Some New Prazosin Analogues

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The synthesis and the pharmacological properties of some new prazosin analogues are described.

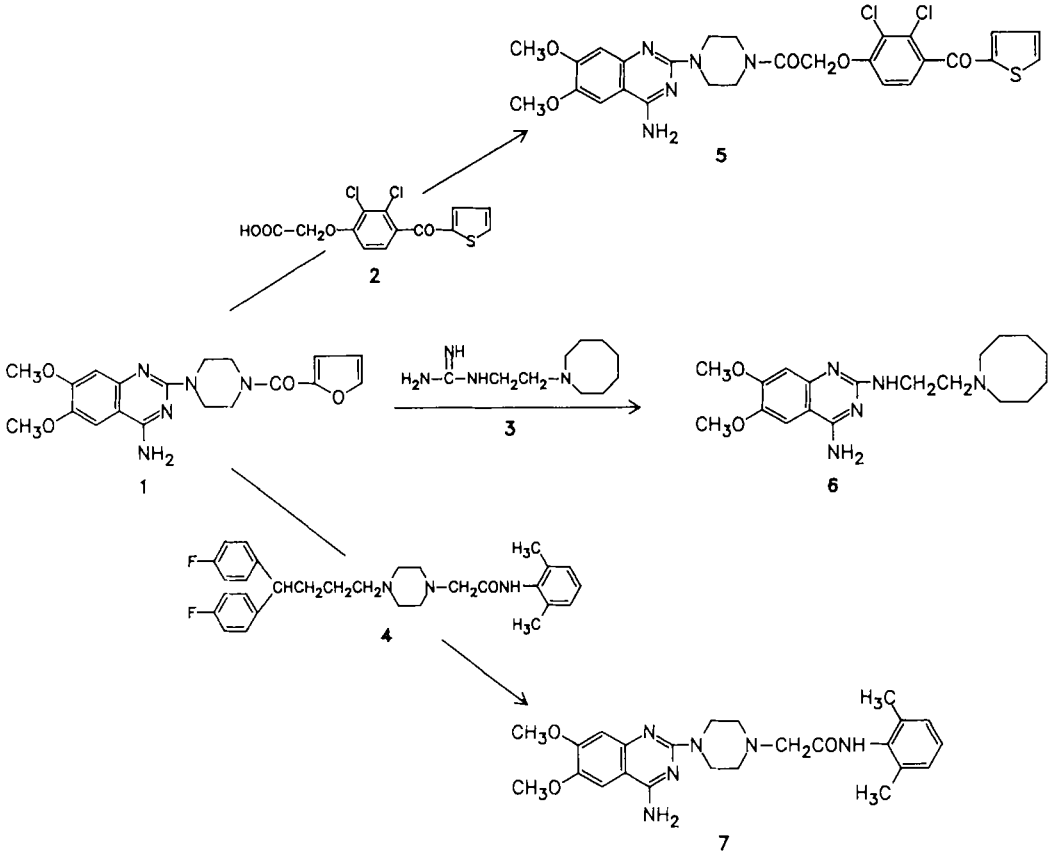
Einige neue Prazosin-Analoge

Einige Prazosin-ähnliche Derivative und ihre pharmakologischen Eigenschaften werden beschrieben.

Prazosin **1**, a well known selective α_1-adrenergic antagonist[1], represents a remarkable improvement in the antihypertensive therapy. However, the short half-life and some side effects restrict its usefullness so that a number of structural modifications have been developed[2]. More interesting are those involving the C-2 side-chain of **1** : e.g. the reduction of the furan ring (terazosin)[3] as well as its replacement with a 1,4-benzodioxan-1-yl one (doxazosin)[4] greatly improved the pharmacokinetic properties of the parent compound. Following this line of research we have studied the substitution of the C-2 side-chain of **1** with peculiar fragments of tienilic acid (**2**) (diuretic and uricosuric), guanethidine (**3**) (hypotensive) and lidoflazine (**4**) (vasodilator, Calcium-antagonist), according to the so called medicinal hybridation conception[5] as shown in Scheme 1.

Chemistry

The new compounds were synthesized by standard procedures as shown in Scheme II. Thus the condensation of 2-chloro-4-amino-6,7-dimethoxyquinazoline[6] (**8**) with **9**, **10** and **11** gave **5**, **6**, and **7**, respectively.



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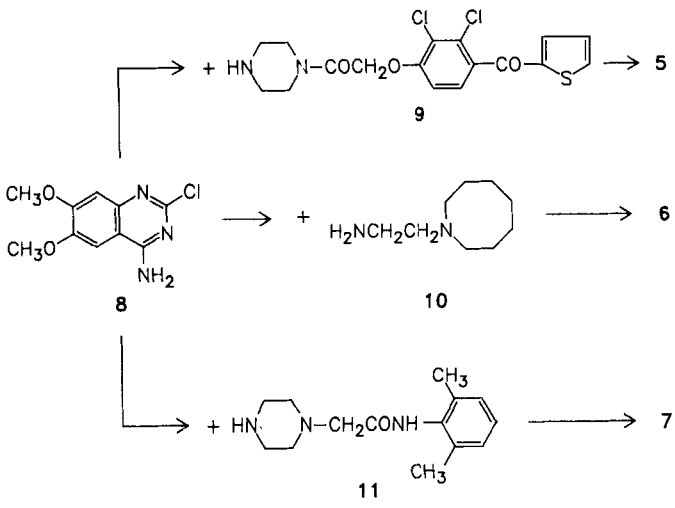
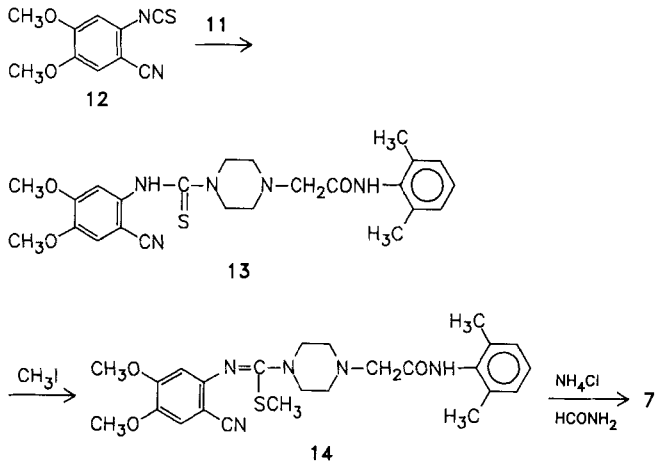


Compound **7** was also obtained starting from 2-cyano-4,5-dimethoxyphenylisothiocyanate[7] **12** (Scheme III):



Pharmacology

Acute toxicity was determined orally in groups of ten albino mice employing all compounds dissolved in saline as HCl salts. The behaviour of the animals was observed during 72 h. The approximate LD_{50} was estimated according to *Litchfield* and *Wilcoxon*[8].

Hypotensive effect was determined in groups of five genetically hypertensive male rats (SHR/NOS, 200-220 g weight). Maximum systolic blood pressure in basic conditions was estimated by BP Recorder 8002 (Basile) in bloodless way (muff on tail) three times for two days before the administration of the compounds under examination. The rats were warmed into a box at 37°C for 40 min before each assessment. The systolic blood pressure was determined 2, 4, 6, 8 and 24 h after oral administration of the compounds dissolved in saline.

Compounds **5**, **6** and **7** were tested at 161.7, 154.0 and 135.2 ng/Kg, respectively. These doses were calculated by multiplying the reference oral dose of **1**[9] (80 ng/Kg) by an appropriate factor, which is obtained by dividing the molecular weight of the compound under examination and the weight of the prazosin fragment contained in it.

The other reference compounds, guanethidine (**3**), tienilic acid (**2**), and lidoflazine (**4**) were used at 2000, 3570 and 5140 ng/Kg, respectively, according to literature[10, 11, 12].

Results and Discussion

The results have been collected in Table 1.

Acute toxicity - The LD_{50} values of **5** and **7** (>4000 mg/Kg orally) were similar to that of prazosin while **6** was more toxic (but about equitoxic with guanethidine) with a prelethal symptomatology characterized by a sedative pattern.

Hypotensive activity - **5** showed the highest hypotensive effect 2 h after oral administration (about 41% more than prazosin). This effect decreased more slowly than that of **1** (Table 1). **7** and **6** were equiactive with prazosin; the latter showed a slower onset of the hypotensive action.

As a conclusion the pharmacological profile of the new compounds does not move away from that of prazosin, the hypotensive activity of which seems differently modulated by the fragment of the C-2 side-chain.

The best results were observed when the furan ring of **1** was replaced by the tienilic residue, leading to **5**.

Therefore, compound **5** even if it has not a slower onset of action, seems to elicit a more long lasting hypotensive activity than prazosin similarly to both terazosin and doxazosin.

Table 1 – Pharmacological properties of Prazosine analogues

Compounds	$LD_{50_{PO}}$ mg/Kg	dose μg/Kg	2 h Δ ± SD	4 h Δ ± SD	6 h Δ ± SD	8 h Δ ± SD	24 h Δ ± SD
Prazosin	>4000	80.0	−42.5±3.5	−27.5±3.5	−17.5±2.5	−15.5±2.0	−12.0±3.1
Guanethidine	1.000 (900–1100)	2000.0	−37.5±5.0	−47.5±3.1	−20.0±1.0	− 5.0±5.0	− 2.0±6.0
6	825 (750–900)	154.0	−23.7±5.0	−31.2±3	−26.2±4.3	− 8.7±5.2	− 8.7±3.5
5	>4000	161.7	−60.0±7.5	−50.0±5.0	−40.0±5.0	−25.0±4.5	−10.0±2.5
7	>4000	135.2	−52.5±3.5	−17.5±5.0	−10.0±4.5	−10.0±2.2	− 7.5±5.0
Tienilic acid	1275	3570.0	− 7.5±3.2	−10.0±4.5	− 5.0±2.6	0	+ 2.5±5.0
Lidoflazine	>2000	5140.0	− 5.0±3.0	− 7.5±3.5	0	0	+ 5.0±2.5

Blood pressure changes (± SD) are given as differences (mm Hg) from the initial base values.

Experimental Part

[2,3-Dichloro-4-(2-thenoyl)]phenoxyacethylpiperazine-HCl (**9**)

To a solution of 1.4 g (0.016 mol) of anhydrous piperazine in 16 ml of EtOH and 2 ml of H_2O were added dropwise 2.7 g (0.016 mol) of 48% aqueous HBr solution mantaining a temp. of 40-45°C. The mixture was stirred at 40° under N_2 and 2.8 g (0.008 mol) of 2,3-dichloro-4-(2-thenoyl)phenoxyacethyl chloride were added over a 10 min period. The slurry was stirred at 80°C for 1.5 h, chilled to 5°C and filtered. The clear filtrate was concentrated *in vacuo* to an oil, diluted with 2 ml of H_2O, the pH adjusted to 10.2 (dil. NaOH) and then extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in EtOH and treated with ethanolic HCl : 2.1 g (30%) of **9** - HCl, m.p. 207-210°C. - $C_{17}H_{17}Cl_3N_2O_3S$ (435.6) Calcd. C 46.8 H 3.9 N 6.4 Cl 24.4 Found C 46.5 H 3.8 N 6.3 Cl 24.1.

3,4-Dimethoxy-6-[4-(2,6-dimethylacetanilido)piperazin-1-yl]thiocarbamido-benzonitrile (**13**)

A solution of 2.7 g (0.012 mol) of **12**[7] in 15 ml of ethyl acetate was added gradually at 0-5°C with stirring to a solution of 3 g (0.012 mol) of **11**[13] in 15 ml of ethyl acetate. The mixture was stirred for 20 h and then filtered. The crystals were washed with cold ethyl acetate and dried: 5.6 g (100%) **13**, m.p. 219-22°C. - $C_{24}H_{29}N_5O_3S$ (467.3) Calcd. C 61.6 H 6.3 N 14.9 Found C 61.6 H 6.2 N 14.8.

Methyl N-(3,4-dimethoxy-6-cyanophenyl)-[4-(2,6-dimethylacetanilido) piperazin-1-yl]-thioformamidate (**14**)

To a stirred solution of 5.6 g (0.012 mol) of **13** in 40 ml of ethyl acetate, 3.3 g (0.023 mol) of methyl iodide were added. The mixture was heated for 20 h at 60°C, cooled and treated with 20 ml of 5% aqueous NaOH. The org. layer was separated, washed with water and evaporated *in vacuo* to dryness: 4.6 (80%) **14** m.p. 62-65°. - $C_{25}H_{31}N_5O_3S$ (481.4) Calcd. C 62.3 H 6.5 N 14.5 Found C 62.4 H 6.2 N 14.4.

2-[4-[2,3-Dichloro-4-(2-thenoyl)]phenoxyacetyl]piperazin-1-yl-4-amino-6,7-dimethoxyquinazoline-HCl (**5**)

A mixture of 0.87 g (0.0036 mol) of **8** and 1.6 g (0.0036 mol) of **9** was heated in 20 ml of isoamyl alcohol for 2.5 h and then cooled. The separated solid was collected by filtration and washed with isoamyl alcohol and acetone; on crystallizing the crude product from MeOH-Et_2O 1.38 g (60%) of **5**, m.p. 190-192°C, was obtained. - $C_{27}H_{26}Cl_2N_5O_5S{\cdot}Cl$ (638.7) Calcd. C 50.7 H 4.1 N 10.9 Cl 16.5 Found C 50.6 H 4.0 N 10.7 Cl 16.5.

2-[2-Heptamethyleneimino]-4-amino-6,7-dimethoxyquinazoline-HCl (**6**)

With the same procedure described for **5**, starting from 1.74 g (0.0072 mol) of **8** and 1.1 g (0.0072 mol) of **10**[14], 1.9 g (63%) of **6** m.p. 265-266° (EtOH) were obtained. - $C_{21}H_{30}ClN_5O_2$ (419.7) Calcd. C 60.0 H 7.2 N 16.7 Cl 8.4 Found C 60.1 H 7.1 N 16.5 Cl 8.6.

2-[4-(2,6-Dimethylacetanilide)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline-HCl (**7**)

With the same procedure as above, starting from 0.97 g (0.004 mol) of **8** and 1 g (0.004 mol) of **11**[13], 1.4 g (70%) of **7** m.p. 308-309° (MeOH-Et_2O) were obtained. - $C_{24}H_{31}ClN_6O_3$ (486.7) Calcd. C 59.1 H 6.4 N 17.2 Cl 7.2 Found C 59.0 H 6.3 N 17.1 Cl 7.1.

The same compound can be prepared as follows : a mixture of 4.8 g (0.01 mol) of **14**, 12 g of NH_4Cl and 50 ml of $HCONH_2$ was heated at 120° for 20 h under N_2. After cooling the mixture was diluted with 25 ml of H_2O, filtered, washed with water and acetone and dried. On crystallizing the crude product from MeOH-Et_2O 3.9 g (80%) of **7** m.p. 308-309° were obtained. The analytical data are consistent.

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