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Chirospecific and Subtype Selective Dopamine Receptor Binding of Heterocyclic Methoxy-naphthamide Analogs

Laura Bettinetti, Harald Hübner, and Peter Gmeiner

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, Erlangen, Germany

Employing the D_3 and D_4 selective methoxynaphthalines nafadotride and FAUC 182, respectively, as lead compounds, the pyrazolo[1,5-a]pyridine-3-carboxamides of type **1a** and **2a** as well as their 2-substituted regioisomers **1b** and **2b** were synthesized when following an ex-chiral pool approach. Dopamine receptor binding studies involving the target compounds (**1a,b**, **2a,b**) and the respective optical antipodes **ent-1a,b** and **ent-2a,b** revealed the heterocyclic carboxamide **2a** as a strong and selective D_4 ligand (K_i = 8.6 nM). According to a mitogenesis assay, **2a** shows D_4 partial agonist effects (29%, EC_{50} = 6.7 nM) and, thus, might be of interest for the treatment of sexual dysfunction.

Keywords: Dopamine; receptor; medicinal chemistry

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Introduction

2-Methoxybenzamides including the aminomethylpyrrolidine derivative sulpiride are known as highly active agents for the treatment of schizophrenia [1]. Due to the affinity of this family of compounds to dopamine D_2 receptors in striatal regions of the brain, their application is associated with extrapyramidal side effects [2]. Structural modifications led to the 2-methoxynaphthalenes nafadotride and FAUC 182 revealing binding preference for the D_3 and D_4 subtype, respectively [3, 4]. Due to their distribution in the brain and a series of functional studies, dopamine D_3 and D_4 receptors seem to be especially involved in the symptoms of schizophrenia [5, 6].

Very recently, we reported that the bioisosteric replacement of the naphthalene subunit of the dopamine D_3 receptor partial agonist BP 897 by a pyrazolopyridine moiety led to the neuroprotective D_3 receptor ligand FAUC 329 [7, 8]. As an extension of these studies, we herein describe the synthesis of the enantiomerically pure pyrazolo[1,5-*a*]pyridine carboxamides **1** and **2** (Figure 1) as well as their optical antipodes **ent-1** and **ent-2**. To investigate the effect of the spatial orientation of the 7*a*-azaindole moiety onto the dopamine receptor binding profiles, both 2- and the 3-substituted regioisomeres should be prepared.

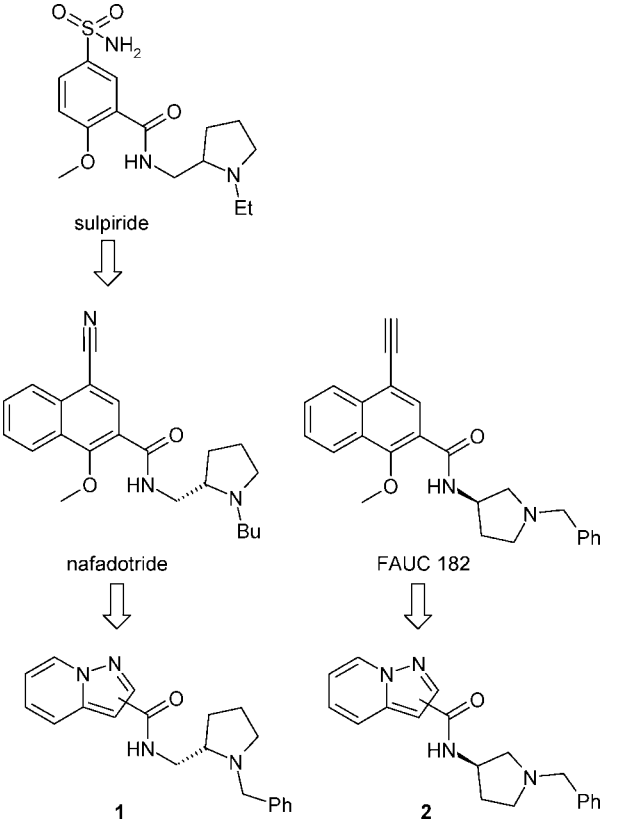
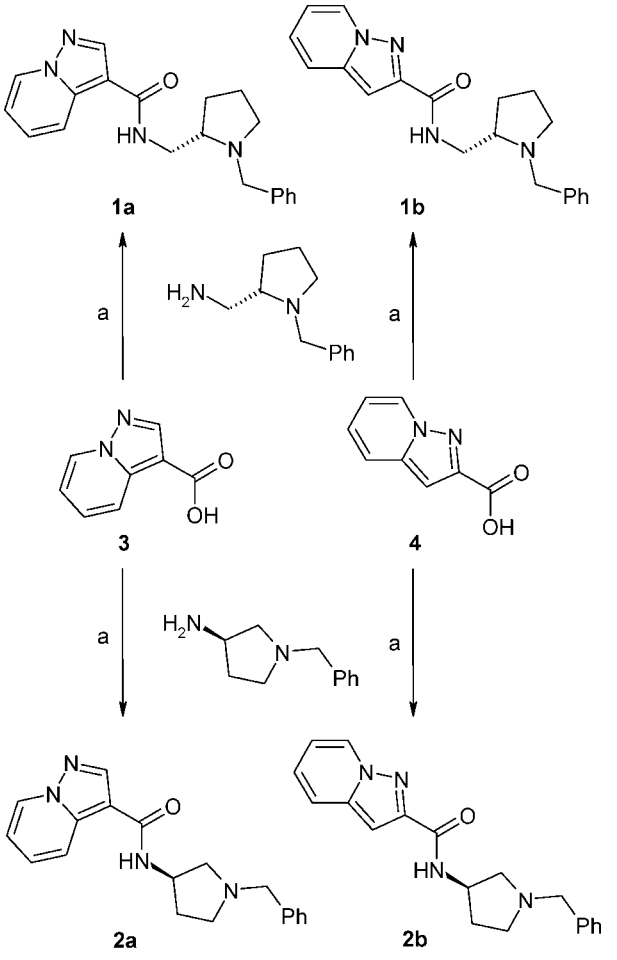


Figure 1. Ratio for structural modifications.

Results and discussion

Chemical synthesis of the building block **3** was done by 1,3-dipolar cycloaddition of *N*-aminopyridinium iodide and

Correspondence: Department of Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, Schuhstraße 19, D−91052 Erlangen, Germany. Phone: +49 9131 8529383, Fax: +49 9131 8522585, e-mail: gmeiner@pharmazie.uni-erlangen.de



Scheme 1. Synthesis routes for **2a** and **2b**.

ethyl propiolate under oxidative conditions and subsequent saponification employing a modified protocol of R. Huisgen's pioneering work [9, 10]. For the preparation of the 2-substituted regioisomer **4**, acetylene dicarboxylate was utilized as a dipolarophile taking advantage of a selective decarboxylation in position 3 [11, 12]. Whereas the benzyl protected 2-aminomethylpyrrolidenes could be derived enantiomerically pure from (*S*)- or (*R*)-*N*-benzylproline ethyl ester by aminolysis and lithium aluminum hydride promoted reduction, chiral *N*-benzyl protected 3-aminopyrrolidine was synthesized in both configurations starting from (*S*)- or (*R*)-aspartic acid following a protocol that we have recently elaborated [4, 13].

Chemical coupling of the two amine building blocks and their enantiomers to the heteroarene carboxylic acids **3** and **4** was accomplished by oxalyl chloride promoted activation and subsequent aminolysis (Scheme 1). Thus, the target compounds **1a**, **1b**, **2a**, **2b**, and their enantiomers **ent-1a**, **ent-1b**, **ent-2a** and **ent-2b** were obtained in 83−99% yield.

The novel 7*a*-azaindole carboxamides were evaluated *in vitro* for their ability to displace [^{3}H]spiperone from the cloned human dopamine receptors D_{2long}, D_{2short} [14], D_3 [15] and D_4 [16] being stably expressed in CHO cells [17]. D_1 affinity was determined by employing porcine striatal membrane preparations and the D_1 selective antagonist [^{3}H]SCH 23390. For comparison of the binding data, the antipsychotic drug sulpiride was investigated under the same conditions (Table 1).

The dopamine receptor binding profiles of the test compounds clearly indicate poor affinities for the D_1, D_2 and D_3 subtypes. Only the (*S*)-aminomethylpyrolidine derivative **1b** displayed a K_i value in the nanomolar range (400 nM for D_3). Comparison of the D_4 binding data shows significantly higher affinities for the 2-aminopyrolidine derivatives (type **2**). For both regioisomers, (*R*)-configuration proved superior to the (*S*)-enantiomers. Interestingly, the pyrazolopyridine-3-carboxamide **2a** showed high and selective D_4 binding leading to a K_i value of 8.6 nM when the selectivity over the subtypes D_1, D_{2long}, D_{2short} and D_3 was higher than 300 fold for any subtype. To investigate the intrinsic effect of the test compound **2a**, an *in vitro* functional assay measuring the [^{3}H]thymidine uptake in growing CHO cells stably expressing the dopamine D_4 receptor was performed when a 29% stimulation of mitogenesis (compared to the full agonist effect of quinpirole and the D_4 antagonist clozapine) was determined (EC_{50} = 6.7 nM compared to 13 nM for quinpirole) indicating that the test compound behaves as a partial agonist (Figure 2) [18].

In conclusion, SAR investigations on the heterocyclic carboxamide regio- and stereoisomers of type **1** and **2** indicated that the *ortho*-methoxy substituent of the lead compounds might be of special importance for D_2 and D_3 but not for D_4 receptor binding. Thus, the D_2 and D_3 receptor recognition was significantly reduced when compared to sulpiride. However, for the D_4 subtype, the (*R*)-configured regioisomers of type **2** displayed substantial receptor binding resulting in a 250 fold lower K_i value than the reference agent. However, it is not clear whether they adopt the same binding modes as the structural family of 2-methoxybenzamides and 2-methoxynaphthamides. Due to recent observations on the dopamine D_4 receptor partial agonist ABT-724 inducing penile erection in rats [19], the pyrazolopyridine carboxamide **2a** is of potential interest for further investigations.

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Table 1. Receptor binding data for the test compounds **1**, **2** and **ent-1,2** and the neuroleptic drug sulpiride to porcine dopamine D_1 and human D_{2long}, D_{2short}, D_3 and D_4 receptors†.

	K_i values in nM ± SEM				
Compound	[3H]SCH 23390 pD_1	hD_{2long}	hD_{2short}	[3H]spiperone hD_3	hD_4
1a	26000 ± 1500	77000 ± 23000	60000 ± 17000	7000 ± 950	4600 ± 800
ent1a	20000 ± 1000	16000 ± 2000	14000 ± 3000	3800 ± 750	4000 ± 150
1b	17000 ± 2000	26000 ± 1500	19000 ± 4000	400 ± 5.0	3800 ± 250
ent1b	23000 ± 1000	11000 ± 2000	7700 ± 150	3800 ± 450	410 ± 35
2a	22000 ± 2000	16000 ± 3000	15000 ± 3000	2900 ± 300	8.6 ± 1.2
ent2a	24000 ± 1000	35000 ± 3500	36000 ± 5000	5100 ± 900	100 ± 8.0
2b	16000 ± 0	35000 ± 7000	24000 ± 1000	4300 ± 350	55 ± 5.0
ent2b	21000 ± 0	34000 ± 9500	25000 ± 3500	5200 ± 3300	160 ± 15
sulpiride	50000 ± 13000	140 ± 22	51 ± 11	89 ± 32	2300 ± 260

† K_i values in nM ± SEM are based on the means of 2−3 experiments each done in triplicate.

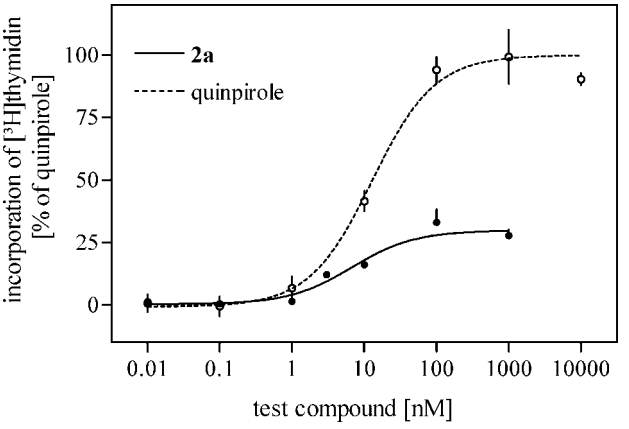

Figure 2. Determination of intrinsic activity of **2a** (29%, EC_{50} = 6.7 nM) compared to the full agonist quinpirole by measuring the incorporation of [3H]thymidine into growing CHO cell expressing the rat $D_{4.2}$ receptor.

Garvan Institute of Medical Research, Sydney) for providing dopamine D_4, D_3 and D_2 receptor expressing cell lines, respectively. This work was supported by the *Fonds der Chemischen Industrie.*

Experimental

General

MS spectra were recorded on FINNIGAN MAT TSQ 70 spectrometer. ^1H NMR (360 MHz) and ^{13}C NMR (90 MHz) spectra were recorded in solution using a BRUCKER AM 360 instrument. Infrared spectra were registered on a JASCO FT/IR 410 instrument, using a film of substance on a NaCl pill. Melting points were determined on a BÜCHI apparatus. CHN elementary analyses were done at the Department of Organic Chemistry (Friedrich Alexander University). Flash chromatography was performed using Silica Gel 60 (40−63 μm). For TLC, Merck 60 F_{254} aluminum plates were used analyzed by UV light (254nm) or by iodine vapor.

Chemistry

[(S)-1-Benzylpyrrolidin-2-yl]-methylamine [20, 21]

(S)-N-Benzylproline ethyl ester (432 mg, 1.85 mmol) in a NH_3 MeOH solution (20 mL) was stirred at RT for 10 days. After evaporation of NH_3 at RT, the solvent was removed *in vacuum* to give 375 mg of a yellow pasty solid which was used without purification.

A suspension of the crude intermediate (153 mg, 0.75 mmol) in abs THF (4 mL) was treated with a 1.0 M $LiAlH_4$ solution in THF (1.26 mL) and stirred under nitrogen atmosphere at RT for 6 h. EtOAc (0.1 mL) and a 2 N NaOH solution (0.2 mL) were added, the obtained solid was removed by filtration and the solution dried (Na_2SO_4). Evaporation of the solvent gave an oil purified by flash chromatography ($CHCl_3$: MeOH = 8:2). Yield: 144 mg (76%). $[\alpha]_D^{20}$: −71.3° (c 1.0, $CHCl_3$), ($[\alpha]_D^{25}$ ($CHCl_3$): −55°) [21]. IR (NaCl) ν: 3367, 3027, 2962, 2792, 1643, 1573, 1118, 740, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.64−1.73 (m, 3H); 1.86−1.94 (m, 1H), 2.17−2.24 (m, 1H), 2.54−2.59 (m, 1H), 2.70 (dd, *J* = 13.0 Hz, 3.4 Hz, 1H), 2.76 (dd, *J* = 12.8 Hz, 5.3 Hz, 1H), 2.91−2.96 (m, 1H), 3.30 (d, *J* = 12.8 Hz, 1H), 3.96 (d, *J* = 13.1 Hz, 1H), 7.23−7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.9, 27.9, 44.0, 54.5, 59.0; 65.4, 126.8, 128.2 (2 C, isochrones), 128.7 (2 C, isochrones), 139.8. MS (EI): *m/z* 190 (M^+).

[(R)-1-Benzylpyrrolidin-2-yl]-methylamine

[(*R*)-1-Benzylpyrrolidin-2-yl]-methylamine was synthesized under the same reaction conditions starting from *(R)-N*-benzylproline ethyl ester; yield: 78.5 mg (55%). $[\alpha]_D^{20}$: +68.8° (c 1.0, $CHCl_3$).

*General procedure for the preparation of carboxamides **1** and **2***

Three equivalents of oxalyl chloride were added to a suspension of the corresponding acid in abs. toluene (2 mL) under nitrogen atmosphere. The mixture was heated slowly to 40 °C until gas development was observed, then stirred for 1 h at RT and finally 4 h at 60 °C. Evaporation of the liquid gave a solid, which was dissolved in abs. CH_2Cl_2 (2 mL) and subsequently added to a solution of 1.1 equivalents of amine in abs. CH_2Cl_2 at −60 °C. The reaction mixture was allowed to warm to RT and stirred for 45 min. A saturated $NaHCO_3$ solution (5 mL) was added, the mixture extracted with CH_2Cl_2, the solvent dried (Na_2SO_4) and evaporated giving a solid, which was purified by flash chromatography.

*N-[(S)-1-Benzylpyrrolidin-2-ylmethyl]-pyrazolo[1,5-a]pyridine-3-carboxamide (**1a**)*

The reaction was carried out using **3** (47.0 mg, 0.29 mmol) in toluene, oxalyl chloride (76 μL, 0.87 mmol) and [(*S*)-1-benzylpyrrolidin-2-yl]-methylamine (60.6 mg, 0.32 mmol) in CH_2Cl_2. The product was purified by flash chromatography (CH_2Cl_2 : MeOH = 90:10) obtaining a white sticky solid. Yield: 86 mg (89%). $[\alpha]_D^{20}$: −119.7° (c 0.4, $CHCl_3$). IR (NaCl) ν: 3328, 2962, 2796, 1639, 1550, 1531, 1272, 748 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.67−1.77 (m, 3H), 1.94−2.02 (m, 1H), 2.29−2.37 (m, 1H), 2.86−2.93 (m, 1H), 3.05−3.10 (m, 1H), 3.36 (ddd, *J* = 13.8 Hz, 4.3 Hz, 3.2 Hz, 1H), 3.43 (d, *J* = 13.1 Hz, 1H), 3.76 (ddd, *J* = 13.8 Hz, 7.4 Hz, 2.8 Hz, 1H), 4.00 (d, *J* = 13.1 Hz, 1H), 6.64 (br s, 1H), 6.90 (br dd, *J* = 7.1 Hz, 6.7 Hz, 1H), 7.23−7.27 (m, 1H), 7.29−7.35 (m, 5H), 8.13 (s, 1H), 8.28 (br d, *J* = 8.9 Hz, 1H), 8.49 (br d, *J* = 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 22.9, 28.2, 39.9, 54.5, 58.5, 62.5, 106.8, 113.4, 119.5, 126.3, 127.1, 128.2, 128.5, 128.6, 128.8 (2 C, isochrones), 138.4, 140.4, 140.5, 162.6. MS (EI): *m/z* 334 (M^+). Anal. Calcd. for $C_{20}H_{22}N_4O \times 3/4\ H_2O$: C, 69.04; H, 6.81; N, 16.10; found C, 69.25; H, 6.79; N, 15.54.

ent-**1a** could be synthesized under the reaction conditions described for **1a**; yield: 83 mg (98%). $[\alpha]_D^{20}$: +121.0° (c 1, $CHCl_3$).

*N-[(S)-1-Benzylpyrrolidin-2-ylmethyl]-pyrazolo[1,5-a]pyridine-2-carboxamide (**1b**)*

The reaction was carried out using **4** (47.0 mg, 0.29 mmol) in toluene, oxalyl chloride (76 μL, 0.87 mmol) and [(*S*)-1-benzylpyrrolidin-2-yl]-methylamine (60.6 mg, 0.32 mmol) in CH_2Cl_2. The product was purified by flash chromatography (CH_2Cl_2 : MeOH = 95:5) obtaining a white solid. Yield: 88 mg (91%). Mp 98 °C. $[\alpha]_D^{20}$: −127.0° (c 1.0, $CHCl_3$). IR (NaCl) ν: 3401, 2962, 2796, 1666, 1546, 1515, 1257, 740 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.67−1.77 (m, 3H); 1.93−2.00 (m, 1H), 2.22−2.29 (m, 1H), 2.82−2.87 (m, 1H), 2.98−3.03 (m, 1H), 3.35−3.41 (m, 1H), 3.37 (d, *J* =13.1 Hz, 1H), 3.78 (ddd, *J* = 13.8 Hz, 7.5 Hz, 3.2 Hz, 1H), 6.85 (br dd, *J* = 7.1 Hz, 6.7 Hz, 1H), 7.05 (s, 1H), 7.13 (ddd, *J* = 8.9 Hz, 6.7 Hz, 1.1 Hz, 1H), 7.24−7.26 (m, 1H), 7.30−7.35 (m, 2H), 7.40−7.43 (m, 2H), 7.58 (br d, *J* = 8.9 Hz, 1H), 7.64 (br s, 1H), 8.42 (br d, *J* = 7.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.8, 28.4, 40.6, 54.3; 58.6, 62.3, 97.7, 113.3, 119.2, 123.5, 126.9, 128.2, 128.3, 128.5, 128.6, 128.8, 139.5, 141.3, 148.1, 162.5. MS (EI): *m/z* 334 (M^+). Anal. Calcd. for $C_{20}H_{22}N_4O \times 1/5\ H_2O$: C, 71.07; H, 6.68; N, 16.57; found C, 71.19; H, 6.84; N 16.23.

ent-**1b** could be synthesized under the reaction conditions described for **1b**; yield: 81 mg (97%). $[\alpha]_D^{20}$: +127.3° (c 1.0, $CHCl_3$).

*N-[(R)-1-Benzylpyrrolidin-3-yl]-pyrazolo[1,5-a]pyridine-3-carboxamide (**2a**)*

The reaction was carried out using **3** (60.6 mg, 0.37 mmol) in toluene, oxalyl chloride (98 μL, 1.12 mmol) and (*3R*)-(−)-1-benzyl-3-aminopyrrolidine (72.5 mg, 0.41 mmol) in CH_2Cl_2. The product was purified by flash chromatography (CH_2Cl_2 : MeOH = 90:10) obtaining a white sticky solid. Yield: 99 mg (83%). $[\alpha]_D^{20}$: +11.8° (c 1.0, $CHCl_3$). IR (NaCl) ν: 3320, 2958, 2796, 1635, 1550, 1531, 1272, 1068, 752 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.73−1.81 (m, 1H), 2.29−2.44 (m, 2H), 2.65 (dd, *J* = 9.9 Hz, 6.4 Hz, 1H), 2.75 (dd, *J* = 9.9 Hz, 2.5 Hz, 1H), 2.91−2.96 (m, 1H), 3.64 (s, 2H), 4.66−4.74 (m, 1H), 6.41 (br d, *J* = 7.8 Hz, 1H), 6.89 (br dd, *J* = 7.1 Hz, 6.7 Hz, 1H), 7.24−7.34 (m, 6H), 8.16 (s, 1H), 8.28 (br d, *J* = 8.9 Hz, 1H), 8.47 (br d, *J* = 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 32.7, 48.4, 52.7, 60.0, 60.9, 106.8, 113.4, 119.5, 126.3, 127.1, 128.2, 128.5, 128.6, 128.8 (2 C, isochrones), 138.4, 140.5, 140.4, 162.6. MS (EI): *m/z* 320 (M^+). Anal. Calcd. for $C_{19}H_{20}N_4O \times 1/4H_2O$: C, 70.24; H, 6.36; N 17.24; found C, 70.47; H, 6.33; N 17.15.

ent-**2a** could be synthesized under the reaction conditions described for **2a**; yield:106 mg (90%). $[\alpha]_D^{20}$: −12.1° (c 1.0, $CHCl_3$).

*N-[(R)-1-Benzylpyrrolidin-3-yl]-pyrazolo[1,5-a]pyridine-2-carboxamide (**2b**)*

The reaction was carried out using **4** (53.0 mg, 0.33 mmol) in toluene, oxalyl chloride (86 μL, 0.99 mmol) and (*3R*)-(−)-1-benzyl-3-aminopyrrolidine (63.5 mg, 0.36 mmol) in CH_2Cl_2. The product was purified by flash chromatography (CH_2Cl_2 : MeOH = 95:5) obtaining a white solid. Yield: 87 mg (83%). Mp 101 °C. $[\alpha]_D^{20}$: −30.4° (c 1.0, $CHCl_3$). IR (NaCl) ν: 3401, 2919, 2796, 1662, 1546, 1515, 1257, 1025, 744. ^1H NMR ($CDCl_3$) δ: 1.74−1.84 (m, 1H), 2.33−2.43 (m, 2H), 2.69 (dd, *J* = 9.6 Hz, 3.5 Hz, 1H,), 2.76 (dd, *J* = 9.7 Hz, 6.6 Hz, 1H), 2.83−2.90 (m, 1H), 3.61−3.69 (m, 2H), 4.65−4.75 (m, 1H), 6.84 (br dd, *J* = 7.1 Hz, 6.7 Hz, 1H), 7.03 (s, 1H), 7.13 (ddd, *J* = 8.9 Hz, 6.7 Hz, 1.1 Hz, 1H), 7.24−7.38 (m, 6H), 7.57 (br d, *J* = 8.9 Hz, 1H), 8.38 (dd, *J* = 7.1 Hz, 1.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 32.5, 48.4, 52.7, 60.1, 60.7, 97.9, 113.5, 119.2, 123.6, 127.0, 128.1, 128.2, 128.4, 128.5, 128.7, 138.7, 141.3, 147.9, 161.4. MS (EI): *m/z* 320 (M^+). Anal. Calcd. for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49; found: C, 71.49; H, 6.38; N, 17.49.

ent-**2b** could be synthesized under the reaction conditions described for **2b**; yield:113 mg (97%). $[\alpha]_D^{20}$: +32.8° (c 1.0, $CHCl_3$).

Receptor binding experiments and data analysis

Receptor binding studies were carried out as described in literature [17]. In brief, the dopamine D_1 receptor assay was done with porcine striatal membranes at a final protein concentration of 40 μg/assay tube and the radioligand [^{3}H]SCH23390 at 0.3 nM (K_d = 0.5 nM). Competition experiments with the human D_{2long}, D_{2short}, D_3 and $D_{4.4}$ receptors were run with preparations of membranes from CHO cells expressing the corresponding receptor and [^{3}H]spiperone at a final concentration of 0.5 nM. The assays were carried out at a protein concentration of 6−30 μg/assay tube and K_d values of 0.10 nM for D_{2long}, D_{2short} and D_3 and 0.10−0.13 nM for $D_{4.4}$.

The resulting competition curves were analyzed by nonlinear regression using the algorithms in PRISM (GraphPad Software, San Diego, USA). The data were fit using a sigmoid model to provide an IC_{50} value, representing the concentration corresponding to 50% of maximal inhibition. IC_{50} values were transformed to K_i values according to the equation of Cheng and Prusoff [22].

Mitogenesis assay

The mitogenesis experiments were done with a CHO10001A cell line stably transfected with the rat dopamine $D_{4.2}$ receptor according to literature [18]. In brief, cells were grown in MEM α-medium supplemented with fetal calf serum, L-glutamine, penicillin G, streptomycin and hygromycin B at 37 °C under a humidified atmosphere of 5% CO_2−95% air at a density of 10,000 cells/well. After 72 h the growth medium was removed and the cells were rinsed twice with serum free medium. Incubation was started by adding seven different concentrations of the test compounds (with a final concentration of 0.01−10,000 nM) diluted in 10 μL of sterile water to each well containing 90 μL serum free medium. Eight wells of every plate contained 100 μL serum free medium or medium supplemented with 10% fetal calf serum to control stimulation of growth. After incubation for 20 h, 0.02 μCi [^{3}H]thymidine (specific activity 25 Ci/mmol) in 10 μL serum free medium was added to each well for 2 h at 37 °C. Finally, cells were trypsinized and har-

vested onto GF/C filters using an automated cell harvester. Filters were washed four times with ice-cold PBS buffer and counted in a microplate scintillation counter.

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