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# Phenylpiperazinylmethylindolecarboxylates and Derivatives as Selective $D_4$-Ligands

Annette Moll, Harald Hübner, Peter Gmeiner and Reinhard Troschütz*

*Department of Medicinal Chemistry, Emil Fischer Center, Friedrich-Alexander University, Schuhstrasse 19, D-91052 Erlangen, Germany*

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**Abstract**—Novel phenylpiperazinylmethylindolecarboxylates were synthesized for evaluation as potential $D_4$-ligands. Test compounds showed high affinity for the human dopamine $D_4$ receptor and great selectivity over the other receptor subtypes. Intrinsic effects of indole derivatives, which indicated most promising binding properties, were investigated in a mitogenesis assay. 

## Introduction

Recently, there have been numerous investigations on the role of the dopaminergic system in mechanisms of neurological and psychiatric disorders such as Parkinson's disease or schizophrenia. New insights were possible because of the advances in molecular biological techniques, which led to the characterization of different dopamine receptor subtypes. The dopamine receptors are classified in two main families—the $D_1$-like, consisting of $D_1$ and $D_5$ subtype, and the $D_2$-like, including the $D_2$, $D_3$ and $D_4$ subtypes. The findings of Seeman et al.,[1] who reported elevated density of dopamine $D_4$ receptors in post-mortem brains of schizophrenic patients, were followed by a controverse discussion.

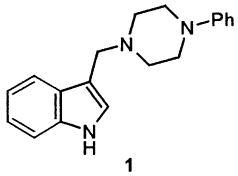
In spite of this, special interest is focused on selective $D_4$ receptor ligands, because it is known that the atypical neuroleptic drug clozapine binds preferentially to this receptor subtype. The selectivity over the $D_2$ receptor is considered responsible for the lack of extrapyramidal motoric symptoms. Following observations by Löber et al.[2] $D_4$ selectivity of phenylpiperazinylmethylpyrazolo[1,5-*a*]pyridines is induced by a certain negative molecular electrostatic potential (MEP).

In the course of synthesis of functionalised indoles, we planned to modify the structure of 3-(4-phenylpiperazin-1-ylmethyl)indole (**1**) (Fig. 1), which shows only moderate $D_4$ selectivity,[3] by introducing an electronegative carboxylate moiety. We report investigations on the effect of the relative topicity of the basic side chain and a carboxylate moiety (**3a**–**e**) on binding properties, as well as the synthesis of target compounds **5** and **6** and the related structures **7** and **8**. Finally the carboxylate group is replaced by other electronegative substituents and results of dopamine receptor binding studies are presented.

## Chemistry

In order to find out the optimum relative topicity of the basic side chain and the carboxylate moiety, the 3-(4-phenylpiperazin-1-ylmethyl)indolcarboxylates **3a**–**e** were prepared. Treatment of the Mannich bases **2a**–**d** [4] with 4-phenylpiperazine in boiling toluene gave **3a-d** by elimination-addition reaction. Compound **3e** was obtained by reductive amination of the methyl 3-formylindole-2-carboxylate **4**, which is known in the literature,[5] with 4-phenylpiperazine and sodium triacetoxyborohydride (Scheme 1).

Results from dopamine receptor binding studies (see Table 1) showed best binding properties for the deriva-




**1**

**Figure 1.**

*Corresponding author. Tel.: +49-9131-852-3923; fax: +49-9131-852-2587; e-mail: troschuetz@pharmazie.uni-erlangen.de

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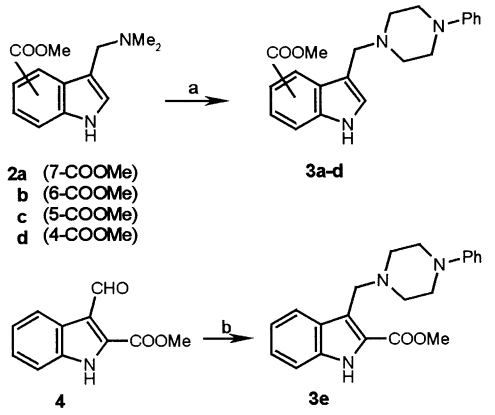
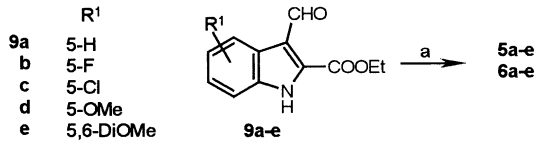



**Scheme 1.** Reagents and conditions: (a) $HNR_2$, toluene, reflux; (b) $HNR_2$, $NaBH(OAc)_3$, DCE, rt.

tive bearing the carboxylate moiety in the indole-2-position (**3e**). Thus indole derivatives **5a**–**e**, **6a**–**e**, as well as their isomeric derivatives **7a**–**d** and **8a**,**b**, were synthesised by reductive amination of the corresponding aldehydes (Fig. 2).

The known aldehydes **9a**–**e**[6–8] were employed as starting material leading to indole derivatives **5a**–**e** and **6a**–**e** using sodium triacetoxyborohydride and the adequate phenylpiperazine in 1,2-dichloroethane (DCE) at room temperature (Scheme 2).[9]




**Scheme 2.** (a) $HNR_2$, $NaBH(OAc)_3$, DCE, rt.

Furthermore, we were interested in the binding properties of the derivatives bearing the piperazinylmethyl side chain in position 2 of the indole. To yield compounds **7a**–**c** and **8a**,**b** the ethyl 2-formylindole-3-carboxylates **12a**–**c** were required. Compound **12a** was obtained in a one pot procedure by treating 1,4-benzoquinone **11** with the enamine **10**[10] in a Nenitzescu indole synthesis using EtOAc/HOAc (10/1) as solvent.[11] The diethyl acetal moiety is cleaved by the acid conditions in this reaction. The dimethylated derivative **12b** could be obtained by methylation of **12a** with MeI and $K_2CO_3$ in acetone. Further reductive amination of the resulting aldehydes **12a**–**b**, as described above, gave **7a**,**b** and **8a**,**b** (Scheme 3).

Results from dopamine receptor binding studies (Table 1) showed loss of affinity with alkylation of the indole-N. Similar effects have been reported by Thurkauf et al.[12] for the affinity of phenylpiperazinylmethyl sub-

**Table 1.** Receptor binding data [$K_i$ values (nM)] of different (4-phenylpiperazin-1-ylmethyl)-indole-derivatives employing bovine $D_1$ and human $D_2$, $D_3$ and $D_{4.4}$ receptors[a]

| Entry | [$^3$H]SCH23390 | [$^3$H]spiperone | | | |
|---|---|---|---|---|---|
| | $D_1$ | $D_{2\ long}$ | $D_{2\ short}$ | $D_3$ | $D_{4.4}$ |
| **1** | 3100 | 570 | 660 | 3400 | 2.9 |
| **19** | | 900 | 820 | 680 | 0.51 |
| Clozapine | 420 | 41 | 28 | 960 | 16 |
| **3a** | 1700 | 870 | 600 | 3000 | 11 |
| **3b** | 920 | 1600 | 450 | 750 | 56 |
| **3c** | 46,000 | 48,000 | 90,000 | >100,000 | 800 |
| **3d** | 4700 | 49,000 | 53,000 | 32,000 | 4400 |
| **3e** | 3000 | 4200 | 1300 | 3500 | 2.5 |
| **5a** | 3700 | 5000 | 5700 | 3800 | 1.9 |
| **5b** | 2400 | 22,000 | 25,000 | 15,000 | 1.5 |
| **5c** | 10,000 | 43,000 | 80,000 | 16,000 | 5.0 |
| **5d** | 12,000 | 36,000 | 32,000 | 17,000 | 5.1 |
| **5e** | 3100 | 45,000 | 50,000 | 56,000 | 6.1 |
| **6a** | 3100 | 4700 | 8900 | 2000 | 2.5 |
| **6b** | 18,000 | 43,000 | 65,000 | 22,000 | 19 |
| **6c** | 21,000 | 44,000 | 48,000 | 31,000 | 19 |
| **6d** | 18,000 | 67,000 | 36,000 | 37,000 | 33 |
| **6e** | 16,000 | 17,000 | 25,000 | 37,000 | 200 |
| **7a** | 970 | 1900 | 1400 | 6700 | 4.8 |
| **7b** | 16,000 | 38,000 | 56,000 | 34,000 | 14,000 |
| **7c** | 2500 | 7600 | 7000 | 4100 | 4.6 |
| **7d** | 5200 | 2000 | 1500 | 2200 | 1.1 |
| **8a** | 570 | 5100 | 6200 | 3900 | 6.9 |
| **8b** | 4900 | 27,000 | 30,000 | 22,000 | 3000 |
| **16a** | 3500 | 2100 | 1600 | 3300 | 0.66 |
| **16b** | 4700 | 4100 | 5600 | 2400 | 1.2 |
| **16c** | 6400 | 2600 | 2900 | 2400 | 1.4 |
| **16d** | 5000 | 4900 | 3200 | 2500 | 0.76 |
| **20a** | 6000 | 910 | 510 | 3500 | 5.4 |
| **20b** | 17,000 | 56,000 | 73,000 | 70,000 | 3.3 |
| **20c** | 24,000 | 13,000 | 14,000 | 13,000 | 7.3 |
| **20d** | 5800 | 1200 | 1300 | 5000 | 4.7 |
| **20e** | 14,000 | 8800 | 14,000 | 3700 | 0.50 |

[a] $K_i$ values are the means of 2–4 independent experiments each carried out in triplicate.

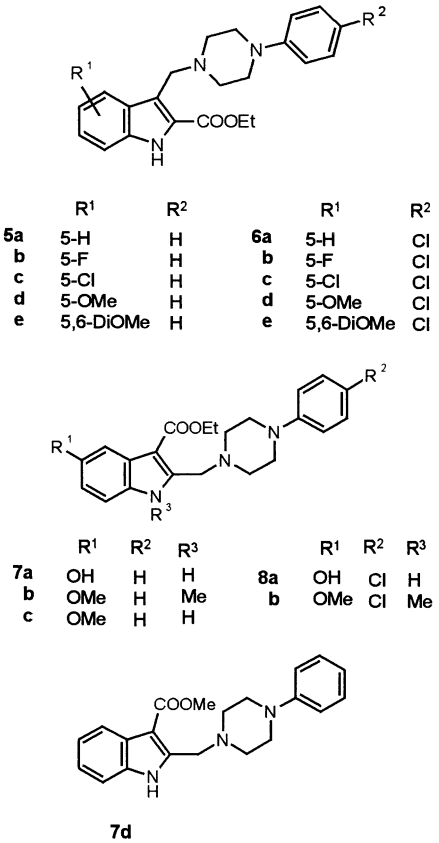
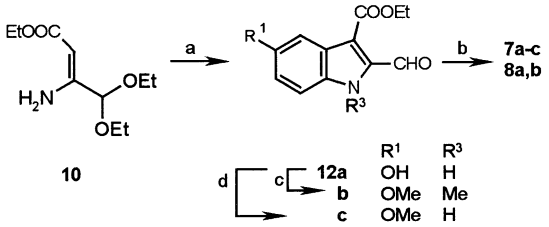
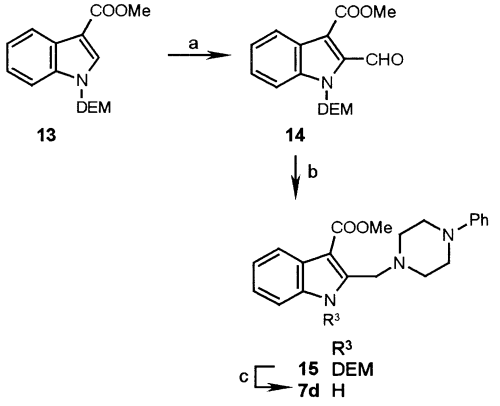



**Figure 2.**



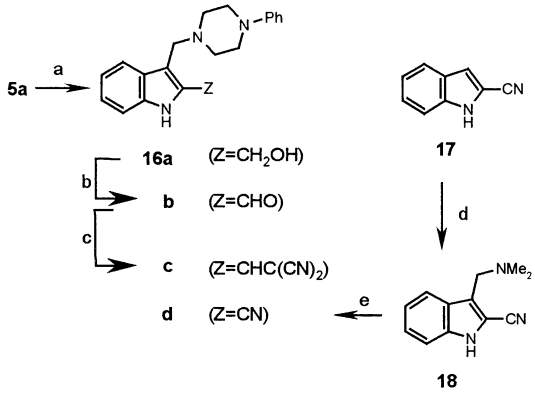

**Scheme 3.** Reagents and conditions: (a) 1,4-benzoquinone (**11**), EtOAc/HOAc (10/1), 50 °C; (b) $HNR_2$, $NaBH(OAc)_3$, DCE, rt; (c) MeI, $K_2CO_3$, acetone, reflux; (d) (i) $HC(OEt)_3$, 160 °C; (ii) see (c); (iii) EtOH, HCl (2 N), rt.

stituted pyrroles to the $D_2$-receptor. To gain the monomethylated derivative **12c**, in order to maintain the NH-function and $D_4$-affinity as well, the NH-group of **12a** had to be protected with the diethoxymethyl-(DEM)-group[13] before being methylated. Deprotection was performed in EtOH/HCl (2 N) at room temperature and led to **12c**, which was used as a crude product in the following reductive amination leading to **7c**. The 5-unsubstituted indole derivative **7d** could not be achieved using the Nenitzescu method. Therefore the formyl group was introduced by *ortho*-lithiation[14,15] in position 2 of the DEM-protected indole **13**, which was treated with DMF and subsequently hydrolysed to the *N*-protected 2-formyl-indole-3-carboxylate **14**. Related structures have yet only been synthesised by oxidative methods.[16,17] Indole derivative **7d** was obtained by reductive amination and following deprotection with EtOH/HCl (2 N) at room temperature (Scheme 4).



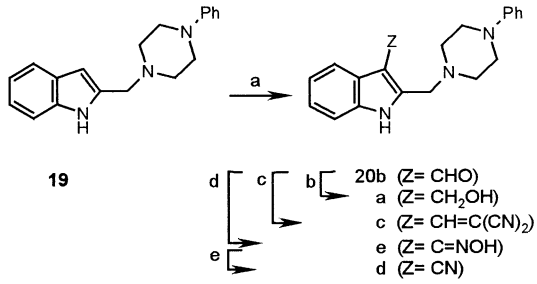

**Scheme 4.** Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; DMF, rt; $NaHCO_3/H_2O$; (b) $HNR_2$, $NaBH(OAc)_3$, DCE, rt; (c) EtOH, HCl (2 N), rt.

In order to get further information about the negative MEP, that seems to induce $D_4$ selectivity, indoles **16a–d** and **20a–e**, containing an electronegative substituent *Z*, were prepared. The indole-2-carboxylate **5a** was reduced with $LiAlH_4$ in THF at room temperature to yield the alcohol **16a**, which could easily be transformed into the aldehyde **16b** by $MnO_2$ oxidation. Following Knoevenagel condensation with malononitrile in EtOH gave rise to the dicyanovinyl derivative **16c**. The indole-2-carbonitrile **16d**, an isomeric compound of previously described 5-cyano -derivatives,[18] could be achieved by amine exchange with 4-phenylpiperazine in boiling toluene from 2-cyanogramine (**18**), which was obtained from 2-cyanoindole (**17**) by aminomethylation (Scheme 5).




**Scheme 5.** Reagents and conditions: (a) $LiAlH_4$, ether, 0 °C; (b) $MnO_2$, $CH_2Cl_2$, rt; (c) $H_2C(CN)_2$, EtOH, $NEt_3$, 0 °C; (d) $H_2C{=}N(CH_3)_2^+Cl^-$, $CH_2Cl_2$, rt; (e) $HNR_2$, toluene, reflux.

3-*Z*-Substituted 2-phenylpiperazinylmethylindoles **20a–e** were obtained from 2-(4-phenylpiperazin-1-ylmethyl)-indole (**19**),[19] a regioisomer of **1**, as starting material. Vilsmeier formylation of **19** gave the aldehyde **20b**. Following reduction of **20b** with $LiAlH_4$ in ether afforded the alcohol **20a**. **20b** was also reacted with malononitrile in EtOH to yield the dicyanovinyl derivative **20c**. Treatment of the aldehyde **20b** with hydroxylamine hydrochloride in EtOH provided the oxime **20e**, which was dehydrated to the nitrile **20d** (Scheme 6).




**Scheme 6.** Reagents and conditions: (a) $POCl_3$, DMF, 0 °C; (b) $LiAlH_4$, THF, rt; (c) $H_2C(CN)_2$, EtOH, $NEt_3$, 0 °C; (d) $NH_2OH$, EtOH, $NEt_3$, rt; (e) $(CF_3CO)_2O$, THF, $NEt_3$, rt.

## Results and Discussion

Dopamine $D_1$ receptor binding was determined by measuring the ability to displace [$^3$H]SCH23390 from bovine $D_1$ receptors.[20] To assess $D_{2\ long}$, $D_{2\ short}$,[21] $D_3$[22] and $D_{4.4}$[23] affinities cloned human dopamine receptor subtypes stably expressed in Chinese hamster ovary cells (CHO)[20] and the radioligand [$^3$H]spiperone were used for competition experiments.

Binding data of the test compounds were depicted in Table 1 and compared to those of lead structure **1** and clozapine. An increased $D_4$-selectivity could be observed due to the introduction of the electronegative carboxylate moiety in target structures **5–8**. Among the indole-2-carboxylates bearing the basic side chain in the indole-

3-position the 5-fluoro (**5b**) and the 5-H (**5a**) derivatives showed highest affinity ($K_i = 1.5$ and 1.9 nM, respectively) to the dopamine $D_4$ receptor and a 10- to 15-fold selectivity over the $D_2$-subtypes in comparison with **1**. A chloro substituent in the side chain neither increased affinity nor selectivity for the $D_4$-subtype in any of the derivatives **6** or **8**.

Variation of the electronegative group led to even more selective dopamine $D_4$-ligands. Best binding properties were provided by the alcohol **16a** ($K_i = 0.66$ nM, about 3200-fold selectivity over $D_{2\ long}$), the nitrile **16d** ($K_i = 0.76$ nM, about 6400-fold selectivity over $D_{2\ long}$) and the oxime **20e** ($K_i = 0.50$ nM, about 28,000-fold selectivity over $D_{2\ short}$).

Intrinsic effects of **5a**, **7d**, **16a**, **16d** and **20e**, which showed most promising binding profiles, were determined by a mitogenesis assay.[18] All of them had partial agonist effects between 32% (**7d**) and 53% (**20e**) compared to quinpirole (100%).

## Experimental

All materials were employed as received from a commercial supplier, unless noted otherwise. Solvents were purified and dried by standard procedures. All anhydrous reactions were performed in oven-dried glassware. Reactions were monitored by thin layer chromatography on analytical plates (Merck, silica gel 60 F, aluminium back) and analysed with 254 nm UV light. Chromatographic purification of the target compounds was performed using silica gel 60 (Merck). Melting points: Büchi melting point apparatus, uncorrected. IR Jasco FT/IR 410 and Perkin-Elmer 1740. MS were run on Finnigan MAT TSQ 70 and 8200 spectrometers with EI (70eV) or on Jeol MS 700 with FD. $^1$H NMR spectra were obtained on a Bruker AM 360 (360 MHz) spectrometer in DMSO-$d_6$ relative to TMS. Microanalyses were performed by the institute of inorganic chemistry (Friedrich Alexander University, Erlangen) using Carlo Erba Elemental Analyser 1108 and are within $\pm 0.4$% of the theoretical values if not noted otherwise.

**Methyl 3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-7-carboxylate (3a).** Methyl 3-dimethylaminomethylindole-7-carboxylate (**2a**) (60 mg, 0.259 mmol) was dissolved in 5 mL of toluene and 4-phenylpiperazine (83.9 mg, 0.518 mmol) was added. The mixture was refluxed for 4 h. After evaporation of the solvent, the residue was purified by column chromatography (cyclohexane/EtOAc = 5:5) to give **3a** (61.0 mg, 68%) as a colourless powder. Mp 133–135 °C; IR 3448, 2915, 2819, 1697, 1500, 1284 cm$^{-1}$; $^1$H NMR δ 2.52–2.55 (m, 4H, ArNC$H_2$CH$_2$), 3.09–3.11 (m, 4H, ArNCH$_2$C$H_2$), 3.72 (s, 2H, ArC$H_2$), 3.95 (s, 3H, OC$H_3$), 6.73–6.77 (m, 1H, H-4′), 6.88–6.92 (m, 2H, H-2′/6′), 7.11–7.20 (m, 3H, H-3′/5′/5), 7.34 (d, $J = 2.5$ Hz, 1H, H-2), 7.78 (dd, $J = 0.7$, 6.7 Hz, 1H, H-6), 8.00 (d, $J = 7.5$ Hz, 1H, H-4), 11.05 (s, br, 1H, NH, exchangeable with $D_2O$). MS (FD) $m/z$: 350 $[M+1]^+$. Anal. $C_{21}H_{23}N_3O_2$ (349.41) calcd C 72.19; H 6.63; N 12.03; found C 72.33; H; 7.10; N 11.91.

**Methyl 3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-6-carboxylate (3b).** Preparation and purification according to **3a** from **2b** gave **3b** (84.8 mg, 94%) as a colourless powder. Mp 191–192 °C; IR 3325, 2819, 1704, 1500, 1280, 1218 cm$^{-1}$; $^1$H NMR δ 2.53–2.55 (m, 4H), 3.09–3.12 (m, 4H), 3.70 (s, 2H), 3.85 (s, 3H), 6.73–6.76 (m, 1H), 6.88–6.92 (m, 2H), 7.17–7.21 (m, 2H), 7.53 (d, $J = 2.5$ Hz, 1H), 7.62 (dd, $J = 1.4$, 8.5 Hz, 1H), 7.75 (d, $J = 8.5$ Hz, 1H), 8.05 (d, $J = 1.4$ Hz, 1H), 11.38 (s, br, 1H). MS (FD) $m/z$: 350 $[M+1]^+$. Anal. $C_{21}H_{23}N_3O_2$ (349.41) C, H, N.

**Methyl 3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-5-carboxylate (3c).** Preparation and purification according to **3a** from **2c** gave **3c** (71.5 mg, 79%) as a colourless powder. Mp 168–169 °C; IR 3340, 2950, 1693, 1511, 1434, 1245 cm$^{-1}$; $^1$H NMR δ 2.54–2.57 (m, 4H), 3.08–3.12 (m, 4H), 3.72 (s, 2H), 3.84 (s, 3H), 6.73–6.77 (m, 1H), 6.89–6.93 (m, 2H), 7.16–7.23 (m, 2H), 7.40 (s, 1H), 7.45 (d, $J = 8.9$ Hz, 1H), 7.74 (d, $J = 8.9$ Hz, 1H), 8.39 (s, 1H), 11.36 (s, br, 1H). MS (FD) $m/z$: 350 $[M+1]^+$. Anal. $C_{21}H_{23}N_3O_2$ (349.41) C, H, N.

**Methyl 3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-4-carboxylate (3d).** Preparation and purification according to **3a** from **2d** gave **3d** (61.5 mg, 68%) as a colourless powder. Mp 155 °C; IR 3345, 2822, 1715, 1598, 1496, 1349, 1269 cm$^{-1}$; $^1$H NMR δ 2.35–2.42 (m, 4H), 2.98–3.03 (m, 4H), 3.68 (s, 2H), 3.84 (s, 3H), 6.73–6.77 (m, 1H), 6.87–6.90 (m, 2H), 7.12–7.20 (m, 3H), 7.30–7.33 (m, 1H), 7.43 (s, br, 1H), 7.58 (d, $J = 7.5$ Hz, 1H), 11.30 (s, br, 1H). MS (FD) $m/z$: 350 $[M+1]^+$. Anal. $C_{21}H_{23}N_3O_2$ (349.41) C, H, N.

**Methyl 3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carboxylate (3e).** To a mixture of **4** (140 mg, 0.691 mmol) and *N*-phenylpiperazine (112 mg, 0.691 mmol) in 5 mL of DCE sodium triacetoxyborohydride (205 mg, 0.967 mmol) was added under nitrogen atmosphere. After 8 h of stirring at room temperature saturated $NaHCO_3$ solution was added and the mixture was extracted with $CH_2Cl_2$. The dried and concentrated organic layer was purified by flash chromatography (cyclohexane/EtOAc = 7:3) to afford **3e** (135 mg, 56%) as a colourless powder. Mp 170–172 °C; IR 3316, 2950, 1685, 1492, 1454, 1234 cm$^{-1}$; $^1$H NMR δ 2.56–2.61 (m, 4H), 3.07–3.11 (m, 4H), 3.89 (s, 2H), 4.07 (s, 3H), 6.73–6.76 (m, 1H), 6.88–6.91 (m, 2H), 7.05–7.09 (dd, $J = 7.1$, 8.2 Hz, 1H), 7.16–7.20 (m, 2H), 7.25–7.29 (dd, $J = 7.1$, 8.2 Hz, 1H), 7.43 (d, $J = 8.2$ Hz, 1H), 7.89 (d, $J = 8.2$ Hz, 1H), 11.71 (s, br, 1H). MS (FD) $m/z$: 350 $[M+1]^+$. Anal. $C_{21}H_{23}N_3O_2$ (349.41) C, H, N.

**Ethyl 3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carboxylate (5a).** Preparation and purification according to **3e** from **9a** gave **5a** (195 mg, 78%) as a colourless powder. Mp 175 °C; IR 3320, 2935, 1681, 1496, 1454, 1226 cm$^{-1}$; $^1$H NMR δ 1.37 (t, $J = 7.1$ Hz, 3H), 2.56–2.59 (m, 4H), 3.07–3.10 (m, 4H), 4.06 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.73–6.77 (m, 1H), 6.87–6.92 (m, 2H), 7.05–7.09 (m, 1H), 7.15–7.20 (m, 2H), 7.22–7.28 (m, 1H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 11.66 (s, br, 1H). MS (EI) $m/z$: 363 $[M]^+$. Anal. $C_{22}H_{25}N_3O_2$ (363.44) C, H, N.

**Ethyl 5-fluoro-3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carboxylate (5b).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **3e** from **9b** gave **5b** (192 mg, 73%) as a colourless powder. Mp 175 °C; IR 3320, 2935, 2850, 1681, 1600, 1500, 1461, 1238 $cm^{-1}$; $^1H$ NMR δ 1.37 (t, $J = 7.1$ Hz, 3H), 2.56–2.58 (m, 4H), 3.08–3.10 (m, 4H), 4.03 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.73–6.77 (m, 1H), 6.88–6.92 (m, 2H), 7.11–7.20 (m, 3H), 7.45 (dd, $J = 4.6$, 8.9 Hz, 1H), 7.61 (dd, $J = 2.5$, 9.9 Hz, 1H), 11.78 (br s, 1H). MS (FD) *m/z*: 416 $[M+1]^+$. Anal. $C_{22}H_{24}N_3O_2F$ (381.43) C, H, N.

**Ethyl 5-chloro-3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carboxylate (5c).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **3e** from **9c** gave **5c** (150 mg, 55%) as a colourless powder. Mp 205–206 °C; IR 3297, 2766, 1682, 1455, 1397, 1260 $cm^{-1}$; $^1H$ NMR δ 1.37 (t, $J = 7.1$ Hz, 3H), 2.56–2.59 (m, 4H), 3.08–3.11 (m, 4H), 4.04 (s, 2H), 4.37 (q, $J = 7.1$ Hz, 2H), 6.73–6.77 (m, 1H), 6.88–6.92 (m, 2H), 7.16–7.21 (m, 2H), 7.27 (dd, $J = 8.8$, 1.8 Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.93 (d, $J = 1.8$ Hz, 1H), 11.88 (br s, 1H). MS (EI) *m/z*: 397 $[M]^+$. Anal. $C_{22}H_{24}N_3O_2Cl$ (397.89) C, H, N.

**Ethyl 5-methoxy-3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carboxylate (5d).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **3e** from **9d** gave **5d** (171 mg, 63%) as a colourless powder. Mp 184 °C; IR 3333, 2769, 1681, 1466, 1385, 1259 $cm^{-1}$; $^1H$ NMR δ 1.36 (t, $J = 7.1$ Hz, 3H), 2.57–2.59 (m, 4H), 3.09–3.12 (m, 4H), 3.76 (s, 3H), 4.04 (s, 2H), 4.34 (q, $J = 7.1$ Hz, 2H), 6.73–6.77 (m, 1H), 6.88–6.91 (m, 2H), 6.93 (dd, $J = 8.9$, 2.5 Hz, 1H), 7.17–7.21 (m, 2H), 7.34 (d, $J = 8.9$ Hz, 1H), 7.34 (d, $J = 2.5$ Hz, 1H), 11.53 (br s, 1H). MS (FD) *m/z*: 394 $[M+1]^+$. Anal. $C_{23}H_{27}N_3O_3$ (393.43) C, H, N.

**Ethyl 5,6-dimethoxy-3-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carboxylate (5e).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **3e** from **9e** gave **5e** (180 mg, 62%) as a colourless powder. Mp 170 °C; IR 3328, 2942, 2842, 1673, 1496, 1234 $cm^{-1}$; $^1H$ NMR δ 1.35 (t, $J = 7.1$ Hz, 3H), 2.55–2.58 (m, 4H), 3.07–3.11 (m, 4H), 3.76 (s, 3H), 3.79 (s, 3H), 4.03 (s, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 6.71–6.74 (m, 1H), 6.87 (s, 1H), 6.87–6.93 (m, 2H), 7.18–7.22 (m, 2H), 7.35 (s, 1H), 11.36 (br s, 1H). MS (FD) *m/z*: 424 $[M+1]^+$. Anal. $C_{24}H_{29}N_3O_4$ (423.47) C, H, N.

**Ethyl 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-1*H*-indole-2-carboxylate (6a).** To a mixture of **9a** (100 mg, 0.461 mmol) and N-(4-chlorphenyl)piperazine (90 mg, 0.461 mmol) in 5 mL of DCE sodium triacetoxyborohydride (137 mg, 0.645 mmol) was added under nitrogen atmosphere. After 8 h of stirring at room temperature saturated $NaHCO_3$ solution was added and the mixture was extracted with $CH_2Cl_2$. The dried and concentrated organic layer was purified by flash chromatography (cyclohexane/EtOAc = 9:1) to afford **6a** (98.6 mg, 58%) as a colourless powder. Mp 153–155 °C; IR 3342, 2772, 1772, 1594, 1498, 1235 $cm^{-1}$; $^1H$ NMR δ 1.37 (t, $J = 7.1$ Hz, 3H), 2.55–2.58 (m, 4H), 3.07–3.10 (m, 4H), 4.05 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.88–6.92 (m, 2H), 7.07 (dd, $J = 8.2$ Hz, 1H), 7.19–7.21 (m, 2H), 7.26 (dd, $J = 8.2$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 11.65 (br s, 1H). MS (EI) *m/z*: 397 $[M]^+$. Anal. $C_{22}H_{24}N_3O_2Cl$ (397.89) (×0.25$H_2O$) C, H, N.

**Ethyl 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-5-fluoro-1*H*-indole-2-carboxylate (6b).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **6a** from **9b** gave **6b** (124 mg, 65%) as a colourless powder. Mp 178–179 °C; IR 3320, 1681, 1496, 1458, 1346, 1241 $cm^{-1}$; $^1H$ NMR δ 1.36 (t, $J = 7.1$ Hz, 3H), 2.54–2.57 (m, 4H), 3.08–3.10 (m, 4H), 4.02 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.88–6.92 (m, 2H), 7.14 (ddd, $J = 2.5$, 8.9, 9.2 Hz, 1H), 7.18–7.22 (m, 2H), 7.45 (dd, $J = 4.6$, 9.2 Hz, 1H), 7.61 (dd, $J = 2.5$, 8.9 Hz, 1H), 11.78 (br s, 1H). MS (FD) *m/z*: 416 $[M+1]^+$. Anal. $C_{22}H_{23}N_3O_2ClF$ (415.88) C, H, N.

**Ethyl 5-chloro-3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-1*H*-indole-2-carboxylate (6c).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **6a** from **9c** gave **6c** (114 mg, 57%) as a colourless powder. Mp 170–171 °C; IR 3320, 2923, 1681, 1496, 1454, 1234 $cm^{-1}$; $^1H$ NMR δ 1.37 (t, $J = 7.1$ Hz, 3H), 2.55–2.59 (m, 4H), 3.08–3.12 (m, 4H), 4.03 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.88–6.93 (m, 2H), 7.18–7.22 (m, 2H), 7.26 (dd, $J = 2.0$, 8.9 Hz, 1H), 7.45 (d, $J = 8.9$ Hz, 1H), 7.92 (d, $J = 2.0$ Hz, 1H), 11.87 (br s, 1H). MS (EI) *m/z*: 432 $[M]^+$. Anal. $C_{22}H_{23}N_3O_2Cl_2$ (432.33) (×2$H_2O$) C, H, N.

**Ethyl 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-5-methoxy-1*H*-indole-2-carboxylate (6d).** Preparation and purification ($CHCl_3$/acetone = 9:1) according to **6a** from **9d** gave **6d** (124 mg, 63%) as a colourless powder. Mp 173–174 °C; IR 3305, 2827, 1677, 1496, 1241 $cm^{-1}$; $^1H$ NMR δ 1.36 (t, $J = 7.1$ Hz, 3H), 2.55–2.59 (m, 4H), 3.09–3.11 (m, 4H), 3.76 (s, 3H), 4.03 (s, 2H), 4.34 (q, $J = 7.1$ Hz, 2H), 6.88–6.93 (m, 2H), 6.93 (dd, $J = 2.3$, 8.7 Hz, 1H), 7.17–7.21 (m, 2H), 7.31–7.35 (m, 2H), 11.52 (br s, 1H). MS (EI) *m/z*: 428 $[M]^+$. Anal. $C_{23}H_{26}N_3O_3Cl$ (427.95) C, H, N.

**Ethyl 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-5,6-dimethoxy-1*H*-indole-2-carboxylate (6e).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **6a** from **9e** gave **6e** (180 mg, 67%) as a colourless powder. Mp 195 °C; IR 3336, 2823, 1673, 1496, 1245 $cm^{-1}$; $^1H$ NMR δ 1.35 (t, $J = 7.1$ Hz, 3H), 2.54–2.57 (m, 4H), 3.08–3.12 (m, 4H), 3.76 (s, 3H), 3.79 (s, 3H), 4.02 (s, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 6.88 (s, 1H), 6.90–6.94 (m, 2H), 7.18–7.21 (m, 2H), 7.33 (s, 1H), 11.36 (br s, 1H); MS (EI) *m/z*: 458 $[M]^+$. Anal. $C_{24}H_{28}N_3O_4Cl$ (457.92) (×0.25$H_2O$) C, H, N.

**Ethyl 5-hydroxy-2-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carboxylate (7a).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **3e** from **12a** gave **7a** (167 mg, 64%) as a colourless powder. Mp 192–194 °C; IR 3289, 2932, 1655, 1466, 1232 $cm^{-1}$; $^1H$ NMR δ 1.35 (t, $J = 7.1$ Hz, 3H), 2.60–2.63 (m, 4H), 3.17–3.19 (m, 4H), 4.05 (s, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 6.65 (dd, $J = 8.5$, 2.5 Hz, 1H), 6.74–6.78 (m, 1H), 6.91–6.95 (m,

2H), 7.17–7.25 (m, 3H), 7.35 (d, $J=2.5$ Hz, 1H), 8.87 (s,1H), 11.78 (br s, 1H); MS (EI) $m/z$: 379 $[M]^+$. Anal. $C_{22}H_{25}N_3O_3$ (379.43) C, H, N.

**Ethyl 5-methoxy-1-methyl-2-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carboxylate (7b).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **3e** from **12b** gave **7b** (213 mg, 76%) as a colourless powder. Mp 166–167 °C; IR 2923, 2820, 2383, 1677, 1531, 1407 $cm^{-1}$; $^1H$ NMR δ 1.38 (t, $J=7.1$ Hz, 3H), 2.60–2.63 (m, 4H), 3.08–3.11 (m, 4H), 3.79 (s, 3H), 3.84 (s, 3H), 4.15 (s, 2H), 4.30 (q, $J=7.1$ Hz, 2H), 6.74–6.78 (m, 1H), 6.88–6.92 (m, 3H), 7.16–7.21 (m, 2H), 7.46 (d, $J=8.9$ Hz, 1H), 7.55 (d, $J=2.5$ Hz, 1H). MS (EI) $m/z$: 407 $[M]^+$. Anal. $C_{24}H_{29}N_3O_3$ (407.48) C, H, N.

**Ethyl 5-methoxy-2-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carboxylate (7c). 12a** (100 mg, 0.429 mmol) was refluxed in ethyl orthoformiate for 8 h. Evaporation of the reagent and purification by column chromatography (cyclohexane/ EtOAc = 94:6) gave a crude product (112 mg, 78%), which was methylated according to **12b**. Chromatographic purification (cyclohexane/ EtOAc = 95:5) afforded (93.5 mg, 80%) of the methylated raw product. Hydrolysis in EtOH/HCl (2 N) according to **7d** gave **12c** (66.2 mg, 100%). Following reductive amination according to **3e** from **12c** (60 mg, 0.25 mmol), *N*-phenylpiperazine (41 mg, 0.25 mmol) and sodium triacetoxyborohydride (74 mg, 0.35 mmol) gave **7c** (65.1 mg, 68%) as colourless crystals. Mp 185–186 °C; IR 3023, 2823, 1596, 1496, 1234 $cm^{-1}$; $^1H$ NMR δ 1.37 (t, $J=7.1$ Hz, 3H), 2.61–2.63 (m, 4H), 3.17–3.20 (m, 4H), 3.77 (s, 3H), 4.07 (s, 2H), 4.28 (q, $J=7.1$ Hz, 2H), 6.74–6.77 (m, 1H), 6.80 (dd, $J=2.5$, 8.5 Hz, 1H), 6.91–6.94 (m, 2H), 7.18–7.23 (m, 2H), 7.35 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=2.5$ Hz, 1H), 11.66 (br s, 1H). MS (FD) $m/z$: 394 $[M+1]^+$. Anal. $C_{23}H_{27}N_3O_3$ (393.43) ($\times 0.25H_2O$) C, H, N.

**Methyl 2-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carboxylate (7d). 15** (30 mg, 0.067 mmol) was dissolved in EtOH. After addition of one drop of aqueous HCl (2 N) and 2 h of stirring at room temperature, the mixture was neutralised by addition of saturated $NaHCO_3$ solution (aq.). Extraction with ether gave **7d** (23.4 mg, 100%) as colourless crystals. Mp 177–178 °C; IR 3401, 2927, 1681, 1454, 1226 $cm^{-1}$; $^1H$ NMR δ 2.62–2.66 (m, 4H), 3.18–3.22 (m, 4H), 3.83 (s, 3H), 4.11 (s, 2H), 6.75–6.79 (m, 1H), 6.92–6.95 (m, 2H), 7.13–7.27 (m, 2H), 7.18–7.23 (m, 2H), 7.45–7.48 (m, 1H), 7.94–7.97 (m, 1H), 11.80 (br s, 1H). MS (FD) $m/z$: 350 $[M+1]^+$. Anal. $C_{21}H_{23}N_3O_2$ (349.41) C, H, N.

**Ethyl 2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-5-hydroxy-1*H*-indole-3-carboxylate (8a).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **6a** from **12a** gave **8a** (139 mg, 73%) as a colourless powder. Mp 203 °C; IR 3286, 2815, 1654, 1461, 1338, 1230 $cm^{-1}$; $^1H$ NMR δ 1.35 (t, $J=7.1$ Hz, 3H), 2.59–2.62 (m, 4H), 3.16–3.19 (m, 4H), 4.04 (s, 2H), 4.26 (q, $J=7.1$ Hz, 2H), 6.64 (dd, $J=8.5$, 2.1 Hz, 1H), 6.93–6.96 (m, 2H), 7.20–7.23 (m, 2H), 7.23 (d, $J=8.5$ Hz, 1H), 7.35 (d, $J=2.1$ Hz, 1H), 8.87 (s,1H), 11.51 (br s, 1H). MS (EI) $m/z$: 413 $[M]^+$. Anal. $C_{22}H_{24}N_3O_3Cl$ (413.90) C, H, N.

**Ethyl 2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-5-methoxy-1-methyl-1*H*-indole-3-carboxylate (8b).** Preparation and purification (cyclohexane/EtOAc = 95:5) according to **6a** from **12b** gave **8b** (152 mg, 75%) as a colourless powder. Mp 146–148 °C; IR 2905, 2813, 1678, 1499, 1382 $cm^{-1}$; $^1H$ NMR δ 1.38 (t, $J=7.1$ Hz, 3H), 2.59–2.62 (m, 4H), 3.08–3.11 (m, 4H), 3.79 (s, 3H), 3.83 (s, 3H), 4.14 (s, 2H), 4.29 (q, $J=7.1$ Hz, 2H), 6.89 (dd, $J=8.9$, 2.5 Hz, 1H), 6.91–6.93 (m, 2H), 7.20–7.23 (m, 2H), 7.46 (d, $J=8.9$ Hz, 1H), 7.54 (d, $J=2.5$ Hz, 1H); MS (EI) $m/z$:441 $[M]^+$. Anal. $C_{24}H_{28}N_3O_3Cl$ (441.95) C, H, N.

**Ethyl 2-formyl-5-hydroxy-1*H*-indole-3-carboxylate (12a).** 1,4-Benzoquinone **11** (648 mg, 6 mmol) was dissolved in EtOAc/HOAc (10:1) and the enamine **10** (434 mg, 2 mmol) was added dropwise at 50 °C; the reaction mixture was stirred at 50 °C for 16 h; after cooling a solution of 1.03g NaOAc in $H_2O$ was added dropwise under stirring at room temperature for 2 h. Then pH was adjusted to 7.5 with 2 N NaOH and a yellow precipitate was collected. Recrystallisation from ethylacetate gave **12a** (242 mg, 52%) of pale yellow crystals. Mp 159–160 °C; IR 3284, 2989, 1676, 1651, 1589, 1235 $cm^{-1}$; $^1H$ NMR δ 1.39 (t, $J=7.1$ Hz, 3H), 4.37 (q, $J=7.1$ Hz, 2H), 6.94 (dd, $J=8.9$, 2.5 Hz, 1H), 7.36 (d, $J=8.9$ Hz, 1H), 7.46 (d, $J=2.5$ Hz, 1H), 9.41 (br s, 1H), 10.45 (s, 1H), 12.50 (br s, 1H). MS (EI) $m/z$: 233 $[M]^+$. Anal. $C_{12}H_{11}NO_4$ (233.22) ($\times 0.25H_2O$) C, H, N.

**Ethyl 2-formyl-5-methoxy-1-methyl-1*H*-indole-3-carboxylate (12b). 12a** (233 mg, 1.0 mmol) was dissolved in acetone. $K_2CO_3$ (276 mg, 2.0 mmol) and MeI (2.5 mL, 40 mmol) were added and the mixture was refluxed for 10 h. After evaporation of the solvent the residue was suspended in $H_2O$. Extraction with ether and crystallisation from EtOH gave **12b** (154 mg, 59%) as pale yellow crystals. Mp 115–116 °C; IR 22987, 1700, 1651, 1493, 1275 $cm^{-1}$; $^1H$ NMR δ 1.41 (t, $J=7.1$ Hz, 3H), 3.83 (s, 3H), 4.04 (s, 3H), 4.39 (q, $J=7.1$ Hz, 2H), 7.15 (dd, $J=9.2$, 2.5 Hz, 1H), 7.56 (d, $J=2.5$ Hz, 1H), 7.65 (d, $J=9.2$ Hz, 1H), 10.60 (s, 1H). MS (EI) $m/z$: 261 $[M]^+$. Anal. $C_{14}H_{15}NO_4$ (261.28) C, H, N.

**Methyl 1-diethoxymethyl-2-formyl-1*H*-indole-3-carboxylate (14). 13** (145.5 mg, 0.5 mmol) was dissolved in THF under nitrogen atmosphere and cooled to-78 °C; *n*-BuLi (1.6 M in hexane) (0.34 mL, 0.55 mmol) was added. The mixture was stirred at −78 °C for 15 min and at room temperature for another 30 min. After cooling again to −78 °C DMF (40 μL, 0.52 mmol) was added. The mixture was allowed to warm and the reaction was stopped after 10 min by addition of $NaHCO_3$ solution. Extraction with ether gave **14** (154 mg, 96%) as a colourless powder. Mp 141–143 °C; IR 2977, 1712, 1673, 1454, 1261 $cm^{-1}$; $^1H$ NMR δ 1.09–1.13 (m, 6H), 3.41–3.50 (m, 2H), 3.67–3.76 (m, 2H), 3.96 (s, 3H), 7.26 (s, 1H), 7.33–7.39 (m, 1H), 7.43–7.49 (m, 1H), 7.95–8.00 (m, 1H), 8.13–8.20 (m, 1H), 10.62 (s, 1H). MS (EI) $m/z$: 305 $[M]^+$. Anal. $C_{16}H_{19}NO_5$ (305.28) C, H, N.

**Methyl 1-diethoxymethyl-2-(4-phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carboxylate (15).** Preparation and purification (cyclohexane/EtOAc = 9:1) according to **3e** from **14** (42 mg, 0.138 mmol), *N*-phenylpiperazine (21.7 mg, 0.138 mmol) and sodium triacetoxyborohydride (40.5 mg, 0.195 mmol) gave **15** (34.2 mg, 55%) as colourless crystals. Mp 159–160 °C; IR 2977, 1700, 1500, 1457, 1222 $cm^{-1}$; $^1H$ NMR δ 1.28–1.33 (m, 6H) 2.62–2.68 (m, 4H), 3.08–3.12 (m, 4H), 3.44–3.52 (m, 2H), 3.76–3.84 (m, 2H), 3.87 (s, 3H), 4.20 (s, 2H), 6.66 (s, 1H), 6.74–6.79 (m, 1H), 6.90–6.93 (m, 2H), 7.17–7.23 (m, 4H), 7.82–7.85 (m, 1H), 8.00–8.03 (m, 1H). MS (EI) *m*/*z*: 452 $[M+1]^+$. Anal. $C_{26}H_{33}N_3O_4$ (451.53) C, H, N.

**[3-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indol-2-yl]-methanol (16a). 5a** (180 mg, 0.496 mmol) was suspended in 5 mL of dry ether (0 °C, nitrogen atmosphere). Dry THF was added until dissolution of **5a**. 0.50 mL of a $LiAlH_4$ solution (1 M in THF) were added. The reaction mixture was stirred for 10 min Saturated $NaHCO_3$ soln was added. Neutralisation with 2 N HCl and extraction with ether gave **16a** (132 mg, 83%) as a colourless powder. Mp 175–177 °C; IR 3231, 2825, 1598, 1455, 1230 $cm^{-1}$; $^1H$ NMR δ 2.52–2.55 (m, 4H), 3.06–3.09 (m, 4H), 3.67 (s, 2H), 4.66 (s, 2H), 5.75 (s, br, 1H), 6.73–6.77 (m, 1H), 6.88–6.91 (m, 2H), 6.95 (ddd, *J* = 1.4, 7.5, 8.5 Hz, 1H), 7.03 (ddd, *J* = 1.4, 7.5, 8.5 Hz, 1H), 7.16–7.21 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 10.97 (s, br, 1H). MS (FD) *m*/*z*: 322 $[M+1]^+$. Anal. $C_{20}H_{23}N_3O$ (321.41) (×0.8$H_2O$) C, H, N.

**3-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carbaldehyde (16b). 16a** (100 mg, 0.31 mmol) was dissolved in $CH_2Cl_2$. $MnO_2$ was added and the mixture stirred for 4 h at room temperature. After filtering off the $MnO_2$ and evaporation of the solvent, the residue was purified by column chromatography (cyclohexane/ethylacetate 8:2) to give **16b** (88.0 mg, 89%) as a colourless powder. Mp 176–177 °C; IR 3286, 2814, 1643, 1454, 1242 $cm^{-1}$; $^1H$ NMR δ 2.57–2.61 (m, 4H), 3.08–3.13 (m, 4H), 4.06 (s, 2H), 6.73–6.77 (m, 1H), 6.88–6.92 (m, 2H), 7.09–7.13 (m, 1H), 7.17–7.21 (m, 2H), 7.31–7.35 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 10.18 (s, 1H), 11.80 (s, br, 1H). MS (FD) *m*/*z*: 320 $[M+1]^+$. Anal. $C_{20}H_{21}N_3O$ (319.40) ×0.75$H_2O$) C, H, N.

**2-[3-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indol-2-yl-methylene]malononitrile (16c). 16b** (40 mg, 0.126 mmol) and malononitrile (16.6 mg, 0.126 mmol) were dissolved in 3 mL of EtOH at 0 °C. One drop of triethylamine was added and the mixture stirred at room temperature. After 3 h, **16c** (38.6 mg, 84%) was collected as a yellow precipitate. Mp 175–176 °C; IR 3367, 2933, 2825, 2221, 1587, 1492 $cm^{-1}$; $^1H$ NMR δ 2.53–2.57 (m, 4H), 3.07–3.11 (m, 4H), 3.95 (s, 2H), 6.73–6.77 (m, 1H), 6.88–6.92 (m, 2H), 7.13–7.21 (m, 3H), 7.38–7.42 (m, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 8.62 (s, 1H), 11.24 (s, br, 1H);. MS (FD) *m*/*z*: 368 $[M+1]^+$. Anal. $C_{23}H_{21}N_5$ (367.45) C, H, N.

**3-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indole-2-carbonitrile (16d). 18** (35 mg, 0.176 mmol) and 4-phenylpiperazine (65 mg, 0.40 mmol) were refluxed in 5 mL of toluene for 3 h. After evaporation of the solvent and column chromatography (cyclohexane/ethylacetate 9:1) **16d** (44.5 mg, 80%) was yielded as a colourless powder. Mp 184–186 °C; IR 3444, 2946, 2221, 1558, 1538, 1234 $cm^{-1}$; $^1H$ NMR δ 2.56–2.58 (m, 4H), 3.10–3.12 (m, 4H), 3.84 (s, 2H), 6.72–6.76 (m, 1H), 6.88–6.91 (m, 2H), 7.13–7.20 (m, 3H), 7.31–7.36 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 12.23 (s, br, 1H). MS (FD) *m*/*z*: 317 $[M+1]^+$. Anal. $C_{20}H_{20}N_4$ (316.21) C, H, N.

**3-Dimethylaminomethyl-1*H*-indole-2-carbonitrile (18).** Indole-2-carbonitrile (**17**) (70 mg, 0.50 mmol) and *N*,*N*-dimethylmethyleneimmonium chloride (56.1 mg, 0.60 mmol) were dissolved in 8 mL of dry $CH_2Cl_2$. After 18 h of stirring at room temperature and neutralisation with $NaHCO_3$ (aq) the mixture was extracted with $CH_2Cl_2$. Purification was performed by column chromatography (cyclohexane/ethylacetate 8:2) to give **18** (86.6 mg, 87%) as a colourless powder. Mp 173–174 °C; IR 3316, 2944, 2825, 2220, 1718, 1455, 1348 $cm^{-1}$; $^1H$ NMR δ 2.17 (s, 6H), 3.68 (s, 2H), 7.13–7.16 (m, 1H), 7.31–7.36 (m, 1H), 7.42–7.45 (m, 1H), 7.76–7.79 (m, 1H), 12.20 (s, br, 1H). MS (FD) *m*/*z*: 200 $[M+1]^+$. Anal. $C_{12}H_{13}N_3$ (199.26) (×0.25$H_2O$) C, H, N.

**[2-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indol-3-yl]-methanol (20a). 20b** (180 mg, 0.564 mmol) was suspended in 5 mL of dry ether (0 °C, nitrogen atmosphere). Dry THF was added until dissolution of **20b**. 0.54 mL of a $LiAlH_4$ solution (1 M in THF) were added. The reaction mixture was stirred for 10 min and quenched with saturated $NaHCO_3$ soln. Neutralisation with 2 N HCl and extraction with ether gave **20a** (166 mg, 92%) as a colourless powder. Mp 189–191 °C; IR 3178, 2823, 1596, 1446, 1245 $cm^{-1}$; $^1H$ NMR δ 2.55–2.58 (m, 4H), 3.12–3.14 (m, 4H), 3.70 (s, 2H), 4.65 (s, 3H), 6.74–6.78 (m, 1H), 6.90–6.93 (m, 2H), 6.96 (ddd, *J* = 1.0, 7.0, 8.1 Hz, 1H), 7.04 (ddd, *J* = 1.0, 7.0, 8.5 Hz, 1H), 7.17–7.22 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 10.92 (s, br, 1H). MS (FD) *m*/*z*: 322 $[M+1]^+$. Anal. $C_{20}H_{23}N_3O$ (321.41) (×0.85$H_2O$) C, H, N.

**2-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carbaldehyde (20b).** To a solution of $POCl_3$ (79.0 mg, 0.515 mmol) in 5 mL of DCE, DMF (37.6 mg, 0.515 mmol) was added at 0 °C. After stirring the mixture at room temperature for 30 min, 2-(4-phenylpiperazin-1-ylmethyl)indole (**19**) (100 mg 0.344 mmol) dissolved in 2 mL of DCE was added followed by 2 more hours of stirring at room temperature. After addition of 0.5 g NaOAc in 1 mL $H_2O$ and 1 h of stirring, the pH was adjusted to 8 ($NaHCO_3$). Extraction with $CH_2Cl_2$ and column chromatography (cyclohexane/ethylacetate 5:5) gave **20b** (84.4 mg, 77%) as a colourless powder. Mp 206–208 °C; IR 3234, 2822, 1627, 1460 $cm^{-1}$; $^1H$ NMR δ 2.61–2.64 (m, 4H), 3.16–3.18 (m, 4H), 4.06 (s, 2H), 6.75–6.79 (m, 1H), 6.90–6.94 (m, 2H), 7.16–7.24 (m, 4H), 7.46–7.48 (m, 1H), 8.10 (m, 1H), 10.21 (s, 1H), 12.09 (s, br, 1H). MS (FD) *m*/*z*: 320 $[M+1]^+$. Anal. $C_{20}H_{21}N_3O$ (319.40) (×0.75$H_2O$) C, H, N.

**2-[2-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indol-3-ylmethylene]malononitrile (20c). 20b** (40 mg, 0.126 mmol) and

malononitrile (16.6 mg, 0.126 mmol) were dissolved in 3 mL of EtOH at 0 °C. One drop of triethylamine was added and the mixture stirred at room temperature. After 3 h **20c** (38.9 mg, 84%) was collected as a yellow precipitate. Mp 211–212 °C; IR 3270, 2923, 2211, 1573, 1502, 1454 $cm^{-1}$; $^1H$ NMR δ 2.59–2.62 (m, 4H), 3.16–3.18 (m, 4H), 4.00 (s, 2H), 6.75–6.79 (m, 1H), 6.91–6.95 (m, 2H), 7.18–7.22 (m, 2H), 7.24–7.33 (m, 2H), 7.51–7.55 (m, 1H), 8.08 (dd, $J = 1.4$, 7.1 Hz, 1H), 8.56 (s, 1H), 12.76 (s, br, 1H). MS (FD) $m/z$: 368 $[M+1]^+$. Anal. $C_{23}H_{21}N_5$ (367.45) C, H, N.

**2-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carbonitrile (20d). 20e** (50 mg, 0.150 mmol) was dissolved in 5 mL of THF (0 °C, $N_2$-atmosphere). After addition of triethylamine (15.2 mg, 0.30 mmol) and trifluoroacetic acid anhydride (15.8 mg, 0.150 mmol) the mixture was stirred for 4 h at room temperature. After extraction with $CH_2Cl_2$ the combined organic layers were washed with water, dried and concentrated in vacuo. Purification was performed by column chromatography (cyclohexane/ethylacetate 7:3) to give **20d** (31.8 mg, 67%) as a colourless powder. Mp 149–150 °C; IR 3259, 2931, 2827, 2213, 1504, 1226 $cm^{-1}$; $^1H$ NMR δ 2.60–2.63 (m, 4H), 3.16–3.19 (m, 4H), 3.60 (s, 2H), 6.75–6.80 (m, 1H), 6.92–6.95 (m, 2H), 7.18–7.25 (m, 4H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.58 (d, $J = 7.1$ Hz, 1H), 12.24 (s, br, 1H). MS (FD) $m/z$: 317 $[M+1]^+$. Anal. $C_{20}H_{20}N_4$ (316.41) C, H, N.

**2-(4-Phenylpiperazin-1-ylmethyl)-1*H*-indole-3-carbaldehyde oxime (20e). 20b** (50 mg, 0.157 mmol) and hydroxylamine hydrochloride (12 mg, 0.174 mmol) were dissolved in EtOH. After addition of one drop of triethylamine, the mixture was refluxed for 3 h. After cooling **20e** (33 mg, 63%) was collected as colourless crystals. Mp 224 °C; IR 3320, 2819, 1596, 1442, 1226, 1133 $cm^{-1}$; $^1H$ NMR δ 2.55–2.59 (m, 4H), 3.13–3.17 (m, 4H), 3.80 (s, 2H), 6.74–6.78 (m, 1H), 6.90–6.93 (m, 2H), 7.03–7.07 (m, 1H), 7.11–7.15 (m, 1H), 7.18–7.22 (m, 2H), 7.37 (d, $J = 8.2$ Hz, 1H), 7.97 (d, $J = 7.8$ Hz, 1H), 8.44 (s, 1H), 10.45 (s, br, 1H), 11.41 (s, br, 1H). MS (FD) $m/z$: 335 $[M+1]^+$. Anal. $C_{20}H_{22}N_4O$ (334.41) ($\times 0.25H_2O$) C, H, N.

## Receptor binding studies

Receptor binding assays at the dopamine $D_1$ receptor were carried out using bovine striatal membranes with a final protein concentration of 25 μg/assay tube and a $K_d$ value of 0.27–0.32 nM considering the radioligand [$^3$H]SCH23390 as previously described.[20] Preparations of membranes from CHO cells expressing human dopamine $D_{2\ long}$, $D_{2\ short}$, $D_3$ and $D_{4.4}$ receptors were employed for competition binding analysis displacing the radioligand [$^3$H]spiperone according to literature.[20] The assays were run with a protein concentration of 5–25 μg/assay tube, with $K_d$ values being 0.10–0.20, 010, 0.20 and 0.10–0.30 nM for the $D_{2\ long}$, $D_{2\ short}$, $D_3$ and $D_{4.4}$ receptors, respectively. Mitogenesis experiments were done employing CHO10001 cells stably expressing the human dopamin $D_{4.2}$ receptor as described previously.[18,24]

In brief, 10,000 cells/well were seeded in a 96-well plate and grown for 75 h. Medium was removed and the test compounds were incubated in medium without serum for 20 h with a final concentration of 0.001–10000 nM. After addition of 0.25 μCi of [$^3$H]thymidine and further incubation for 2 h, cells were trypsinised, harvested onto GF/C filters and the incorporated radioactivity was counted in a 96-well scintillation counter.

Protein concentration was established by the method of Lowry using bovine serum albumin as standard.[25]

## Data analysis

The resulting competition curves of the receptor binding experiments were analysed by nonlinear regression using the algorithms in PRISM (GraphPad Software, San Diego, CA, USA). The data were fit in accordance to a sigmoid model to provide an $IC_{50}$ value, representing the concentration corresponding to 50% of maximal inhibition, and then transformed to $K_i$ values applying the equation of Cheng and Prusoff.[26] Data resulting from experiments investigating the stimulation of mitogenesis were each normalised and then combined to get a mean curve. Analysing this curve as described above yielded an $EC_{50}$ value expressing the concentration, which caused half of the maximal rate of incorporation of the radioactive marker to derive the rate of agonistic effect for each test compound in correlation to the reference agonist quinpirole.

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