α_1-Adrenoceptor Blocking Activity of Some Ring-open Analogues of Prazosin

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Synthesis and structural characterization of some ring-open analogues of Prazosin containing either the guanidine substructure or urea-equivalent groups are described. The opening of the pyrimidine ring in Prazosin is very important as far as the affinity for α_1-adrenoceptor is concerned. The pA_2 values of the ring-open derivatives are 10^4-10^5 fold lower than that of the parent. It is probable that the affinity decrease principally reflects a negative influence of the conformational factors in the interaction with the α_1-receptor. The derivative **5** containing the guanidine moiety, charged at physiological pH, is as active as the other derivatives containing the uncharged urea-equivalent groups. This behaviour indicates, in this class of compounds, the importance of H-bonding interactions with the receptor. When in the ring-open models the ethanediamino substructure is substituted for the piperazine ring additional decrease in activity occurs.

Hemmung der α_1-Adrenozeptoraktivität durch ringoffene Analoge des Prazosins

Die Synthese und die Strukturanalyse von Analogen des Prazosins, die einen geöffneten Ring haben, werden beschrieben. Diese Analogen haben eine Guanidin-Struktur oder eine gleichwertige Harnstoffgruppe. Die Öffnung des Pyrimidinringes des Prazosins ist sehr wichtig für die Affinität zum α_1-Adrenorezeptor. Die pA_2 Werte dieser Folgeprodukte sind 10^4-10^5 niedriger als die von Prazosin. Die Abnahme der Affinität beruht wahrscheinlich auf einer negativen konformativen Einwirkung auf die α_1-Rezeptoren. Das Derivat **5** enthält eine Guanidingruppe, die bei physiologischem pH geladen ist. **5** hat dieselbe Aktivität wie die anderen 1-Derivate, die eine gleichwertige Harnstoffgruppe beinhalten und nicht geladen sind. Das zeigt die Wichtigkeit von Wasserstoffbindungen mit dem Rezeptor. Wenn in dieser Verbindungsklasse der Piperazinering durch die Ethanediaminostruktur ausgewechselt wird, beobachtet man eine zusätzliche Abnahme der Aktivität.

Structure-activity relationships in prazosin (**1**), an effective agent used in the management of hypertension, have been the object of several studies. At physiological pH, **1** is partially protonated (**1a**, pk_a = 7.2) at the endocyclic nitrogen N-1. It has been suggested that the 2,4-diamino-6,7-dimethoxyquinazolinium nucleus acts as a conformationally restricted form of the noradrenaline cation and that its high affinity for the α_1-adrenoceptor is due both to hydrophobic interactions involving the aryl ring and to the charge-reinforced H-bond between the anionic receptor site (carboxylate ion) and protonated N-1[1].

In addition the role of the piperazine ring in α-blocking activity has been demonstrated. On the basis of the effect of replacing the piperazine ring with alkanediamine moieties the existence on the α_1-adrenoceptor of a lipophilic pocket located between the binding sites for quinazoline and furoyl substructures was hypothesized[2].

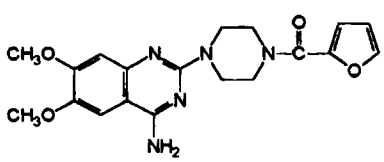
In this paper we describe synthesis and α_1-adrenoceptor blocking activity of a series of prazosin analogues in which guanidine (**5**), cyanoguanidine (**14**), thiourea (**19**), and nitroethenediamino (**24**) systems were substituted in **1** for the diaminopirimidine ring, and of their derivatives **10**, **15**, **20**, **25** in which the piperazine moiety was opened to the ethylenediamine chain.

Chemistry

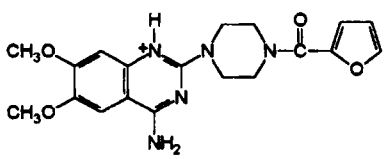
The compounds were synthetized by standard procedures.

The guanidine derivative **5** was obtained according to Scheme 1a. The intermediate **3** was prepared by reaction of *N*-benzoyl-diphenylimidocarbonate **2** with 3,4-dimethoxyaniline. Reaction of piperazine with **3** gave the intermediate **4** which was hydrolyzed with HCl and, after treatment with $KHCO_3$, reacted with 2-furoyl chloride to afford **5**.

Compound **10**, the ring-open analogue of **5** at the piperazine ring, was prepared according to Scheme 1b. The intermediate **7** was synthesized from *N*-3,4-dimethoxyphenylthiourea (**6**) by action of 30% H_2O_2. Reaction in acetonitrile solution of **7** with **9**, obtained from 2-furoyl chloride and 1,2-ethanediamine *emi*-protected by *t*-butyloxycarbonyl group **8**, gave the expected product **10**.



1



1a

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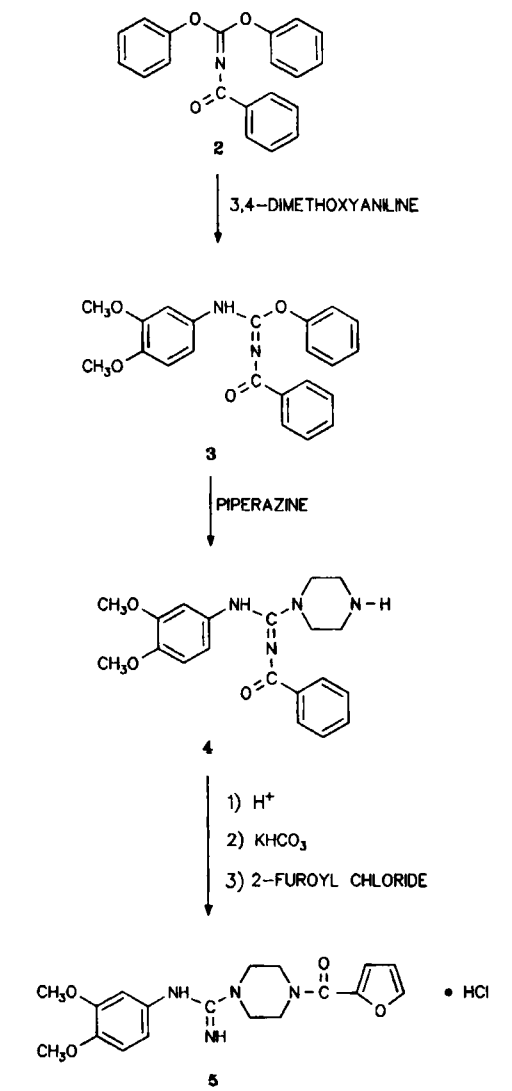
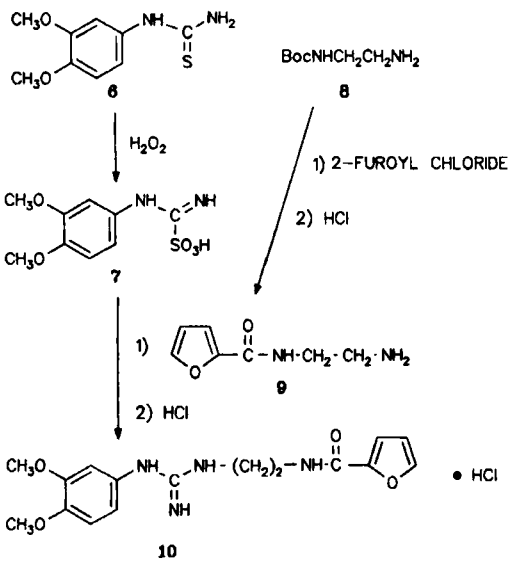


Scheme 1a



Scheme 1b

The synthesis of the cyanoguanidine models **14** and **15** is reported in Scheme 2. The intermediates **11** and **12** were prepared, with slight changes, according to ref.[3] (Experim. Part). In a similar way **13** was obtained from **11** and 1,2-ethanediamine. Reaction in methanol solution of 2-furoyl chloride on these derivatives afforded the final products.

For the thiourea models **19**, **20** see Scheme 3. Addition of the amino derivative **9** or **17** to an ethyl acetate solution of 3,4-dimethoxyphenylisothiocyanate (**18**) gave the expected compounds. The intermediate **17** was prepared by action of 2-furoyl chloride on 1-*t*-butyloxycarbonylpiperazine (**16**).

Finally, by nucleophilic substitution of the methylthio group present in **22** with the appropriate amino derivative, the nitroethenediamino analogues **24** and **25** were obtained (Scheme 4).

Pharmacology

Table 1 summarizes the biological properties at α_1- and α_2-receptors of ring-open analogues of 1. α_1-Adrenoceptor blocking activity was assessed by antagonism of (-)-noradrenaline induced contractions of rat aortic strips. α_2-Adrenoceptor blocking activity was determined by antagonism of clonidine induced depression of the twitch responses of field stimulated prostatic portion of rat vas deferens.

Tab. 1: Functional antagonism of the compounds studied towards α_1 and α_2 adrenoceptors.

	α_1		α_2	
Compd.	$pA_2 \pm 95\%$ CL	slope ± 95 % CL	$pA_2 \pm 95$ % CL	slope ± 95 % CL
1	9.81 ± 0.27	0.89 ± 0.15	5.43 ± 0.13 #	1.00
5	6.01 ± 0.23	0.96 ± 0.22	4.54 ± 0.10	1.19 ± 0.11
10	4.89 ± 0.24	1.10 ± 0.24	-	-
14	5.00 ± 0.17	1.01 ± 0.27	-	-
15	-	-	-	-
19	5.77 ± 0.33	0.98 ± 0.30	-	-
20	-	-	-	-
24	6.24 ± 0.23	0.91 ± 0.20	-	-
25	-	-	-	-

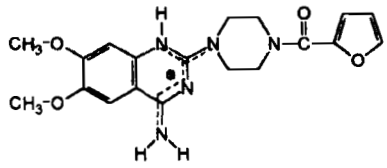
- Inactive at 10^{-4} M

Taken from ref. 2.

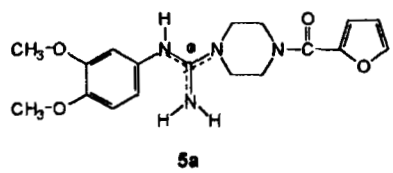
β_1-Adrenoceptor blocking activity was studied by antagonism of isoprenaline induced positive chronotropic effect on guinea-pig right atrium. None of the compounds modified the effect of isoprenaline.

Results and discussion

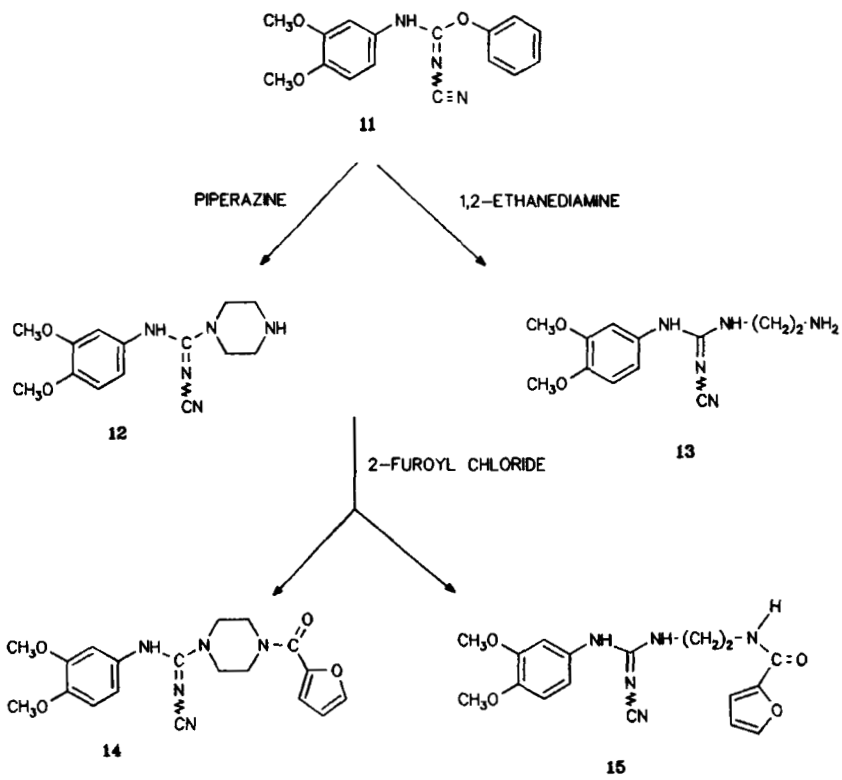
As pointed out prazosin (**1**) is partially ionized at physiological pH. The positive charge in the cation **1a** is delocalized over the 2,4-diaminopyrimidinium substructure. Also **5** must undergo protonation at physiological pH at the imino moiety giving **5a** and the positive charge is delocalized on the guanidinium substructure. Therefore, **5** can be considered a ring-open analogue of **1**.



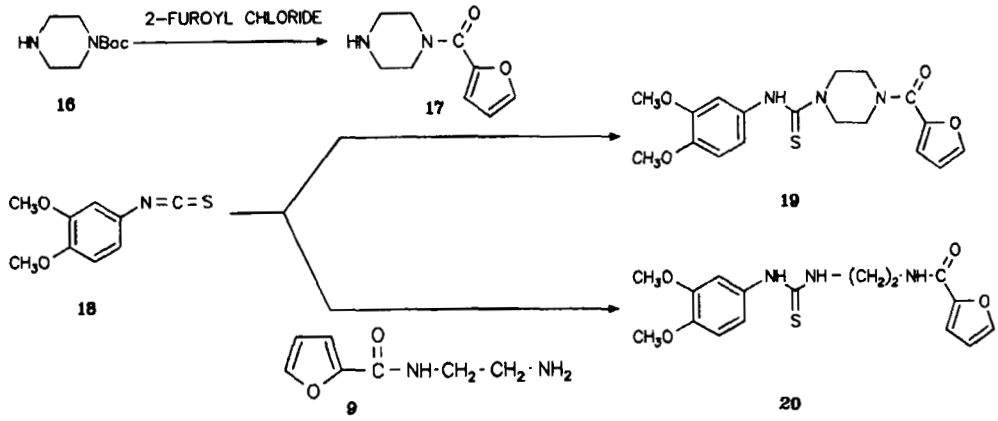
1a



5a

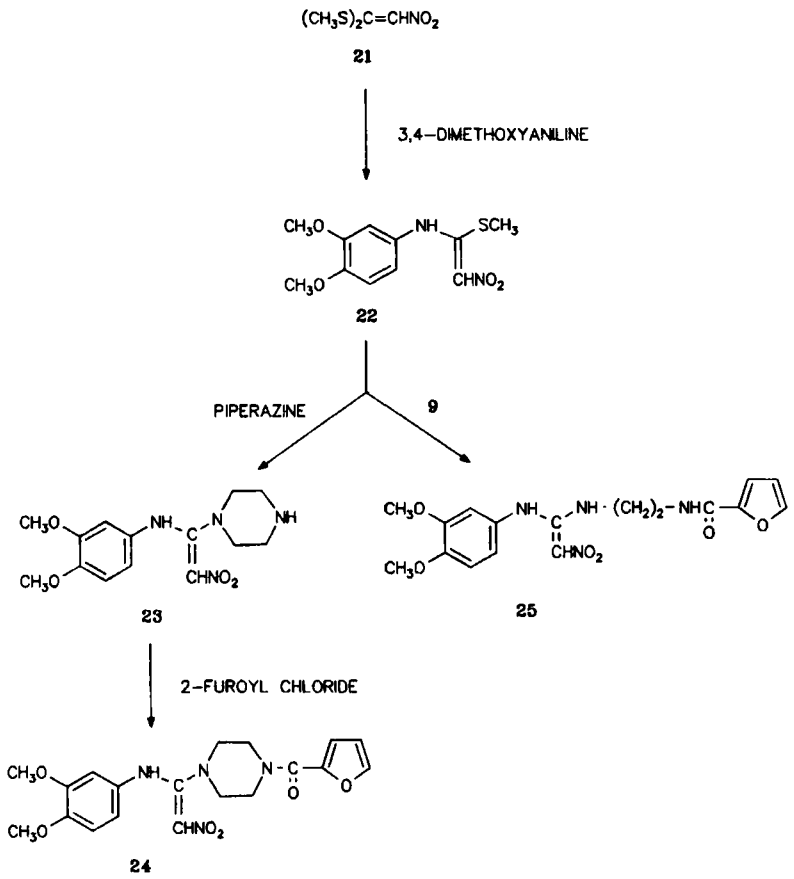


Scheme 2



Scheme 3

The opening of the pyrimidine ring in **1** has a dramatic influence on the affinity for the α_1-adrenoceptor: the pA_2 value of **5** is about 10^4 fold lower than that of prazosin. Hydrophobic effects should not play a relevant role in this decrease because they involve principally the interaction of the dimethoxyphenyl ring[1], a moiety common to both molecules. Perhaps the affinity decrease could be partially due to the reduced tendency of **5a** to give charge reinforced



Scheme 4

H-bonds in comparison with **1a**. Indeed the H on the N-atom adjacent to the phenyl ring in **5a** is less acidic than the corresponding H on N-1 of prazosin cation, because the protonation site in **5a** is located on the imino substructure. But probably the low affinity of **5** principally reflects a negative influence of the conformational factors in its interaction with the α_1-adrenoceptor. In fact while the substituted quinazolinium ring of **1a** displays a high degree of complementarity for the coplanar hydrophilic and anionic sites of the α_1-adrenoceptor[1], this does not occur for the phenylguanidinium moiety of **5a** which is a flexible structure. The weak affinity shown by **5** for the α_2-adrenoceptor seems to confirm this interpretation. Indeed SAR studies suggest that the hydrophobic binding area and the carboxylate anion in the α_2-adrenoceptor could lie in ortogonal planes[1,4].

Substitution in **5** of thiourea or nitroethenediamino moieties for the guanidine substructure does not substantially change the pA_2 value, while introduction of the cyanoguanidine moiety results in a 10 fold decrease in the affinity. Since these functions are not charged at physiological pH but are able to give strong H-bonding interactions with the anionic sites[5], we conclude that there is no reason to emphasize in **5a** the role of direct coulombionic interactions with the receptor.

Derivatives **10**, **15**, **20**, **25** are analogues of **5**, **14**, **19**, and **24**, respectively, in which an ethanediamino chain is substituted for the piperazine ring. Only **10** displays a weak α_1-antagonist activity. This behaviour underlines the crucial role of the conformational restricted piperazine ring for the antagonistic activity in the ring-open analogues of prazosin (**1**).

Experimental Part

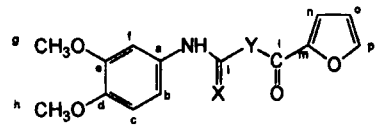
Chemistry

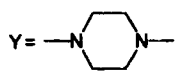
Melting points: Büchi 530 capillary melting point apparatus, uncorrected.- Differential Scanning Calorimetric measurement for compound **10**: DSC 7 Perkin Elmer.- IR: Perkin-Elmer 781.- Mass spectrometry: Varian CH7 MAT.- 200-MHz ^{1}H-NMR: Bruker AC 200.- 50-MHz. ^{13}C-NMR: spectral data (Bruker AC 200) of the final compounds are compiled in Table 2.- 27-MHz ^{17}O-NMR spectrum (Bruker AC 200) was performed for compound **7**.- CC: Silica gel (Merck, Kieselgel 100), 70-230 mesh ASTM.- Petroleum ether (b.p. 40-60°C) was used for chromatography purification and crystallizations. $MgSO_4$ was used as drying agent. Compounds **2**[6], **6**[7], **8**[8], **18**[7], **21**[9], were synthetized according to lit. methods.- Analyses of new compounds were performed by REDOX (Cologno M.).

N-Benzoyl-N'-(3,4-dimethoxyphenyl)-O-phenylisourea (**3**)

3,4-Dimethoxyaniline (2.29 g, 15 mmol) was added under stirring to a conc. dichloromethane solution of **2** (4.75 g, 15 mmol). The mixture was

Tab. 2: ^{13}C-NMR chemical shifts of the prazosin analogues ([D$_6$]DMSO, TMS int. ref.)[a]





A

—NH—CH_2—CH_2—NH— B

Compound	X	Y	a	b+	c	d⊛	e⊛	f	g•	h•	i	l	m⊛	n	o+	p	A or B	X
5	NH	A	129,0	111,5	117,0	146,8	147,4	109,4	55,8	55,7	155,3	158,5	149,2	116,3	112,3	145,1	45.9; 42 v.br	
10	NH	B	127,7	112,0	118,0	147.8	147,8	110,2	55,7	55,6	155,5	158,3	149,2	113,7	112,2	145.2	40,8; 37.8	
14	NCN	A	131.7	111,3	116.0	145.7	146.8	109,3	55,9	55,8	158.0	158,5	148.9	113,4	111,7	145.0	46.1; 43 v. br	117,5
15	NCN	B	129,9	111,9	117,3	146,9	148,0	109,9	55,9	55,4	158,2	158,7	148,9	113,5	111,9	145,0	44,6; 34.8	117,6
19	S	A	134,0	111,4	117,9	146,3	146,9	110,9	55,7	55,6	161,7	158,5	148,1	115,9	111,4	144,9	47,4; 43 v.br	
20	S	B	131,6	111,6	116,5	146,4	148.0	109,4	55,6	55,4	160,6	158,1	148,7	113,3	112,0	144,9	43,6; 38.3	
24	$CHNO_2$	A	132,1	111,3	116,0	146,3	146,7	106,6	55,6	55,7	156,6	158,4	149,3	113,9	112,4	144,9	47,6; 43 v. br	102,7
25	$CHNO_2$	B	128,6	111,7	118,6	147,7	147,9	110,9	55,6	55,7	155,6	158,2	149,4	113,4	112,4	144,8	40,7; 37.9	98,3

a) The values in the labelled column are tentatively assigned

kept for 3 h at room temp., then washed with 2 N NaOH, N HCl, water, and dried. Removal of the solvent left a residue which was purified on a short silica gel column, to afford **3** as a white solid (5.00 g, 90% yield) which was recrystallized from benzene/petroleum ether and melted, after initial softening, at 125-126°C (sample introduced into the bath at 50°C, heating rate 1-2°C/min).- $C_{22}H_{20}N_2O_4$ (376.4) Calcd. C 70.2 H 5.36 O 7.4 Found C 70.1 H 5.36 N 7.4. Mol. Mass 376 (ms).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 177.8; 160.1; 151.5; 149.1; 147.0; 136.8; 131.9; 129.3; 129.0; 127.9; 125.7; 121.9; 114.9; 111.2; 107.0; 55.9 (2C).

N-Benzoyl-N'-(3,4-dimethoxyphenyl)-1-piperazinecarboximidamide (**4**)

An ethyl acetate solution of **3** (3.76 g, 10 mmol), was added to piperazine (3.44 g, 40 mmol) dissolved in 2-propanol (20 ml) and ethyl acetate (10 ml). The mixture was stirred overnight and extracted with N HCl. The aqueous phase was washed with ethyl acetate, basified with $NaHCO_3$ and extracted with dichloromethane. The org. layer was dried and the solvent evaporated under vacuum. The crude product, purified by column chromatography (dichloromethane-methanol 10-30%), gave **4** as a white solid (2.60 g, 70%). An analytical sample was characterized as picrate, m.p. 188-190°C (aqueous ethanol).- $C_{26}H_{27}N_7O_{10}\cdot H_2O$ (615.5) Calcd. C 50.7 H 4.75 N 15.9 Found C 50.9 H 4.56 N 15.9.- ^{13}C-NMR (DMSO): δ (ppm) = 173.2; 160.9; 158.8; 148.9; 145.8; 141.9; 132.2; 131.2; 128.8; 128.5; 128.0; 125.3; 124.3; 113.4; 112.1; 106.4; 55.7; 55.3; 44.9; 44.0; 43.2; 42.6.

N-(3,4-Dimethoxyphenyl)-4-(2-furoyl)-1-piperazinecarboximidamide hydrochloride (**5**)

A solution of **4** (3.69 g, 10 mmol) in 5 M HCl (30 ml) was refluxed for 4 h. After cooling benzoic acid was removed by repeated extraction with ether and the aqueous solution was evaporated to dryness *in vacuo*. Drying of the residue *in vacuo* afforded *N*-(3,4-dimethoxyphenyl)-1-piperazinecarboximidamide dihydrochloride (2.48 g; 74%) as a hygroscopic solid which was used for the next step without further purification: 1.00 g was dissolved in methanol/water 10/2 (30 ml) containing $KHCO_3$ (0.60 g; 6 mmol); then, 2-furoyl chloride (0.3 ml, d = 1.32, 3 mmol) dissolved in the minimum amount of anhydrous tetrahydrofuran, was added dropwise. After removal of the solvent *in vacuo* the residue was purified by flash chromatography (dichloromethane/methanol 8/2) and triturated twice with an anhydrous mixture of 2/1 acetone/isopropanol (0.92 g; 78%). M.p. 223-224°C dec.- $C_{18}H_{22}N_4O_4\cdot HCl \cdot 0.5\ H_2O$ (403.9) Calcd. C 53.5 H 5.99 N 13.9 Found C 53.6 H 5.81 N 13.8.

Imino-(3,4-dimethoxyphenylamino)methanesulfonic acid (**7**)

6 (2.12 g; 10 mmol) was suspended in water (5 ml) containing NaCl (0.23 g; 4 mmol) and Na_2MoO_4 dihydrate (0.04 g; 0.15 mmol). 30% H_2O_2 (20 mmol) was added dropwise keeping the temp. < 20°C. When the addition was complete (total addition time 1 h), a further 10 mmol 30% H_2O_2 were added and the temp. maintained at 40°C for 1 h. The mixture was cooled and filtered. The solid so obtained was washed with ice-cold water and dried under vacuum (2.39 g, 92%). An analytical sample was crystallized from DMSO/water. M.p. 163-164°C dec.- $C_9H_{12}N_2O_5S$ (260.2) Calcd. C 41.5 H 4.65 N 10.8 Found C 40.9 H 4.77 N 10.5.- ^{13}C-NMR (DMSO): δ (ppm) = 165.6, 149.4, 148.7, 126.7, 117.6, 112.3, 109.3, 55.8, 55.7.- ^{17}O-NMR (CH_3CN/DMSO): δ (ppm) = 178.6 (relative to water)[10].

N-(2-Furoyl)-1,2-ethanediamine (**9**)

2-Furoyl chloride (0.98 ml; d = 1.32, 10 mmol) in anhydrous THF (5 ml) was added dropwise at room temp. to anhydrous THF (35 ml) containing **8** (1.60 g; 10 mmol) and triethylamine (1.38 ml; d = 0.73; 10 mmol). After 2 h, the mixture was cooled in an ice bath and conc. HCl (35 ml) was added. Afterwards the temp. was allowed to rise to 20°C. After a further 2 h the solution was reduced to one half *in vacuo*, washed with dichloromethane, basified under cooling with NaOH pellets and extracted many times with dichloromethane. The combined org. layers, dried and evaporated, afforded **9** as a yellow oil (1.27 g, 83%). An analytical sample in isopropanol was treated with an excess of HCl to give the hydrochloride, which was recrystallized from ethanol. M.p. 161-163°C dec., lit.[11]: 155-159°C (ethanol).- ^{13}C-NMR (DMSO): δ (ppm) = 158.3; 147.7; 145.2; 113.9; 111.9; 38.3; 36.4.

N-(3,4-Dimethoxyphenyl)-N'-[2-(2-furoylamino)ethyl]guanidine hydrochloride (**10**)

A solution of **7** (2.60 g, 10 mmol) and **9** (2.00 g, 13 mmol) in acetonitrile (8 ml) was refluxed for 30 min. After cooling a solid separated which was filtered and dissolved in 5 ml N HCl. The aqueous solution was

evaporated to dryness *in vacuo* and afforded a hygroscopic solid (2.29 g, 62% yield). Compound **10** was recrystallized from anhydrous isopropanol/ether and vitrified on heating: its m.p., checked by capillary apparatus and DSC instrument, resulted undefined.- $C_{16}H_{20}N_4O_4 \cdot HCl \cdot 0.5\ H_2O$ (377.8) Calcd. C 50.9 H 5.86 N 14.8 Found C 50.8 H 5.98 N 14.8.

N-Cyano-N'-(3,4-dimethoxyphenyl)-O-phenylisourea (**11**)

3,4-Dimethoxyaniline (12.00 g; 78 mmol) was added to a mixture of *N*-cyanodiphenylimidocarbonate[12] in isopropanol (300 ml) and the mixture was stirred at room temp. for 90 min. Then the mixture was filtered and the residue was washed with isopropanol and dried: 20.40 g (89%), m.p. 166°C from ethanol, lit.[3]: 163-164°C.- ^{13}C-NMR (DMSO): δ (ppm) = 161 (v.br); 151.7; 148.6; 147.3; 129.9; 129.0; 126.2; 120.9 (br); 116.5; 113.6; 111.7; 109.1; 55.7 (2C).

N-Cyano-N'-(3,4-dimethoxyphenyl)-1-piperazinecarboximidamide (**12**)

Compound **11** (7.40 g; 25 mmol) was added to a solution of piperazine (4.30 g; 50 mmol) in isopropanol (30 ml) and ethyl acetate (15 ml) and the mixture was stirred at room temp. for 6 h. Then the mixture was filtered and the residue was washed with isopropanol and dried: 6.20 g (86%), m.p. 181-182°C from ethanol, lit.[3]: 181-182°C from ethanol.- ^{13}C-NMR (DMSO): δ (ppm) = 158.2; 149.0; 145.6; 132.3; 116.7; 113.7; 112.2; 106.7; 55.8; 55.6; 47.9; 45.5.

N-(2-Aminoethyl)-N'-cyano-N''-(3,4-dimethoxyphenyl)guanidine (**13**)

13 was prepared from **11** as described for **12**: 89%. M.p. 142-145°C from ethanol.- $C_{12}H_{17}N_5O_2 \cdot 0.5\ H_2O$ (272.6) Calcd. C 52.9 H 6.62 N 25.7 Found C 53.3 H 6.56 N 25.7. Mol. Mass: 263 (ms).- ^{13}C-NMR (DMSO): δ (ppm) = 159.0; 148.8; 146.3; 130.8; 117.8; 116.0; 112.0; 108.8; 55.8; 55.6; 45.0; 41.4.

N-Cyano-N'-(3,4-dimethoxyphenyl)-4-furoyl-1-piperazinecarboximidamide (**14**)

Compound **12** (1.25 g; 4.32 mmol) and triethylamine (0.60 ml; d = 0.73, 4.32 mmol) were dissolved in anhydrous methanol (50 ml). To the ice-cold and stirred solution, 2-furoyl chloride (0.51 ml; d = 1.32, 5.18 mmol) was added dropwise.- The white precipitate was filtered, washed with methanol and dried: 1.19 g (72%), m.p. 183-184°C from methanol.- $C_{19}H_{21}N_5O_4$ (383.7) Calcd. C 59.5 H 5.52 N 18.3 Found C 59.3 H 5.50 N 18.3. Mol. Mass 383 (ms).

N-Cyano-N'-(3,4-dimethoxyphenyl)-N''-[2-(2-furoylamino)ethyl]guanidine (**15**)

15 was prepared from **13** as described for **14**: 73%, m.p. 200-201°C from methanol.- $C_{17}H_{19}N_5O_4$ (357.4) Calcd. C 57.1 H 5.36 N 19.6 Found C 57.0 H 5.34 N 19.6. Mol. Mass 357 (ms).

1-tert-Butoxycarbonylpiperazine (**16**)

Di-*tert*-buthyldicarbonate (2.45 g; 11 mmol), dissolved in dioxane (70 ml), was added during 2.5 h to a solution of piperazine (7.49 g; 87 mmol) in dioxane (30 ml). The mixture was stirred for 24 h. After removal of solvent, water (50 ml) was added and the mixture was filtered to remove the insoluble bis-substituted derivative. The aqueous solution was extracted with dichloromethane. The org. layer was dried and the solvent evaporated *in vacuo* to yield **16** (1.70 g; 83%) as a viscous oil that gradually solidified in a dessicator. The crude product was used for the next step without purification.- ^{1}H-NMR-spectrum of a sublimed sample was identical to that reported in ref.[13].- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 154.7; 79.4; 45.6; 44.6 (broad), 28.3.

1-(2-Furoyl)piperazine (**17**)

17 was prepared from **16** as described for **9**: 85%, m.p. 205-206°C from ethanol, lit.[14]: 202-204°C from ethanol.- ^{13}C-NMR (DMSO): δ (ppm) = 158.5; 146.4; 145.3; 116.4; 111.5; 42.7; 40.8 (broad).

N-(3,4-Dimethoxyphenyl)-4-(2-furoyl)-1-piperazinecarbothioamide (**19**)

Compound **17** (0.46 g; 2.56 mmol) dissolved in ethyl acetate (10 ml) was added dropwise to a solution of 3,4-dimethoxyphenylisothiocyanate (**18**) (0.50 g; 2.56 mmol) in ethyl acetate (10 ml). During the addition, the temp. was kept < 5°C. The precipitate was filtered off, washed with ethyl acetate and dried to give **19** (0.83 g; 87%). M.p. 186-187°C from ethanol (sintering at 182°C).- $C_{18}H_{21}N_3O_4S$ (375.4) Calcd. C 57.6 H 5.64 N 11.2 Found C 57.6 H 5.65 N 11.2. Mol. Mass 375 (ms).

N-(3,4-Dimethoxyphenyl)-N'-[2-(2-furoylamino)ethyl]thiourea (**20**)

20 prepared from **9** as for **19**: 58%, m.p. 166-168°C from ethanol.- $C_{16}H_{19}N_3O_4S$ (349.4) Calcd. C 55.0 H 5.48 N 12.0 Found C 55.0 H 5.50 N 12.0. Mol. Mass 349 (ms).

1-(3,4-Dimethoxyphenylamino)-1-methylthio-2-nitroethene (**22**)

A solution of **21** (5.00 g; 30 mmol) and 3,4-dimethoxyaniline (4.64 g; 30 mmol) in ethanol (225 ml) was refluxed for 8 h. After cooling the precipitate was filtered, washed with ether and dried (7.13 g; 88%). Crude **22** so obtained was recrystallized from ethanol. M.p. 162-163°C.- $C_{11}H_{14}N_2O_4S$ (270.3) Calcd. C 48.9 H 5.22 N 10.4 Found C 48.9 H 5.28 N 10.3. Mol. Mass 270 (ms).- ^{13}C-NMR (DMSO): δ (ppm) = 164.7; 148.9; 148.5; 129.4; 118.8; 111.6; 110.7; 107.0; 55.8 (2C); 14.3.

1-[1-(3,4-Dimethoxyphenylamino)-2-nitroethen-1-yl]piperazine (**23**)

A solution of **22** (2.03 g; 7.5 mmol) and piperazine (2.60 g; 30 mmol) in acetonitrile (80 ml) was refluxed for 6.5 h. After cooling, solvent removal *in vacuo* left a residue which was purified by flash chromatography (CH_2Cl_2/MeOH 9/1) to give **23** as a yellow solid (1.83 g; 79%). M.p. 124-125°C (methanol).- $C_{14}H_{20}N_4O_4 \cdot 0.75\ H_2O$ (321.8) Calcd. C 52.2 H 6.73 N 17.4 Found C 52.2 H 6.43 N 17.3. Mol. Mass 308 (ms).- ^{13}C-NMR (DMSO): δ (ppm) = 156.5; 149.0; 146.0; 32.2; 113.4; 112.0; 106.3; 102.4; 55.5; 55.4; 49.2; 44.6.

1-[1-(3,4-Dimethoxyphenylamino)-2-nitroethen-1-yl]-4-(2-furoyl)piperazine (**24**)

23 (0.50 g; 1.6 mmol) and triethylamine (0.22 ml; d = 0.73; 1.6 mmol) were dissolved in anhydrous methanol (30 ml). To the stirred solution 2-furoyl chloride (0.16 ml; d = 1.32; 1.6 mmol), dissolved in anhydrous tetrahydrofuran, was added dropwise; when the addition was complete the mixture was poured into water and extracted with ethyl acetate. The org. layer, dried and evaporated, afforded **24** (0.49 g; 76%). M.p. 161-162°C from ethylacetate.- $C_{19}H_{22}N_4O_6$ (402.4) Calcd. C 56.7 H 5.51 N 13.9 Found C 56.6 H 5.52 N 13.9.- Mol. Mass 402 (ms).

N-(3,4-Dimethoxyphenyl)-N'-[2-(2-furoylamino)ethyl]-2-nitro-1,1-diaminoethene (**25**)

A solution of **22** (0.50 g; 1.85 mmol) and **9** (0.30 g; 2 mmol) in ethanol (25 ml) was refluxed for 6 h. After cooling to 0°C for 1 h, **25** precipitated and was collected by filtration (0.21 g; 30% yield). M.p. 200-203°C dec. (sample introduced into the bath at 185°C, heating rate 3°C/min).- $C_{17}H_{20}N_4O_6$ (376.6) Calcd. C 54.3 H 5.36 N 14.9 Found C 54.3 H 5.40 N 14.7. Mol. Mass 376 (ms).

Pharmacology

Functional antagonism at α_1-adrenoceptors

The α_1-adrenoceptor blocking activity has been investigated in thoracic aorta isolated from male Wistar rats weighing 250-300 g. The vessels were helically cut, the endothelium was removed and two strips were obtained from each aorta. The tissues were suspended under a tension of 1 g in organ baths containing 30 ml of *Krebs-Henseleit* solution: NaCl 137; KCl 2.68; $MgCl_2$ 0.5; $CaCl_2$ 5.44; NaH_2PO_4 0.54; $NaHCO_3$ 8.93; glucose 8.3; ascorbic acid 0.1 mM. Desmethylimipramine x HCl 1 x 10^{-7} M, deoxycorticosterone acetate 5 x 10^{-6} M, propranolol 5 x 10^{-6} M, and yohimbine x HCl 1 x 10^{-7} M were added to the solution to prevent neuronal and extraneuronal uptake of noradrenalin and to block β- and α_2-adrenoceptors, respectively. The medium was gassed with 95% O_2 - 5% CO_2 at 37°C (pH = 7.4). The aortic strips were allowed to equilibrate for 2 h before starting the experiments.

Agonist induced contractions were determined cumulatively in the absence or presence of antagonist incubated for 30 min. One of the two strips cut from each aorta served as a control while, on the other one, a dose-response curve in the presence of antagonist was performed.

Functional antagonism at α_2-adrenoceptors

The α_2-adrenoceptor blocking activity was assessed on the prostatic portion of the rat vas deferens by antagonism to clonidine which inhibits twitch responses of the field-stimulated vas deferens by acting on the α_2-adrenoceptors. The tissues were mounted in organ baths containing 30 ml of *Krebs* solution: NaCl 118.4; KCl 4.7; $CaCl_2$ 2.52; $MgSO_4$ 0.6; KH_2PO_4 1.2; $NaHCO_3$ 25.0; glucose 11.1 mM. The solution was maintained at 37°C and continuously gassed with 95% O_2 - 5% CO_2 (pH = 7.4).

The preparations were stretched to a resting tension of 1 g (isometric transducers) and allowed to equilibrate for at least 60 min before addition of any drug. A first clonidine dose-response curve, taken as control, was obtained cumulatively. Thus, after incubation with antagonist for 30 min a second dose-response curve was obtained.

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