Kurzmitteilungen:

Enantiomerically Pure Aminoindolizines: Bicyclic Ergoline Analogues with Dopamine Autoreceptor Activity

Enantiomerenreine Aminoindolizine: Bizyklische Ergolin-Analoge mit Aktivität am Dopamin-Autorezeptor

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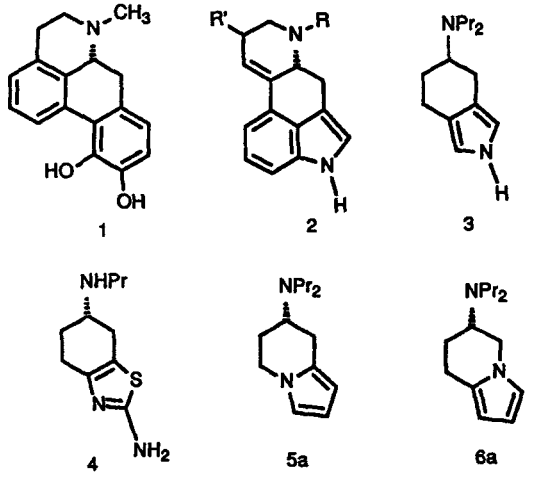
The development of drugs which stimulate selectively the prejunctional dopamine receptor has become a major challenge in recent years[1,2]. These autoreceptor agonists decrease synthesis and release of dopamine (DA). Thus, the symptoms of schizophrenia originated from dopamine hyperactivity in the mesolimbic system should be reduced. On the other hand, it has been shown that DA autoreceptor agonists fail to reveal classical DA antagonist side effects like catalepsy, when given to animals[3].

Since the highly sensitive DA autoreceptor is assumed to resemble the postsynaptic D-2 receptor[4,5], we planned to develop novel autoreceptor agonists by specific structural modifications of known D-2 agonists. One major characteristic of these compounds is an X-H moiety (X = O, N) connected to an aromatic ring, which can mimic a catechol hydroxyl group of the genuine transmitter dopamine[4,5]. Typical examples are (*R*)-apomorphine (**1**) and compounds with ergoline (**2**) or ergoline partial structure (**3**)[6,7]. An aromatic X-H substructure is also included in previous representatives of DA autoreceptor agonists (*e.g.* SND 919 (**4**)[8,9])[10]. In some cases, these groups cause a reduced bioavailability, due to a metabolic degradation or an inability to pass through the blood-brain barrier[5].



Pr: n-C_3H_7

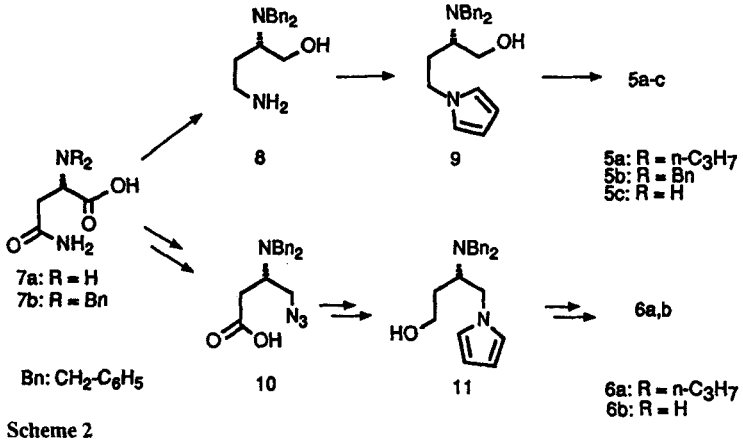
Scheme 1

In this paper we report on the aminoindolizine regioisomers **5a** and **6a**, as bioisosters of DA active bicyclic ergoline analogues. One of them (**5a**) turned out to be the first strong and selective DA autoreceptor agonist, which is devoid of an aromatic NH or OH moiety.

Since DA receptor - ligand interactions are known to proceed stereoselectively[4,5,9] pure enantiomers should be investigated.

The synthesis of both regioisomeric aminotetrahydroindolizines (**5a** and **6a**) was performed starting from L-asparagine, which was used likewise as an α-amino acid for the synthesis of the 7-aminoindolizine **5a**, or as a β-amino acid equivalent when the 6-amino regioisomer **6a** was approached.

For the synthesis of **5a-c** *N,N*-dibenzylasparagine **7b**, readily available from natural L-asparagine (**7a**), was first reduced with borane/THF to afford the diaminobutanol derivative **8**. Then the pyrrole unit was introduced by a modified *Paal-Knorr* procedure to give the cyclization precursor **9**. Subsequent trifluoromethanesulfonic anhydride assisted ring closure yielded **5b**, which could be deprotected by catalytic

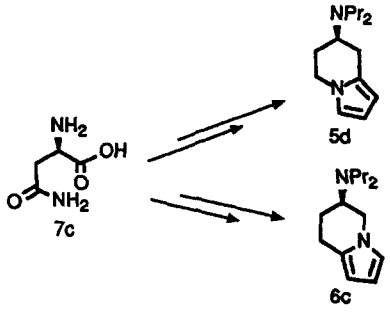


Scheme 2

  0365-6233/92/0101-0057 $ 3.50 + .25/0

hydrogenation (H_2, $Pd(OH)_2$) to afford the primary amine **5c**[11]. The synthesis was accomplished by conversion of **5c** into the dipropylamine **5a** using an excess of propionic aldehyde and $NaCNBH_3$. Following the same reaction conditions the 6-dipropylaminoindolizine **6a** was prepared from the primary amine **6b**. **6b** was synthesized by application of our β-amino acid methodology[12,13] *via* the azide **10** and the 1,3 diamino alcohol **11** as the key intermediates[14].

Analogously, we obtained the (*R*)-configurated enantiomers **5d** and **6c** from D-asparagine (**7c**).



Scheme 3

The aminotetrahydroindolizine derivatives **5a-d** and **6a,c** were chosen for receptor binding studies, when their ability to displace [^{3}H]-SCH 23390, [^{3}H]-spiroperidol and [^{3}H]-SND 919 as specific radioligands labeling D-1, D-2, and DA-autoreceptor binding sites was investigated (Table 1). All compounds tested failed to reveal remarkable affinity to the postsynaptic D-1 and D-2 sites. However, evaluation of their autoreceptor binding showed modest to strong and highly selective affinity. The most potent derivative turned out to be **5a** (IC_{50} = 30 nmol) showing a 240 and 500-fold preference, compared to the D-1 and D-2 binding sites. The autoreceptor - ligand complexes are formed stereoselectively, indicated by a 24-fold higher IC_{50} value of **5d**. Discrimination between the enantiomers was also observed for the less active 6-amino derivatives **6a** and **6c** when, in contrast to **5a/5d**, the eutomer (**6c**) has reversed configuration. These data indicate that the position of the pyrrole nitrogen, and so the contribution of the electron density at the aromatic region, is important for the receptor binding.

As expected, the IC_{50} values show that the dipropylamine is a valuable structural unit[15].

Table 1: Receptor Binding Data

	IC_{50} [nM]		
compd	D-1[a]	D-2[b]	DA-autoreceptor[c]
5a	7.100	15.000	30
5b	>100.000	>100.000	34.000
5c	33.000	>100.000	2.200
5d	33.000	22.000	730
6a	>100.000	>100.000	6.900
6c	>100.000	72.000	350

[a] 3H-ligand: SCH 23390; [b] 3H-ligand: spiroperidol; [c] 3H-ligand: SND 919.

To evaluate whether the autoreceptor affinity of **5a** is connected with an intrinsic activity, the ability of **5a** to inhibit γ-butyrolactone (GBL) induced acceleration of DA synthesis in rat corpus striatum was examined. In fact, a 62% lower L-DOPA level was measured after injecting 10 mg/kg of **5a**. This indicates DA autoreceptor agonistic effects.

Treatment of mice with **5a** did not produce catalepsy (a typical extrapyramidal side effect of postsynaptic DA antagonists) nor stereotyped behavior (due to postsynaptic striatal DA receptor stimulation), up to 100 mg/kg. At 10 mg/kg reduced locomotor activity was observed. After injection of doses > 40 mg/kg of **5a** excitation was shown when the mice were stimulated acoustically. Our CNS screening with mice[16] indicated that the primary amine **5c** is also strongly CNS active, unless the affinity to the DA receptors was fairly low. The compound exhibited a strong sedative effect (extremely reduced locomotor activity, depressed pinna reflex) at doses between 5 and 50 mg/kg.. Additionally, *Straub* tail and mydriasis were observed. It is worthy to note, that **5c** gave an ED_{50} value of 1.8 mg/kg (1.0 - 3.3 mg/kg, p. > 0.05) in the writhing test[16], indicating that **5c** might have central analgesic properties.

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Experimental Part

General Remarks see ref. 13.

(S)-4-Amino-2-N,N-dibenzylaminobutanol(**8**)

To a solution of **7b**[13] (15.6 g, 50 mmol) in THF (400 ml) was added BH_3 x THF (300 ml of a 1 molar solution of THF) at 0°C. After 1 h at 0°C the mixture was refluxed for 4 h. Then the mixture was acidified to pH 1 with 6 N aqueous HCl and subsequently adjusted to pH 12 with 2 N aqueous NaOH. After addition of Et_2O the org. layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography ($CHCl_3$-MeOH-Et_3N 85:10:7) to give 12.2 g (86%) of pure **8** as a colorless oil; $[\alpha]_D^{23}$ + 32.5° (c = 1.0, $CHCl_3$).- $C_{18}H_{24}N_2O$ (284.4) Calcd. C 76.0 H 8.51 N 9.85 Found C 75.7 H 8.91 N 10.01.- IR (NaCl): 3280; 3240; 3030; 2930; 1600 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.41-1.50 (m, 1H, H-3), 1.89-1.97 (m, 1H, H-3), 2.62-2.82 (m, 3H, H-1 and H-4), 3.50 (d, J = 13.3 Hz, 2H, NCH_2Ph), 3.51 (dd, J = 10.5, 6.0 Hz, 1H, H-1), 3.61 (dd, J = 10.5, 8.0 Hz, 1H, H-1), 3.74 (d, J = 13.3 Hz, 2H, NCH_2Ph), 7.20-7.32 (m, 10 H, Ar).

(R)-**8**($[\alpha]_D^{23}$ - 33° (c = 1.0, $CHCl_3$) was prepared from (R)-**7b**[13] following the same procedure.

(S)-2-N,N-Dibenzylamino-4-N-pyrrolylbutanol(**9**)

To a mixture of **8** (12.8 g, 45 mmol) and NaOAc x 3 H_2O (122 g, 900 mmol) in acetic acid (650 ml) was added dimethoxytetrahydrofuran (6.6 g, 50 mmol) at room temp.. Then the temp. was slowly raised to 70°C and stirring was continued for 75 min. After the mixture was concentrated it was basified with 2 N aqueous NaOH and extracted with Et_2O. The org. layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether - EtOAc 4:1) to give 11.3 g (75%) of pure **9** as a colorless oil; $[\alpha]_D^{23}$ + 67° (c = 1.0, $CHCl_3$).- $C_{22}H_{26}N_2O$ (334.5) Calcd. C 79.0 H 7.84 N 8.38 Found C 79.4 H 7.74 N 8.07.- IR (NaCl): 3600-3200; 3030; 2930; 1600 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.63-1.69 (m, 1H, H-3), 2.14-2.22 (m, 1H, H-3), 2.76-2.84 (m, 1H, H-2), 3.39 (d, J = 13.2 Hz, 2H, NCH_2Ph), 3.42 (dd, J = 10.8, 5.2 Hz, 1H, H-1),

3.46 (dd, J = 10.8, 10.5 Hz, 1H, H-1), 3.67 (d, J = 13.2 Hz, 2H, NCH_2Ph), 3.80-3.93 (m, 2H, H-4), 6.15-6.16 (m, 2H, NCHCH), 6.58-6.59 (m, 2H, NCH), 7.17-7.32 (m, 10 H, Ar).

(R)-**9** ($[\alpha]_D^{23}$ - 68° (c = 1.0, $CHCl_3$) was prepared from (R)-**8** following the same procedure.

(S)-7-N,N-Dibenzylamino-5,6,7,8-tetrahydroindolizine(**5b**)

To a mixture of **9** (10 g, 30 mmol) in CH_2Cl_2 (400 ml) was added trifluoromethanesulfonic anhydride (17.4 g, 61.7 mmol) at 0°C. After stirring for 16 h at room temp. saturated aqueous $NaHCO_3$ and Et_2O were added. The org. layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether - Et_2O 95:5) to give 8.9 g (94%) of pure **5b** as a colorless solid; mp. 95-97°C; $[\alpha]_D^{23}$ - 50° (c = 1.0, $CHCl_3$).- $C_{22}H_{24}N$ (316.4) Calcd. C 83.5 H 7.65 N 8.86 Found C 83.3 H 7.61 N 8.87.- IR (NaCl): 3030; 2960; 1600 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.00 (ddd, J = 12.5, 12.5, 5.4 Hz, 1H, H-6), 2.13-2.18 (m, 1H, H-6), 2.85 (dd, J = 15.5, 11.8 Hz, 1H, H-8), 3.00-3.12 (m, 2H, H-7 and H-8), 3.66 (d, J = 14.0 Hz, 2H, NCH_2Ph), 3.73 (d, J = 14.0 Hz, 2H, NCH_2Ph), 3.77 (ddd, J = 12.5, 12.5, 4.4 Hz, 1H, H-5), 4.10 (ddd, J = 12.5, 5.4, 2.2 Hz, 1H, H-5), 5.82-5.83 (m, 1H, H-1), 6.08-6.09 (m, 1H, H-2), 6.45-6.46 (m, 1H, H-3), 7.20 (t, J = 7.3 Hz, 2H, *p*-Ar), 7.28 (t, J = 7.3 Hz, 4H, *m*-Ar), 7.37 (d, J = 7.3 Hz, 4H, *o*-Ar).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 25.50 (H_2C-8), 26.08 (H_2C-6), 45.17 (H_2C-5), 53.51 (HC-7), 53.89 (NCH_2Ph), 104.66 (HC-1), 108.24 (HC-2), 118.30 (HC-3), 126.88 (HC-Ar), 128.27 (HC-Ar), 128.58 (HC-Ar), 128.85 (C-8a); 140.14 (C-Ar).

(R)-**5b** ($[\alpha]_D^{23}$ + 51° (c = 1.0, $CHCl_3$) was prepared from (R)-**9** following the same procedure.

(S)-7-Amino-5,6,7,8-tetrahydroindolizine(**5c**)

A mixture of **5b** (0.95 g, 3 mmol) and 20% $Pd(OH)_2/C$ (0.70 g) in EtOAc (35 ml) and MeOH (35 ml) was stirred under a balloon of H_2 for 5 h at room temp.. The mixture was filtered through celite, the filtrate was evaporated carefully and the residue was purified by flash chromatography (CH_2Cl_2-MeOH 4:1) to give 0.35 g (85%) of pure **5c** as a colorless solid; mp. 150°C (dec.); $[\alpha]_D^{23}$ - 64° (c = 0.5, MeOH).- $C_8H_{12}N_2$ (136.2) Calcd. C 70.7 H 8.88 N 20.57 Found C 70.5 H 9.12 N 20.36.- IR (NaCl): 3400-2800; 2930 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.83-1.92 (m, 1H, H-6), 2.10-2.17 (m, 1H, H-6), 2.56 (dd, J = 15.7, 8.8 Hz, 1H, H-8), 3.08 (dd, J = 15.7, 4.4 Hz, 1H, H-8), 3.28-3.31 (m, 1H, H-7), 3.89-3.97 (m, 1H, H-5), 4.05-4.11 (m, 1H, H-5), 5.85-5.86 (m, 1H, H-1), 6.12-6.14 (m, 1H, H-2), 6.53-6.54 (m, 1H, H-3).

(R)-**5c** ($[\alpha]_D^{23}$ + 64.5° (c = 0.5, MeOH) was prepared from (R)-**5b** following the same procedure.

(S)-7-N,N-Dipropylamino-5,6,7,8-tetrahydroindolizine(**5a**)

To a solution of **5c** (136 mg, 1 mmol) in MeOH (15ml) was added propionic aldehyde (581 mg, 10 mmol) and then $NaCNBH_3$ (126 mg, 2 mmol) at 0°C. After the mixture was stirred for 20 h at room temp. it was acidified to pH 1 with 2 N aqueous HCl and subsequently basified with saturated aqueous $NaHCO_3$. After addition of Et_2O the org. layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2 - MeOH 97:3) to give 158 mg (72%) of pure **5a** as a colorless oil; $[\alpha]_D^{23}$ - 35° (c = 0.5, $CHCl_3$).- $C_{14}H_{24}N_2$ (220.4) Calcd. C 76.3 H 10.98 N 12.71 Found C 76.5 H 10.97 N 12.52.- IR (NaCl): 2960 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.88 (t, J = 7.3 Hz, 6H, $NCH_2CH_2CH_3$), 1.47 (sext., J = 7.3 Hz, 4H, NCH_2CH_2), 1.79-1.95 (m, 1H, H-6), 2.05-2.10 (m, 1H, H-6), 2.45-2.50 (m, 4H, NCH_2), 2.65 (dd, J = 15.4, 11.0 Hz, 1H, H-8), 2.94-3.07 (m, 2H, H-7 and H-8), 3.88 (ddd, J = 11.7, 11.7, 4.4 Hz, 1H, H-5), 4.11 (ddd, J = 11.7, 5.2, 2.0 Hz, 1H, H-5), 5.82-5.83 (m, 1H, H-1), 6.11-6.13 (m, 1H, H-2), 6.49-6.50 (m, 1H, H-3).

5d ($[\alpha]_D^{23}$ + 34.5° (c = 0.4, $CHCl_3$) was prepared from (R)-**5c** following the same procedure.

(S)-6-N,N-Dipropylamino-5,6,7,8-tetrahydroindolizine(**6a**)

6b[14] (136 mg, 1 mmol) in MeOH (15 ml) as well as propionic aldehyde (581 mg, 10 mmol) and $NaCNBH_3$ (126 mg, 2 mmol) were reacted and worked up as described above for **5a** to give 150 mg (68%) of pure **6a** as a colorless oil; $[\alpha]_D^{23}$ - 32° (c = 0.9, $CHCl_3$).- $C_{14}H_{24}N_2$ (220.4) Calcd. C 76.3 H 10.98 N 12.71 Found C 76.7 H 11.02 N 12.50.- IR (NaCl): 2960 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.88 (t, J = 7.3 Hz, 6H, $NCH_2CH_2CH_3$), 1.43-1.46 (m, 4H, NCH_2CH_2), 1.60-1.69 (m, 1H, H-7), 2.00-2.05 (m, 1H, H-7), 2.44-2.49 (m, 4H, NCH_2), 2.66 (ddd, J = 16.1, 16.1, 5.0 Hz, 1H, H-8), 2.95 (ddd, J = 16.1, 5.2, 3.0 Hz, 1H, H-8), 3.09-3.16 (m, 1H, H-6), 3.72 (dd, J = 11.5, 11.5 Hz, 1H, H-5), 4.23 (dd, J = 11.5, 5.9 Hz, 1H, H-5), 5.80-5.81 (m, 1H, H-1), 6.12-6.13 (m, 1H, H-2), 6.49-6.50 (m, 1H, H-3).

6c ($[\alpha]_D^{23}$ + 31.5° (c = 0.9, $CHCl_3$) was prepared from (R)-**6b**[14] following the same procedure.

Receptor Binding Assay

DA receptor binding was performed as described[17,18] using [^{3}H]-SCH 23390 and [^{3}H]-spiroperidol as radioligands in concentrations of 0.3 nM and 0.5 nM, respectively. In the receptor binding assay for the characterization of the DA autoreceptor, [^{3}H]-SND 919 (51 Ci/mmol specific activity) was used in a concentration of 0.5 nM. The experimental procedure was performed in analogy to the binding assay with [^{3}H]-spiroperidol as radioligand. For all receptor binding tests rat brain striatum was used.

Determination of DA Synthesis Rate

For the determination of the DA synthesis rate the inhibition of the GBL-induced L-DOPA accumulation was measured as described[19,20].

In vivo Screening with Mice

The behavioural activity screening with mice was carried out according to ref. 16.

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