cardiotachometer (Sanei, 2336A) triggered by a lead II electrocardiogram. Mean blood pressure was measured with a pressure transducer (Sanei, 45266). The body temperature was maintained at 37–38 °C with a heating pad.

When the vertebral arterial blood flow was measured, arterial blood taken from the left femoral artery was led to the right vertebral artery. An electromagnetic flow probe (Nihon Kohden, Model MFV-1200) of the extracorporeal type was inserted into this circuit.

In the case of femoral blood flow, an electromagnetic flow probe of extracorporeal type (Nihon Kohden, Model MFV-1200) was inserted into the left femoral artery.

Compounds in a volume of 10 μL were injected with a microinjector into a rubber tube connected to the arterial cannula over a period of 5 s. Despite drug injections, neither blood pressure nor heart rate changed. At least three different amounts of each test compound were injected and the changes in blood flow were assessed. After and before the administration of three doses of each compound, 100 μg of trapidil was administered as a relative control. At least three dose–response curves per compound were obtained. From these dose–response curves, the dose that gave the same increasing effect on the femoral arterial blood flow as 100 μg of trapidil was calculated.

The increments in femoral and vertebral blood flow by trapidil were 165 ± 73% (SD) (n = 30) and 130 ± 78% (SD) (n = 30), respectively.

Intravenous Injection. In order to monitor the vertebral or coronary arterial blood flow, arterial blood of an anesthetized mongrel dog taken from the left femoral artery was led to the right vertebral or coronary artery. An electromagnetic flow probe was inserted into the circuit. Heart rate and mean blood pressure were monitored with a cardiotachometer and pressure transducer in a manner similar to that for intraarterial injection. Compounds in a volume of 100 μL were injected (0.3 mg/kg). Changes in cardiovascular parameters, heart rate, mean blood pressure, and femoral or vertebral blood flow were monitored and evaluated as a percentage.

Acknowledgment. We thank Masami Yanagita for his assistance in the biological testing, members of the Department of Medicinal Chemistry for their assistance in synthesis work, and Barrett B. Madrigal for his critical reading of the manuscript.

Registry No. **2**, 84468-17-7; **2**·HCl, 116970-50-4; **6**, 116700-33-5; **7**, 116700-34-6; **8**, 111541-58-3; **9**, 116970-51-5; **10**, 116970-52-6; **11**, 111541-55-0; **12**, 116970-53-7; **13**, 116970-54-8; **14**, 92564-42-6; **14**·2HCl, 116700-35-7; **15**, 84468-18-8; **15**·HCl, 116970-55-9; **16**, 84468-16-6; **16**·HCl, 116970-56-0; **17**, 84477-66-7; **17**·HCl, 116970-57-1; **18**, 116971-01-8; **18**·2HCl, 116970-58-2; **19**, 117254-10-1; **19**·2HCl, 116970-59-3; **20**, 116971-02-9; **20**·2HCl, 116970-60-6; **21**, 116971-03-0; **21**·2HCl, 116970-61-7; **22**, 84478-11-5; **22**·HCl, 116970-62-8; **23**, 116970-89-9; **23**·HCl, 116970-63-9; **24**, 116970-90-2; **24**·HCl, 116970-64-0; **25**, 116970-91-3; **25**·HCl, 116970-65-1; **26**, 116970-92-4; **26**·HCl, 116970-66-2; **27**, 116970-93-5; **27**·HCl, 116970-67-3; **28**, 116970-94-6; **28**·2HCl, 116970-68-4; **29**, 116970-95-7; **29**·2HCl, 116970-69-5; **30**, 116970-96-8; **30**·HCl, 116970-70-8; **31**, 116970-97-9; **31**·2HCl, 116970-71-9; **32**, 116970-98-0; **32**·2HCl, 116970-72-0; **33**, 116970-99-1; **33**·2HCl, 116970-73-1; **34**, 116971-00-7; **34**·2HCl, 116970-74-2; **35**, 116971-04-1; **35**·2HCl, 116970-75-3; **36**, 116971-05-2; **36**·HCl, 116970-76-4; **37**, 116971-06-3; **37**·HCl, 116970-77-5; **38**, 116971-07-4; **38**·HCl, 116970-78-6; **39**, 116971-08-5; **39**·HCl, 116970-79-7; **40**, 111541-20-9; **40**·HCl, 116970-80-0; **41**, 111541-21-0; **41**·HCl, 116970-81-1; **42**, 111541-25-4; **42**·HCl, 116970-82-2; **43**, 111540-96-6; **43**·HCl, 116970-83-3; **44**, 116971-09-6; **44**·HCl, 116970-84-4; **45**, 111540-97-7; **45**·HCl, 116970-85-5; **46**, 111540-98-8; **46**·HCl, 116970-86-6; **47**, 111540-99-9; **47**·HCl, 111541-46-9; **48**, 111541-00-5; **48**·HCl, 116970-87-7; **49**, 111541-01-6; **49**·HCl, 116970-88-8; $NH_2(CH_2)_2OH$, 141-43-5; $CH_3NH(CH_2)_2OH$, 109-83-1; $CH_3CH_2NH(CH_2)_2OH$, 110-73-6; $(CH_3)_2CHNH(CH_2)_2OH$, 109-56-8; $CH_3(CH_2)_3NH(CH_2)_2OH$, 111-75-1; $CH_3(CH_2)_5NH(CH_2)_2OH$, 54596-69-9; $CH_3(CH_2)_7NH(CH_2)_2OH$, 32582-63-1; $C_6H_5CH_2NH(CH_2)_2OH$, 104-63-2; $CH_3CH_2NH(CH_2)_2NHCH_2CH_3$, 111-74-0; $NH_2(CH_2)_3NH_2$, 109-76-2; $NH_2(CH_2)_4NH_2$, 110-60-1; $NH_2(CH_2)_6NH_2$, 124-09-4; $NH_2(CH_2)_2NHCH_3$, 108-00-9; $CH_3NH(CH_2)_2NHCH_3$, 110-70-3; $C_6H_5CH_2NH(CH_2)_2NHCH_2C_6H_5$, 140-28-3; o-$ClC_6H_4CH_2Cl$, 611-19-8; m-$ClC_6H_4CH_2Cl$, 620-20-2; p-$ClC_6H_4CH_2Cl$, 622-95-7; $CH_3(CH_2)_5NH_2$, 111-26-2; $CH_3(CH_2)_4NH_2$, 110-58-7; $CH_3(CH_2)_7NH_2$, 111-86-4; $CH_3(CH_2)_9NH_2$, 2016-57-1; c-$C_6H_{11}NH_2$, 108-91-8; $C_6H_5CH_2NH_2$, 100-46-9; p-$CH_3OC_6H_4CH_2NH_2$, 2393-23-9; 3,4-$(CH_3O)_2C_6H_3CH_2NH_2$, 5763-61-1; $C_6H_5(CH_2)_2NH_2$, 64-04-0; c-$C_6H_{11}NHCH_3$, 100-60-7; $CH_3(CH_2)_5NH(CH_2)_2CH_3$, 20193-73-1; $[CH_3(CH_2)_5]_2NH$, 143-16-8; p-$NO_2C_6H_4CH_2Br$, 100-11-8; isoquinolinesulfonic acid, 27655-40-9; 5-isoquinolinesulfonyl chloride hydrochloride, 105627-79-0.

Structure–Activity Relationships in Prazosin-Related Compounds. Effect of Replacing a Piperazine Ring with an Alkanediamine Moiety on α_1-Adrenoreceptor Blocking Activity

Dario Giardinà,* Livio Brasili, Maurizio Gregori, Maurizio Massi,† Maria T. Picchio, Wilma Quaglia, and Carlo Melchiorre*

Department of Chemical Sciences and Institute of Pharmacology and Pharmacognosy, University of Camerino, 62032 Camerino (MC), Italy. *Received April 18, 1988*

Several prazosin-related compounds were synthesized in which the piperazine ring of prazosin (1) was replaced by an alkanediamine chain and were evaluated for their blocking activity on α_1- and α_2-adrenoreceptors in isolated rat vas deferens. All the compounds investigated proved highly selective toward the α_1-adrenoreceptor owing to a very low affinity for α_2-adrenoreceptors. Furthermore, compounds **2**, **9**, and **13** were also investigated in vivo to determine their hypotensive effect on anesthetized rats, which were compared with that of prazosin (1). It was confirmed that the piperazine moiety of 1 is not essential for potency. However, optimum activity depends on two parameters: carbon-chain length of the alkanediamine moiety and N-methylation of both the amide and the 2-amino functions. In the desmethyl series, optimum activity was associated with the lower homologues (**2**–**4**) bearing a chain of two to four methylenes whereas in the N,N'-dimethyl series peak potency was observed with a six-carbon chain as in **13**. Compound **13** proved the most active of the series and was more potent than prazosin (1) in both in vivo and in vitro assays. It is hypothesized that the α_1-adrenoreceptor incorporates a lipophilic area that is located between the binding sites for the quinazoline and the furoyl moieties and is able to accommodate a polymethylene chain.

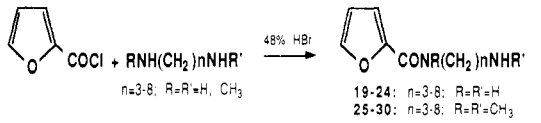
Prazosin (1) is a potent and highly selective α_1-adrenoreceptor antagonist.[1] At clinically relevant concentrations, it acts as a peripheral vasodilator by competitively antagonizing the vascular postsynaptic α_1-adrenoreceptor and is used to treat patients with hypertension and congestive

† Institute of Pharmacology and Pharmacognosy.

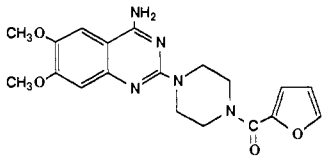
(1) Cambridge, D.; Davey, M. J.; Massingham, R. *Br. J. Pharmacol.* **1977**, *59*, 514P.

0022-2623/89/1832-0050$01.50/0 © 1988 American Chemical Society

Scheme I

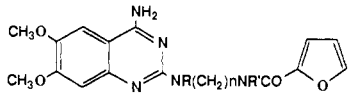


heart failure. In contrast to nonselective α-antagonists and direct-acting vasodilators, **1** does not give rise to undesirable side effects such as tachycardia, increased renin release, and increase in circulating levels of norepinephrine because of its low affinity for α_2-adrenoreceptors. The utility of **1** as an antihypertensive agent is also associated with beneficial effects on serum lipid levels such as decrease in cholesterol and triglycerides and increase in high-density lipoproteins as well as cholesterol ratio.[2] These effects are very important during long-term hypertension treatment.



Prazosin (1)

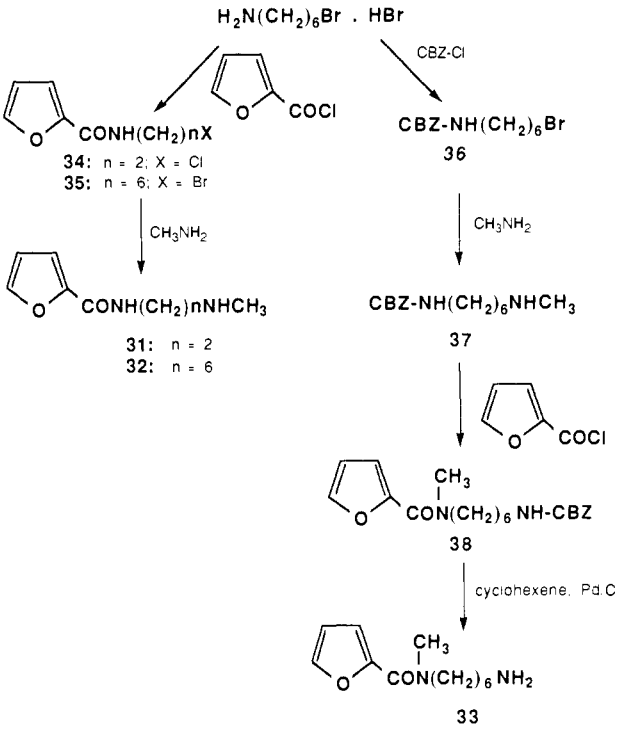
Recently, we have shown that the piperazine ring of **1** may not be essential for α-blocking activity.[3] In fact, its replacement by an ethanediamine moiety gave **2**, which proved to be a potent and highly selective α_1-adrenoreceptor antagonist. In contrast, methylation of both nitrogens of the ethanediamine chain of **2**, to give **9**, caused a significant decrease in activity. However, it has been reported that with the homologous compound **10** a marked increase in antihypertensive activity was observed in rats.[4] In order to investigate fully the effects of chain length and N-methylation on α_1-adrenoreceptor blocking activity, we prepared two series of prazosin-related compounds bearing respectively secondary (**3–8**) or tertiary nitrogen atoms in the polymethylenediamine chain (**10–15**). Furthermore, compounds **16–18** were included in this study to evaluate the effect of mono-N-methylation.



2-8 n=2-8, R=R'=H
9-15 n=2-8, R=R'=CH3
16 n=2, R=CH3, R'=H
17 n=8, R=CH3, R'=H
18 n=6, R=H, R'=CH3

Chemistry. All the compounds were synthesized by standard procedures. The *N*-(2-furoyl)alkanediamines **19–30**[5] were prepared by acylation of the appropriate α,ω-alkanediamine with 2-furoyl chloride following a slightly modified procedure reported for *N*-(2-furoyl)-piperazine[7] (Scheme I). The prerequisite diamines were

Scheme II[a]



[a] CBZ- = $C_6H_5CH_2OCO$.

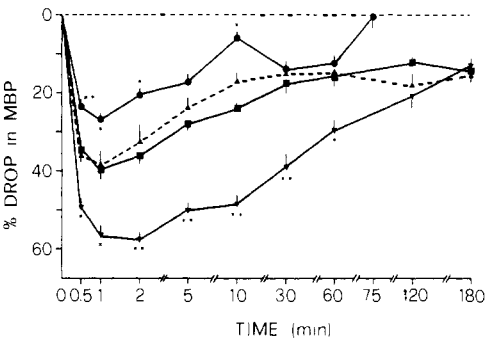


Figure 1. Percent drop in mean blood pressure (MBP) of anesthetized rats following intravenous injection of 100 μg/kg body weight of prazosin (1) (▲), **2** (■), **9** (●), and 13 (▼). Each point is the mean ± SEM of six subjects for prazosin and of five subjects for the other three compounds. Difference from prazosin values: *, $p < 0.05$; **, $p < 0.01$; where not indicated, the difference was not statistically significant. Pretreatment MBP levels of rats treated with **1**, **2**, **9**, and **13** were respectively 82 ± 3.4, 83.7 ± 4.4, 75.3 ± 5.0 and 82.3 ± 6.2 mmHg.

either commercially available (R = R′ = H, n = 3–8 and R = R′ = Me, n = 3, 6) or were synthesized as already described[6] (R = R′ = Me, n = 4, 5, 7, 8). Acylalkanediamines **31–33** were synthesized following the two routes shown in Scheme II. Finally, *N*-(4-amino-6,7-dimethoxy-2-quinazolinyl)-*N*′-(2-furoyl)alkanediamines **3–8** and **10–18**[5] were synthesized as hydrochloride salts through the reaction of the appropriate alkanediamine derivative (**19–33**) with 2-chloro-4-amino-6,7-dimethoxyquinazoline.

Pharmacology. The biological profile of the compounds listed in Table I at α_1- and α_2-adrenoreceptors was assessed on isolated rat vas deferens.[8,9] α_1-Adrenoreceptor blocking activity was assessed by antagonism of (−)-nor-

(2) For review see: (a) Colucci, W. S. *Ann. Int. Med.* **1982**, *97*, 67. (b) Colucci, W. S. *Am. J. Cardiol.* **1983**, *51*, 639. (c) Graham, R. M. *Am. J. Cardiol.* **1984**, *53*, 16A.

(3) Giardinā, D.; Bertini, R.; Brancia, E.; Brasili, L.; Melchiorre, C. *J. Med. Chem.* **1985**, *28*, 1354.

(4) Manoury, P. M.; Binet, J. L.; Dumas, A. P.; Lefevre-Borg, F.; Cavero, I. *J. Med. Chem.* **1986**, *29*, 19.

(5) Compounds **3**, **4**, **10**, **11**, **19**, **20**, **25**, and **26** were included in a general formula reported by: (a) Manoury, P.; Michel, J. Ger. Offen. 2904445; *Chem. Abstr.* **1980**, *92*, 6552c. (b) Michel, J.; Manoury, P. Fr. Demande 2389613; *Chem. Abstr.* **1980**, *92*, 94421*n*.

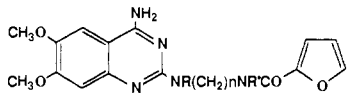
(6) Devinsky, F.; Lacko, I.; Krasmel, L. *Synthesis* **1980**, *4*, 303.

(7) Althuis, T. H.; Hess, H. J. *J. Med. Chem.* **1977**, *20*, 146.

(8) McGrath, J. C. *J. Physiol.* **1978**, *23*, 283.

(9) Brown, C. M.; McGrath, J. C.; Summers, R. J. *Br. J. Pharmacol.* **1979**, *66*, 553.

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



no.	R	R'	n	α_1 pA_2 against norepinephrine (slope)	α_2 pA_2 against clonidine (slope)	α_1/α_2[b] selectivity ratio
1				8.54 ± 0.05 (1.08 ± 0.08)	5.43 ± 0.13 (0.82 ± 0.09)	1288
2	H	H	2	8.28 ± 0.03 (1.02 ± 0.07)	5.37 ± 0.06 (0.99 ± 0.16)	813
3	H	H	3	8.01 ± 0.05 (1.00 ± 0.11)	5.99 ± 0.03 (1.14 ± 0.06)	105
4	H	H	4	8.25 ± 0.05 (1.00 ± 0.12)	6.03 ± 0.07 (1.09 ± 0.17)	170
5	H	H	5	7.72 ± 0.05 (1.06 ± 0.12)	5.01 ± 0.04[c]	513
6	H	H	6	7.88 ± 0.05 (1.05 ± 0.12)	4.51 ± 0.04[c]	2344
7	H	H	7	7.54 ± 0.06 (1.20 ± 0.12)	5.04 ± 0.06[c]	316
8	H	H	8	7.22 ± 0.03 (0.99 ± 0.09)	4.78 ± 0.03[c]	273
9	CH_3	CH_3	2	6.70 ± 0.04 (0.85 ± 0.15)	5.52 ± 0.04 (1.15 ± 0.08)	15
10	CH_3	CH_3	3	7.41 ± 0.04 (1.04 ± 0.10)	6.45 ± 0.05 (1.19 ± 0.12)	9
11	CH_3	CH_3	4	8.15 ± 0.06 (1.02 ± 0.05)	6.50 ± 0.09 (0.99 ± 0.24)	45
12	CH_3	CH_3	5	8.83 ± 0.05 (1.09 ± 0.10)	6.68 ± 0.07 (0.86 ± 0.17)	141
13	CH_3	CH_3	6	8.93 ± 0.04 (1.13 ± 0.09)	6.84 ± 0.06 (0.93 ± 0.14)	123
14	CH_3	CH_3	7	8.60 ± 0.05 (1.14 ± 0.11)	6.55 ± 0.05 (1.12 ± 0.11)	112
15	CH_3	CH_3	8	8.10 ± 0.03 (1.00 ± 0.07)	6.31 ± 0.07 (1.28 ± 0.14)	62
16	CH_3	H	2	8.03 ± 0.05 (1.00 ± 0.12)	5.20 ± 0.06 (0.79 ± 0.12)	676
17	CH_3	H	6	8.53 ± 0.05 (0.98 ± 0.10)	5.98 ± 0.04 (0.89 ± 0.08)	355
18	H	CH_3	6	8.17 ± 0.05 (0.83 ± 0.09)	5.76 ± 0.06 (0.90 ± 0.14)	257

[a] pA_2 values plus or minus standard error of estimate were calculated according to Arunlakshana and Schild,[10] unless otherwise specified, constraining the slope to −1 (ref 19). pA_2 is defined as the negative logarithm to the base 10 of that dose of antagonist that requires a doubling of the agonist dose to compensate for the action of the antagonist. [b] The α_1/α_2 selectivity ratio is the antilog of the difference between pA_2 values at α_1- and α_2-adrenoceptors. [c] Calculated according to van Rossum (ref 20) since it was not possible to investigate three different concentrations owing to the inhibition of twitch responses of electrically stimulated tissue at concentrations higher than 100 μM.

epinephrine-induced contractions of the epididymal portion, while α_2-adrenoreceptor blocking activity was determined by antagonism of the clonidine-induced depression of the twitch responses of the field-stimulated prostatic portion of rat vas deferens. The potency of the drugs was expressed as pA_2 values.[10]

The most potent member of the series, **13**, was examined in vivo and its antihypertensive effects were compared with those of **1**, **2**, and **9**. The experiments were carried out on anesthetized rats. Percent reduction in mean blood pressure was measured at different time intervals in order to determine both potency and duration of action. The results are reported in Figure 1.

Results and Discussion

The results assembled in Table I show that all the compounds studied displayed significant and competitive α-adrenoreceptor blocking activity with a marked selectivity toward α_1-adrenoreceptors. Compounds **12–14** were more potent than prazosin (**1**) whereas **6** was the most selective, although it was less active.

In the *N,N'*-dimethyl series a gradual increase in activity was observed by increasing the polymethylene chain length up to a maximum of six carbons as in **13**, while a slight decrease was found for the higher homologues **14** and **15**. On the other hand, increasing the chain length in the unsubstituted series (**2–8**) had a different effect. In fact, the most potent compounds proved to be the lower homologues **2–4**, which were almost as active as **1**, whereas the higher homologues were significantly less active when compared to **2** as well as to the corresponding *N,N'*-dimethyl analogues. Thus, it is evident that N-methylation is relevant for potency but is strictly dependent on the carbon-chain length. This derives from the finding that N-methylation of **6** ($n = 6$) to give the monomethyl analogues **17** and **18** and the dimethyl compound **13** resulted in a gradual and significant increase in activity whereas N,N'-dimethylation of **2** ($n = 2$) giving **9** caused a significant decrease in activity; N-methylation, to give **16**, did not modify significantly ($p > 0.05$) potency.

A recent theoretical model[11,12] for the α_1-adrenoreceptor, while considering a common binding site for norepinephrine and the quinazoline nucleus, focuses on the

(10) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.
(11) Campbell, S. F. *X-Ray Crystallography and Drug Action*; Horn, A. S., De Ranter, C. F., Eds.; Clarendon: Oxford, 1984; p 347.
(12) Campbell, S. F.; Davey, M. J. *Drug. Des. Delivery* **1986**, *1*, 83.

directional flexibility displayed by a carboxylic acid moiety that accepts a partially charged hydrogen atom from the protonated nitrogen of the quinazoline system. Since the quinazoline moiety contains a 2,4-diaminopyrimidine ring with increasing basicity going from 2-amino to 2-methylamino and to 2-dimethylamino derivatives (pK_a = 7.4, 7.55, and 7.64, respectively),[13] an overall increase in the extent of protonation would be expected for tertiary amines as compared to secondary ones. The increased proportion of protonated species should give an enhanced charge-reinforced hydrogen bond between the quinazoline moiety and the receptor, and this should result in increased potency. This holds for **12–15** compared to the corresponding desmethyl analogues **5–8** whereas it does not apply to the lower homologues **9–11** vs **2–4**. Thus, in order to rationalize their relative potencies, factors other than N-methylation should be taken into account.

Recently we reported that the high activity displayed by the opened analogue **2** might be the result of formation of an intramolecular hydrogen bond between the amide function and the 2-amino group which stabilizes a conformation for optimal interaction with the receptor.[3] This reasoning may also apply to the monomethyl analogue **16** and to the homologues **3** and **4**, which proved to be about as active as **2**. The dramatic drop in activity observed for the *N,N'*-dimethyl analogue **9** was explained by way of steric hindrance between the two *N*-methyl groups which would prevent hydrogen bond formation.[3] This effect could be responsible for the lower α_1-adrenoreceptor blocking activity of **9** when compared to **2**. Perhaps, **10** was less active than **3** for the same reason although the effect of steric hindrance becomes less pronounced on increasing the chain length. For n = 4, compound **11** was as active as the corresponding desmethyl analogue **4** whereas, for n = 5, the effect due to basicity is greater than that of possible steric hindrance and as a consequence **12** is significantly more potent than the desmethyl analogue **5**.

Although the quinazoline nucleus may play a crucial role in receptor recognition, structure–activity relationship (SAR) studies of prazosin-like compounds revealed that the 2-substituent also contributes to the affinity for the receptor through interaction with a secondary site where, for example, the furoyl group of **1** binds.[3,4,11,12,14] The increasing potency observed for **9–13** by increasing the chain length may suggest the existence of a lipophilic area located between the two binding sites for the quinazoline and furoyl rings that can accommodate the polymethylene chain and allow optimal interaction for n = 6 (**13**).

The results obtained with the monomethyl analogues **17** and **18**, which proved to be less active than the dimethyl analogue **13**, clearly suggest that optimum activity is associated with both tertiary amine and tertiary amido functions. However, N-methylation of the amide contributes less to α-adrenoreceptor blocking activity than N-methylation of the amine group (Table I).

Comparative in vivo screening for hypotensive activity of **13**, the most potent member of the series, and prazosin (**1**), **2**, and **9** was carried out. The four compounds tested displayed a marked and reproducible hypotensive effect. As shown in Figure 1, **2** proved to be equipotent to **1**. Also the time course of their effect was very similar, reaching a maximum at 1 min after injection and slowly declining afterwards, but remaining statistically significant even at 3 h after drug administration.

In agreement with in vitro data, the hypotensive effect of **9** appeared to be less potent and of shorter duration than that of **1**. In fact, 75 min after drug injection the mean blood pressure of treated animals was back to pretreatment level. On the other hand, **13** proved to be the most potent hypotensive agent among the compounds tested. Its effect reached a maximum 2 min after drug injection with a 57.5% reduction in mean blood pressure compared to a 38.5% maximum reduction for **1**. Variance analysis showed a statistically significant difference between the effect of **13** and that of **1** $F(1,9) = 16.86$; $p < 0.005$. Accordingly, pairwise comparisons showed that the effect of **13** was statistically larger than that of **1** over the first 30 min following drug treatment.

The hypotensive effects produced by **13** and by prazosin (**1**) proved to be statistically significant ($p < 0.05$) even 3 h after drug treatment.

In conclusion, the present results confirm and extend the view that the piperazine ring of **1** is not essential for activity[3] and can be replaced by a suitable carbon-chain length without affecting potency toward α_1-adrenoreceptors. However, this structural manipulation caused a decrease in α_1-selectivity with the only exception being **6**. Compound **13** proved to be more active than prazosin (**1**) in both in in vitro and in vivo experiments.

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Büchi SMP-20 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian EM-390 instruments, respectively. Although the IR and NMR 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 microanalyses were performed by the Microanalytical Laboratory of our department, and the elemental compositions of the compounds agreed to within ±0.4% of the calculated value. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040–0.063 mm, Merck) by flash chromatography. R_f values were determined with silica gel TLC plates (Kieselgel 60 F_{254}, layer thickness 0.25 mm, Merck). The eluting solvents were (A) petroleum ether–ethyl acetate–methanol–28% ammonia (3:7:2:0.2), (B) chloroform–petroleum ether–methanol–28% ammonia (8:8:1.5:0.1), (C) petroleum ether–ethyl acetate–methanol–28% ammonia (8:6:2:0.2), (D) petroleum ether–ethyl acetate–methanol–28% ammonia (8:6:2:0.1), (E) chloroform–petroleum eter–methanol–28% ammonia (12.5:7.5:2.5:0.2), (F) petroleum ether–ethyl acetate–methanol–28% ammonia (6:9:1:0.1), (G) ethyl acetate–cyclohexane (1:1), (H) chloroform–petroleum ether–methanol–28% ammonia (12.5:7.5:6:0.4); (I) ethyl acetate–cyclohexane (3:7), (J) ethyl acetate–cyclohexane (6;4), (K) petroleum ether–ethyl acetate–methanol–28% ammonia (3:8:6:1.5), (L) petroleum ether–ethyl acetate–methanol–28% ammonia (8:6:2:0.15). Petroleum ether refers to the fraction with a boiling point of 40–60 °C. The term "dried" refers to the use of anhydrous sodium sulfate.

General Procedure for the Synthesis of 19–30. The procedure adopted for the synthesis of **21** is described.

Hydrobromic acid (48%) (25.3 g, 150 mmol) was added dropwise to a stirred (40 °C) solution of 1,5-pentanediamine (21.9 g, 210 mmol) in ethanol (152 mL) and water (18 mL), followed by the addition over 15 min of 2-furoyl chloride (10 g, 77 mmol). The resulting mixture was stirred at 80 °C for 1.5 h, concentrated, diluted with water, made strongly basic with NaOH pellets, and extracted with chloroform (3 × 50 mL). Removal of dried solvents gave an oil that was purified by column chromatography; eluting with mixture K yielded 9.34 g (62%) of **21** as an oil.

Similarly **19**, **20**, and **22–30** (free bases) were obtained as oils or hygroscopic solids in 40–60% yields from suitable starting

(13) (a) Roth, B.; Strelitz, J. Z. *J. Org. Chem.* **1969**, *34*, 821. (b) Brown, D. J.; Jacobsen, N. W. *J. Chem. Soc.* **1962**, 3172. (c) Brown, D. J.; Teitei, T. *J. Chem. Soc.* **1965**, 755.

(14) (a) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49. (b) Alabaster, V. A.; Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 999. (c) Campbell, S. F.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 1794.

materials (Scheme I) and were used in the next step without further purification.

***N*-(2-Furoyl)-*N'*-methyl-1,2-ethanediamine (31).** A solution of **34**[15] (1.0 g, 5.78 mmol) in ethanol (5 mL) and 20% methylamine in ethanol (9 mL, 58 mmol) was heated at 110 °C for 24 h in a sealed glass tube. After cooling, the solvent was evaporated and the residue taken up with 2 N HCl and washed with ethyl ether. The aqueous solution was made basic with NaOH pellets and extracted with chloroform (3 × 50 mL). Removal of dried solvents gave a residue that was purified by column chromatography; eluting with mixture **F** yielded 0.48 g (50%) of **31** as an oil (R_f 0.23), which was used in the next step without further purification.

***N*-(2-Furoyl)-*N'*-methyl-1,6-hexanediamine (32).** A stirred mixture of 2-furoyl chloride (0.6 g, 4.6 mmol) and 6-bromo-1-aminohexane hydrobromide (1.2 g, 4.6 mmol) in dry benzene (70 mL) was heated under reflux for 24 h. After cooling, it was diluted with ethyl ether and washed with 2 N NaOH and finally with water. Removal of dried solvents gave an oil that was purified by column chromatography; eluting with mixture G yielded 0.65 g (52%) of intermediate **35** as an oil (R_f 0.35), which was dissolved in ethanol (10 mL) and treated with 20% methylamine in ethanol (3.22 mL, 20.8 mmol). The resulting mixture was sealed in a glass tube and heated to 110 °C for 24 h. Removal of the solvent gave a residue, which was taken up in 2 N HCl and washed with ethyl ether. The aqueous solution was made basic with NaOH pellets and extracted with chloroform. Removal of dried solvents gave an oil that was purified by column chromatography; eluting with mixture H yielded 0.33 g (71%) of **32** as an oil (R_f 0.26), which was used in the next step without further purification.

***N*-[(Benzyloxy)carbonyl]-*N'*-methyl-1,6-hexanediamine (37).** Benzyl chloroformate (1.06 g, 6.0 mmol) was added to a mechanically stirred and cooled (0 °C) solution of 6-bromo-1-aminohexane hydrobromide (1.25 g, 4.8 mmol) and $NaHCO_3$ (0.41 g, 4.9 mmol) in water (15 mL), followed by portionwise addition over 20 min of 1 N NaOH (4.9 mL, 4.9 mmol). Stirring was continued for 1 h and the mixture was extracted with chloroform. Removal of dried solvents gave a residue that was purified by column chromatography; eluting with mixture I yielded 0.72 g (48%) of intermediate **36** (R_f 0.42; mp 47–49 °C), which was dissolved in ethanol (10 mL) and treated with 20% methylamine in ethanol (10.36 mL, 66.9 mmol). The resulting mixture was heated in a sealed glass tube at 50 °C for 48 h and then evaporated to dryness to give a residue which was treated with 2 N NaOH and extracted with chloroform. Removal of dried solvents gave a residue that was purified by column chromatography; eluting with mixture H yielded 0.45 g (76%) of **37** as an oil (R_f 0.39), which was used in the next step without further purification.

***N*-[(Benzyloxy)carbonyl]-*N'*-(2-furoyl)-*N'*-methyl-1,6-hexanediamine (38).** Dry pyridine (2 mL) was added to a stirred and cooled (ice) solution of **37** (2.19 g, 8.3 mmol) in dry benzene (10 mL) followed by dropwise addition over 20 min of 2-furoyl chloride (1.08 g, 8.3 mmol) in dry benzene (5 mL). After 20 h of stirring at room temperature, the mixture was poured into water, the benzene layer separated, and the aqueous phase extracted with ethyl ether. Removal of dried solvents gave a residue, which was purified by column chromatography; eluting with mixture J yielded 1.61 (54%) g of **38** as an oil (R_f 0.31), which was used in the next step without further purification.

***N*-(2-Furoyl)-*N*-methyl-1,6-hexanediamine (33).** A mixture of cyclohexene (3.16 g, 38.5 mmol), 10% palladium on charcoal (1.17 g), and **38** (1.17 g, 3.27 mmol) in methanol (40 mL) was heated under reflux for 1 h. After cooling, the catalyst was filtered off and the solution evaporated to give a residue that was purified by column chromatography; eluting with mixture H yielded 0.5 g (68%) of **33** as an oil (R_f 0.40), which was used in the next step without further purification.

General Procedure for the Synthesis of 3–8 and 10–18. The procedure adopted for the synthesis of **3** is described.

A stirred mixture of 2-chloro-4-amino-6,7-dimethoxyquinazoline (0.4 g, 1.7 mmol) and **19** (0.57 g, 3.4. mmol) in isoamyl alcohol (10 mL) was heated under reflux for 36 h. After cooling, the precipitate was filtered, washed with isoamyl alcohol and dry ether, and then purified by column chromatography; eluting with mixture A yielded **3** as the free base. Compound **3** was treated with an excess of hydrogen chloride in ethanol to give the hydrochloride salt, which then was recrystallized in 58% yield.

Similarly **4–8** and **10–18** were obtained from suitable starting materials. However, compounds **6**, and **10**, **11**, **15**, **17**, **18**, and **14**, and **16**, and **7**, **8** were purified by column chromatography eluting with mixtures B, C, D, E, and L, respectively, whereas compound **12** was purified directly by recrystallization of the crude solid obtained after filtration of the cooled reaction mixture. Furthermore, when compounds **4**, **7**, **8**, and **18** were synthesized, after the reaction mixture was heated under reflux, the solvent was evaporated in vacuo to give a residue, which then was worked up as for **3**. Yields were in the range of 30–50%.

The physical characteristics of **3–8** and **10–18** are reported in Table II.

Table II. Physical Characteristics of Open-Chain Analogues of Prazosin (1)

compd	mp,[a] °C	recrystn solvent	formula[b]
3	245–248	MeOH	$C_{18}H_{22}ClN_5O_4 \cdot 0.5H_2O$
4	198–201	MeOH	$C_{19}H_{24}ClN_5O_4 \cdot H_2O$
5	207–210	MeOH/*i*-PrOH	$C_{20}H_{26}ClN_5O_4 \cdot 2H_2O$
6	227–230	MeOH	$C_{21}H_{28}ClN_5O_4 \cdot 0.5H_2O$
7	190–194	MeOH/Et_2O	$C_{22}H_{30}ClN_5O_4 \cdot H_2O$
8	223–225	*i*-PrOH	$C_{23}H_{32}ClN_5O_4$
10	200–203	*i*-PrOH	$C_{20}H_{26}ClN_5O_4 \cdot 1.5H_2O$
11	228–230	MeOH/*i*-PrOH	$C_{21}H_{28}ClN_5O_4$
12	215–218	MeOH/*i*-PrOH	$C_{22}H_{30}ClN_5O_4$
13	209–211	MeOH/*i*-PrOH	$C_{23}H_{32}ClN_5O_4$
14	178–180	MeOH/*i*-PrOH	$C_{24}H_{34}ClN_5O_4$
15	181–184	EtOH	$C_{25}H_{36}ClN_5O_4$
16	182–186	MeOH/*i*-PrOH	$C_{18}H_{22}ClN_5O_4 \cdot H_2O$
17	216–220	MeOH/*i*-PrOH	$C_{22}H_{30}ClN_5O_4$
18	190–192	*i*-PrOH	$C_{22}H_{30}ClN_5O_4$

[a] The heating rate was 1 °C/min. [b] Analyses for C, H, N were within ±0.4% of the theoretical value required.

Pharmacology. Owing to low solubility, some of the compounds under investigation were solubilized with a mixture of solvents containing alcohols or dimethyl sulfoxide (DMSO), as cosolvents, together with water. Thus in in vitro tests, the following vehicles were used: water for **10**, **11**, and **14**; 9% MeOH for **3**, **12**, **13**, **15**, **17**, and **18**; 23% MeOH for **2**, **4**, **5**, and **9**; 9% DMSO for **6** and **16**. For the in vivo experiments compounds **1**, **2**, **9**, and **13** were dissolved in EtOH–0.9% NaCl solution (3:7). In all cases solutions were made by first dissolving the compound in the cosolvent and then adding the proper amount of water or saline solution.

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

Field stimulation of the tissue was carried out by means of two platinum electrodes, placed near the top and bottom of the vas deferens, at 0.1 Hz with square pulses of 3-ms duration at a voltage of 10–35 V. The stimulation voltage was fixed throughout the experiments.

Propranolol hydrochloride (1 μM) and cocaine hydrochloride (10 μM) were present in the Krebs solution throughout the experiments outlined below to block β-adrenoreceptors and neuronal uptake mechanisms, respectively.

α_1-Adrenoreceptor Blocking Activity. Postsynaptic α_1-adrenoreceptor blocking activity was determined on the epididymal portion of the vas deferens. The tissues were allowed to equilibrate for at least 1 h before the addition of any drug. Norepinephrine dose–response curves were obtained cumulatively, the first one being discarded and the second one taken as a conrol.

(15) Vlahov, A.; Volf, D. *Chem. Abstr.* **1984**, *101*, 230268b.

After incubation with the antagonist for 30 min, a third dose–response curve was obtained. Responses were expressed as a percentage of the maximal response obtained in the control curve. Parallel experiments, in which tissues did not receive any antagonist, were run in order to correct for time-dependent changes in agonist sensitivity.[16] It was generally verified that the third dose–response curve was identical with the second because the change in dose ratio was less than 2, which usually represents a minimal correction.

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

α_2-Adrenoreceptor Blocking Activity. This was assessed on the prostatic portion of the vas deferens by antagonism to clonidine, which inhibits twitch responses of the field-stimulated vas deferens by acting on the α_2-adrenoreceptor.[17,18]

The tissues were allowed to equilibrate for at least 1 h before the addition of any drug. A first clonidine dose–response curve, taken as control, was obtained cumulatively, avoiding the inhibition of more than 90% of twitch responses. Under these conditions it was possible to obtain a second dose–response curve that was not significantly different from the first one. Thus, after incubation with the antagonist for 30 min, a second dose–response curve was obtained and dose ratio (DR) values were determined from the concentration causing 50% inhibition of the twitch response in the absence and presence of antagonist. Parallel experiments, in which tissues did not receive any antagonist, were run in order to correct for time-dependent changes in agonist sensitivity and to determine the concentration of agonist causing 100% inhibition of twitch responses.

The results are expressed as dissociation constants.

Determination of Dissociation Constants. Dose ratios at the EC_{50} values of the agonists were calculated at three antagonist concentrations, and each concentration was tested five times. Dissociation constants (pA_2 values, Table I) were estimated by Schild plots[10] constrained to slope −1.0, as required by the theory.[19] When this method was applied, it was always verified that the experimental data generated a line whose derived slope was not significantly different from unity ($p > 0.05$). Compounds **5**–**8**, however, were tested at only two concentrations when determining α_2-adrenoreceptor blocking activity because of their low affinity for this receptor. In this case, pA_2 values were calculated according to van Rossum.[20]

Data are presented as the mean ±SE of n experiments. Differences between mean values were tested for significance by Student's t test.

Anesthetized Rat. Hypotensive Activity. Male Wistar rats (Charles River, Calco (CO), Italy) weighing 400–490 g were employed. Under equithesin anesthesia (9.6 g of nembutal sodium, 42.6 g of chloral hydrate, 21.2 g of magnesium sulfate, 400 mL of propylene glycol, 50 mL of ethyl alcohol, and water to 1000 mL), 3 mL/kg body weight, an intraveneous catheter (PE 10) for drug injection was inserted into the left jugular vein. Blood pressure was measured from the right common carotid artery through a PE 50 catheter connected to a pressure transducer (P23 ID, STATHAM, Hato Rey, Puerto Rico). After surgery, rats received a further dose of equithesin (0.8 mL/kg body weight) by intraperitoneal (ip) injection. Following this anesthetic administration, the animal was left for about 20 min before testing began. During the experiments, supplementary doses of equithesin (about 20% of the initial dose) were given ip at intervals of 90–120 min. The drugs tested were administered by pulse intravenous injection at the dose of 100 μg/kg in a constant volume of 30 μL. After drug injection, the intravenous cannula was flushed with 100 μL of isotonic NaCl solution. Drug injection was always preceded by control administration of the vehicle alone. Each animal received only a single drug injection.

The percent decrease in mean arterial blood pressure following drug administration was measured and expressed as mean ±SE. Statistical analysis of the time course of the hypotensive effect of each drug was performed by means of paired t test. Comparison of the effects of the four drugs tested was performed by split-plot analysis of variance with comparisons between groups for drug treatment and comparisons within groups for time (after drug injection). Planned pairwise comparisons between groups were carried out by t tests. Statistical significance was set at $p < 0.05$.

Acknowledgment. This work was supported by a grant from the Regione Marche (Contributo Ricerca Sanitaria, 1985) and Consiglio Nazionale delle Ricerche (Grant No. 87.00746.03.). A generous gift of prazosin from Pfizer (Rome) is gratefully acknowledged.

Registry No. 1, 19216-56-9; **2**, 96649-54-6; **3**, 116784-53-3; **3**·HCl, 116784-54-4; **4**, 116784-55-5; **4**·HCl, 116784-56-6; **5**, 116784-57-7; **5**·HCl, 116784-58-8; **6**, 116784-59-9; **6**·HCl, 116784-60-2; **7**, 116784-61-3; **7**·HCl, 116784-62-4; **8**, 116784-63-5; **8**·HCl, 116784-64-6; **9**, 96649-38-6; **10**, 98902-44-4; **10**·HCl, 65189-43-7; **11**, 116784-65-7; **11**·HCl, 116784-66-8; **12**, 116784-67-9; **12**·HCl, 116784-68-0; **13**, 116784-69-1; **13**·HCl, 116784-70-4; **14**, 116784-71-5; **14**·HCl, 116784-72-6; **15**, 116784-73-7; **15**·HCl, 116784-74-8; **16**, 116784-75-9; **16**·HCl, 116784-76-0; **17**, 116784-77-1; **17**·HCl, 116784-78-2; **18**, 116784-79-3; **18**·HCl, 116784-80-6; **19**, 116784-81-7; **20**, 116784-82-8; **21**, 116784-83-9; **22**, 116784-84-0; **23**, 116784-85-1; **24**, 116784-86-2; **25**, 116784-87-3; **26**, 116784-88-4; **27**, 116784-89-5; **28**, 116784-90-8; **29**, 116784-91-9; **30**, 116784-92-0; **31**, 116784-93-1; **32**, 116784-94-2; **33**, 116784-95-3; **34**, 63003-69-0; **35**, 116784-96-4; **36**, 116784-97-5; **37**, 116784-98-6; **38**, 116784-99-7; $H_2N(CH_2)_3NH_2$, 109-76-2; $H_2N(CH_2)_4NH_2$, 110-60-1; $H_2N(CH_2)_5NH_2$, 462-94-2; $H_2N(CH_2)_6NH_2$, 124-09-4; $H_2N(CH_2)_7NH_2$, 646-19-5; $H_2N(CH_2)_8NH_2$, 373-44-4; $MeNH(CH_2)_3NHMe$, 111-33-1; $MeNH(CH_2)_4NHMe$, 16011-97-5; $MeNH(CH_2)_5NHMe$, 56992-95-1; $MeNH(CH_2)_6NHMe$, 13093-04-4; $MeNH(CH_2)_7NHMe$, 15411-11-7; $MeNH(CH_2)_8NHMe$, 33563-54-1; CH_3NH_2, 74-89-5; CBzCl, 501-53-1; 2-furoyl chloride, 527-69-5; 6-bromo-1-aminohexane hydrobromide, 14502-76-2; 2-chloro-4-amino-6,-7-dimethoxyquinazoline, 23680-84-4.

(16) Furchgott, R. F. *Catecholamines*; Blanschko, H., Muscholl, E., Eds., Springer-Verlag: Berlin, 1972; p 283.
(17) Drew, G. M. *Eur. J. Pharmacol.* **1977**, *42*, 123.
(18) Doxey, J. C.; Smith, C. F. C.; Walker, J. M. *Br. J. Pharmacol.* **1977**, *60*, 91.
(19) Tallarida, R. J.; Murray, R. B. *Manual of Pharamcologic Calculations with Computer Programs*, Springer-Verlag: New York, 1987.
(20) van Rossum, J. M. *Arch. Int. Pharmacodyn.* **1963**, *143*, 299.