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Dopaminergic 7-Aminotetrahydroindolizines: Ex-Chiral Pool Synthesis and Preferential D3 Receptor Binding

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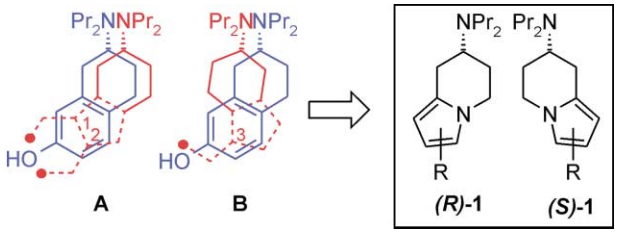
Abstract—Starting from both isomers of enantiopure asparagine, heterocyclic bioisosteres of the preferential dopamine D3 receptor agonist (*R*)-7-OH-DPAT were investigated when SAR studies led to the 3-formyl substituted aminoindolizine (***S*)-1e** (FAUC 54) displaying a K_i value of 6.0 nM for the high affinity D3 binding site. In contrast, D3 affinity of the enantiomer (***R*)-1e** was 300 fold lower. © 2001 Elsevier Science Ltd. All rights reserved.

The existence of two families of dopamine receptors has been established by recent advances in classical pharmacology and molecular biology.[1] It is generally accepted that the D2, D3, and D4 subtypes belong to the D2-like family, while the D1-like family comprises D1 and D5 receptors.[2] There is strong evidence that D2 and D3 receptors exist postsynaptically and also as autoreceptors controlling dopamine synthesis, release and neuronal firing.[1] The D3 receptor[3] appears an important target for the development of drug candidates since it is selectively expressed in the brain limbic system, which is thought to be involved in mood and cognitive disturbances as well as drug dependence.[4] Most of the recent SAR studies on preferential dopamine D3 receptor agonists are based on (*R*)-7-OH-dipropylaminotetralin as a lead compound.[5] In recent reports, we described novel DPAT regioisomers[6] and heterocyclic bioisosteres including enantiomerically pure dipropylaminotetrahydroindolizines revealing autoreceptor activity.[7] Structural alignment of (*R*)-7-OH-DPAT and tetrahydroindolizines led us to the assumption that a hydrogen bond acceptor connected with one atom distance to the aromatic moiety of the aminoindolizine framework could simulate the sp^3 oxygen of (*R*)-7-OH-DPAT. Depending on the absolute stereochemistry of the heterocyclic bioisostere, spatial overlap can result from substitution in the positions 1 or 2 (superimposition A) or 3 (superimposition B).

In this communication, we report on EPC synthesis and subtype selective dopamine receptor binding of hydroxymethyl and formyl substituted 7-dipropylaminoindolizines of type (***R*)-1** and (***S*)-1**. In order to estimate the influence of the hydrogen bond acceptor, 1-, 2- or 3-methyl derivatives were evaluated, too.



The synthesis of the target compounds bearing (*S*)-configuration relied on the employment of natural asparagine as a chiral building block (Scheme 1). For the preparation of the 1- and 2-substituted indolizines we approached the formylpyrrole **3a** as a central intermediate. In practice, reductive *N,N*-dibenzylation and subsequent treatment with borane•THF furnished the primary amine **2** that could be reacted with 3-formyl-2,5-dimethoxytetrahydrofuran.[8] Using HOAc as a solvent for the Paal–Knorr reaction, the primary alcohol **3a** was formed along with the acetate **3b** that was converted to **3a** under aqueous basic conditions.

Transformation of the carbaldehyde function into a methyl group was accomplished by Wolff–Kishner reduction resulting in formation of the cyclization

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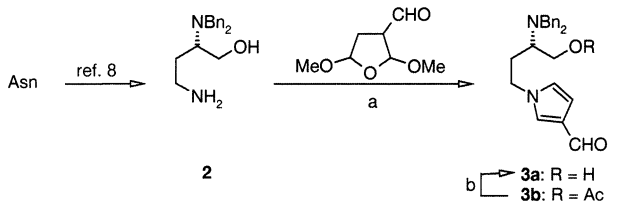
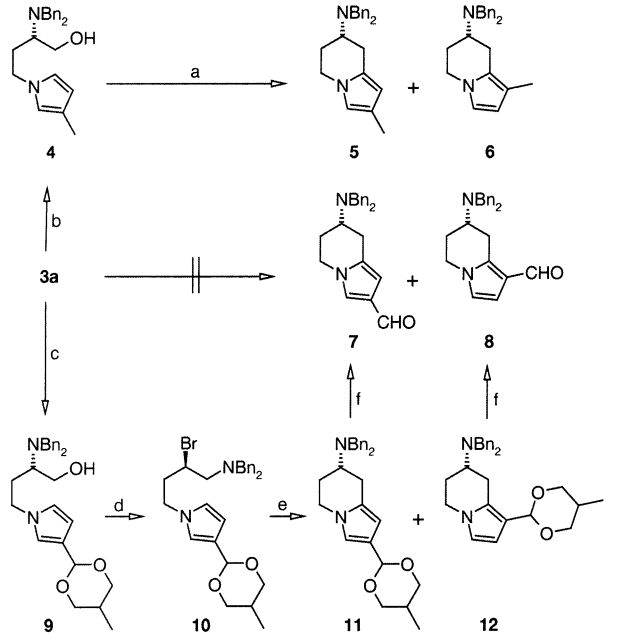


Scheme 1. (a) HOAc/NaOAc, 70°, 75 min (**3a**: 48%; **3b**: 10%); (b) K_2CO_3, H_2O, rt, 24 h (100%).

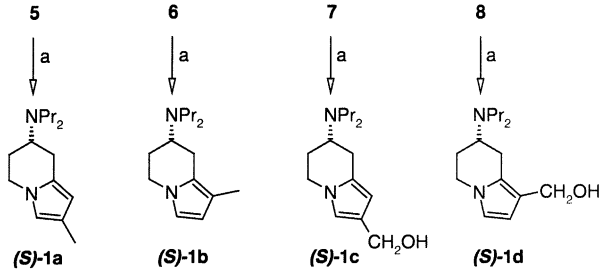
precursor **4** in 70% yield (Scheme 2). In accordance to our recently described observations on stereoelectronically controlled cationic cyclizations,[9] formation of a six-membered ring was induced by activation of the terminal alcohol group. Thus, treatment of **4** with trifluoromethanesulfonic anhydride gave the 2-methyl indolizine **5** and the 1-methyl substituted heterocycle **6** as a 1:10 mixture of regioisomers reflecting the influence of the electron donating properies of the methyl group onto the site-selectivity of the electrophilic attack. 5-*Exo* attack of the intermediately formed aziridinium salt could not be detected.

Due to the electron accepting effect of the carbaldehyde function, Tf_2O activation of the pyrrole **3a** did not result in cationic π-cyclization. In order to increase the electron density of the aromatic region, the protected derivative **9**, which was readily available by acid catalyzed acetalization, was selected as a cyclization precursor. However, Tf_2O induced sulfonylation of **9** caused decomposition that we put down to impurities of TfOH being able to activate the acetal function for side reactions. Seeking for a smooth alternative, we tried to transform the alcohol function into a bromide using neutral Appel conditions. Subsequent treatment with AgOTf was envisaged to form a reactive triflate giving access to the indolizines **7**,**8**. In fact, bromide formation was observed in 71% yield. Careful NMR studies clearly proved the structure of the secondary bromide **10**[10] which was obviously formed by rearrangement via an aziridinium intermediate. Similar reactions have been observed and described by us in detail.[11] Anticipating the reversibility of the migration, we subjected the bromide **10** to AgOTf. In fact, formation of the indolizines **11** and **12** as a 1:2 mixture of regioisomers was observed. Subsequent deprotection led to the carbaldehydes **7** and **8** which were readily separable by flash chromatography.[12] Employing one-pot conditions, the reaction sequence afforded a 39% yield of the main regioisomer **8** and 20% of the 2-substituted isomer **7**. The optical integrity of the synthesis was proved by coupling of the carbaldehyde **8** with (*R*)- and (*S*)-alanine methyl ester under reductive conditions ($NaBH_3CN$, MeOH) when ^1H and ^{13}C NMR investigations of the resulting secondary amines indicated an isomeric excess >95%. Exchange of the *N,N*-dibenzyl protecting groups by the pharmacophoric *N,N*-dipropyl substitution pattern was intended by hydrogenolysis and subsequent reductive alkylation (Scheme 3). Thus, the methyl substituted dibenzylaminoindolizines could be readily transformed into the primary amines upon hydrogenation in presence of Pearlman's catalyst. Subsequent treatment with an excess of propionaldehyde and $NaBH_3CN$ afforded the final products (***S*)-1a** and (***S*)-1b**. Subjecting the carbaldehydes **7** and **8** to identical hydrogenation conditions resulted in debenzylation and reduction of the formyl group into a mixture of hydroxymethyl and methyl derivatives when careful optimization of the reaction time and the solvent accomplished the 1- and 2-hydroxymethyl substituted aminoindolizines in satisfactory yield. Finally, reductive dipropylation was performed to give the target compounds (***S*)-1c** and (***S*)-1d**.

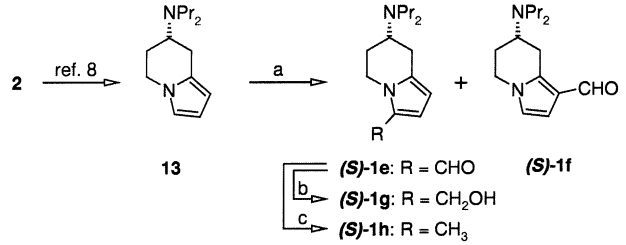


Scheme 2. (a) Tf_2O, CH_2Cl_2, rt, 48 h (**5**: 5%, **6**: 50%); (b) hydrazine hydrate, diethylene glycol, 130°, 1 h; +KOH, 170°, 4 h (70%); (c) 2,2,-dimethylpropan-1,3-diol, $TsOH{\cdot}H_2O$, benzene, reflux, 4 h (85%); (d) CBr_4, PPh_3, CH_2Cl_2, rt, 16 h (71%); (e) AgOTf, CH_2Cl_2, 0°, 75 min; (f) CF_3COOH, MeOH, 0 °C, 75 min (**7**: 20%, **8**: 39%, based on **9**).

Modification of the 3-position of the indolizine framework was planned by regiocontrolled formylation of the unsubstituted *N,N*-7-dipropylaminoindolizine **13** (Scheme 4) which was synthesized from the asparagine derived building block **2** applying a previously described reaction sequence.[8] Subjecting **13** to Vilsmeier–Haack reaction conditions gave preferential formylation in position 3 when 42% of pure carbaldehyde (***S*)-1e** was isolated.[13] As a minor regioisomer, the 1-formyl derivative (***S*)-1f** was obtained (5% yield). Reductive modification of the 3-formylindolizine (***S*)-1e** was



Scheme 3. (a) (1) H_2, $Pd(OH)_2$/C, MeOH–EtOAc 1:1, rt, 6 h; (2) propionaldehyde, MeOH, 0°, 90 min for **5**, **6**, 180 min for **7**, **8** (19–41%).



Scheme 4. (a) DMF, $POCl_3$, 0° to rt, 4 h [(***S***)-**1e**: 42%, (***S***)-**1f**: 5%]. (b) $NaBH_4$, isopropanol, rt, 19 h (89%); (c) $LiAlH_4$, THF, 0° to reflux, 48 h (44%).

Table 1. Receptor binding data for the target compounds (***R***)-**1** and (***S***)-**1** compared to the D2 autoreceptor agonist **13** and the D3 agonist (*R*)-7-OH-DPAT employing bovine D1 and D2 and human D3 receptors. K_i values [nM] are given based on the means of 2–8 experiments each performed in triplicate, the results of which did not vary more than 25%, except for (***R***)**1b** (35%). For (***S***)-**1e** and (R)-7-OH-DPAT, a clear differentiation between a high affinity binding site (representing the ternary complex) and a low affinity binding site was observed for D2 and D3 when labeled with [^{3}H]spiperone

Compd	R	bD1 [^{3}H] SCH23390	bD2$_{high}$ [^{3}H] pram.	bD2 [^{3}H]spip.	hD3 [^{3}H]spip.
(***R***)-**1a**	2-CH_3	83,000	800	17,000	1300
(***S***)-**1a**	2-CH_3	44,000	640	9600	770
(***R***)-**1b**	1-CH_3	71,000	1000	12,000	2100
(***S***)-**1b**	1-CH_3	68,000	380	4000	750
(***R***)-**1c**	2-CH_2OH	> 100,000	1000	34,000	1400
(***S***)-**1c**	2-CH_2OH	> 100,000	13,000	> 100,000	8600
(***R***)-**1d**	1-CH_2OH	100,000	200	6100	330
(***S***)-**1d**	1-CH_2OH	> 100,000	8000	55,000	9700
(***R***)-**1e**	3-CHO	47,000	1700	21,000	1800
(***S***)-**1e**	3-CHO	26,000	21	(high) 90 (low) 6500	(high) 6,0 (low) 150
(***R***)-**1f**	1-CHO	80,000	380	12,000	510
(***S***)-**1f**	1-CHO	> 100,000	1600	5900	3600
(***R***)-**1g**	3-CH_2OH	> 100,000	4700	37,000	7400
(***S***)-**1g**	3-CH_2OH	13,000	87	5500	420
(***R***)-**1h**	3-CH_3	12,000	430	1300	590
(***S***)-**1h**	3-CH_3	29,000	150	3800	430
13	H	> 100,000	150	4100	560
(*R*)-7-OH-DPAT		n.d.	3,5	n.d.	(high) 0,8 (low) 9,5

accomplished employing the complex metal hydrides $NaBH_4$ and $LiAlH_4$ to afford the alcohol (***S***)-**1g** and the methyl derivative (***S***)-**1h**, respectively.

Employing the identical procedures, we synthesized the optical antipodes (***R***)-**1a**–**h** starting from unnatural (*R*)-asparagine.

The final products of type **1** were evaluated in vitro for their abilities to displace [^{3}H]spiperone from cloned human dopamine D3 receptors[14] being stably expressed in CHO cells (Table 1).[15] D1 and D2 affinities were determined by employing bovine striatal membrane preparations and the D1 selective antagonists [^{3}H]SCH 23390 and [^{3}H]spiperone, respectively. Additionally, the selective dopamine D2 autoreceptor agonist [^{3}H]pramipexole was utilized for competition experiments at the high affinity binding site.[16,17] Employing (*R*)-7-OH DPAT as an internal standard, similar affinities could be determined when compared to cloned human D2 receptors stable expressed in CHO cells ($K_{i high} = 10$ for $D2_{long}$ and $K_{i high} = 3.3$ for $D2_{short}$). The investigation of the D3 receptor binding of the test compounds indicated K_i values ranging only in micromolar or submicromolar concentrations. As expected, the methylindolizines **1a,b,h** showed binding properties that were similar to those of the unsubstituted 7-aminoindolizine **13**. It is interesting to note, that the (*R*)-enantiomers of the 2- and 1-hydroxymethyl substituted ligands **1c** and **1d** displayed higher D3 (and also D2) affinity than its optical antipodes. This is contrary to the 3-hydroxymethyl derivative **1g** revealing significantly higher binding of the (*S*)-enantiomer. Comparison of the 1-formylindolizine **1f** with the 3-formyl regioisomer **1e** shows the same relationship clearly corroborating an analogy of binding modes as indicated in the schematic superimpositions A and B. (***S***)-**1e** (FAUC 54) exhibited the best binding properties and a Hill coefficient $n_H = -0.68$ that was identical to that we obtained for the D3 receptor agonist 7-OH-DPAT. The biphasic binding curves clearly indicated agonist properties for (***S***)-**1e** when differentiation between a high affinity site representing the ternary receptor G-protein complex and a low affinity binding site is typical. Detailed analysis of the binding curves of (***S***)-**1e** provided a $K_{i high} = 6.0 \pm 1.3$ nM and a $K_{i low} = 150 \pm 20$ nM.

In conclusion, the ability of the hydroxyl function of (*R*)-7-OH DPAT interacting with serine residues in TM5 of the D3 receptor protein as an H-bond acceptor may be best adopted by a formyl group when positioned at C3 of the (*S*)-7-dipropylaminotetrahydroindolizine core structure. Based on FAUC 54 [(***S***)-**1e**], further SAR studies, functional experiments and investigations of the bioactive conformation will be published without delay.

Acknowledgements

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References and Notes

1. Neve, K. A., Neve, R. L. Eds.; *The Dopamine Receptors*. Humana Press: Totowa, New Jersey, 1997.
2. Kebabian, J. W.; Tarazi, F. I.; Kula, N. S.; Baldessarini, R. J. *Drug Discovery Today* **1997**, *2*, 333.
3. Sokoloff, P.; Giros, P.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. *Nature* **1990**, *347*, 146.
4. For review, see: Sokoloff, P.; Griffon, N.; Sautel, F.; Lévesque, D.; Pilon, C.; Schwartz, J.-C.; Ridray, S.; Diaz, J.; Simon, P.; Costentin, J.; Mann, A.; Wermuth, C. G.; Caine, S. B.; Parsons, L. H.; Koob, G. F. *Biomed. Health Res.* **1998**, *19 (Dopamine Receptor Subtypes)*, 118.
5. Gonzalez, A. M.; Sibley, D. R. *Eur. J. Pharmacol.* **1995**, *272*, R1. For examples, see: Glase, S. A.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *J. Med. Chem.*

1995, *38*, 3132. Van Vliet, L. A.; Tepper, P. G.; Dijkstra, D.; Damsma, G.; Wikström, H.; Pugsley, T. A.; Akunne, H. C.; Heffner, T. G.; Glase, S. A.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 4233. Murray, P. J.; Helden, R. M.; Johnson, M. R.; Robertson, G. M.; Scopes, D. I. C.; Stokes, M.; Wadman, S.; Whitehead, J. W. F.; Hayes, A. G.; Kilpatrick, G. J.; Large, C.; Stubbs, C. M.; Turpin, M. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 403. Dubuffet, T.; Newman-Tancredi, A.; Cussac, D.; Audinot, V.; Loutz, A.; Millan, M. J.; Lavielle, G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2059.

6. Gmeiner, P.; Hummel, E.; Mierau, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2589.

7. Gmeiner, P.; Mierau, J.; Höfner, G. *Arch. Pharm. (Weinheim)* **1992**, *325*, 57.

8. Gmeiner, P.; Lerche, H. *Heterocycles* **1990**, *31*, 9.

9. Lehmann, T.; Gmeiner, P. *Heterocycles* **2000**, *53*, 1371.

10. Analytical data: **10**: $[\alpha]_D^{23} = +21.5°$ ($c = 1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 0.76 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.73 (dddd, $J = 14.9$, 8.3, 8.1, 2.7 Hz, 1H, H-3), 2.35 (dddd, $J = 14.9$, 10.2, 5.6, 4.7 Hz, 1H, H-3), 2.66 (dd, $J = 13.0$, 9.0 Hz, 1H, H-1), 2.76 (dd, $J = 13.0$, 6.0 Hz, 1H, H-1), 3.47 (d, $J = 13.4$ Hz, 2H, NCH_2ar), 3.57 (d, $J = 11.0$ Hz, 2H, CH_2O), 3.60 (d, $J = 13.4$ Hz, 2H, NCH_2ar), 3.68 (d, $J = 11.0$ Hz, 2H, CH_2O), 3.69–3.83 (m, 1H, H-2), 3.80–3.93 (m, 2H, H-4), 5.35 (s, 1H, OCH), 6.20 (dd, $J = 2.5$, 1.8 Hz, 1H, H-4-pyrrole), 6.52 (dd, $J = 2.5$, 2.5 Hz, 1H, H-5-pyrrole), 6.73 (dd, $J = 2.5$, 1.8 Hz, 1H, H-2-pyrrole), 7.18–7.42 (m, 10H, ar). Anal. calcd for $C_{28}H_{35}N_2O_2Br$: C 65.75, H 6.90, N 5.48; Found: C 65.65, H 6.96, N 5.45.

11. Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766. Weber, K.; Kuklinkski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647.

12. Analytical data: **7**: $[\alpha]_D^{23} = -132.8°$ ($c = 1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) = 2.00 (dddd, $J = 12.0$, 12.0, 11.5, 5.5 Hz, 1H, H-6_{ax}), 2.16–2.24 (m, 1H, H-6_{eq}), 2.83 (ddd, $J = 15.5$, 11.5, 1.0 Hz, 1H, H-8_{ax}), 3.03 (ddd, $J = 15.5$, 5.0, 1.0 Hz, 1H, H-8_{eq}), 3.10 (dddd, $J = 11.5$, 11.5, 5.0, 2.5 Hz, 1H, H-7), 3.67 (d, $J = 14.0$ Hz, 2H, NCH_2ar), 3.74 (d, $J = 14.0$ Hz, 2H, NCH_2ar), 3.82 (ddd, $J = 12.5$, 12.0, 4.5 Hz, 1H, H-5_{ax}), 4.14 (ddd, $J = 12.5$, 5.5, 2.0 Hz, 1H, H-5_{eq}), 6.28 (brs, 1H, H-1), 7.08 (d, $J = 1.5$ Hz, 1H, H-3), 7.19–7.25 (m, 2H, p-ar), 7.27–7.33 (m, 4H, m-ar), 7.38 (m, 4H, o-ar), 9.65 (s, 1H, CHO). Anal. calcd for $C_{23}H_{24}N_2O$: C 80.20, H 7.02, N 8.13; found: C 80.05, H 6.88, N 7.99. **8**: $[\alpha]_D^{23} = -168.0°$ ($c = 1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) = 2.05 (dddd, $J = 13.0$, 12.5, 12.5, 5.5 Hz, 1H, H-6_{ax}), 2.17–2.25 (m, 1H, H-6_{eq}), 3.03 (dd, $J = 17.0$, 11.5 Hz, 1H, H-8_{ax}), 3.14 (dddd, $J = 12.5$, 11.5, 5.0, 2.5 Hz, 1H, H-7), 3.47 (ddd, $J = 17.0$, 5.0, 1.5 Hz, 1H, H-8_{eq}), 3.68 (d, $J = 14.0$ Hz, 2H, NCH_2ar), 3.78 (d, $J = 14.0$ Hz, 2H, NCH_2ar), 3.83 (ddd, $J = 12.5$, 12.5, 4.5 Hz, 1H, H-5_{ax}), 4.10 (ddd, $J = 12.5$, 5.5, 2.0 Hz, 1H, H-5_{eq}), 6.41 (d, $J = 3.0$ Hz, 1H, H-3), 6.53 (d, $J = 3.0$ Hz, 1H, H-2), 7.20–7.25 (m, 2H, p-ar), 7.27–7.33 (m, 4H, m-ar), 7.39 (m, 4H, o-ar), 9.78 (s, 1H, CHO). HRMS (EI) calcd for $C_{23}H_{24}N_2O$ (M^+): 344.1888; found: 344.1882.

13. Analytical data: (***S***)**-1e:** $[\alpha]_D^{23} = -17.3°$ ($c = 0.1$, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) = 0.88 (t, $J = 7.3$ Hz, 6H, $NCH_2\underline{CH_2}\underline{CH_3}$), 1.45 (sext., $J = 7.3$ Hz, 4H, $NCH_2\underline{CH_2}CH_3$), 1.86 (dddd, $J = 13.0$, 12.1, 11.9, 5.5 Hz, 1H, H-6_{ax}), 2.07–2.16 (m, 1H, H-6_{eq}), 2.40–2.50 (m, 4H, $N\underline{CH_2}CH_2CH_3$), 2.72 (dd, $J = 16.1$, 10.6 Hz, 1H, H-8_{ax}), 2.98 (ddd, $J = 16.1$, 4.7, 2.1 Hz, 1H, H-8_{eq}), 3.05 (dddd, $J = 11.9$, 10.6, 4.7, 2.8 Hz, 1H, H-7), 4.03 (ddd, $J = 13.5$, 13.0, 4.8 Hz, 1H, H-5_{ax}), 4.84 (ddd, $J = 13.5$, 5.5, 2.4 Hz, 1H, H-5_{eq}), 5.98 (d, $J = 3.9$ Hz, 1H, H-1), 6.87 (d, $J = 3.9$ Hz, 1H, H-2), 9.40 (s, 1H, CHO). Anal. calcd for $C_{15}H_{24}N_2O$ (248.37): C 72.54, H 9.74, N 11.28; found: C 72.42, H 9.77, N 11.21.

14. Sokoloff, P.; Andrieux, M.; Besancon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. *Eur. J. Pharmacol.* **1992**, *225*, 331.

15. Receptor binding studies were carried out as described in ref 16. In brief, competition experiments with the bovine dopamine receptors were run with striatal membranes at a final protein concentration of 100 μg/mL and the radioligand [^{3}H]SCH 23390 at 0.3 nM ($K_d = 0.27$ nM) for D1 and with 90 μg/mL and the antagonist [^{3}H]spiperone at 0.5 nM ($K_d = 0.65$–0.85 nM) for D2. Competition experiments specifically labeling the high affinity binding site of the bovine D2 receptor were done with the agonist [^{3}H]pramipexole at 0.5 nM ($K_d = 1.2$–2.8 nM) and a protein concentration of 200 μg/mL. Preparations of membranes from CHO cells expressing the human D3 receptor (30–70 μg/mL) were employed with [^{3}H]spiperone at 0.5 nM ($K_d = 0.1$–0.4 nM).

16. Ohnmacht, U.; Tränkle, C.; Mohr, K.; Gmeiner, P. *Pharmazie* **1999**, *54*, 294.

17. Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.