8. [c] See ref 15.

Table 3. Affinity of Selected Compounds for α_1-Adrenoceptor Subtypes

	K_i (nM), animal clones		
compd	α_{1a}	α_{1b}	α_{1d}
10	10.99	5.43	8.17
11	5.68	4.43	19.38
13	1.48	1.57	1.59
14	18.95	8.56	18.95
15	36.20	9.05	23.72
16	7.5	0.45	10.34
18	155.6	14.7	112.8
1	0.72	0.46	1.39

respect to compounds **3** and **27**. The QSAR model derived in that paper refers to a supermolecule obtained by superpositioning compounds **1**−**3** and all the accessible conformations of the flexible compound **4** (Chart 1), chosen within 0.5 kcal mol^{-1} of its absolute minimum (i.e., 19 conformers). The regression obtained in ref 26:

$$pA = 5.321(\pm 1.801)V_{dif} - 2.426(\pm 0.679)$$
$$n = 14,\ r = 0.834,\ s = 0.302,\ F = 27.3 \qquad \text{(a)}$$

where p*A* is the negative logarithm of the binding affinity of a generic compound normalized with respect to prazosin (IC_{50} = 2 nM), provided a p*A* value for compound **28** (V_{dif} = 0.4045) of −0.27, which corresponds to an IC_{50} of 3.7 nM. The experimental result (IC_{50} = 1.6 nM) confirms the soundness of the model used to predict these values.

Quantitative Structure−Affinity Relationship Analysis. Successful correlation equations can be obtained for the α_1-AR binding affinity by means of theoretical descriptors derived on a single structure (i.e., molecular orbital indices and charged partial surface area descriptors) and ad hoc derived descriptors computed with respect to a supermolecule obtained by superimposing the highest affinity ligands (see Computational Procedures section).

The data values of the molecular descriptors used in the selected correlation equations are listed in Table 4, together with the cologarithmic form of the α_1-AR binding affinity (pIC_{50}) of the considered ligands. An exhaustive definition of the descriptor involved in the selected QSAR models is given in the Computational Procedures section. A quantitative overview of the collinearities existing between the theoretical descriptors of Table 4 is shown in Table 5, where the respective intercorrelation coefficients are given. The descriptors involved in the rationalization of the α_1-adrenoceptor binding affinity emphasize (a) the role of the quinazoline N^1-nitrogen atom as a hydrogen-bonding donor with respect to a suitable amino acid residue of the receptor (eqs 2 and 3), (b) the hydrogen-bonding acceptor propensity (eqs 4 and 5) of the ligands, and (c) the dispersive and steric interactions realized by the quinazoline substituents (eq 1).

The critical role of the quinazoline protonated N^1-nitrogen is well-described by the valency of its hydrogen atom V_f(H). In fact, the negative value of the regression coefficient indicates that ligands with lower values for minimum valency give stronger hydrogen bonds. The V_f(H) values for compounds **7**, **19**, and **29** have not been reported in Table 4 since their minimum valency is not due to the protonated N^1-nitrogen but to a substituent hydrogen, whereas compound **8** has been omitted from eq 2 since it is an outlier with overpredicted binding affinity. The role of a long-range electrostatic interaction as a preliminary recognition step in the ligand−receptor complex formation is further emphasized by the nucleophilic index computed on the protonated nitrogen atom (S^1(N)) (eq 3). This index, which provides a numerical differentiation of the capability of the ligand to donate the proton, explains 60% of the variation in the binding affinity, by omitting compounds **7**, **24**, and **25**.

Equation 1 involves the ad hoc derived size and shape descriptor V_{dif}, which, by taking into account in its

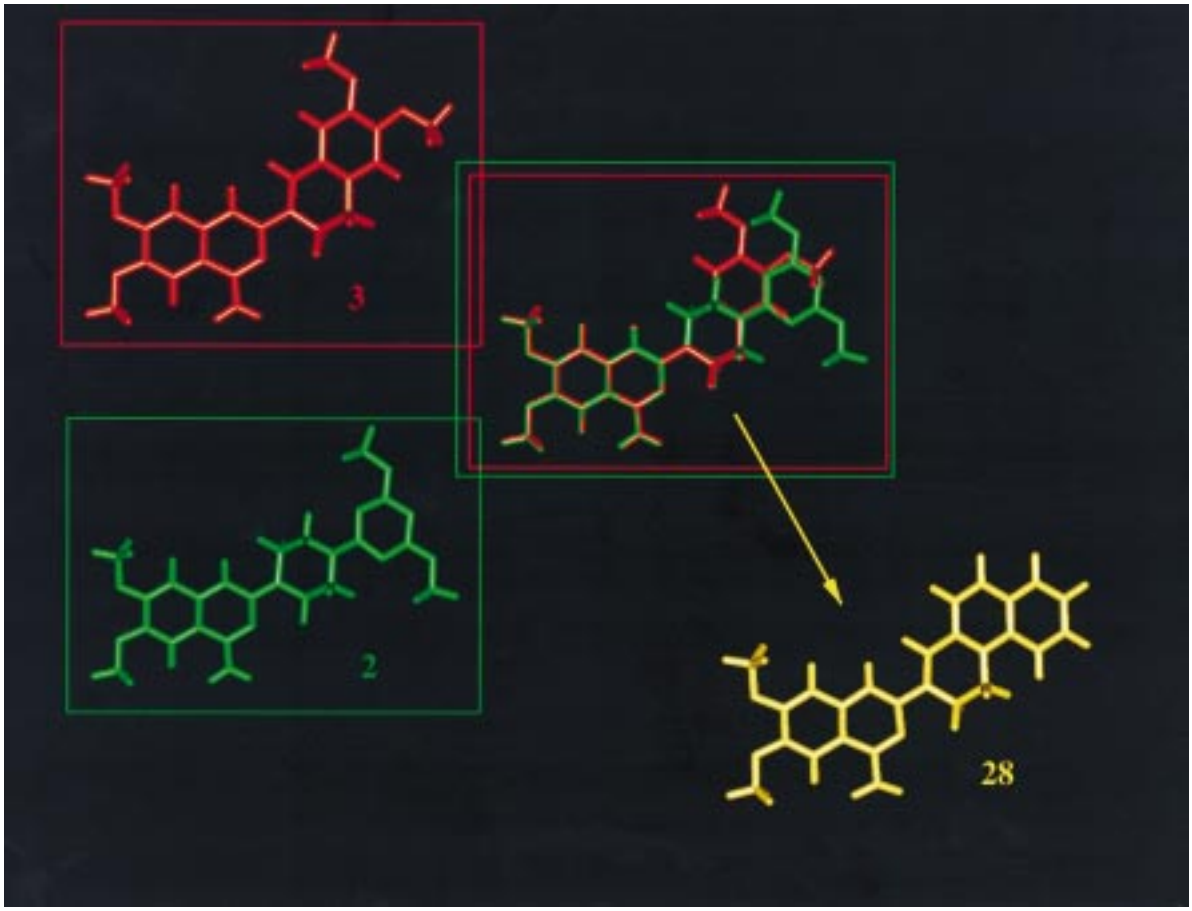


Figure 1. Structural design of compound **28**, based on the superimposition of compound **3** to compound **2**.

Table 4. Binding Affinities (pIC_{50}) and Theoretical Descriptors of the Protonated Forms of the Quinazoline-like Ligands

compd	pIC_{50}	V_{mol} (Å^3)	V_{in} (Å^3)	V_{out} (Å^3)	V_{dif}	V_f(H)	HACA-1 (Å^2)	HACA-1/TMSA ($\times 10^{-3}$)	S_L(N) (eV^{-1})	ΔE_{prot} (kcal/mol)
5	6.47	246.50	243.63	2.87	0.4528	0.9253	3.4882	6.05	0.0152	−191.07
9	8.34	330.75	314.88	15.87	0.5623	0.9236	2.4363	3.24	0.0164	−188.70
27	8.39	285.13	285.13	0.00	0.5362	0.9224	2.3817	3.74	0.0170	−190.50
3	9.70	331.88	331.88	0.00	0.6241	0.9224	2.1270	2.97	0.0168	−189.12
23	6.95	337.75	287.25	50.50	0.4452	0.9241	2.1909	2.95	0.0165	−187.98
1	8.70	314.00	314.00	0.00	0.5905	0.9237	2.3759	3.30	0.0163	−189.13
17	7.31	402.13	318.75	83.38	0.4426	0.9243	2.4330	3.00	0.0159	−189.69
16	8.40	417.75	356.13	61.62	0.5539	0.9233	2.3125	2.65	0.0165	−188.54
18	6.91	438.63	335.75	102.88	0.4379	0.9242	2.4951	2.82	0.0160	−189.51
19	5.93	450.38	300.88	149.50	0.2847		2.4386	2.81	0.0154	−192.53
13	8.85	429.63	429.63	0.00	0.8080	0.9235	2.3756	2.69	0.0164	−188.58
11	7.82	378.13	339.63	38.50	0.5663	0.9237	2.5686	3.04	0.0164	−188.85
10	8.14	363.25	323.00	40.25	0.5317	0.9235	2.3094	2.91	0.0166	−187.74
8	6.47	327.75	284.50	43.25	0.4537	0.9240	2.3792	3.43	0.0161	−189.54
6	7.35	280.13	279.38	0.75	0.5240	0.9235	2.3159	3.57	0.0165	−188.38
7	5.29	339.50	274.13	65.37	0.3926		3.5630	5.06	0.0170	−187.84
20	7.49	329.63	314.50	15.13	0.5630	0.9242	2.1852	3.04	0.0158	−190.78
12	8.49	413.38	365.63	47.75	0.5978	0.9235	2.1894	2.56	0.0162	−189.25
21	7.40	397.13	339.25	57.88	0.5291	0.9240	2.1909	2.67	0.0156	−191.29
25	7.07	375.63	304.88	70.75	0.4403	0.9243	2.5053	3.18	0.0143	−190.31
14	7.77	374.50	338.88	35.62	0.5703	0.9233	2.3156	2.75	0.0165	−188.64
28	8.80	324.88	324.88	0.00	0.6110	0.9221	2.5698	3.67	0.0167	−190.68
29	6.59	377.50	294.88	82.62	0.3992		2.7671	3.58	0.0148	−193.56
24	7.15	280.25	260.00	20.25	0.4509	0.9247	2.4433	3.83	0.0147	−190.24
26	5.50	355.13	250.75	104.38	0.2753	0.9253	2.5772	3.22	0.0150	−187.95
15	8.22	452.00	361.63	90.37	0.5101	0.9233	2.3156	2.67	0.0162	−189.80

formulation both the inner and outer molecular volumes of the ligands considered with respect to the reference volume of the supermolecule, indicates that once the main docking has been accomplished the binding affinity might be modulated by the optimization of the short-range intermolecular interactions and dispersion contributions of the quinazoline substituents. In this respect, it is worth noting that the selected supermolecule, being obtained by superimposing the highest affinity ligands (**1**, **3**, **13**, and **28**) for the native α_1-adrenoceptor, is a good template for the α_1 binding site, but not for the α_1 subtypes. In fact, the selective α_{1b}-

Table 5. Correlation Matrix between Experimental Binding Affinity and Theoretical Descriptors Reported in Table 4

	pIC_{50}	V_{mol}	V_{in}	V_{out}	V_{dif}	$V_f(H)$	HACA-1	HACA-1/TMSA	$S_L(N)$	ΔE_{prot}
pIC_{50}	1.000									
V_{mol}	0.038	1.000								
V_{in}	0.648	0.689	1.000							
V_{out}	−0.596	0.689	−0.051	1.000						
V_{dif}	0.858	0.000	0.725	−0.725	1.000					
$V_f(H)$	−0.838	−0.097	−0.478	0.416	−0.647	1.000				
HACA-1	−0.561	−0.296	−0.468	0.061	−0.365	0.466	1.000			
HACA-1/TMSA	−0.415	−0.690	−0.667	−0.283	−0.265	0.336	0.871	1.000		
$S^L(N)$	0.487	−0.035	0.353	−0.401	0.520	−0.791	−0.146	−0.113	1.000	
ΔE_{prot}	0.165	−0.060	0.144	−0.227	0.256	−0.048	−0.104	−0.134	0.542	1.000

Table 6. Regression Models for the Correlation between Theoretical Molecular Structure Descriptors and α_1-Adrenoceptor Binding Affinity

eq	descriptor	$x \pm D_x$	*t*-test	*n*	R^2	R^2_{CV}	s^2	*F*
1	intercept	3.23 ± 0.53	6.03					
	V_{dif}	8.47 ± 1.03	8.18	26	0.736	0.651	0.324	66.96
2	intercept	905.4 ± 122.1	7.42					
	$V_f(H)$	−971.8 ± 132.2	−7.35	22	0.730	0.655	0.250	54.05
			omitted: **8**					
3	intercept	−15.08 ± 3.94	−3.82					
	$S^L(N)$	1410.7 ± 244.8	5.76	23	0.613	0.536	0.439	33.20
			omitted: **7**, **24**, and **25**					
4	intercept	5.99 ± 1.06	5.65					
	V_{dif}	7.44 ± 0.97	7.66					
	HACA-1	−0.90 ± 0.31	−2.90	26	0.807	0.723	0.248	48.04
5	intercept	11.39 ± 0.59	19.21					
	V_{out}	−0.02 ± 0.003	−6.80					
	HACA-1/TMSA	−891.1 ± 160.2	−5.56	26	0.725	0.643	0.353	30.29

adrenoceptor derivatives **16** and **18** are well-accomodated by eq 1 (Table 6) for their native α_1 binding affinity, whereas no interpolation can be done for their α_{1b}-adrenoceptor binding affinity by making use of the same equation.

A significant improvement in the stability of the regression involving V_{dif} is obtained in eq 4 by including the HACA-1 index, as underlined by the cross-validated correlation coefficient ($R_{CV}^2 = 0.723$). It is worth noting that this descriptor contributes to the regression with a negative sign; therefore proliferation of hydrogen bond acceptor centers in the ligands seems to not be essential for the modulation of the binding affinity. The HACA-1 index is also involved, together with V_{out}, in eq 5, where it is normalized for the total molecular surface area of the ligands. Notwithstanding this correlation shows worse statistical parameters with respect to eq 4, the predictive power for the ligands showing higher affinity is notably improved (compare Figures 2 and 3, where the experimental and calculated α_1 binding affinity for eq 4 (Table 6) and eq 5 (Table 6) are plotted).

Functional Selectivity. Compounds **10**, **11**, **13**, and **16** were tested in a dog model[38] aiming to evaluate the effects on stimulated urethral contractility in parallel to hypotension. Prazosin was tested as a reference standard, as shown in Table 7. None of the tested compounds showed selectivity for the lower urinary tract. Compound **10** was the only derivative showing in vivo potency close to that of prazosin.

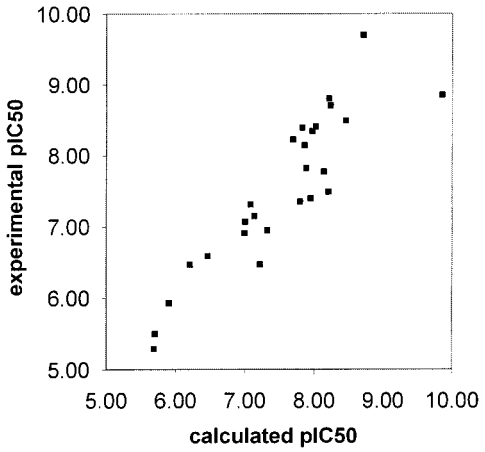


Figure 2. Plot of the predicted versus experimental α_1 binding affinity for eq 4.

Conclusions

In addition to confirmation of the pivotal role of protonation of N^1 in the quinazoline ring, the obtained results allowed us to define other relevant features for the affinity of 4-amino-2-(1-piperazinyl)-6,7-dimethoxyquinazolines for the α_1-adrenoceptor, such as the negative effect given by acylation of the 4-amino group and the modulating role of the piperazine N^4 susceptibility to protonation. Tolerance to bulky substituents introduced at the piperazine N^4 was also confirmed, with some exceptions. Moreover, the use of theoretical descriptors derived on a single structure and ad hoc defined size and shape descriptors in deriving QSAR models provided elucidation of the role of the main pharmacophoric components for α_1-AR recognition and binding. In fact, the electrostatic interactions between the protonated amine function and a primary nucleophilic site of the receptor necessary for recognition are described by the nucleophilic superdelocalizability and the free valency of the protonated N^1-nitrogen atom, while the short-range attractive and repulsive intermolecular interactions mainly responsible for the modulation of the binding affinities are described by charged partial surface area descriptors computed on the whole molecules (polar forces) and by ad hoc defined size and

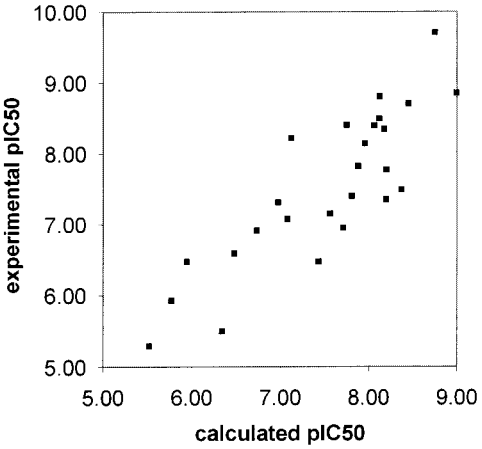


Figure 3. Plot of the predicted versus experimental α_1 binding affinity for eq 5.

Table 7. In Vivo Effects of Selected Compds after Intravenous Administration in the Dog Model

compd	UP (ED_{50})		DBP (ED_{25})		ratio (DBP/UP)
10	10.6	(6.8−16.4)	8.1	(6.7−9.8)	0.7
11	35	(27.6−44.7)	132	(73−240)	3.77
13[a]	31	(25−37)	23	(18−29)	0.74
16[a]	65	(51−82)	183	(96−347)	2.82
1[a]	3.6	(3.1−4.2)	6.6	(4.2−10)	1.83

[a] These data have already been published, see ref 55.

shape descriptors (dispersive and steric forces). Finally, the predictive ability of previously reported QSAR models obtained by employing ad hoc derived size and shape descriptors has been corroborated by the experimental binding affinity of compound **28**.

Experimental Section

Chemistry. Melting points were determined with a Buchi 535 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker AC 200; chemical shifts are reported as δ values relative to tetramethylsilane as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Analytical TLC was performed on silica 60 F_{254} plates (Merck), and the spots were made visible by a UV lamp or iodine vapor or were sprayed with Dragendorff's reagent. Flash chromatography was performed on silica gel (Merck 70−230 mesh). Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values and were performed by Redox s.n.c. Unless stated otherwise, starting materials were used as high-grade commercial products.

The compound **5** was synthesized by a published procedure. The physical data are in agreement with those given in ref 39. Intermediates *N*-methyl-3,3-diphenylpropylamine[40] used for **25**, (*R*)-1-methyl-2-(3-aminosulfonyl-4-methoxyphenyl)ethylamine[41] used for **26**, 1,2,3,4-tetrahydrobenz[*f*]isoquinoline[42] used for **28**, and 4,4-diphenylpiperidine[43] used for **29** were synthesized by published procedures.

Method A. 1-Acetyl-4-(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine Hydrochloride·2.5H_2O (6). To a suspension of **5** (5.78 g, 0.02 mol), $CHCl_3$ (120 mL), and triethylamine (4.86 mL, 0.0347 mol) was dropped in 15 min a solution of acetyl chloride (2.24 mL, 0.031 mol) in $CHCl_3$ (20 mL). The mixture was stirred at 22−25 °C for 8 h and then was washed with H_2O (3 × 50 mL); the organic layer was dried (anhydrous Na_2SO_4) and evaporated to dryness in vacuo. The residue was suspended into boiling EtOH (150 mL), and ethanolic HCl was added to the mixture obtaining a solution followed by precipitation of the solid, which was collected and crystallized from EtOH affording 5.5 g (66%) of the desired product as a white solid: mp 244−245 °C; ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H), 3.35−3.55 (m, 4H), 3.60−3.80 (m, 4H), 3.79 (s, 3H), 3.83 (s, 3H), 6.75 (s, 1H) 7.17 (bs, 2H), 7.44 (s, 1H).

1-Acetyl-4-(4-acetylamino-6,7-dimethoxy-2-quinazolinyl)piperazine (7). A mixture of **5** (4.63 g, 0.016 mol) and Ac_2O (100 mL) was stirred at reflux for 1 h. The reaction was poured into H_2O (300 mL), was alkalinized with 12 N NaOH (190 mL) in 15 min, and after cooling to room temperature was extracted with $CHCl_3$ (3 × 140 mL). The organic layer was washed with H_2O (2 × 100 mL) and dried (anhydrous Na_2SO_4) and the solvent evaporated to afford a crude that was purified by flash chromatography ($CHCl_3$−MeOH gradient 100:1 to 100:5) followed by crystallization from DMF−H_2O (1:2) to afford 3.7 g (62%) of a white solid: mp >270 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H), 2.41 (s, 3H), 3.45−3.60 (m, 4H), 3.71−3.81 (m, 4H), 3.84 (s, 3H), 3.89 (s, 3H), 6.90 (s, 1H), 7.47 (s, 1H), 10.46 (s, 1H).

The following compounds were prepared by method A, above.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-pivaloylpiperazine hydrochloride·0.75H_2O (8): ^{1}H NMR (DMSO-d_6) δ 1.25 (s, 9H), 3.30−4.30 (m, 8H), 3.80 (s, 7.5H), 7.45 (s, 1H), 7.60 (s, 1H), 8.20−8.80 (bs, 2H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(3,3-diphenylpropionyl)piperazine hydrochloride (13): ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 6H), 3.00−4.10 (m, 10H), 4.20−4.70 (m, 1H), 6.90−7.30 (m, 10H), 7.50−7.80 (m, 2H), 8.10−9.20 (bb, 2H), 12.00−12.60 (bb, 1H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2-isopropyl-6-methoxyphenoxy)acetyl]piperazine hydrochloride (16): ^{1}H NMR (DMSO-d_6) δ 1.30 (d, 6H), 3.10−4.90 (m, 9H), 4.30 (s, 3H), 4.35 (s, 3H), 5.15 (s, 2H), 7.40−7.90 (m, 3H), 8.50−8.80 (m, 2H), 9.50−10.00 (bb, 2H), 13.70−14.70 (bb, 1H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2-isopropyl-6-methoxyphenoxy)propionyl]piperazine hydrochloride·0.4H_2O (18): ^{1}H NMR (DMSO-d_6) δ 1.10−1.70 (m, 9H), 3.50−5.00 (m, 10.8H), 4.30−4.35 (m, 9H), 7.60−8.10 (m, 3H), 8.70−9.00 (m, 2H), 9.50−10.60 (bb, 2H), 13.60−15.00 (bb, 1H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2-isopropyl-6-methoxyphenoxy)-2-methylpropionyl]piperazine hydrochloride (19): ^{1}H NMR (DMSO-d_6) δ 1.50 (d, 6H), 1.75 (s, 6H), 3.50−5.30 (m, 9H), 4.45 (s, 3H), 4.70 (s, 6H), 8.00−8.60 (m, 3H), 9.10−9.50 (m, 2H), 9.80−11.20 (bb, 2H), 14.70−15.30 (bb, 1H).

Method B. 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(benzoylacetyl)piperazine (10). To a suspension of 97% DCC (10.5 g, 0.05 mol), DMAP (0.37 g, 0.003 mol), **5** (8.7 g, 0.03 mol), and anhydrous $CHCl_3$ (140 mL) was dropped in 3 min a solution of benzoylacetic acid (8.2 g, 0.05 mol) in anhydrous $CHCl_3$ (30 mL). The mixture was stirred at 22−25 °C for 6 h and then was diluted with CH_2Cl_2 (200 mL) and MeOH (16 mL), and the insoluble DCU was filtered off. The solvents were evaporated to dryness, and the residue was purified by flash chromatography (CH_2Cl_2−MeOH, 100:3) followed by crystallization from ACN to afford 7.8 g (60%) of a white solid: mp 214−215 °C; ^{1}H NMR (DMSO-d_6) δ 3.00−4.00 (m, 8H), 2.75 (s, 6H), 4.20 (s, 2H), 6.65 (s, 1H), 6.80−7.10 (bs, 2H), 7.30 (s, 1H), 7.20−7.50 (m, 3H), 7.60−7.90 (m, 2H).

The following compounds were prepared by method B, above.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-[(3-benzoyl)propionyl]piperazine hydrochloride monohydrate (11): ^{1}H NMR (DMSO-d_6) δ 2.50−2.90 (m, 2H), 3.80 (s, 6H), 3.00−4.00 (m, 12H), 7.20−7.90 (m, 7H), 8.20−8.90 (bb, 2H), 11.50−12.50 (bb, 1H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(2,2-diphenylacetyl)piperazine hydrochloride·0.75H_2O (12): ^{1}H NMR (DMSO-d_6) δ 3.20 (s, 1.5H), 3.30 (s, 6H), 3.40−4.00 (m, 8H), 5.50 (s, 1H), 7.10 (s, 10H), 7.50 (s, 1H), 7.60 (s, 1H), 8.20−8.80 (bb, 2H), 11.20−12.70 (bb, 1H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2-methoxyphenoxy)acetyl]piperazine hydrochloride (14): ^{1}H NMR (DMSO-d_6) δ 2.90−4.20 (m, 8H), 3.70 (s, 3H), 3.80 (s,

6H), 4.75 (s, 2H), 6.75 (s, 4H), 7.50 (s, 1H), 7.60 (s, 1H), 8.30−8.70 (bb, 2H), 11.70−12.30 (bb, 1H).

Method C. 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-[2-(2-methoxyphenoxy)-2-methylpropionyl]piperazine Hydrochloride (17). A mixture of **37** (2.78 g, 0.01 mol), 4-amino-2-chloro-6,7-dimethoxyquinazoline (2.39 g, 0.01 mol), and isoamyl alcohol (50 mL) was stirred at reflux temperature for 5 h. After cooling to 0−5 °C the mixture was kept resting for 30 min; then the precipitate was collected by filtration, washed first with isoamyl alcohol and second with acetone. The crude was suspended in H_2O (50 mL) and $CHCl_3$ (50 mL), alkalinized with 20% aqueous Na_2CO_3, and stirred at 22−25 °C until two phases became clear. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography (EtOAc−MeOH gradient 10:0 to 10:1). The crude base (4.45 g) was dissolved in boiling EtOH (90 mL), the solution acidified with ethanolic HCl, and the solid crystallized from 80% EtOH to afford 2.93 g (57%) of a white solid: mp 288 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 6H), 3.30−3.70 (m, 2H), 3.98 (s, 3H), 4.02 (s, 6H), 3.70−4.03 (m, 8H), 7.00−7.40 (m, 4H), 7.96 (s, 1H), 8.08 (s, 1H), 8.70−9.30 (bs, 1H).

The following compounds were prepared by method C, as above.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-benzylpiperazine dihydrochloride emihydrate (20): ^{1}H NMR (DMSO-d_6) δ 3.00−3.60 (m, 4H), 3.85 (s, 7H), 4.00−4.80 (m, 6H), 7.40 (s, 5H), 7.50 (s, 1H), 7.60 (s, 1H), 8.40−9.10 (bb, 2H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-benzhydrylpiperazine dihydrochloride emihydrate (21): ^{1}H NMR (DMSO-d_6) δ 2.20−2.60 (m, 4H), 3.50−4.00 (m, 4H), 3.75 (s, 3H), 3.80 (s, 3H), 4.10 (s, 1H), 5.25−5.45 (bs, 2H), 6.70 (s, 1H), 6.80 (s, 1H), 6.90−7.40 (m, 10H).

4-Amino-6,7-dimethoxy-2-(*N*-benzylmethylamino)-quinazoline hydrochloride (24): ^{1}H NMR (DMSO-d_6) δ 3.30 (s, 3H), 3.90 (s, 6H), 5.00 (s, 2H), 7.30 (s, 5H), 7.75 (s, 1H), 7.85 (s, 1H), 8.50−8.85 (bs, 2H), 11.50−12.40 (bb, 1H).

4-Amino-6,7-dimethoxy-2-[*N*-(3,3-diphenylpropyl)-methylamino]quinazoline hydrochloride (25): ^{1}H NMR (DMSO-d_6) δ 2.30−2.80 (m, 2H), 3.20 (s, 3H), 3.40−4.30 (m, 3H), 3.90 (s, 6H), 6.80−7.40 (m, 10H), 7.70 (s, 2H), 8.00−8.80 (bb, 2H), 11.20−11.70 (bb, 1H).

(*R*)-4-Amino-6,7-dimethoxy-2-[1-methyl-2-(3-aminosulfonyl-4-methoxyphenyl)ethylamino]quinazoline hydrochloride·0.8H_2O (26): ^{1}H NMR (DMSO-d_6) δ 1.25 (d, 3H), 2.80−3.20 (m, 3.6H), 3.90 (s, 9H), 4.10−4.70 (m, 1H), 6.90−7.20 (m, 4H), 7.30−8.20 (m, 5H), 8.30−9.10 (bb, 2H).

4-Amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydrobenz[*f*]isoquinolin-2-yl)quinazoline·0.25C_2H_5OH (28): ^{1}H NMR (DMSO-d_6) δ 3.17 (t, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 4.17 (t, 2H), 5.02 (s, 2H), 6.80 (s, 1H), 7.19 (s, 2H), 7.36 (d, 1H), 7.44 (s, 1H), 7.48−7.55 (m, 2H), 7.75−8.02 (m, 3H).

4-Amino-6,7-dimethoxy-2-(4,4-diphenyl-1-piperidinyl)-quinazoline hydrochloride·0.65H_2O (29): ^{1}H NMR (DMSO-d_6) δ 2.20−2.70 (m, 4H), 3.30−4.00 (m, 5.3H), 3.80 (s, 6H), 6.80−7.30 (m, 10H), 7.50−7.75 (m, 2H), 8.30−8.75 (bs, 2H), 10.00−11.00 (bb, 1H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-benzylpiperazine N^4-Oxide·2HCl·0.75H_2O (22). To a stirred solution of **20** (5.32 g, 0.014 mol) in MeOH (70 mL) was dropped in 30 min at 0−5 °C a solution of 83% Mg monoperoxyphthalate·6H_2O (4.34 g, 0.0073 mol) in H_2O (40 mL). After 1 h of stirring the mixture was evaporated to dryness, and the residue was purified by flash chromatography ($CHCl_3$−5 N methanolic NH_3, 100:3). The crude base was dissolved into EtOH (50 mL), the solution acidified with ethanolic HCl and diluted with Et_2O (100 mL), and the precipitate collected by filtration and dried to afford 5 g (86%) of a white solid: mp 219−221 °C; ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 6H), 3.00−4.50 (m, 6H), 4.50−5.40 (m, 4H), 7.10−7.60 (m, 7H), 8.30−9.20 (bs, 2H), 11.40−12.90 (bb, 1H). After D_2O addition all exchangeable protons were evaluated as HDO peak. A sample of the crude base was crystallized from EtOAc to give a white solid: mp 188 °C; for $C_{21}H_{25}N_5O_3$·0.25H_2O, calcd (found) C, 63.06 (63.19); H, 6.43 (6.41); N, 17.51 (17.26); H_2O, 1.13 (0.79); ^{1}H NMR (DMSO-d_6) δ 2.80 (d, 2H), 3.30 (t, 2H), 3.56 (t, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 4.33 (s, 2H), 4.50 (s, 2H), 6.74 (s, 1H), 7.15−7.35 (bs, 2H), 7.30−7.45 (m, 3H), 7.45 (s, 1H), 7.50−7.65 (m, 2H).

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(benzyloxy)piperazine (23). Compound **22** (2.2 g, 0.0056 mol) was heated at 220−225 °C for 5 min. The brown crude was purified by flash chromatography ($CHCl_3$−5 N methanolic NH_3, 100:1.5) followed by crystallization from ACN to afford 0.24 g (11%) of a white solid: mp 179−180 °C; ^{1}H NMR (DMSO-d_6) δ 2.48 (d, 2H), 2.97 (t, 2H), 3.29 (t, 2H), 3.78 (s, 3H), 3.82 (s, 3H), 4.57 (d, 2H), 4.71 (s, 2H), 6.73 (s, 1H), 7.13 (bs, 2H), 7.31−7.37 (m, 5H), 7.42 (s, 1H). For the interpretation of this spectrum, it was very helpful looking up the source of ref 44.

Ethyl 2-Methoxy-6-isopropylphenoxyacetate (30). To a stirred suspension of 50% NaH (0.6 g, 0.0125 mol) in anhydrous benzene (50 mL) was dropped in 15 min at 22−25 °C a solution of 2-methoxy-6-isopropylphenol[45] (1.7 g, 0.010 mol) in anhydrous benzene (20 mL). After 30 min of stirring at 22−25 °C and 3 h at reflux, H_2O (1.2 mL) was added to the mixture and the solvents were evaporated in vacuo. The green residue was dissolved into isobutyl methyl ketone (50 mL), and a solution of ethyl bromoacetate (2.3 mL, 0.014 mol) in isobutyl methyl ketone (5 mL) was added. The mixture was stirred at 22−25 °C for 2 h and at 100−105 °C for 14 h. After that period, ethyl bromoacetate (0.67 mL, 0.006 mol) was added, and stirring at 100−105 °C was continued for an additional 8 h. After cooling to 22−25 °C, the mixture was cautiously diluted with 2 N HCl (30 mL), the organic phase was separated, and the aqueous phase was extracted with Et_2O. The residue obtained after evaporation of the reunited organic phases was purified by flash chromatography (*n*-hexane−Et_2O gradient 100:5 to 100:20) to afford 1.78 g (71%) of a yellowish thick oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 6H), 1.40 (t, 3H), 3.20−3.90 (m, 1H), 4.00 (s, 3H), 4.20−4.70 (m, 2H), 4.80 (s, 2H), 6.90−7.40 (m, 3H).

2-Methoxy-6-isopropylphenoxyacetic Acid (31). To a well-stirred mixture of NaOH (20 g, 0.5 mol), TEBA (1.1 g, 0.005 mol), 2-methoxy-6-isopropylphenol (8.4 g, 0.05 mol), H_2O (30 mL), and toluene (40 mL) was dropped in 15 min a solution of ethyl bromoacetate (11.1 mL, 0.1 mol) in toluene (10 mL). The mixture was stirred at 22−25 °C for 2 h, at 60−65 °C for 2 h, and at reflux for 1.5 h. After that, a solution of ethyl bromoacetate (5.5 mL, 0.05 mol) in toluene (10 mL) was added to the mixture, and refluxing was continued for an additional 5 h. After cooling to room temperature, H_2O (250 mL) was added and the phases were separated. The aqueous phase was washed with Et_2O (3 × 50 mL), acidified with 37% HCl, and extracted with Et_2O (3 × 50 mL). The organic phase was washed with H_2O (3 × 30 mL) and extracted with 20% Na_2CO_3 solution (40 mL) stirring at room temperature for almost 15 min. The alkaline phase was washed with Et_2O (2 × 30 mL), acidified with 37% HCl, and extracted with Et_2O (3 × 40 mL). The ethereal solution was dried (Na_2SO_4) and evaporated to dryness to afford 8 g (72%) of **31** as a yellowish oil. The analytical sample was obtained by distillation (190 °C/7 mmHg): ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 6H), 3.20−3.70 (m, 1H), 3.90 (s, 3H), 4.65 (s, 2H), 6.70−7.40 (m, 3H), 10.30−10.60 (bs, 1H).

1-[2-(2-Methoxyphenoxy)-2-methylpropionyl]-piperazine·HCl·H_2O (37). To a boiling solution of 2-(2-methoxyphenoxy)-2-methylpropionic acid[46] (10.5 g, 0.05 mol) in anhydrous $CHCl_3$ (50 mL) was dropped within 30 min a solution of $SOCl_2$ (5.4 mL, 0.074 mol) in anhydrous $CHCl_3$ (20 mL). The mixture was stirred at reflux for 2 h and then was evaporated to dryness to give 11.5 g (100%) of the 2-(2-methoxyphenoxy)-2-methylpropionyl chloride as a light-brown oil: ^{1}H NMR ($CDCl_3$) δ 1.70 (6H, s), 4.00 (3H, s), 7.10−7.50 (4H, m). To a stirred solution of anhydrous piperazine (12.9 g, 0.15 mol), 95% EtOH (50 mL), and H_2O (15 mL) was added at room temperature 48% HBr (25.3 g, 0.15 mol). After cooling to 10 °C a solution of the above acid chloride (11.5 g, 0.05 mol) in THF (50 mL) was dropped in 30 min without exceeding 20 °C. The mixture was stirred for 1.5 h at the same temperature

and then for 3 h at reflux, diluted with THF (50 mL), and cooled to 0−5 °C for 30 min. The piperazine salts were separated by filtration, the filtrate was evaporated to dryness, and the residue was treated with 1 N HCl (100 mL) and Et_2O (100 mL). The insoluble 1,4-bis[2-(2-methoxyphenoxy)-2-methylpropionyl]piperazine was separated by filtration; the aqueous phase was neutralized with NaOH, washed with Et_2O (4 × 50 mL), alkalinized with concentrated NaOH, and extracted with Et_2O (5 × 50 mL). The organic phase was acidified with HCl in EtOH and evaporated to dryness. The residue was crystallized from MEK to give 5.6 g (33%) of **37** as a white solid: mp 95−98 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 6H), 2.90−3.50 (m, 4H), 3.90 (s, 3H), 3.90−4.60 (m, 4H), 6.80−7.60 (m, 6H).

Computational Procedures. Geometry optimization: Conformational analysis of the N^1-protonated form of some quinazoline derivatives was recently performed,[26] and the resulting absolute minimum structure of prazosin (**1**) was considered in this study as the starting geometry. The substituents were constructed within the Editor module of the Quanta96 program.[47] Then, the protonated structures were fully optimized by means of molecular orbital calculations (AM1),[48] using the MOPAC 6.0 (QCPE 455) program.

Molecular superimposition: The most structurally different ligands which show the highest affinity for the α_1-adrenoceptor (**1**, **3**, **13**, and **28**) were chosen for the construction of the reference supermolecule and were superimposed, by a rigid fit procedure on the quinazoline moiety. The Quanta96 molecular modeling software was utilized for molecular comparisons, matching, and computation of van der Waals volumes.

Molecular descriptors and statistical treatment of data: The MOPAC output files were loaded into the CODESSA program[49] along with the α_1-adrenoceptor binding affinity data values. A large number of global and fragment descriptors (constitutional, topological, electrostatic, geometrical, and quantum-chemical) were generated for each compound. The ad hoc defined molecular size and shape parameters, described above, were added as external descriptors.[31,50]

The search for the best correlation equation was achieved by means of the heuristic method, which accomplished a preselection of descriptors on the basis of their statistical significance.[51,52] Default values for control parameters and criteria were used: minimum squared correlation coefficient to consider one-parameter correlation significant, $R_{min} = 0.1$; *t*-test value to consider descriptor significant in one-parameter correlation, $t_1 = 1.5$; *t*-test value to consider descriptor significant in multiparameter correlation, $t_2 = 3.0$; highest pair correlation coefficient of two descriptors scales, $r_{full} = 0.99$; significant intercorrelation level, $r_{sig} = 0.80$. Evaluation of the best correlation models was carried out by validation of each model by cross-validation techniques. The QSAR models reported in this paper were selected on the basis of the best statistical parameters and the largest diversity of the descriptors involved.

Definition of the descriptors[53] used in the selected QSAR models: $S^L(N)$ is the nucleophilic superdelocalizability on the protonated nitrogen atom. Being computed on the lowest unoccupied molecular orbital (LUMO), it characterizes the hydrogen bond donor propensity. $V_f(H)$, the free valency for the H atom of the protonated nitrogen, characterizes the hydrogen-bonding donor capability of the ligands. ΔE_{prot} is the energy difference between the protonated and neutral forms of the ligands considered in the vapor phase. HACA-1[54] is calculated according to the following formula: HACA-1 = $S_A q_A S_A$, where q_A is the charge on the hydrogen-bonding acceptor atom and S_A is its surface area. The atomic partial charges used in this formula were calculated using a Zefirov empirical method. The HACA-1/TMSA parameter represents the ratio of the surface area of the hydrogen acceptor atoms to the total surface area of the molecule (TMSA). V_{in} and V_{out} are ad hoc defined size and shape descriptors[26] and represent, respectively, the intersection and the outer van der Waals volumes of the ligands considered with respect to a supermolecule constituted by the most structurally different ligands which show the highest binding affinity for the α_1-adrenoceptor (**1**, **3**, **13**, and **28**). V_{dif} is computed according to the following formula: $V_{dif} = V_{in} - V_{out}/V^{sup}$, where V^{sup} is the resultant van der Waals volume of the reference supermolecule (531.75 Å^3). According to the ligand pharmacophore similarity−target receptor complementarity paradigm, this approach assumes that the volume obtained by superimposing the most structurally different ligands which show the highest affinities for the same receptor might reflect the overall shape and the conformational flexibility of the high-affinity receptor binding site.

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