# Synthesis and Dopamine Receptor Binding Studies of Homochiral 8-Aminopyrido[1,2-*a*]indoles

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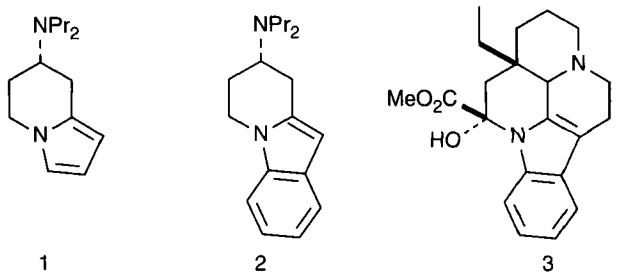
## Summary

Starting from L-aspartic acid the preparation of 8-aminopyrido[1,2-*a*]indole derivatives as benzo-fused analogs of the dopamine autoreceptor agonist **1** is reported. The key step of the synthesis is the $Tf_2O$ induced cyclization of the 1,2-amino alcohol **6**. Receptor binding studies indicated selective affinity for the D-2 autoreceptor. Among the tested compounds, the dipropylamino derivative **2** showed the highest affinity for the D-2 receptor labelled with the selective autoreceptor agonist pramipexole ($IC_{50}$ value: 450 nM). Thus, **2** is 15 times less potent than the aminoindolizine **1**.




1 2 3

**Scheme 1**

## Introduction

A landmark in dopamine receptor research was the demonstration that the dopamine receptors exist in two receptor subfamilies[1,2]. These are the D-1 receptors which activate the enzyme adenylyl cyclase and increase intracellular levels of cAMP and the D-2 receptors which show an inhibitory effect on this enzyme. D-2 receptors are also supposed to be linked to additional second messenger systems including inhibition of phosphatidylinositol turnover and modulation of $K^+$ and $Ca^{2+}$ channels[3]. Furthermore, D-2 receptors exist not only postsynaptically but also as supersensitive autoreceptors when they exert an inhibitory effect on dopamine synthesis by influencing tyrosine hydroxylase activity.[4] Phosphorylation of $Ca^{2+}$/calmodulin sensitive protein kinase 2 leading to coupling of dopamine vesicles to the sites of exocytosis and thus dopamine release is also controlled by dopamine autoreceptors[5]. Selective dopamine autoreceptor agonists are of particular interest as atypical neuroleptics exerting antipsychotic effects without causing adverse motor side effects[6]. We have previously reported that the *(S)*-configured aminoindolizine **1** [7] is able to reduce dopamine synthesis, induces reduction of locomotor activity in mice, and shows potent and selective affinity to the D-2 receptor, when labelled with pramipexole, a compound which in functional *in vivo* experiments turned out to be a selective dopamine autoreceptor agonist.[8,9] As a part of our structure activity studies on the dopamine autoreceptor [10-13] we herein report EPC synthesis and receptor binding and of the tricyclic heterocycle **2** as a benzo fused analog of **1** (Scheme 1). Thus, it should be investigated whether a π-system which is expanded to the "south side" of the molecules (when drawn as in Scheme 1) leads to an increased binding to the D-2 autoreceptor.

## Synthesis

Although the 6,7,8,9-tetrahydro-pyrido[1,2-*a*]indole moiety is a substructure of a number of natural products including vincamine (**3**)[14], there are only two reports of synthetic studies on 8-amino derivatives in the literature. These communications on the synthesis of some racemic derivatives, required as intermediates for inhibitors of protein kinase C, described a Dieckmann ring closure approach [15,16].

We envisioned construction of the tricyclic ring system by employing the 1,2-amino alcohol **6** (Scheme 2) as a cyclization precursor when the terminal HO-group should be activated for ring closure by trifluoromethanesulfonic anhydride ($Tf_2O$). According to the methodology we recently reported, the *N,N*-dibenzyl protected amino alcohol **6** was synthesized from L-aspartic acid by regioselective functionalization of the enantiomerically pure building block **4** through the intermediate **5**[17,18]. Subsequent treatment of **6** with $Tf_2O$ led to the corresponding sulfonate which entered into an intramolecular electrophilic attack on the indole 2 position, resulting in **7a** (86 % yield). Both reaction steps were carried out in a one-pot procedure. It is worthy of note that the cyclization works only in presence of triethylamine as a proton scavenger whereas indolizine formation of the respective pyrrole analogs gives a good yield only in the absence of $Et_3N$[19]. For the completion of the synthesis, **7a** was debenzylated by catalytic hydrogenolysis. Subsequent reductive alkylation by propionaldehyde and $NaBH_3CN$ afforded the target compound **2** and the hexahydropyrido[1,2-*a*]indole **8** as a side product. The relative configuration of **8** was established by NMR spectroscopy, including $^1H^1H$ COSY and $^1H^{13}C$ COSY experiments as well as analysis of the coupling con-

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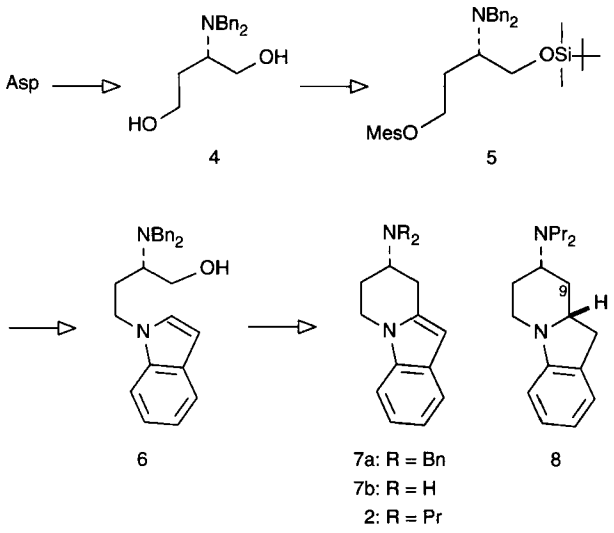
stants of the $^1H$ NMR spectrum. The most diagnostic signal was observed for the axial proton in position 9 (1.50 ppm, ddd, $J$ = 12.4, 12.4, 12.4 Hz) indicating an antiperiplanar arrangement of 9-$H_{ax}$ with respect to 9a-H and 8-H.




**Scheme 2**

## Receptor Binding Studies

We evaluated the abilities of the test compounds **2, 7b** and **8** to displace the radioactively labelled ligands [$^3$H]-SCH 23390 [20] and [$^3$H]-spiperone [21] from D-1 and D-2 binding sites as well as [$^3$H]-pramipexole, a compound which proved to be a selective D-2 autoreceptor agonist[9]. Table 1 shows that **2, 7b** and **8** failed to shown significant affinity for the D-1 receptor and for the D-2 sites labelled by the antagonist [$^3$H]-spiperone. However, the dipropylamines **2** and **8** were able to displace [$^3$H]-pramipexole resulting in $IC_{50}$ values of 450 nM and 1410 nM, respectively. Compared to the D-2 agonists (–)-PPP [22] and **1**, the test compounds are clearly less potent.

## Conclusions

The results indicate that the enlargement of the aromatic π-system of **1** by replacement of the pyrrole fragment by indole in the described manner does not increase the binding affinity to the dopamine D-2 autoreceptor. This is convincingly demonstated by the expansion of the π-system to the "south side" which can be visualized by comparison of the three-dimensional molecular electrostatic potential (MEP) maps of the aromatic core structures (the respective computation has been performed based on *ab initio* calculations at the RHF level of theory when the 6-31G* basis set was employed). Obviously, the benzo-fused ring system of **2, 7b** and **8** gives repulsive interactions with the binding site.

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## Experimental Section

*General.* $CH_2Cl_2$ was distilled from $CaH_2$, immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted reactions were conducted under dry $N_2$. Evaporations of final product solutions were done under vacuum with a rotatory evaporator. Flash chromatography was carried out with 230–400 mesh silica gel.– Melting points: Büchi melting point apparatus, uncorrected.– IR spectra: Perkin Elmer 881 spectrometer.– Mass spectra: Varian CH7 instrument.– NMR spectra: Jeol JNM-GX 400 spectrometer at 400 MHz, spectra were measured as $CDCl_3$ solutions using tetramethylsilane as internal standard.– Elemental analyses: Heraeus CHN Rapid instrument.– *Ab initio* calculations were performed on a Silicon Graphics Indigo 2 Extreme R4400 workstation computer using the TURBOMOL 2.300 program system (BIOSYM Tech. Inc., San Diego).

*(S)-8-N,N-Dipropylamino-6,7,8,9-tetrahydropyrido[1,2-a]indole* (**2**), *(8S,9aS)-8-N,N-Dipropylamino-1,6,7,8,9,9a-hexahydropyrido[1,2-a]indole* (**8**)

To a solution of **7b** (86 mg, 0.46 mmol) in MeOH (6 ml) was added popionic aldehyde (266 mg, 4.60 mmol) and then $NaCNBH_3$ (58 mg, 0.92 mmol) at 0 °C. After the mixture was stirred for 5 **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 (petroleum ether EtOAc 85:15) to give **2** (92 mg, 74 %) followed by **8** (12 mg, 10 %). **2**: colorless solid, mp 69–74 °C; $[\alpha]_D^{23}$ = –21 ($c$ = 0.25 in $CHCl_3$).– IR (KBr): ν = 2950 $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 0.83 (t, $J$ = 7.3 Hz, 6H, $CH_3$), 1.41 (sext., $J$ = 7.3 Hz., 4H, $CH_2\underline{CH_2}CH_3$), 1.88–1.98 (m, 1H, 7-$H_{ax}$), 2.12–2.17 (m, 1H, 7-$H_{eq}$), 2.43 (t, $J$ = 7.3 Hz, 4H, $N\underline{CH_2}CH_2CH_3$), 2.77 (dd, $J$ = 13.9, 11.0, 1H, 9-$H_{ax}$), 2.97–3.09 (m, 2H, 9-$H_{eq}$, 1H, 8-H), 3.78 (ddd, $J$ = 11.7, 11.7, 4.4 Hz, 1H, 6-$H_{ax}$), 2.29 (ddd, $J$ = 11.7, 5.8, 2.2 Hz, 6-$H_{eq}$), 6.12 (s, 1H, 1-H), 7.00 (t, $J$ = 7.2 Hz, 1H, Ar), 7.06 (t, $J$ = 7.2 Hz, 1H, Ar), 7.18 (d, $J$ = 7.2 Hz, 1H, Ar), 7.44 (d, $J$ = 7.2 Hz, 1H, Ar).– $C_{18}H_{26}N_2$ (270.4) Calcd. C 79.95 H 9.69 N 10.36; Found C 79.93 H 9.80 N 10.18. Mol.-mass 271 (CIMS).

**8**: colorless oil, $[\alpha]_D^{23}$ = –82 ($c$ = 1 in $CHCl_3$).– IR (NaCl): ν = 2960, 1610 $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 0.81 (t, $J$ = 7.3 Hz, 6H, $CH_3$), 1.40–1.45 (m, 4H, $CH_3\underline{CH_2}CH_2N$), 1.50 (ddd, $J$ = 12.4, 12.4, 12.4 Hz, 1H, 9-$H_{ax}$), 1.55 (dddd, $J$ = 12.4, 12.4, 12.4, 4.4 Hz, 1H, 7-$H_{ax}$), 1.71-1.76 (m, 1H, 7-$H_{eq}$), 1.85–1.90 (m, 1H, 9-$H_{eq}$), 2.35–2.40 (m, 4H, $N\underline{CH_2}CH_2CH_3$), 2.54 (dd, $J$ = 14.5, 7.4 Hz, 1H, 1-$H_a$), 2.61 (ddd, J = 11.7, 11.7, 2.5 Hz, 1H, 6-$H_{ax}$), 2.67–2.73 (m, 1H, 8-H), 2.91 (dd, J = 14.5, 9.5 Hz, 1H, 1-$H_b$), 3.17–3.24 (m, 1H, 9a-H), 3.62 (ddd, J = 11.7, 4.4, 1.4 Hz, 1H, 6-$H_{eq}$), 6.36 (d, $J$ = 7.3 Hz,

**Table 1:** Receptor binding data.

| compound | $IC_{50}$ [nM] ± S.E.M. D-1 ([$^3$H]-SCH 23390) | D-2 ([$^3$H]-spiperone) | D-2 ([$^3$H]-pramipexole) |
|---|---|---|---|
| **2** | >100 000 | 72 000 ± 0 | 450 ± 90 |
| **7b** | >100 000 | >100 000 | 28 000 ± 3 950 |
| **8** | >100 000 | >100 000 | 1 410 ± 200 |
| **(–)-PPP** | — | 7 800 ± 1000 | 14 ± 3 |
| **1** | 7 100 ($n$ = 2) | 15 000 ($n$ = 2) | 30 ($n$ = 2) |

1H, ar), 6.57 (t, $J$ = 7.3 Hz, 1H, ar), 6.96–7.00 (m, 2H, ar).– $^{13}$C NMR ($CDCl_3$): δ = 11.8 ($CH_3$), 22.0 ($CH_3\underline{CH_2}CH_2N$), 26.7 (C-7), 32.7 (C-9), 35.4 (C-1), 43.9 (C-6), 52.8 ($N\underline{CH_2}CH_2CH_3$), 58.9 (C-8), 64.3 (C-9a), 106,1 (ar), 106.1 (ar), 117.6 (ar), 124.6 (ar), 127.3 (ar), 129.4 (ar).– $C_{18}H_{28}N_2$ (272.4) Calcd. C 79.36 H 10.36 N 10.28; Found C 79.08 H 10.70 N 10.22. Mol.-mass 273 (CIMS).

*(S)-8-N,N-Dibenzylamino-6,7,8,9-tetrahydropyrido[1,2-a]indole* (**7a**)

To a mixture of **6** (200 mg, 1.56 mmol) [18] and $Et_3N$ (205 mg, 2.03 mmol) in $CH_2Cl_2$ (60 ml) was added $Tf_2O$ (506 mg, 1.80 mmol) at 0 °C. After stirring for 3 d 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 **7a** (384 mg, 86 %) as a colorless solid, mp 118–120 °C; $[\alpha]_D^{23}$ = –17 ($c$ = 0.5 in $CHCl_3$).– IR (KBr): ν = 3030, 2930, 1600 $cm^{-1}$.– $^1$H NMR ($CDCl_3$): δ = 2.12 (dddd, $J$ = 11.7, 11.7, 11.7, 5.1 Hz, 1H, 7-$H_{ax}$), 2.31–2.35 (m, 1H, 7-$H_{eq}$), 3.04 (dd, $J$ = 13.2, 11.5 Hz, 1H, 9-$H_{ax}$), 3.11–3.24 (m, 2H, 9-$H_{eq}$, 8-H), 3.70–3.78 (m, 1H, 6-$H_{ax}$), 3.72 (d, $J$ = 13.9 Hz, 2H, $NCH_2Ph$), 3.78 (d, $J$ = 13.9 Hz, 2H, $NCH_2Ph$), 4.26–4.31 (m, 1H, 6-$H_{eq}$), 6.19 (s, 1H, 1-H), 6.99–7.49 (m, 14H).– $C_{26}H_{26}N_2$ (366.5) Calcd. C 85.21 H 7.15 N 7.64; Found C 85.09 H 7.42 N 7.42. Mol.-mass 366 (EIMS).

*(S)-8-N,N-Amino-6,7,8,9-tetrahydropyrido[1,2-a]indole* (**7b**)

A mixture of **7a** (360 mg, 0.98 mmol) and 20 % $Pd(OH)_2/C$ (230 mg) in EtOAc (12 ml) and MeOH (12 ml) was stirred under a balloon of $H_2$ for 2 d at room temp. The mixture was filtered through celite, the filtrate was evaporated carefully and the residue was purified by flash chromatography ($CHCl_2$ – MeOH 9:1) to give **7b** (145 mg, 79 %) as a colorless solid, mp 55–58 °C; $[\alpha]_D^{23}$ = +43 ($c$ = 0.74 in MeOH).– IR (KBr): ν = 3240, 3030, 2930 $cm^{-1}$.– $^1$H NMR ($CDCl_3$): δ = 1.84–1.94 (m, 1H, 7-$H_a$), 2.14–2.22 (m, 1H, 7-$H_b$), 2.63–2.74 (m, 1H, 9-$H_a$), 3.13–3.30 (m, 2H, 9-$H_b$, 8-H), 3.81–3.91 (m, 1H, 6-$H_a$), 4.18–4.24 (m, 1H, 6-$H_b$), 6.15 (s, 1H, 1-H), 7.00 (t, $J$ = 7.2 Hz, 1H, Ar), 7.07 (t, $J$ = 7.2 Hz, 1H, Ar), 7.19 (d, $J$ = 7.2 Hz, 1H, Ar), 7.45 (d, $J$ = 7.2 Hz, 1H, Ar).– $C_{12}H_{14}N_2$ (186.3) Calcd. C 77.38 H 7.57 N 15.04; Found C 77.34 H 7.65 N 14.83. Mol.-mass 187 (CIMS).

*Dopamine Receptor Binding*

DA receptor binding was performed as previously described using [$^3$H]-SCH 23390 [20] and [$^3$H]-spiperone [21] 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]-pramipexole (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]-spiperone as a radioligand. For all receptor binding tests rat brain striatum was used.

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