Kurzmitteilung:

Synthesis and Antihypertensive Properties of Some Dopamino-pyridazin-3(2*H*)-one Derivatives

Synthese und antihypertensive Aktivität einiger Dopamino-pyridazin-3(2*H*)one

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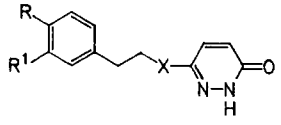
Great attention has been paid to compounds containing the 3(2*H*)-pyridazinone moiety due to their biological activities[1,2].

In addition to the positive inotropic properties, some compounds show a vasodilatory effect on the peripheral vascular system which is in connection with an inhibitory effect on the α-adrenergic receptor[3]. Stimulation of the peripheral dopamine receptors DA_1 and DA_2 gives an hypotensive response[4,5]. So far many agonist for dopamine receptor have been synthesized which show antihypertensive activity[6,7].

We considered the synthesis of compounds interesting in which the pyridazinone ring is linked to derivatives of dopamine. Therefore, we have synthesized a series of new compounds of the general formula:



where R, R^1 are OCH_3, OH, or ester. X are NH, NH-CH_3, piperazine ring or *N,N'*-dimethylethylenediamine.

The scheme shows the method employed for the preparation of these compounds. Alkylation of compounds **1** and **2** with 3,6-dichloropyridazine (**3**), followed by hydrolysis with glacial acetic acid gave compounds **6** and **7**. Subsequently **6** and **7** were treated with 48% (v/v), HBr solution, affording compounds **8** and **9**, which gave compounds **10** and **11** with butyryl chloride.

With the same procedure, starting from 2-(3,4-dimethoxyphenyl)-ethylpiperazine (**12**), compounds **14** and **15** have been prepared.

The synthesis of **18**, where the piperazine ring has been substituted by *N,N'*-dimethylethylenediamine was prepared by alkylation of **16** with 3,6-dichloropyridazine, followed by hydrolysis with glacial acetic acid.

Experimental Part

MP: Reichert microhostage devise, uncorr.- IR-spectra: Beckman Acculab 5 (CCl_4).- ^{1}H-NMR-spectra: Varian EM 390, 90 MHz, $CDCl_3$, DMSO-d_6, TMS int. stand.- Purity was checked by TLC.

6-[2-(3,4-Dimethoxyphenyl)-ethylamine]-3-chloropyridazine (**4**) *and compound* **5**

A mixture of 2.44 g ($1.3 \cdot 10^{-2}$ mole) of 2-(3,4-dimethoxyphenyl)-ethylamine, and 2 g ($1.3 \cdot 10^{-2}$ mole) of 3,6-dichloropyridazine (**3**) in 15 ml of isoamylic alcohol was stirred and refluxed for 12 h. The solvent was removed under reduced pressure and the residue was diluted with water, alkalinized with N-NaOH, and extracted with CH_2Cl_2. Removal of solvent after drying (Na_2SO_4) gave a solid which was purified by flash-chromatography using diethyl ether/ethyl acetate (1/9 v/v); yield 40%, m.p. 158-162°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.9 (t, 2H; J = 6 Hz, CH_2), 3.6 (t, 2H; J = 6 Hz, CH_2), 3.8 (s, 6H; 2 OCH_3), 5.0 (s, 1H; NH), 6.4-6.7 (m, 4H; 3H-aromatic, H-pyridazine), 7.0 (d, 1H; J = 8.5 Hz, H-pyridazine).

6-{N-[2-(3,4-Dimethoxyphenyl)-ethyl]-N-methylamino}-3-chloropyridazine (**5**)

Yield 40%, m.p. 78-84°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.8 (t, 2H; J = 6 Hz, CH_2), 3.0 (s, 3H; N-CH_3), 3.7 (t, 2H; J = 6 Hz, CH_2), 3.9 (s, 6H; 2 OCH_3), 6.5-7.0 (m, 5H; 3H-aromatic, 2H-pyridazine).

6-[2-(3,4-Dimethoxyphenyl)-ethylamine]-pyridazin-3(2H)-one (**6**) *and compound* **7**

A solution of 0.9 g ($3 \cdot 10^{-3}$ mole) of **4** in 15 ml of glacial acetic acid was refluxed for 12 h. The acetic acid was removed under reduced pressure, and the residue was chromatographed on alumina *Brockmann* II using CH_2Cl_2/MeOH (9.5/0.5) m.p. 150-153°C, yield 40%.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.8 (t, 2H; J = 6 Hz, CH_2), 3.4 (t, 2H; J = 6 Hz, CH_2), 3.8 (s, 6H; 2 OCH_3), 4.9 (s, 1H; NH), 6.6-6.8 (m, 5H; 3H-aromatic, C<u>H</u>=C<u>H</u>), 12.5 (s, 1H; NH).- $C_{14}H_{17}N_3O_3$ (275) Calc. C 61.1 H 6.1 N 15.2 Found C 61.1 H 6.5 N 14.8.

6-{N-[2-(3,4-Dimethoxyphenyl)-ethyl]-N-methylamino}-pyridazin-3(2H)-one (**7**)

Yield 50%, m.p. 175-178°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.75 (t, 2H; J = 6 Hz, CH_2), 2.9 (s, 3H; N-CH_3), 3.6 (t, 2H; J = 6 Hz, CH_2), 3.8 (s, 6H; 2 OCH_3), 6.5-7.0 (m, 5H; 3H-aromatic, C<u>H</u>=C<u>H</u>), 11.5 (s, 1H; NH).- $C_{15}H_{19}N_3O_3$ (289) Calc. C 62.3 H 6.57 N 14.5 Found C 61.8 H 6.96 N 14.7.

6-[2-(3,4-Dihydroxyphenyl)-ethylamine]-pyridazin-3(2H)-one (**8**) *and compound* **9**

Under N_2, 0.6 g ($2 \cdot 10^{-3}$ mole) of **6** was refluxed with 10 ml of 48% (v/v) HBr solution for 2 h under stirring. After cooling the solution was concentrated under reduced pressure. The residue was treated with ethanol

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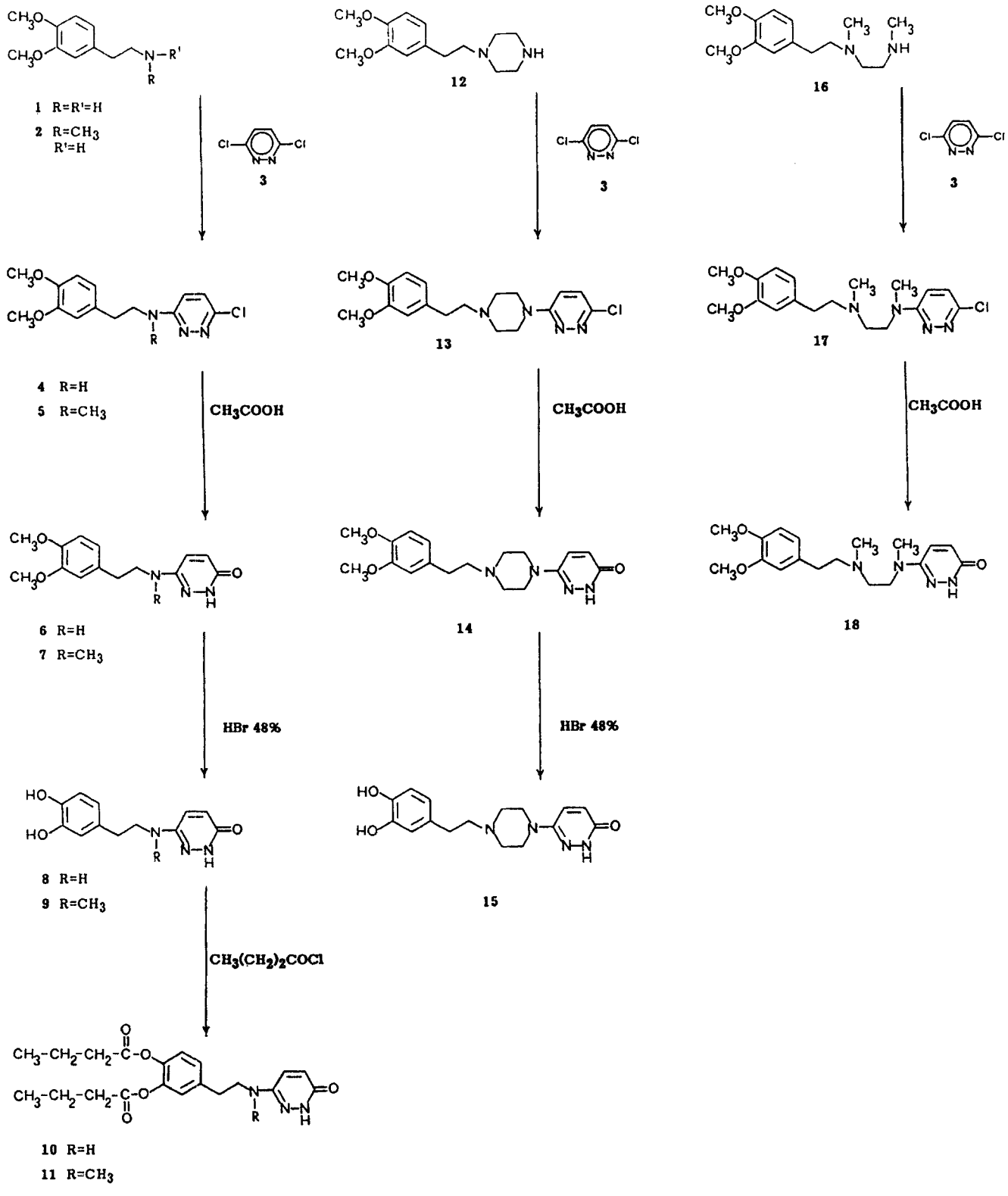

and then evaporated. Traces of acid were eliminated with 0.1 N NaOH. The mixture was concentrated, extracted with CH_2Cl_2, dried, and evaporated i.vac.. The residue was crystallized with EtOH, m.p. 300-305°C; yield 50%.- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.7 (t, 2H; J = 6 Hz, CH_2), 3.3 (t, H; J = 6 Hz, CH_2), 4.5-5.0 (m, 3H; 2 OH, NH), 6.4-6.8 (m, 5H; 3H-aromatic, CH=CH), 12.0 (s, 1H; NH).

6-{N-[2-(3,4-Dihydroxyphenyl)-ethyl]-N-methylamino}-pyridazin-3(2H)-one (**9**)

M.p. 207-210°C; yield 50%.- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.8 (t, 2H; J = 6 Hz, CH_2), 3.0 (s, 3H; N-CH_3), 3.8 (t, 2H; J = 6 Hz, CH_2), 5.4 (s, 2H; 2 OH), 6.4-6.8 (m, 3H; aromatic), 7.1 (d, 1H; J = 9.5 Hz, CH=CH), 7.6 (d, 1H; J = 9.5 Hz, CH=CH).

6-[2-(3,4-Dibutyryloxyphenyl)-ethylamino]-pyridazin-3(2H)-one (**10**) *and compound* **11**

Under N_2 0.5 g ($2 \cdot 10^{-3}$ mole) of **8** were added to a solution of butyryl chloride 0.68 g ($6.4 \cdot 10^{-3}$ mole) in trifluoroacetic acid (8 ml). The solution was stirred at room temp. for 1.5 h. Excess of butyryl chloride and trifluoroacetic acid were removed i.vac. The residue was diluted with water and alkalinized with N-NaOH, and extracted with CH_2Cl_2; removal of solvent after drying gave a solid which was crystallized with hexane/ether. Yield 50%, m.p. 123-126°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.0 (t, 6H; 2 CH_3), 1.6-1.9 (m, 4H; 2 CH_2), 2.5 (t, 4H; 2 CH_2), 2.8 (t, 2H; J = 6 Hz, CH_2), 3.4 (t, 2H; J = 6 Hz, CH_2), 4.3 (s, 1H; NH), 6.7-7.1 (m, 5H; 3H-aromatic, CH=CH).- **$C_{20}H_{23}N_3O_3$ (378) Calc. C 62.0 H 6.4 N 10.9 Found C 61.5 H** 6.15 N 10.45.

6-{N-[2-(3,4-Dibutyryloxyphenyl)-ethyl]-N-methylamino}-pyridazin-3(2H)-one (**11**)

It was crystallized with ethyl acetate, m.p. 129-135°C, yield 50%.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.0 (t, 6H; 2 CH_3), 1.8 (m, 4H; 2 CH_2), 2.5 (t, 4H; 2 CH_2), 2.7-2.9 (m, 5H; N-CH_3, CH_2), 3.5 (t, 2H; J = 6 Hz, CH_2), 6.6-7.0 (m, 5H; 3H-aromatic, CH=CH), 11.5 (s, 1H; NH).- $C_{21}H_{27}N_3O_5$ (401) Calc. C 62.8 H 6.73 N 10.5 Found C 62.6 H 6.92 N 10.9.

4-[2-(3,4-Dimethoxyphenyl)-ethyl]-piperazine (**12**)

A mixture of 4.5 g ($2.2 \cdot 10^{-2}$ mole) of 2-(3,4-Dimethoxyphenyl)-ethylchloride and 2.08 g ($2.4 \cdot 10^{-2}$ mole) of piperazine in anhydrous ethanol was stirred and refluxed for 24 h. After cooling the solvent was evaporated under reduced pressure. The residue was purified on alumina *Brockmann* II eluting with CH_2Cl_2/EtOH; yield 60%.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.6-3.1 (m, 9H; H-piperazinic, NH), 3.1-3.4 (m, 4H; 2 CH_2), 3.9 (s, 6H; 2 OCH_3), 6.6-6.8 (m, 3H; aromatic).

6-{4-[2-(3,4-Dimethoxyphenyl)-ethyl]-piperazinyl}-3-chloropyridazine (**13**) *and compound* **16**

A mixture of 0.7 g ($1.9 \cdot 10^{-3}$ mole) **12** in 20 ml of 2-butanone and 1 g of anhydrous K_2CO_3 and 0.5 g ($3.3 \cdot 10^{-3}$ mole) of 3,6-dichloropyridazine was stirred under reflux for 24 h. It was cooled and filtered. The filtrate was evaporated *in vacuo*, the residue was purified by flash-chromatography using, CH_2Cl_2/EtOH (9/1); yield 55%; m.p. 113-118°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.5-2.9 (m, 8H; H-piperazine), 3.5-3.7 (m, 4H; 2 CH_2), 3.9 (s, 6H; 2 OCH_3), 6.6 (s, 3H; aromatic), 6.8 (d, 1H; J = 8.5 Hz, H-pyridazine), 7.2 (d, 1H; J = 8.5 Hz, H-pyridazine).

N-[2-(3,4-Dimethoxyphenyl)ethyl]-N,N-dimethylethylenediamine (**16**)

16 was prepared from 2-(3,4-dimethoxyphenyl)-ethylchloride and *N, N'*-dimethylethylenediamine and purified on alumin *a Brockmann* II using CH_2Cl_2/EtOH (9/1) as eluent; yield 40%.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.2 (s, 3H; N-CH_3), 2.4 (s, 3H; N-CH_3), 2.5-2.8 (m, 7H; 3 CH_2, NH), 2.9 (t, 2H; J = 6 Hz, CH_2), 3.8 (s, 6H; 2 OCH_3), 6.7 (s, 3H; aromatic).

6-{4-[2-(3,4-Dimethoxyphenyl)-ethyl]-piperazinyl}-pyridazin-3(2H)-one (**14**) *and compound* **18**

A solution of 0.7 g ($1.9 \cdot 10^{-3}$ mole) of **13** in 15 ml of glacial acetic was refluxed under stirring for 7 h. The acetic acid was removed *in vacuo* and the solid was treated with water, alkalinized with N-NaOH, and extracted with CH_2Cl_2. Removal of the solvent after drying gave a solid which was crystallized with ethyl acetate/EtOH; m.p. 207-208°C; yield 40%.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.5-2.9 (m, 8H; H-piperazine), 3.2-3.4 (m, 4H; 2CH_2), 3.8 (s, 6H; 2 OCH_3), 6.6 (s, 3H, aromatic), 6.8 (d, 1H; J = 9.5 Hz, CH=CH), 7.2 (d, 1H; J = 9.5 Hz, CH=CH), 12.0 (s, 1H, NH).- $C_{18}H_{24}N_4O_3$ (344) Calc. C 62.8 H 6.97 N 16.3 Found C 62.8 H 7.02 N 16.1. The corresponding hydrochloride shows m.p. 228-231°C.

N-[2-(3,4-Dimethoxyphenyl)-ethyl]-N'-[pyridazin-3(2H)-onyl]-N,N'-dimethylethylenediamine (**18**)

Yield 40%.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.3 (s, 3H; N-CH_3), 2.5-2.7 (m, 6H; 3 CH_2), 2.9 (s, 3H; N-CH_3), 3.4 (t, 2H; J = 6 Hz, CH_2), 3.8 (s, 6H; 2 OCH_3), 6.6-6.9 (m, 4H; 3H-aromatic, CH=CH), 7.2 (d, 1H; J = 9.5 Hz, CH=CH), 12 (s, 1H; NH).- $C_{18}H_{26}N_4O_3$ (346) Calc. C 62.4 H 7.51 N 16.2 Found C 62.1 H 7.69 N 15.9. The corresponding hydrochloride shows m.p. 80-85°C.

6-{4-[2-(3,4-Dihydroxyphenyl)-ethyl]-piperazinyl}-pyridazin-3(2H)-one (**15**)

Under N_2 1.4 g ($4 \cdot 10^{-3}$ mole) of **14** were treated with 25 ml of 48% (v/v) HBr solution at 125-130°C for 2 h. After cooling the solution was concentrated i.vac. The residue was treated with anhydrous EtOH and then evaporated. The residue was crystallized from EtOH, m.p. 275-280°C; yield 50%.- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.8-3.1 (m, 8H; H-piperazine), 3.2-3.4 (m, 4H; 2 CH_2), 5.3 (s, 2H; 2 OH), 6.6-7.2 (m, 5H; 3H-aromatic, CH=CH).

N-[2-(3,4-Dimethoxyphenyl)-ethyl]-N'-(3-chloropyridazinyl)-N,N'-dimethylethylenediamine (**17**)

A mixture of 0.9 g ($3.9 \cdot 10^{-3}$ mole) of **16** and 0.65 g ($4.4 \cdot 10^{-3}$ mole) of 3,6-dichloropyridazine (**3**) in 15 ml of isoamylic alcohol was refluxed for 12 h. The solvent was evaporated i.vac. The residue was diluted with water and alkalinized with N-NaOH and extracted with CH_2Cl_2. The org. phase was washed, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash-chromatography using CH_2Cl_2/EtOH (8/2), giving an oil; yield 40%.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.3 (s, 3H; N-CH_3), 2.5-2.8 (m, 6H; 3 CH_2), 3.0 (s, 3H; N-CH_3), 3.5 (t, 2H; J = 6 Hz, CH_2), 3.8 (s, 6H; 2 OCH_3), 6.5-6.7 (m, 4H; 3H-aromatic, H-pyridazine), 7.1 (d, 1H; J = 8.5 Hz, H-pyridazine).

Pharmacology

Materials and Methods

Male Wistar rats were employed (medium weight of 250-300 g). Experiments involved 55 male Wistar rats randomized into 11 experimental groups of 5 animals each. Prior to investigation, all animals were subjected to femoral artery cannulation, during ethyl ether anesthesia, employing a PE 50 catheter. The catheter was applied on the dorsal portion of the neck and was maintained previous by washing at the time of implant and measurement of arterial pressure with small amounts of heparin containing saline solution. Surgical preparation of the animals was performed one day prior to drug treatment; the animals were also kept fasting for 12 h and had free access to water. In all animal groups, drug administration was by oral route by employing a gastric probe. The first group served as a control and received distilled water at 10 ml/Kg. Second group was treated with the reference drug Prazosin at 10 mg/Kg. The remaining 9 groups were given the drugs under investigation at the dose of 10 mg/Kg in 10 ml/Kg volumes of distilled water. Direct measurement of mean arterial pressure was performed in conscious animals by means of a Statham transductor and a "S&W 8041" polygraph. In particular, for each animal of each experimental group, the first 10 min of MAP recording provided background values which were followed by drug administration. Subsequent MAP recording was performed for 120 min after treatment and represented the period of experimental observation.

Discussion

The hypotensive activities of all compounds were determined and compared with Prazosin (Table). The results show that only compound **7** shows a weak hypotensive activity lower than that of Prazosin. We believe that this compound does not stimulate DA_1 and DA_2 receptors because

Table: Values of mean arterial pressure (PAM) in mm Hg directly measurement for 120 minutes after the treatment

Compound	rats	dose mg/Kg	basal	10 m	20 m	30 m	40 m	50 m	60 m	80 m	100 m	120 m
H_2O Control	5	10 mg	108.40±2.50	105.20±2.76	105.80±3.72	104.20±2.71	107.40±2.09	105.40±2.54	106.60±2.29	103.00±3.24	102.20±2.92	103.80±2.18
Prazosin	5	10 mg	115.04±2.41	87.00±5.69	87.00±6.70	84.60±6.52	84.40±5.22	88.00±4.62	91.60±5.08	95.40±4.18	97.80±3.84	100.00±3.54
6	5	10 mg	105.80±4.63	104.00±3.63	102.20±2.71	105.40±2.46	108.40±3.17	103.20±2.58	106.40±3.52	107.40±5.35	106.20±3.98	103.20±3.40
8	5	10 mg	107.40±3.78	114.00±3.56	110.40±1.36	110.80±1.98	109.80±2.75	107.40±2.23	107.80±2.96	105.40±3.12	107.40±3.52	105.60±3.17
10	5	10 mg	104.93±1.66	101.33±0.88	104.33±2.03	102.00±0.58	98.33±1.45	103.00±2.65	98.00±2.65	99.00±1.73	97.00±2.65	96.67±2.33
7	5	10 mg	110.44±1.72	101.40±2.34	95.40±1.81	102.60±4.96	103.60±3.54	102.40±3.56	102.60±2.89	100.20±3.22	102.00±2.61	100.80±3.56
9	5	10 mg	108.88±2.48	105.80±1.20	103.40±1.83	102.20±2.40	101.80±3.38	99.80±1.50	99.20±1.93	99.40±2.36	100.80±3.79	96.20±3.20
11	5	10 mg	103.72±1.09	103.00±1.64	104.20±3.65	101.60±2.89	102.80±2.89	99.60±1.94	100.60±2.36	98.80±2.92	100.80±3.28	103.60±1.25
14	5	10 mg	106.08±2.17	103.40±2.96	104.40±3.33	103.60±4.11	102.60±3.08	100.60±2.42	103.40±3.14	99.00±2.02	99.00±1.14	98.00±2.92
15	5	10 mg	105.48±2.68	102.20±1.98	103.60±1.12	102.80±0.97	99.00±1.18	100.60±1.29	99.80±1.59	101.80±3.29	97.80±1.59	97.80±2.13
18	5	10 mg	104.40±1.74	103.00±2.07	104.20±2.58	104.00±1.90	105.40±2.73	104.00±2.77	102.60±2.96	100.20±3.15	98.40±1.60	101.00±5.22

PAM = mean arterial pressure

two OCH_3-groups are present. Therefore, the activity of compound **7** should be attributed to an inhibitory effect on receptor α_1 of the pyridazinone moiety. Compound **14** and **18** do not show an hypotensive effect, probably because they do not have an inhibitory effect on the α_1 receptor.

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