Eur J Med Chem (1994) 29, 899–902

Laboratory note

Synthesis and hypotensive activities of octahydropyrazino[1',2':1,2]pyrido[3,4-*b*]indoles and 15-azayohimbanes

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(Received 20 June 1994; accepted 5 August 1994)

Summary — The hypotensive activities in rats of indolic compounds **1–9** were compared with that of reserpine. In spite of differences in their structure, all 9 showed similar hypotensive activities to that of reserpine. New octahydropyrazinopyridoindoles **3–6** and the tetrahydro-β-carboline **7** were synthesized.

octahydropyrazino[1',2':1,2]pyrido[3,4-*b*]indole / 15-azayohimbane / tetrahydro-β-carboline / hypotensive activity

Introduction

We have recently reported the synthesis of several hexahydro- and octahydropyrazino[1',2':1,2]pyrido-[3,4-*b*]indoles (**1**, **2**) [1–3] and 15-azayohimbanes (**8** and **9**) [4], all containing the nuclei of tetrahydro-β-carboline and piperazine. These heterocyclic compounds are structural analogues of reserpine and, in addition to having an indole nucleus, they also contain the piperazine ring, like the antihypertensive agent atiprosine [5]. The purpose of this paper is to describe the hypotensive effects of the heterocycles indicated in figure 1. New heterocyclic derivates were thus synthesized (compounds **3–6**). These compounds are structurally related to the hexahydroaryl[*a*]quinolizidines (*eg*, WY-26703) [6, 7]. Moreover, the tetrahydro-β-carboline **7**, a secoderivative of the pyrazinopyridoindole, was also synthesized.

Chemistry

Reduction of pyrazinopyridoindoles **10** and **2** [1, 2] with $LiAlH_4$ led to diamines **4** and **3** in good yields (scheme 1). The *N*-alkylation of amine **3** with ethyl bromoacetate produced compound **5**. Sulphonamide **6** was obtained from the amine **3** with methanesulphonyl chloride.

Tetrahydro-β-carboline **7** was prepared by the Pictet–Spengler reaction between tryptamine and *N*-(2,2-diethoxyethyl)benzamide (**11**) in aqueous acetic acid. Intermediate **11** was obtained by Schotten–Baumann acylation of the amino acetaldehyde diethylacetal with benzoyl chloride (scheme 2).

Pharmacology

The results summarized in figure 2 demonstrate that all the compounds tested show similar hypotensive activity[1] to the reserpine model, reaching the highest hypotensor effect at a dose of around 1 μM/kg.

The ED_{25} values found for each of the products tested are shown in table I.

Discussion

Compounds **1–9** are structural analogues of reserpine. They all contain the indole nucleus, and they are differentiated from each other by the degree of basicity and/or in the distance from the basic center (N_b) of reserpine to the indole nucleus.

[1]The cestocide activity of the pyrazinopyridoindoles was also examined since these structures are analogues of the recognized anthelmintic agent praziquantel. Compounds **1**, **2**, **7** and **10** were administered to mice experimentally infected with *Hymenollepis nana*, in a single oral dose of 100 or 200 μg/g. The anthelmintic results show that the synthesized compounds were well tolerated, but were only weakly active or inactive.

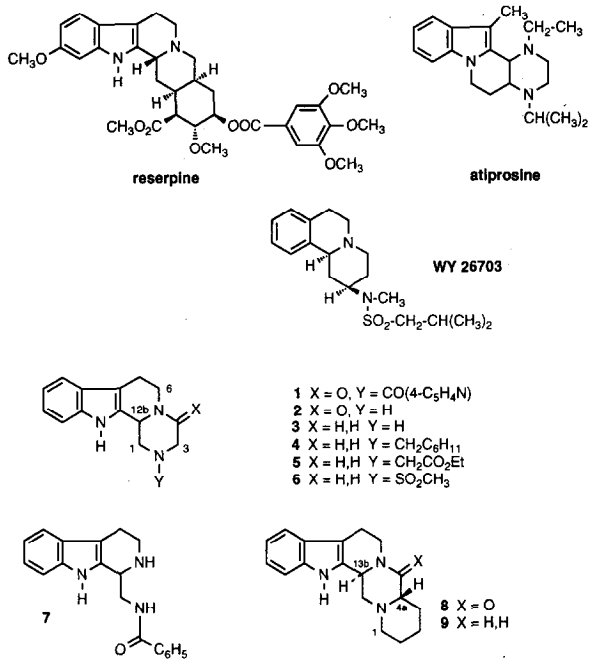
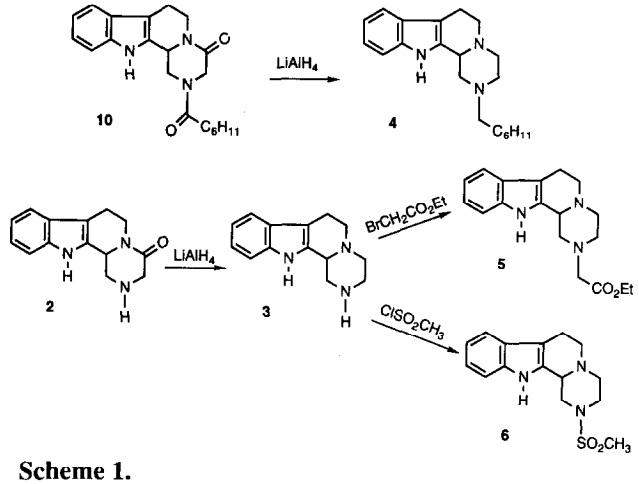
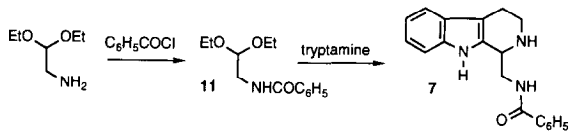


Fig 1. Structural analogues of reserpine.



Scheme 1.

Compound **1** is the least active, possibly because of the pyridine weakly basic nitrogen, which cannot be protonated at physiological pH. Compounds **3–5** and **9** contain 2 basic nitrogens: one in tetrahydro-β-carboline **7** is similar to that of reserpine; and the other is equivalent to the basic nitrogen of compound **8**. The presence of these 2 tertiary amines does not



Scheme 2.

lead to an increase in hypotensive activity, since compounds **8** have a comparable potential to that of compound **7**, which only possesses the basic nitrogen (N_b) of tetrahydro-β-carboline, like reserpine.

Compound **7**, a simplified analogue of reserpine, shows marked hypotensive activity, but this increases if the basic nitrogen is further from the aromatic ring, as in the rigid analogues **2** and **8**, which are the most active compounds of the series (see fig 2).

Experimental protocols

Chemistry

IR spectra (cm^{-1}) were recorded on a Perkin Elmer 1600 FTIR spectrometer. ^{1}H-NMR spectra were recorded on Varian XL-200 (200 MHz) or Perkin Elmer R-24 (60 MHz) instruments; chemical shifts in δ (ppm) are given relative to internal TMS; *J* values are reported in Hz. All ^{13}C-NMR spectra were determined on a Varian XL 200 (50.3 MHz). TLC was performed on SiO_2 (silica gel 60, F_{254}, Macherey–Nagel), and the spots were visualized with UV light or iodoplatinate reagent. Flash column chromatography (FC) was carried out on SiO_2 (silica gel 60, 0.040–0.063 mm, Macherey-Nagel). Melting points were determined in a capillary tube on a CTP-MP 300 hotplate apparatus. Analyses indicated by the elemental symbols were within ± 0.4% of the theoretical values and were performed on a Carlo Erba 1106 analyzer by the Departamento de Química Orgánica Biológica, CSIC, Barcelona, Spain.

*Synthesis of compounds **1**, **2**, **8** and **9***

The syntheses of the tetracyclic compounds **1** and **2** and the pentacyclic derivatives **8** and **9** have been described elsewhere [1, 2, 4]. Hydrochloride of **1**: mp 292–294°C (EtOH/Et_2O). Hydrochloride of **2**: mp 232–234°C (EtOH/Et_2O). Tartrate of **8**: mp 204°C (EtOH). Dihydrochloride of **9**: mp 320–323°C (EtOH/Et_2O).

*1,2,3,4,6,7,12,12b-Octahydropyrazino[1',2':1,2]pyrido[3,4-b]-indole **3***

$LiAlH_4$ (3.5 g, 92 mmol) was added to a suspension of **2** [1, 2] (1 g, 4 mmol) in anhydrous THF (250 ml) under N_2. The mixture was refluxed for 24 h. After cooling, H_2O and a saturated solution of sodium potassium tartrate (100 ml) were slowly added. The aqueous phase was separated and extracted with THF and CH_2Cl_2. Evaporation of the combined organic phases followed by column chromatography ($CHCl_3$/EtOH 1:1), gave **3** (830 mg, 87%) as a yellow solid, mp 125–130°C (lit [8], 126–128°C), IR (KBr): 3300, 3200 (NH), 2800, 2740 (CH Bohlmann's bands). ^{1}H-NMR ($CDCl_3$): 2.2–3.1 (m, 10H); 3.35 (dd, *J* = 12.0 and 2,8, 1H, H-12b); 3.39 (s, 1H, NH); 7.0–7.5 (m, 4H, indole); 8.1 (s, 1H, NH indole). ^{13}C-NMR (DMSO-d_6): 21.3 (C-7); 45.4 (C-3); 48.6 (C-1); 52.5 (C-6);

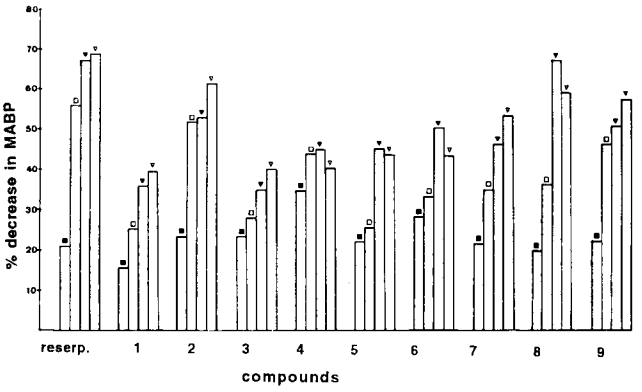


Fig 2. Hypotensive activity of compounds **1–9** at different doses, and the standard reserpine, expressed as the percentage reduction of arterial blood pressure (MABP). Doses ■: 0.01 μM/kg; □ : 0.1 μM/kg; ▼ : 1 μM/kg; ▽ : 10 μM/kg.

Table I. ED_{25} (μM/kg) values obtained for the compounds synthesized.

Compound·HCl	*ED_{25} (μM/kg)*[a,b]
1	$1 \pm 0.2 \times 10^{-1}$
2	$1.2 \pm 0.5 \times 10^{-2}$
3	$2.7 \pm 0.4 \times 10^{-2}$
4	$1.5 \pm 0.5 \times 10^{-3}$
5	$7.9 \pm 0.6 \times 10^{-2}$
6	$5.7 \pm 0.7 \times 10^{-2}$
7	$1.9 \pm 0.3 \times 10^{-2}$
8[c]	$2.2 \pm 0.4 \times 10^{-2}$
9	$1.2 \pm 0.3 \times 10^{-2}$
Reserpine	$1.3 \pm 0.5 \times 10^{-2}$

[a]ED_{25} is the dose that produced 25% of the hypotensive effect, as determined from the 4 doses of different compounds shown in figure 2 using the least-squares regression formulae. [b]Significantly different from control reserpine according to paired one-tailed Student's *t*-test, in all cases $p < 0.0005$. [c]Compound **8** is a tartrate.

54.8 (C-4); 60. 1 (C-12b); 106.7 (C-7a); 110.9 (C-11); 117.3 (C-8); 118.2 (C-9); 120.3 (C-10); 127.4 (C-7b); 133.6 (C-12a); 135.9 (C-11a). Dihydrochloride of **3**: mp 302–304°C dec (MeOH). Anal $C_{14}H_{19}N_3Cl_2 \cdot H_2O$ (C, H, N).

*2-Cyclohexylmethyl-1,2,3,4,6,7,12,12b-octahydropyrazino-[1',2':1,2]pyrido[3,4-b]indole **4***

In the same way as above, amidolactam **10** [1, 2] afforded diamine **4** in 76% yield, mp 123–127°C. IR (KBr): 3380 (NH), 2820, 2780, 2760 (Bohlmann's bands). ^{1}H-NMR (200 MHz, DMSO-d_6): 0.8–1.9 (m, 11H); 2.1–3.2 (m, 12H); 3.51 (dd, J = 11.4 and 2.3, 1H, H-12b); 7.0–7.5 (m, 4H, indole); 7.80 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): 21.6 (C-7); 26,1 (C-3') and (C-5'); 26.8 (C-4'); 32.0 (C-2') and (C-6'); 35.0 (C-1'); 52.2 (N CH_2 cyclohexyl); 53.4 (C-6); 54.1 (C-4); 56.9 (C-3); 58.8 (C-12b); 65.7 (C-1); 108.8 (C-7a); 110.8 (C-11); 118.1 (C-8); 119.4 (C-9); 121.4 (C-10); 127.4 (C-7b); 132.8 (C-12a); 136.0 (C-11a). Dihydrochloride of **4**: mp 292–295°C (EtOH/Et_2O). Anal $C_{21}H_{26}N_3O_2Cl$ (C, H, N).

*2-Ethoxycarbonylmethyl-1,2,3,4,6,7,12,12b-octahydropyrazino[1',2': 1,2]pyrido[3,4-b]indole **5***

Ethyl bromoacetate (0.2 ml, 0.3 g, 2 mmol) and Et_3N (0.34 ml, 0.5 g, 5 mmol) was added to a solution of **3** (450 mg, 2 mmol) in EtOH. The mixture was stirred at room temperature for 16 h and then evaporated, and the resulting solid residue was subjected to FC (Et_2O/MeOH 19:1): **5** (37 mg, 60%). IR (KBr): 3310 (NH), 2810 and 2740 (Bohlmann's bands), 1730 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.29 (t, J = 7.5, 3H, CH_3); 2.3–3.2 (m, 10H); 3.25 and 3.35 (2d, J_{ab} = 17.5, 2H, NCH_2CO); 3.61 (br d, J = 10, 1H, H-12b); 4.21 (q, J = 7.5, 2H, CH_2OCO); 7.0–7.5 (m, 4H, indole); 8.2 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): 14.2 (CH_3); 21.3 (C-7); 51.9 (CH_2CO); 53.0 (C-6); 51.3 (C-4); 55.8 (C-3); 58.3 (C-12b); 52.2 (C-1); 60.8 (CH_2O); 108.6 (C-7a); 111.0 (C-11); 118.1 (C-8); 119.3 (C-9); 121.4 (C-10); 127.3 (C-7b); 132.4 (C-12a); 136.2 (C-11a); 170.5 (CO). Dihydrochloride of **5**: mp 212–215°C (EtOH/Et_2O). Anal $C_{18}H_{25}N_3O_2Cl_2 \cdot 1/2\ H_2O$ (C, H, N).

*2-Methylsulphonyl-1,2,3,4,6,7,12,12b-octahydropyrazino-[1',2':1,2]pyrido[3,4-b]indole **6***

A solution of methanesulphonyl chloride (3.5 g, 30 mmol) in CH_2Cl_2 (47 ml) was added slowly to a solution of **3** (450 mg, 2.2 mmol) and Et_3N (3 g, 30 mmol) in CH_2Cl_2 (7 ml). The mixture was stirred at rt for 17 h. The organic phase was separated and washed with brine, dried and evaporated to give the *N*-sulphonylate **6** (400 mg, 58%), mp 232–233°C (EtOH). IR (KBr): 3360 (NH), 2815, 2780, 2740 (Bohlmann's bands), 1320, 1150 (SO_2). ^{1}H-NMR (200 MHz, DMSO-d_6): 2.5–3.1 (m, 8H, H-1ax, H-3ax-, H-4, H-6, H-7; 2.89 (s, 3H, CH_3); 3.50 (br t, 2H, H-1eq, H-3eq); 4.22 (br d, J = 10.7, H-12b); 6.9–7.4 (m, 4H, indole). ^{13}C-NMR (DMSO-d_6): 21.4 (C-7); 33.9 (CH_3); 45.5 (C-3); 48.3 (C-1); 51.4 (C-6); 52.9 (C-4); 58.1 (C-12b); 107.6 (C-7a); 111.1 (C-11); 117.7 (C-8); 118.5 (C-9); 120.8 (C-10); 126.5 (C-7b); 131.8 (C-12a); 136.1 (C-11a). Hydrochloride of **6**: mp 227–228°C (EtOH/Et_2O). Anal $C_{15}H_{20}N_3O_2SCl \cdot 3/2H_2O$ (C, H, N).

*N-(2,2-Diethoxyethyl)benzamide **11***

Benzoyl chloride (0.87 ml, 1 g, 7.5 mmol) was added to stirred solution of aminoacetaldehyde diethyl acetal (1 g, 7.5 mmol) in $CHCl_3$ (20 ml) and 1 N aqueous K_2CO_3 solution (20 ml). Stirring was continued at rt for 16 h. The phases were then separated. The aqueous phase was extracted with $CHCl_3$ (3 x 40 ml) and the combined organic phases were dried, filtered and evaporated. The resulting oily residue gave **11** (1.7 g, 98%). IR (film): 3310 (NH), 1640 (CO). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.2 (t, J = 7, 6H, CH_3); 3.2–3.8 (m, 4H, CH_2O); 3.52 (d, J = 6, 2H, CH_2NCO); 4.5 (t, J = 6, 1H, CH); 6.8 (br s, CONH); 7.0–7.8 (m, 5H, Ph).

*1-(Benzoylaminomethyl)tetrahydro-β-carboline **7***

A mixture of **11** (3.2 g, 13.6 mmol) and tryptamine (2.9 g, 18.2 mmol) in AcOH (46 ml) and H_2O (20 ml) was refluxed for 2 h under N_2. After evaporation, the crude product was treated with EtOH/H_2O. The precipitate was filtered and gave **7** (3.3 g,

80%), mp 189–195°C (MeOH). IR (KBr): 3280 (NH), 1630 (CO). ^{1}H-NMR (200 MHz, DMSO-d_6): 2.70 (br s, 1H, NH); 2.9–3.1 (m, 2H, NCH_2CH_2-In), 3.3–3.6 (m, 2H, NCH_2CH_2-In); 3.8–4.0 (m, 1H, NCH_AH$_B$); 4.2–4.4 (m, 1H, NCH$_A$CH_B); 7.2–8.1 (m, 10H, Ar-H and NH); 10.0 (s, NH, indole). ^{13}C-NMR (DMSO-d_6): 22.1 (C-4); 40.1 (CH_2); 43.2 (C-3); 51.7 (C-1); 108.1 (C-9a); 111.1 (C-8); 117.5 (C-5); 118.3 (C-6); 120.6 (C-7); 126.9 (C-4b); 127.3 (C-3' and C-5'); 128.2 (C-2'); 131.1 (C-4'); 134.3 (C-4a); 134.6 (C-1'); 135.9 (C-8a); 166.7 (CO). Hydrochloride of **7**: mp 232–233°C (EtOH). Anal $C_{19}H_{20}N_3OCl \cdot 1/2H_2O$ (C, H, N).

Pharmacology. Hypotensive activity

Hypotensive activity was determined by direct blood-pressure measurement on normotensive Sprague–Dawley male rats weighing between 250 and 300 g. They were anaesthetized with an aqueous solution of urethane (500 mg/kg ip). The trachea was cannulated in all rats, and 2 polyethylene catheters were inserted through the right femoral vein. The animals were heparinized (2.5 mg/kg iv) and the right common carotid artery was then catheterized and connected *via* a pressure transducer (Model FTT 1280 C) to a polygraph Hewlett Packard (Model 7702 B) for continuous monitoring of arterial pressure. Each rat was left undisturbed for at least 20 min after completion of the surgical procedures to permit cardiovascular parameters to stabilize.

After an additional 10 min period, during which control readings were recorded, 7 rats received an iv injection of compounds (in 0.2 ml isotonic solution) at the doses indicated. Injections of different doses of compound were separated by 30 min intervals in all cases. Under these conditions, the hypotensive effect is indicated by a reduction in the initial mean arterial blood pressure (MABP); the changes were evaluated for statistical significance by using the paired one-tailed Student's *t*-test.

Acknowledgments

This work was supported by the CIRIT (Catalonia) through Grant AR 87/191 and the FIS (Spain) through Grant 87/1252. We thank Laboratorio Farmacologia, Facultad Medicina (UB), for the use of their facilities.

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