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Clozapine derived 2,3-dihydro-1*H*-1,4- and 1,5-benzodiazepines with D4 receptor selectivity: synthesis and biological testing

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Abstract—Novel 4-arylpiperazin-1-yl-substituted 2,3-dihydro-1*H*-1,4- and 1*H*-1,5-benzodiazepines and their aza-analogues were synthesized as debenzoclozapine derivatives for evaluation as potential D4-ligands. While K_i values of some of the title compounds came within the range of clozapine, they showed an impressively greater selectivity over other dopamine receptor subtypes, especially D2. For the most promising compounds, intrinsic activity and binding properties to serotonin 5-HT1$_A$ and 5-HT2 were also determined.

1. Introduction

The neurotransmitter dopamine plays an important role in the development of several neurological and psychiatric disorders such as schizophrenia,[1,2] Huntington's disease, and Parkinson's disease.[3] Thus, the investigation of the dopaminergic system has become an important target in research in order to understand the etiology of these diseases and to find efficient drugs for their treatment. Making use of modern molecular biological techniques, five dopamine receptor subtypes (D1–D5) were characterized and divided into two main families, the D1-like (including the D1 and D5 subtype) and the D2-like (D2, D3, and D4).[4,5]

Clozapine (**1**) (Fig. 1), an important atypical neuroleptic agent, blocks preferentially the D4 receptor with significant selectivity versus the D2 subtypes. This is considered to be one of the main reasons causing almost no extra pyramidal motoric disturbance. In vivo, supported by antagonistic effects on serotonin, muscarine, adrenaline, and histamine receptors, amelioration of positive and negative psychotic symptoms as well as of treatment-resistant schizophrenia has been observed.[6] Unfortunately the therapeutic use of clozapine is limited by a particular incidence of agranulocytosis (0.05–2%).[7]

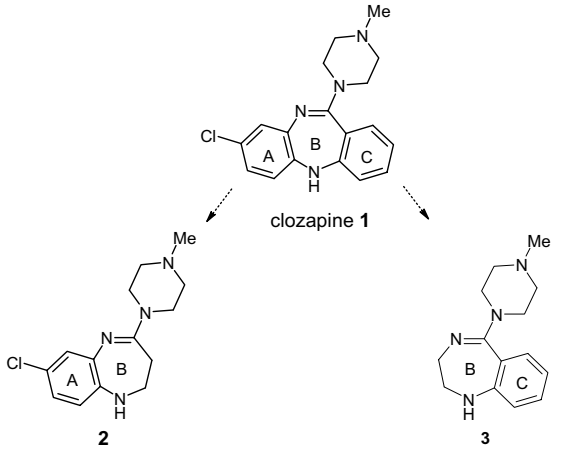

Figure 1.

In the course of our search for new D4 ligands,[8] we planned extensive structure modifications of the tricyclic clozapine (**1**) by formal elimination of ring C as well as ring A giving the bicyclic debenzoclozapines **2** and **3**, respectively.

As their biological testing showed only low D4 affinity (about 17% displacement of radioligand at a concentration of 10 μM for **2** and about 30% for **3**), we decided to attempt further structural variations. Kulagowski et al.[9] have reported that the attachment of a differently substituted *N*-phenylpiperazinylmethyl group in indole

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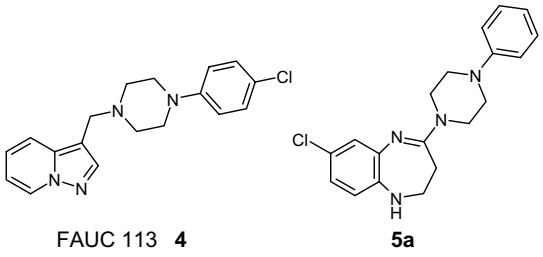


Figure 2.

and 7-azaindole raises the affinity to D4 receptors enormously. Löber et al.[10] have confirmed this observation by synthesizing and testing FAUC 113 (**4**) (Fig. 2), a pyrazolo[1,5-*a*]pyridine derivative with high affinity for the D4 receptor and good selectivity over the other dopamine receptors. Inspired by these results, we replaced the methyl group in **2** with a phenyl group giving the 7-chloro-4-(4-phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**5a**) (Fig. 2). Preliminary calculations in a comparative molecular field analysis (CoMFA) based on D4 ligands of the heteroarylmethylpiperazinylaryl type[11] have predicted a pK_i value of 7.28 for compound **5a**.

For further structure–activity relationship (SAR) studies we prepared a series of 2,3-dihydro-1*H*-1,5-benzodiazepines by altering substituents at ring A (R^1 in **5a**–**d**), at the nitrogen atom in position 5 (R^2 in **5e**,**f**) as well as at the phenyl group of the piperazine side chain (R^3 in **6a**–**f**) or even by changing the phenyl to the benzyl (**6g**) or the pyridin-2-yl (**6h**) group. Finally, we exchanged the benzene ring A in **5a** to a more polar pyridine moiety, which we introduced in two different ways. The 8-chloro-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepine **7b** represents an aza-analogue of **5a**. In the pyridodiazepine **8** the nitrogen atom at position 8 should seize the role of the electronegative chloro residue as realized in **5a** (Fig. 3).

In a similar manner, title compounds **9** and **10** were deduced from 2,3-dihydro-1*H*-1,4-benzodiazepine **3** (Fig. 4).

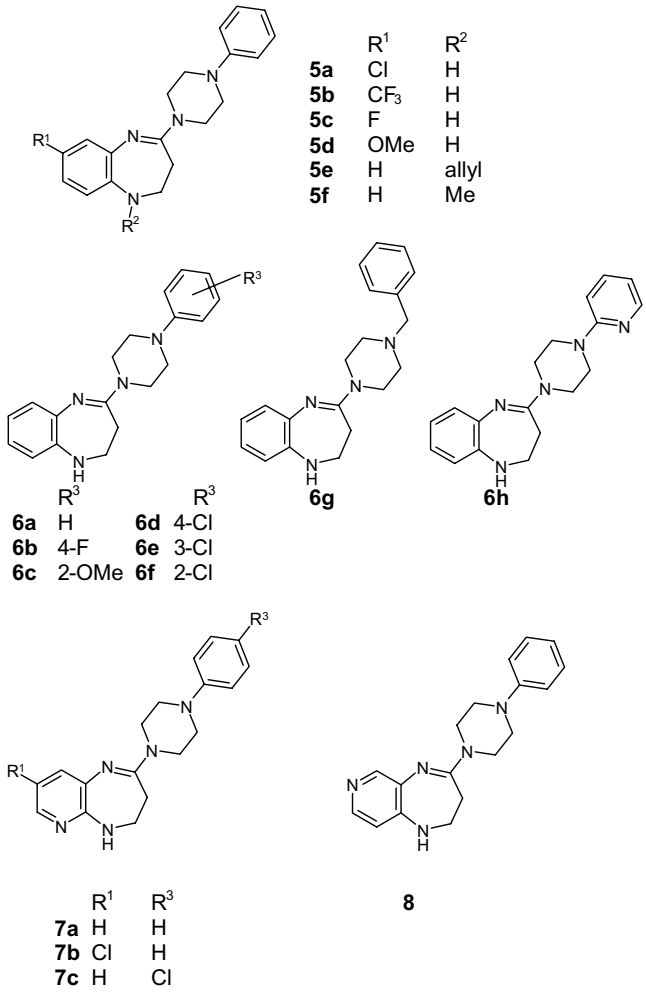


Figure 3.

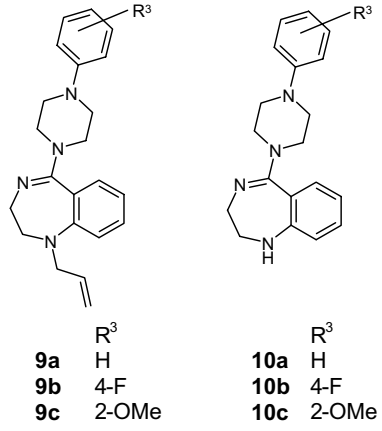


Figure 4.

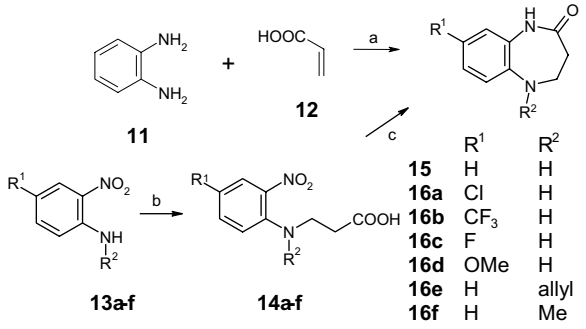
2. Chemistry

After retro synthetic considerations, we planned the synthesis of the title compounds **5**–**10** similar to that of clozapine (**1**)[12] by first preparing the lactams **15**, **16a**–**f**, **26a**,**b**, **30**, and **34**, which should be connected to the appropriate 4-phenylpiperazines in the final step.

2.1. Preparation of lactams 15, 16a–f, 26a,b, 30, and 34

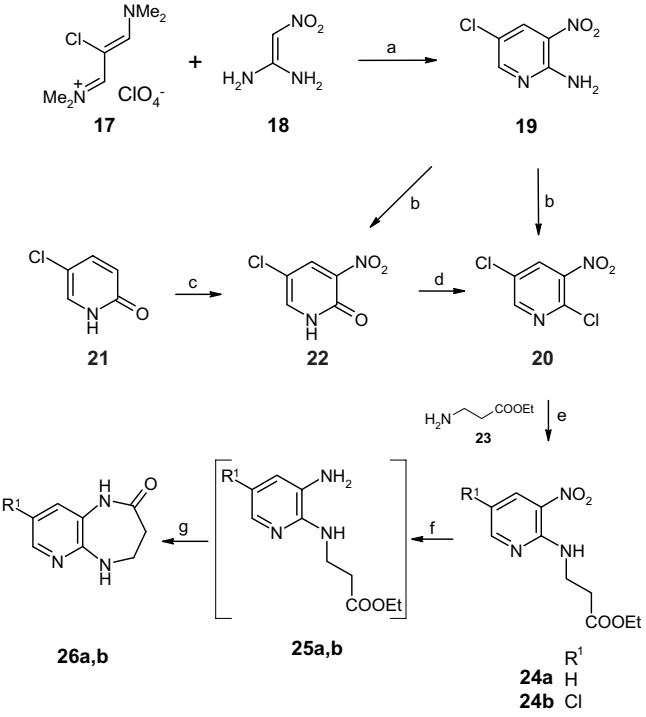
Lactam **15** was prepared from *o*-phenylenediamine (**11**) and acrylic acid (**12**) as described in literature.[13] In analogy to the synthesis of the known lactams **16a**,**b**[14] the nitro anilines **13c**–**f** were treated with acrylic acid in concd H_2SO_4 giving the β-alaninates **14c**–**f**. *N*-Allylnitroaniline (**13e**) was prepared from 2-fluoronitrobenzol and *N*-allylamine.[15] The reduction of the nitro group in **14c**–**f** with zinc powder and concd H_3PO_4 in refluxing dioxane and following ring closure[6] gave rise to the lactams **16c**–**f** (Scheme 1).

In order to obtain the pyridodiazepinones **26a**,**b** and **30**, we needed the *N*-(3-nitropyridin-2-yl)-β-alaninates **24a**,[16]**b** as well as the *N*-(3-nitropyridin-4-yl)-β-alaninate **28** as starting material. Our synthesis of pyridodiazepi-



Scheme 1. Reagents and conditions: (a) EtOH, reflux; (b) acrylic acid (**12**), concd H_2SO_4, 75–80 °C, 15 min; (c) Zn, dioxane, reflux, 2 h.

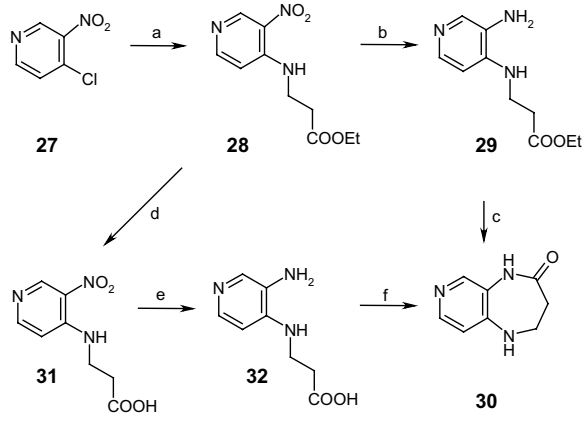
none **26b** started with the cyclocondensation of vinamidinium perchlorate[17] **17** and 2-nitroethen-1,1-diamine (**18**) in abs BuOH[18] giving aminonitropyridine **19** in a good yield. Thus, this new access can be considered as an acceptable alternative to that reported in patent literature.[19] Compound **19** was transformed to the known chloronitropyridine **20**[20] in the next step. To obtain **20** we also performed the nitration of commercially available chloropyridone **21** and following chlorination by treating **22** with PCl_5 in $POCl_3$. However, this way was not favored because of its low yield. According to a method in literature[8] the activated chloro moiety in position 2 of **20** was substituted with ethyl β-alaninate (**23**) in boiling EtOH/Et_3N leading to **24b**. Intramolecular cyclization of **24a**,**b** to the corresponding lactams **26a**,**b** was easily achieved by reducing the nitro group in abs EtOH/Pd–C and refluxing in HOAc (96%) (Scheme 2).



Scheme 2. Reagents and conditions: (a) BuOH, reflux, 4 h; (b) $NaNO_2$, concd HCl, −15 °C; (c) concd HNO_3, concd H_2SO_4, 70 °C, 3 h; (d) PCl_5, $POCl_3$, reflux; (e) ethyl β-alaninate HCl (**23**–HCl), NEt_3, EtOH, reflux, 2 h; (f) H_2, Pd–C (5%), EtOH, 1500 hPa; (g) AcOH (96%), reflux, 4 h.

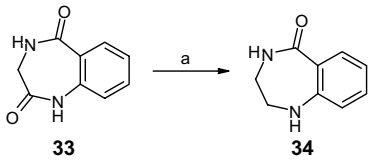
In a similar manner, we prepared pyridodiazepinone **30** starting from the known 4-chloro-3-nitropyridine (**27**)[21] and ethyl β-alaninate (**23**) in boiling EtOH/Et_3N giving **28**. After reduction of the nitro group, the 3-aminopyridine **29** surprisingly did not cyclize well. By varying conditions, for use of numerous solvents and reaction temperature, different kind of acid and base, the formation of **30** succeeded finally in an unsatisfactory yield of 26% using EtOH/concd HCl at 70 °C.

Thus, we thought about an alternative way[22] to effect closure of the seven-membered ring. Hydrolysis of the ethyl ester **28** in 1 N NaOH/THF led to acid **31**, which was reduced in EtOH/Pd–C producing amino acid **32**. In the next step the carboxylic group was activated with 1,3-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) leading to ring closure to 1,2,3,5-tetrahydro-4*H*-pyrido[3,4-*b*][1,4]diazepin-4-one (**30**) (Scheme 3).



Scheme 3. Reagents and conditions: (a) ethyl β-alaninate HCl (**23**–HCl), NEt_3, EtOH, reflux, 2h; (b) H_2, Pd–C (5%), EtOH, 1500 hPa, 2 h; (c) EtOH, HCl, 70 °C, 12 h; (d) THF, 1 N NaOH, 50 °C, 4 h; (e) H_2, Pd–C (5%), EtOH, 3000 hPa, 6 h; (f) DIC, HOBt, DMF, rt, over night.

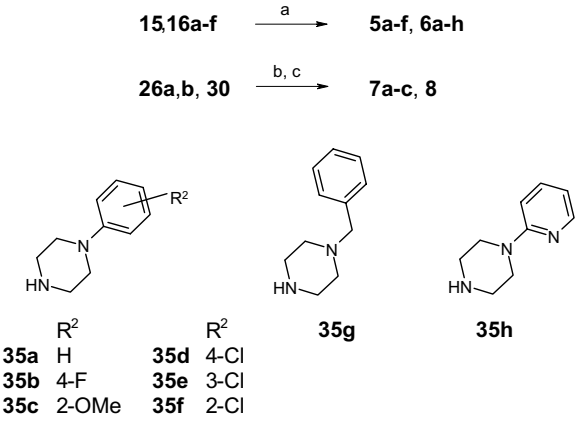
The preparation of lactam **34**, a 1,4-benzodiazepine-5-one, was easily performed by a regioselective reduction[23] of dilactam **33**[24] with $LiAlH_4$ in refluxing THF (Scheme 4).



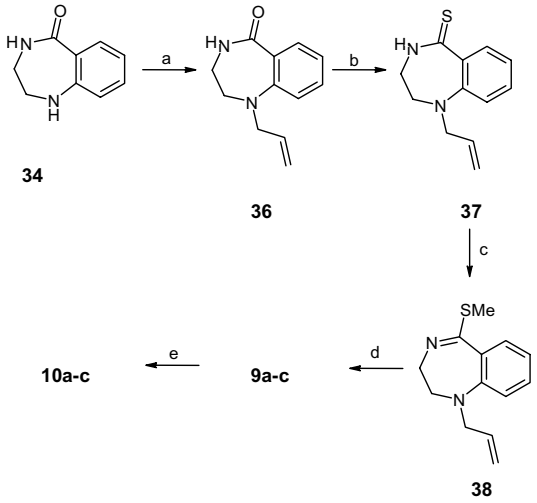
Scheme 4. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 14 h.

2.2. Preparation of title compounds 5–10

Finally, the lactams **15** and **16a**–**f** were converted into the title compounds **5a**–**f**, **6a**–**h** by heating in toluene at



Scheme 5. Reagents and conditions: (a) **35a**–**f**, $TiCl_4$, toluene, 80 °C, 4 h; (b) $PCl_5/POCl_3$, pyridine, reflux, 4 h; (c) **35a**–**d**, EtOH, reflux, 4 h.



Scheme 6. Reagents and conditions: (a) Allyl bromide, triethylamine, benzene, reflux, 2 h; (b) P_2S_5, pyridine, reflux, 2.5 h; (c) NaOEt, MeI, EtOH, reflux, 2 h; (d) **35a**–**c**, AcOH, 120 °C, 12 h; (e) Pd/C (10%), methanesulfonic acid, EtOH, reflux, 2 h.

80 °C after addition of excess of arylpiperazines **35a**–**g** and $TiCl_4$.[25] Due to the minor solubility in toluene, lactams **26a**,**b** and **30** could not be treated in the same way. Hence, they were at first transformed to the reactive imidoyl chlorides using PCl_5 in $POCl_3$/pyridine. These intermediates subsequently reacted with the appropriate phenylpiperazines **35a**–**d** in boiling EtOH to the pyridoazepines **7a**–**c** and **8** in acceptable yields (Scheme 5).[26]

Lactam **34** did not react with any arylpiperazines **35** neither in the presence of $TiCl_4$ nor after treating with $PCl_5/POCl_3$. Thus, we activated the lactam group by preparing the thiolactimmethylether **38**.[27] Therefore, the secondary amine moiety in position 1 of **34** first was protected with an allyl group to prevent from methylation by methyliodide. *N*-Allyllactam **36** was transformed to thiolactam **37** by means of P_2S_5 in pyridine.[28,29] Deprotonation with sodium ethoxide and treatment with methyl iodide led to thiolactimmethylether **38**,[30] which was stirred in a great excess of the phenylpiperazines **35a**–**c** to exchange the methylsulfanyl group into a phenylpiperazine side chain giving **9a**–**c**.[27] Cleavage of the *N*-allyl protecting group was performed in almost quantitative yield by heating **9a**–**c** in ethanol with Pd/C (10%) in the presence of equimolar amounts of methanesulfonic acid[31] yielding the title compounds **10a**–**c** (Scheme 6).

3. Results and discussion

Dopamine D1 receptor binding was determined by measuring the ability to displace [^{3}H]SCH 23390 from porcine D1 receptors.[32] To assess $D2_{long}$, $D2_{short}$,[33] D3,[34] and D4.4[35] affinities cloned human dopamine receptor subtypes stably expressed in Chinese hamster ovary cells (CHO)[32] and the radioligand [^{3}H]spiperone were used for competition experiments. Serotonin 5-$HT1_A$ and 5-HT2 receptor binding was determined utilizing [^{3}H]8-OH–DPAT, [^{3}H]ketanserin and porcine cortical membranes.[36]

Dopamine receptor binding data of the title compounds **5a**–**f**, **6a**–**h**, **7a**–**c**, and **8** are depicted in Table 1. With a K_i value of 11 nM for the dopamine D4 subtype **6a** comes within the range of clozapine (**1**) and shows highest affinity of all test compounds for this receptor subtype. Small substituents, for example, a chloro (**5a**) and fluoro group (**5c**) at position 8 in benzene ring A are tolerated by dopamine D4 receptor, yet. A larger trifluoromethyl (**5b**) or methoxy (**5d**) group at the same position effects in a dramatic decrease of D4 affinity.

A methyl or allyl group at the nitrogen atom in position 1 of the dihydrobenzo-1*H*-1,5-diazepine substructure (**5e**,**f**) results in a moderate reduction of D4 binding in comparison to **6a**.

Substituents at the phenyl ring of the piperazine side chain are accepted in *ortho* position (**6c**,**f**) with almost no decline of affinity for D4. Substitution in *meta*- or *para* position is more or less not tolerated by the D4 receptor. Compounds carrying a benzyl (**6g**) or pyridin-2-yl (**6h**) group instead of a phenyl group in the piperazine side chain are less recognized by the D4 receptor.

While in comparison to clozapine there is nearly no improvement in terms of affinity on D4 receptor, some of the novel synthesized dihydro-1*H*-1,5-benzodiazepines of type **5** and **6** show a remarkable increase in selectivity for D4 especially over the D2 and D3 subtypes. As specified in Table 1, $D2_{long}/4$ and $D2_{short}/4$ ratio of K_i values for clozapine (**1**) result approximately in a factor 2 and D3/4 ratio in about factor 60. In contrast, compounds **5c**, **6a**, and **c** show a 450–700-fold higher binding on D4 than to D2 and 100–170-fold higher binding on D4 than to D3 subtype. Best binding properties were provided by compound **6a**. ($K_i = 11$ nM for D4, about 740-fold selectivity over $D2_{long}$). In this context we like to mention, that compound **6g** is the most selective one tested (D2/4 ratio of K_i values >2700, D3/4 ratio of K_i values = 340).

Table 1. Receptor binding data (K_i values [nM]) of compound **5a–f**, **6a–h**, **7a–c**, and **8** employing porcine D1 and human D2, D3, and D4 receptors[a]

Entry	[^{3}H]SCH23390	[^{3}H]spiperone				Ratio of K_i values		
	D1	$D2_{long}$	$D2_{short}$	D3	D4	$D2_{long}$/4	$D2_{short}$/4	D3/4
5a	1200	4700	3 000	3400	31	150	97	110w
5b	6900	30,000	30,000	10,000	2400	13	13	4.2
5c	530	5500	4800	1300	12	450	400	110
5d	25,000	23,000	160,000	28,000	7600	3.0	21	3.7
5e	3500	8200	5600	3600	33	250	170	110
5f	2900	7000	9800	2200	59	120	170	37
6a	3400	8100	5900	1900	11	740	530	170
6b	4600	31,000	34 000	7000	86	360	400	81
6c	9200	5800	8000	2000	13	440	610	150
6d	5100	1300	1100	3000	600	2.2	1.8	5.0
6e	710	910	690	1100	1000	0.89	0.67	1.1
6f	1700	7400	6 600	1100	27	270	240	41
6g	Nd[b]	>100,000	>100,000	16,000	47	>2100	>2100	340
6h	26,000	63,000	46,000	13,000	3500	18	13	3.7
7a	6400	18,000	15,000	2300	320	55	45	7.2
7b	14,000	37,000	20,000	14,000	140	260	150	100
7c	2200	25,000	21,000	5000	350	71	60	14
8	19,000	33,000	30,000	3700	220	150	140	17
Clozapine (**1**)	420	41	28	960	16	2.6	1.8	60

[a] K_i values are the means of two independent experiments each carried out in triplicate.
[b] Nd = not determined.

Bioisosteric exchange of benzene ring A for a pyridine moiety as realized in **7a–c** and **8** is accompanied by a loss of D4 affinity and selectivity.

In screening tests dihydro-1*H*-1,4-benzodiazepines **9a–c** and **10a–c** already show no appreciable binding to dopamine receptors. Therefore, no K_i values were determined.

To investigate the intrinsic effects of representative examples the compounds **5c**, **6a**, and **6c**, which showed the most promising binding properties, were taken a mitogenesis assay.[37] All of them had partial agonist effects (**5c**: 37%, $EC_{50} = 12$ nM; **6a**: 22%, $EC_{50} = 13$ nM; **6c**: 45%, $EC_{50} = 24$ nM) in comparison to quinpirole (full agonist).

To get a more detailed binding profile the most promising compounds **5a**,**c** and **6a**,**c** were tested for affinity to serotonin 5-$HT1_A$ and 5-HT2 receptors. The binding results listed in Table 2 are quite different. Best binding properties are achieved for **5c** and **6a**. In comparison to clozapine (**1**), fluoro compound **5c** shows a 10-fold high affinity to 5-$HT1_A$, whereas binding to the 5-HT2 receptor was reduced by factor 4. Larger substituents like a chloro group on ring A in **5a** or a methoxy group in the phenylpiperazine side chain in **6c** lead to a decreased K_i value especially for 5-HT2.

Table 2. Receptor binding data (K_i values [nM]) of compound **5a**,**c**, **6a**, and **6c** employing porcine 5-$HT1_A$ and 5-HT2 receptors[a]

Entry	[^{3}H]8-OH–DPAT	[^{3}H]ketanserin
	5-$HT1_A$	5-HT2
5a	3700	9 050
5c	48	58
6a	105	52
6c	250	2 550
Clozapine (**1**)	460	12

[a] K_i values are the means of two independent experiments each carried out in triplicate.

4. Experimental

Starting materials were obtained from commercial sources and were used without further purification. Solvents were dried by standard procedures. All anhydrous reactions were performed in oven-dried glassware. Reaction progress was observed by thin layer chromatography making use of commercial silica gel plates (Merck, silica gel F_{254} on aluminum sheets). Column chromatography was done on silica gel 60 (Merck). Melting points were determined in open capillary tubes on a Buechi 510 melting point apparatus and are uncorrected. Elemental analyzes were performed by the Institut für Organische Chemie (university of Erlangen/Nuremberg) using Carlo Erba Elemental Analyzer 1108. They are within ±0.4% of the theoretical values if not noted otherwise. ^{1}H Nuclear magnetic resonance (^{1}H NMR) spectra were determined with a Bruker AM 360 (360 MHz) spectrometer in appropriate deuterated solvents and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (J), and number of protons. Mass spectra (MS) were taken with a Finnigan MAT TSQ 70 mass spectrometer in the electron impact mode (70 eV). Significant infrared (IR) spectra were obtained on a Jasco FT/IR 410 or Perkin–Elmer 1740 spectrometer.

4.1. *N*-Allyl-2-nitroaniline (13e)

2-Fluoronitrobenzene (11.29 g, 80 mmol) and allylamine (4.56 g, 80 mmol) were refluxed in dry THF (50 mL) for

12 h. Solvent and excess of educts were removed in vacuum. The residue was purified by flash chromatography (cyclohexane/EtOAc = 9:1) to obtain **13e** as an orange oil (10.0 g, 63%). ^{1}H NMR ($CDCl_3$) 3.97 (d, 2H, $J = 6.3$ Hz), 5.14–5.21 (m, 2H), 5.85–5.94 (m, 1H), 6.63 (m, 1H), 6.81 (m, 1H), 7.41 (m, 1H), 8.03–8.32 (m, 2H); MS m/z 178 [M^+]. Anal. $C_9H_{10}N_2O_2$ (178.07) C, H, N.

4.2. *N*-(4-Fluoro-2-nitrophenyl)-β-alanine (14c)

4-Fluoro-2-nitroaniline (**13c**) (7.80 g, 50 mmol) was suspended in acrylic acid (10.8 g, 150 mmol). Concd H_2SO_4 (98%, 5 mL) was added portion-wise and the mixture heated to 75–80 °C and stirred for 15 min. Water (50 mL) was added cautiously so that the temperature did not rise over 80 °C. After cooling, the precipitate was filtered off, washed well with water, and dried in vacuum. The yielded crystals (10.7 g, 93%) were used without further purification in the next step. For analytical purposes crystallization from EtOH/water (2:1) was performed. Mp 145–146 °C (154–155 °C)[38] (EtOH/H_2O); IR 3737, 3378, 3116, 1705, 1523 cm^{-1}; ^{1}H NMR ([d_6]DMSO) 2.61 (t, 2H, $J = 6.8$ Hz), 3.58 (dt, 2H, $J = 6.8$, 5.0 Hz), 7.17 (m, 1H), 7.54 (m, 1H), 7.86 (m, 1H), 8.15 (t, br, 1H, $J = 5.0$ Hz, exchangeable with D_2O), 12.48 (s, br, 1H, exchangeable with D_2O); MS m/z 228 [M^+]. Anal. $C_9H_9FN_2O_4$ (228.18) C, H, N.

4.3. *N*-(4-Methoxy-2-nitrophenyl)-β-alanine (14d)

Preparation and purification according to **14c** from 4-methoxy-2-nitroaniline (**13d**) (8.41 g, 50 mmol) gave **14d** (10.1 g, 84%). Mp 130–131 °C (129–131 °C)[39] (EtOH/H_2O); ^{1}H NMR ([d_6]DMSO) 2.61 (t, 2H, $J = 6.6$ Hz), 3.57 (dt, 2H, $J = 6.6$, 4.5 Hz), 3.75 (s, 3H), 7.10 (m, 1H), 7.29 (m, 1H), 7.50 (m, 1H), 8.10 (t, br, 1H, $J = 4.5$ Hz, exchangeable with D_2O), 12.39 (s, br, 1H, exchangeable with D_2O); MS m/z 240 [M^+]. Anal. $C_{10}H_{12}N_2O_5$ (240.22) C, H, N.

4.4. *N*-Allyl-*N*-(2-nitrophenyl)-β-alanine (14e)

Preparation and purification according to **14c** from *N*-allyl-2-nitroaniline (**13e**) (8.90 g, 50 mmol) gave **14e** (9.5 g, 76%) as bright orange oil. ^{1}H NMR ([d_6]DMSO) 2.37 (t, 2H, $J = 7.3$ Hz), 3.31 (d, 2H, $J = 7.3$ Hz), 3.69 (d, 2H, $J = 6.0$ Hz), 5.10–5.24 (m, 2H), 5.69–5.81 (m, 1H), 7.10 (m, 1H), 7.37 (m, 1H), 7.54 (m, 1H), 7.73 (m, 1H), 12.19 (s, br, 1H, exchangeable with D_2O); MS m/z 250 [M^+]. Anal. $C_{12}H_{14}N_2O_4$ (250.26) C, H, N.

4.5. *N*-Methyl-*N*-(2-nitrophenyl)-β-alanine (14f)

Preparation and purification according to **14c** from *N*-methyl-2-nitroaniline (**13f**) (7.90 g, 50 mmol) gave **14f** (9.7 g, 87%). Mp 188–189 °C (EtOH/H_2O); ^{1}H NMR ([d_6]DMSO) 2.49 (t, 2H, $J = 7.3$ Hz), 2.75 (s, 3H), 3.36 (t, 2H, $J = 7.3$ Hz), 6.96 (m, 1H), 7.27 (m, 1H), 7.51 (m, 1H), 7.74 (m, 1H), 12.27 (s, br, 1H, exchangeable with D_2O); MS m/z 224 [M^+]. Anal. $C_{10}H_{12}N_2O_4$ (224.22) C, H, N.

4.6. 8-Fluoro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (16c)

Compound **14c** (7.98 g, 35 mmol) was heated to 80 °C in a mixture of dioxane (90 mL) and H_3PO_4 (85%, 20 mL). Zinc powder (17.1 g, 262.5 mmol) was added portion-wise within 1 h. The suspension was refluxed for another hour. After cooling, firm components were filtered off and washed profoundly with dioxane. The filtrate was neutralized cautiously with concd NH_3 (25%) under ice cooling. Newly formed precipitate was filtered off and washed profoundly with dioxane once again. The filtrate was concentrated in vacuum. The residue was slurred in 2 N NH_3 solution. The crude product was precipitated by cooling in the refrigerator over night, filtered off, and washed with water. Recrystallization from EtOH and drying in vacuum gave pure **16c** (4.37 g, 69%). Mp 144–146 °C (EtOH); IR 3321, 3217, 2924, 2854, 1670, 1608 cm^{-1}; ^{1}H NMR ([d_6]DMSO) 2.49 (t, 2H, $J = 6.0$ Hz), 3.40 (t, 2H, $J = 2.8$, 6.0 Hz), 5.56 (t, br, 1H, $J = 2.8$ Hz, exchangeable with D_2O), 6.69–6.79 (m, 3H), 9.51 (s, br 1H, exchangeable with D_2O); MS m/z 180 [M^+]. Anal. $C_9H_9FN_2O$ (180.18) C, H, N.

4.7. 8-Methoxy-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (16d)

Preparation and purification according to **16c** from **14d** (8.40 g, 35 mmol) gave **16d** (4.03 g, 87%). Mp 137–138 °C;[40] ^{1}H NMR ([d_6]DMSO) 2.43 (t, 2H, $J = 6.0$ Hz), 3.40 (dt, 2H, $J = 3.0$, 6.0 Hz), 3.64 (s, 3H), 5.12 (t, br, 1H, $J = 3.0$ Hz, exchangeable with D_2O), 6.48–6.79 (m, 3H), 9.37 (s, br, 1H, exchangeable with D_2O); MS m/z 192 [M^+]. Anal. $C_{10}H_{12}N_2O_2$ (192.22) C, H, N.

4.8. 5-Allyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (16e)

Preparation and purification according to **16c** from **14e** (8.76 g, 35 mmol) gave **16e**(4.03 g, 87%). Mp 93–95 °C; ^{1}H NMR ([d_6]DMSO) 2.31 (t, 2H, $J = 6.7$ Hz), 3.37 (t, 2H, $J = 6.7$ Hz), 3.72 (d, 2H, $J = 6.1$ Hz), 5.12–5.29 (m, 2H), 5.74–5.86 (m, 1H), 6.89–7.10 (m, 4H), 9.44 (s, br, 1H, exchangeable with D_2O); MS m/z 202 [M^+]. Anal. $C_{12}H_{14}N_2O$ (202.26) C, H, N.

4.9. 5-Methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (16f)

Preparation and purification according to **16c** from **14f** (7.98 g, 35 mmol) gave **16f**(3.63 g, 58%). Mp 122–123 °C; ^{1}H NMR ([d_6]DMSO) 2.29 (t, 2H, $J = 6.8$ Hz), 2.73 (s, 3H), 3.38 (t, 2H, $J = 6.8$ Hz), 6.89–7.13 (m, 4H), 9.45 (s, br, 1H, exchangeable with D_2O); MS m/z 176 [M^+]. Anal. $C_{10}H_{12}N_2O$ (176.22) C, H, N.

4.10. 5-Chloro-3-nitropyridin-2-amine (19)

2-Nitroethene-1,1-diamine (**18**) (3.09 g, 30 mmol) and *N*-[(2*Z*)-2-chloro-3-(dimethylamino)prop-2-en-1-ylidene]-*N*-methyl-methanaminium perchlorate (**17**) (7.83 g, 30 mmol) were refluxed in dry *n*-BuOH for 4 h. After cooling, the solvent was removed in vacuum. The residue was separated between EtOAc and saturated Na_2CO_3 solution. The organic layer was collected, washed with saturated Na_2CO_3 solution, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography (cyclohexane/EtOAc = 7:3) to obtain **19** (3.03 g, 58%). Mp 188–189 °C; IR 3467, 3278, 3140, 1651, 1554, 1512 cm^{-1}; ^1H NMR ([d_6]DMSO) 8.06 (s, br, 2H, exchangeable with D_2O), 8.45 (d, 1H, $J = 2.5$ Hz); MS m/z 173 [M^+]. Anal. $C_5H_4ClN_3O_2$ (173.56) C, H, N.

4.11. 5-Chloro-3-nitro-1*H*-pyridin-2-one (22)

While stirring oleum (65% SO_3, $d = 1.99$ g/cm^3, 14 mL) was dropped cautiously to ice-cooled HNO_3 (100%, $d = 1.52$ g/cm^3, 10 mL). 5-Chloro-1*H*-pyridin-2-one (**21**) was added portion-wise so that the temperature did not rise over 10 °C. The resulting suspension was allowed to warm slowly to room temperature, and was stirred for another 3 h. The mixture was poured onto crushed ice. The precipitate was filtered off, washed well with water, and dried at 50 °C in vacuum to get **22** (1.83 g, 17%). Mp 225–226 °C; IR 3072, 1705, 1655, 1589, 1539, 1510 cm^{-1}; ^1H NMR ([d_6]DMSO) 8.22 (s, 1H), 8.53 (s, 1H), 13.27 (s, br, 1H, exchangeable with D_2O); MS m/z 174 [M^+]. Anal. $C_5H_3ClN_2O_3$ (174.54) C, H, N.

4.12. Ethyl *N*-(5-chloro-3-nitro-pyridin-2-yl)-β-alaninate (24b)

2,5-Dichloro-3-nitropyridine (**20**) (4.05 g, 21 mmol), ethyl 3-aminopropionate HCl (**23**–HCl) (5.83 g, 31.5 mmol), and triethylamine (5.83 g, 57.7 mmol) were refluxed in dry EtOH (30 mL) for 2 h. After cooling, the solvent was removed in vacuum. The residue was separated between EtOAc and water. The organic layers were collected, washed twice with water, and dried over Na_2SO_4. After evaporation of the solvent the residue was purified by flash chromatography (cyclohexane/EtOAc = 8:2) to obtain **24b** (3.51 g, 61%) as yellow powder. Mp 126–127 °C; IR 3390, 3082, 2981, 1732, 1616 cm^{-1}; ^1H NMR ([d_6]DMSO) 1.18 (t, 3H, $J = 7.1$ Hz), 2.66 (t, 2H, $J = 6.9$ Hz), 3.77 (q, 2H, $J = 7.1$ Hz), 3.81 (dt, 2H, $J = 6.9$, 5.6 Hz), 8.47 (d, 1H, $J = 2.5$ Hz), 8.54 (d, 1H, $J = 2.5$ Hz), 8.61 (t, br, 1H, $J = 5.6$ Hz, exchangeable with D_2O); MS m/z 273 [M^+]. Anal. $C_{10}H_{12}ClN_3O_4$ (273.68) C, H, N.

4.13. 4,5-Dihydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-2(3*H*)-one (26a)

Ethyl 3-(3-nitropyridin-2-ylamino)-propionate (**24a**) (4.78 g, 20 mmol) was hydrogenated in dry EtOH (150 mL) with Pd/C (5%, 300 mg) at 1.5 bar and room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated in vacuum to obtain crude **21a**, which was directly refluxed in HOAc (96%, 100 mL) for 4 h. After cooling, the solvent was evaporated in vacuum. The residue was picked up in 2 N NH_3. The crude product was precipitated by cooling in the refrigerator over night and was separated by filtration. Recrystallization from EtOH/water and drying in vacuum gave **26a** (1.99 g, 61%). Mp 253–255 °C (EtOH/H_2O); IR 3232, 3051, 3008, 1670, 1604 cm^{-1}; ^1H NMR ([d_6]DMSO) 2.59 (t, 2H, $J = 4.9$ Hz), 3.46 (dt, 2H, $J = 4.9$, 3.0 Hz), 6.58 (dd, 1H, $J = 7.7$, 4.8 Hz), 6.62 (t, br 1H, $J = 3.0$ Hz, exchangeable with D_2O), 7.18 (dd, 1H, $J = 7.8$, 1.4 Hz), 7.74 (dd, 1H, $J = 4.8$, 1.4 Hz), 9.52 (s, br, 1H, exchangeable with D_2O); MS m/z 163 [M^+]. Anal. $C_8H_9N_3O$ (163.18) C, H, N.

4.14. 8-Chloro-4,5-dihydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-2(3*H*)-one (26b)

Preparation and purification according to **26a** from **24b** (5.47 g, 20 mmol) gave **26b** (1.54 g, 39%). Mp >270 °C (EtOH/H_2O); ^1H NMR ([d_6]DMSO) 2.62 (t, 2H, $J = 4.6$ Hz), 3.44 (dt, 2H, $J = 4.6$ Hz, 3.5 Hz), 6.92 (t, br, 1H, $J = 3.5$ Hz, exchangeable with D_2O), 7.24 (d, 1H, $J = 2.5$ Hz), 7.74 (d, 1H, $J = 2.5$ Hz), 9.63 (s, br, 1H, exchangeable with D_2O); MS m/z 197 [M^+]. Anal. $C_8H_8ClN_3O$ (197.63) C, H, N.

4.15. Ethyl *N*-(3-nitropyridin-4-yl)-β-alaninate (28)

Preparation and purification (cyclohexane/EtOAc/MeOH = 5:4:1) according to **24b** from **27** (3.33 g, 21 mmol) gave **28** (3.11 g, 62%) as yellow powder. Mp 75–76 °C; IR 3311, 2755, 1721, 1622 cm^{-1}; ^1H NMR ([d_6]DMSO) 1.18 (t, 3H, $J = 7.1$ Hz), 2.69 (t, 2H, $J = 6.4$ Hz), 3.67 (dt, 2H, $J_2 = 6.4$ Hz, $J_2 = 5.4$ Hz), 4.09 (q, 2H, $J = 7.1$ Hz), 7.07 (d, 1H, $J = 6.4$ Hz), 8.28 (d, 1H, $J = 6.4$ Hz), 8.47 (t, br, 1H, $J = 5.4$ Hz, exchangeable with D_2O), 9.03 (s, 1H); MS m/z 239 [M^+]. Anal. $C_{10}H_{13}N_3O_4$ (239.12) C, H, N.

4.16. Ethyl *N*-(3-aminopyridin-4-yl)-β-alaninate (29)

Compound **28** (2.37 g, 10 mmol) was hydrogenated in abs EtOH (100 mL) over Pd/C (5%, 200 mg) at 1500 hPa (22 psi) and room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated in vacuum to get pure colorless crystals (1.92 g, 92%). Mp 116–118 °C (EtOH); IR 3211, 3016, 2966, 1721, 1607 cm^{-1}; ^1H NMR ([d_6]DMSO) 1.19 (t, 3H, $J = 7.2$ Hz), 2.61 (t, 2H, $J = 6.6$ Hz), 3.36 (dt, 2H, $J = 5.5$, 6.6 Hz), 4.08 (q, 2H, $J = 7.2$ Hz), 4.54 (s, br, 2H, exchangeable with D_2O), 5.40 (t, br, 1H, $J = 5.5$ Hz, exchangeable with D_2O), 6.38 (d, 1H, $J = 5.4$ Hz), 7.60 (d, 1H, $J = 5.4$ Hz), 7.65 (s, 1H); MS m/z 209 [M^+]. Anal. $C_{10}H_{15}N_3O_2$ (209.25) C, H, N.

4.17. *N*-(3-Nitropyridin-4-yl)-β-alanine (31)

NaOH (1 N, 50 mL) was added to a solution of **28** (3.59 g, 15 mmol) in THF (50 mL). The mixture was

stirred vigorously for 4 h. The aqueous layer was separated. The organic layer was extracted twice with aqueous 1 N NaOH. Aqueous layers were combined, cooled in an ice bath, and cautiously adjusted to pH 3–4 by adding concd HCl. The precipitate was filtered off and washed with water. Recrystallization from EtOH gave pure **31** (2.25 g, 71%) as colorless crystals. Mp 144–146 °C (EtOH); IR 3350, 3114, 1698, 1633, 1560 cm^{-1}; ^1H NMR ([d_6]DMSO) 2.62 (t, 2H, $J = 6.4$ Hz), 3.62 (dt, 2H, $J = 5.6$, 6.4 Hz), 7.07 (d, 1H, $J = 6.4$ Hz), 8.27 (d, 1H, $J = 6.4$ Hz), 8.47 (t, br, 1H, $J = 5.6$ Hz, exchangeable with D_2O), 9.03 (s, 1H); MS m/z 211 [M^+]. Anal. $C_8H_9N_3O_4$ (211.18) C, H, N.

4.18. *N*-(3-Aminopyridin-4-yl)-β-alanine (32)

Compound **31** (2.37 g, 10 mmol) was hydrogenated in dry EtOH (150 mL) over Pd–C (5%, 300 mg) at 3000 hPa (44 psi) and room temperature for 6 h. The catalyst was filtered off and the filtrate was concentrated in vacuum to get pure colorless crystals (2.25 g, 81%). Mp 159–161 °C (EtOH); IR 3267, 3099, 2765, 1703 cm^{-1}; ^1H NMR ([d_6]DMSO) 2.63 (t, 2H, $J = 6.4$ Hz), 3.49 (t, 2H, $J = 6.4$ Hz), 5.61 (s, br, 2H, exchangeable with D_2O), 6.71 (d, 1H, $J = 6.0$ Hz), 7.21 (s, br, 1H, exchangeable with D_2O), 7.61 (s, 1H), 7.78 (d, 1H, $J = 6.0$ Hz); MS m/z 181 [M^+]. Anal. $C_8H_{11}N_3O$ (181.20) C, H, N.

4.19. 1,2,3,5-Tetrahydro-4*H*-pyrido[3,4-*b*][1,4]diazepin-4-one (30)

Method A. Compound **29** (1.67 g, 8 mmol) was heated to 70 °C in a mixture of dry EtOH (50 mL) and concd HCl (36%, 5 mL) for 12 h. The resulting solution was cooled in an ice bath and pH was adjusted to 6–7 by adding aqueous concd NH_3 solution. After evaporation to dryness, the residue was sonicated with MeOH. Firm components were filtered off and washed well with methanol. The filtrate was concentrated in vacuum and purified by flash chromatography (CH_2Cl_2/MeOH = 3:1) gives **30** (235 mg, 18%) as colorless powder.

Method B. 1,3-Diisopropylcarbodiimide (3.53 g, 28 mmol) and 1-hydroxybenzotriazol·H_2O were added to a solution of **32** (1.27 g, 7 mmol) in abs DMF (30 mL). The mixture was stirred over night at room temperature. After evaporation to dryness the residue was extracted with MeOH and purified as described under method A to get **30** (639 mg, 56%) as colorless powder. Mp >300 °C (decomposition); IR 3221, 2924, 1694, 1643, 1570 cm^{-1}; ^1H NMR ([d_6]DMSO) 2.64 (t, 2H, $J = 4.6$ Hz), 3.49 (dt, 2H, $J = 4.6$, 4.6 Hz), 6.74 (d, 1H, $J = 6.0$ Hz), 7.79 (d, 1H, $J = 6.0$ Hz), 7.84 (t, br, 1H, $J = 4.6$ Hz, exchangeable with D_2O), 7.95 (s, 1H), 9.71 (s, 1H); MS m/z 163 [M^+]. Anal. $C_8H_8N_3O$ (163.18) C, H, N.

4.20. 7-Chloro-4-(4-phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (5a)

N-Phenylpiperazine (**35a**) (0.5 g) was added to a solution of $TiCl_4$ (189 mg, 1 mmol) in dry toluene (10 mL). After stirring for 10 min a solution of **16a** (99 mg, 0.5 mmol) in dry toluene (10 mL) was added. While stirring the mixture was heated under a nitrogen atmosphere to 80 °C for 4 h. After cooling water (10 mL) was added cautiously and pH was adjusted to 7–8 with concd NH_3. The precipitate was filtered off and washed well with $CHCl_3$. The aqueous layer of the filtrate was separated and extracted with $CHCl_3$. Combined organic layers were washed with 2 N NH_3, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography (CH_2Cl_2/MeOH = 97:3) to yield **5a** (59 mg, 42%) as light yellow powder. Mp 170–172 °C; IR 3429, 2954, 2819, 1597, 1500 cm^{-1}; ^1H NMR ([d_6]DMSO) 2.62 (t, 2H, $J = 6.0$ Hz), 3.19 (t, 4H, $J = 4.6$ Hz), 3.55 (dt, 2H, $J = 3.0$, 6.0 Hz), 3.68 (t, 4H, $J = 4.6$ Hz), 5.09 (t, 1H, NH, $J = 3.0$ Hz, exchangeable with D_2O), 6.68–7.29 (m, 8H); MS m/z 340 [M^+]. Anal. $C_{15}H_{21}ClN_4$ (340.86) C, H, N.

4.21. 4-(4-Phenylpiperazin-1-yl)-7-trifluoromethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (5b)

Preparation and purification (CH_2Cl_2/MeOH = 96:4) according to **5a** from **16b** (115 mg, 0.5 mmol) gave **5b** (103 mg, 55%) as light yellow powder. Mp 190–192 °C; ^1H NMR ([d_6]DMSO) 2.71 (t, 2H, $J = 5.5$ Hz), 3.19 (t, 4H, $J = 4.9$ Hz), 3.57 (dt, 2H, $J = 2.7$, 5.5 Hz), 3.69 (t, 4H, $J = 4.9$ Hz), 5.80 (t, br, 1H, $J = 2.7$ Hz, exchangeable with D_2O), 6.73–7.32 (m, 8H); MS m/z 374 [M^+]. Anal. $C_{20}H_{21}F_3N_4$ (374.41) C, H, N.

4.22. 7-Fluoro-4-(4-phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (5c)

Preparation and purification (CH_2Cl_2/MeOH = 96:4) according to **5a** from **16c** (90 mg, 0.5 mmol) gave **5c** (122 mg, 38%) as light yellow powder. Mp 164–165 °C; ^1H NMR ([d_6]DMSO) 2.58 (t, 2H, $J = 5.5$ Hz), 3.19 (t, 4H, $J = 4.9$ Hz), 3.55 (dt, 2H, $J = 2.9$, 5.5 Hz), 3.69 (t, 4H, $J = 4.9$ Hz), 4.77 (t, br, 1H, $J = 2.9$ Hz, exchangeable with D_2O), 6.45–7.39 (m, 8H); MS m/z 324 [M^+]. Anal. $C_{19}H_{21}FN_4$ (324.40) C, H, N.

4.23. 7-Methoxy-4-(4-phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (5d)

Preparation and purification (CH_2Cl_2/MeOH = 95:5) according to **5a** from **16d** (115 mg, 0.5 mmol) gave **5d** (86 mg, 51%) as light yellow powder. Mp 168–170 °C; ^1H NMR ([d_6]DMSO) 2.44 (t, 2H, $J = 5.8$ Hz), 3.20 (t, 4H, $J = 2.8$, 5.0 Hz), 3.52 (t, 2H, $J = 5.3$ Hz), 3.64 (s, 3H), 3.66 (t, 4H, $J = 5.3$ Hz), 5.29 (t, br, 1H, $J = 2.8$ Hz, exchangeable with D_2O), 6.67–7.27 (m, 8H); MS m/z 336 [M^+]. Anal. $C_{20}H_{24}N_4O$ (336.44) C, H, N.

4.24. 1-Allyl-4-(4-phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (5e)

Preparation and purification (CH_2Cl_2/MeOH = 97:3) according to **5a** from **16e** (88 mg, 0.5 mmol) gave **5e**

(66 mg, 41%) as light yellow powder. Mp 117–119 °C; ^{1}H NMR ($CDCl_3$) 2.75 (t, 4H, $J = 5.0$ Hz), 2.99–3.14 (m, 4H), 3.23(t, 4H, $J = 5.0$ Hz), 4.76–4.81 (m, 2H), 4.97 (d, 1H, $J = 8.6$ Hz), 5.24 (d, 2H, $J = 5.3$ Hz), 5.90–6.02 (m, 1H), 6.82–9.97 (m, 3H), 7.20–7.31 (m, 4H), 7.69–7.78 (m, 1H). MS m/z 346 [M$^+$]. Anal. $C_{22}H_{26}N_4$ (346.48) C, H, N.

4.25. 1-Methyl-4-(4-phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (5f)

Preparation and purification (CH_2Cl_2/MeOH = 97:3) according to **5a** from **16f** (88 mg, 0.5 mmol) gave **5f** (66 mg, 41%) as light yellow powder. Mp 161–163 °C; ^{1}H NMR ([d_6]DMSO) 2.49 (t, 2H, $J = 6.4$ Hz), 2.63 (s, 3H), 3.21 (t, 4H, $J = 5.0$ Hz), 3.37 (t, 2H, $J = 6.4$ Hz), 3.68 (t, 4H, $J = 5.0$ Hz), 6.72–7.29 (m, 9H); MS m/z 320 [M$^+$]. Anal. $C_{20}H_{24}N_4$ (320.44) C, H, N.

4.26. 4-(4-Phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (6a)

Preparation and purification (CH_2Cl_2/MeOH = 95:5) according to **5a** from 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**15**) (81 mg, 0.5 mmol) and *N*-phenylpiperazine (**35a**) (0.5 g) gave **6a** (64 mg, 42%) as light yellow powder. Mp 185–187 °C; ^{1}H NMR ($CDCl_3$) 2.67 (t, 2H, $J = 6.3$ Hz), 3.29 (t, 4H, $J = 5.3$ Hz), 3.77 (t, 2H, $J_2 = 2.9$ Hz, $J_2 = 6.3$ Hz), 3.81 (t, 4H, $J = 5.3$ Hz), 6.71–7.23 (m, 9H), 7.09 (t, br, 1H, $J = 2.9$ Hz, exchangeable with D_2O); MS m/z 306 [M$^+$]. Anal. $C_{19}H_{22}N_4$ (306.41) C, H, N.

4.27. 4-[4-(4-Fluorophenyl)piperazin-1-yl]-2,3-dihydro-1*H*-1,5-benzodiazepine (6b)

Preparation and purification (CH_2Cl_2/MeOH = 97:3) according to **5a** from **15** (81 mg, 0.5 mmol) and N-(4-fluorophenyl)piperazine (**35b**) (0.5 g) gave **6b** (83 mg, 51%) as light yellow powder. Mp 115–116 °C; ^{1}H NMR ([d_6]DMSO) 2.59 (t, 2H, $J = 6.0$ Hz), 3.13 (t, 4H, $J = 5.0$ Hz), 3.55 (t, 2H, $J = 2.9$, 6.0 Hz), 3.65 (t, 4H, $J = 5.0$ Hz), 4.90 (s, br, 1H, $J = 2.9$ Hz, exchangeable with D_2O), 6.65–7.16 (m, 8H); MS m/z 324 [M$^+$]. Anal. $C_{19}H_{21}FN_4$ (324.40) C, H, N.

4.28. 4-[4-(2-Methoxyphenyl)piperazin-1-yl]-2,3-dihydro-1*H*-benzodiazepine (6c)

Preparation and purification (CH_2Cl_2/MeOH = 96:4) according to **5a** from **15** (81 mg, 0.5 mmol) and *N*-(2-methoxyphenyl)piperazine (**35c**) (0.5 g) gave **6c** (73 mg, 43%) as light yellow powder. Mp 170–171 °C; ^{1}H NMR ([d_6]DMSO) 2.58 (t, 2H, $J = 6.0$ Hz), 3.01 (t, 4H, $J = 4.7$ Hz), 3.56 (t, 2H, $J = 2.8$, 6.0 Hz, H-2), 3.64 (t, 4H, $J = 4.7$ Hz), 3.81 (s, 3H), 4.90 (t, br, 1H, $J = 2.8$ Hz, exchangeable with D_2O), 6.66–7.00 (m, 8H); MS m/z 340 [M$^+$]. Anal. $C_{19}H_{21}ClN_4$ (340.86) C, H, N.

4.29. 4-[4-(4-Chlorophenyl)piperazin-1-yl]-2,3-dihydro-1*H*-1,5-benzodiazepine (6d)

Preparation and purification (CH_2Cl_2/MeOH = 95:5) according to **5a** from **15** (81 mg, 0.5 mmol) and *N*-(4-chlorophenyl)piperazine (**35d**) (0.5 g) gave **6d** (84 mg, 49%) as light yellow powder. Mp 149–150 °C; ^{1}H NMR ([d_6]DMSO) 2.59 (t, 2H, $J = 5.7$ Hz), 3.19 (t, 4H, $J = 4.7$ Hz), 3.55 (t, 2H, $J = 2.8$, 5.7 Hz), 3.65 (t, 4H, $J = 4.7$ Hz), 4.90 (s, br, 1H, $J = 2.8$ Hz, exchangeable with D_2O), 6.50–7.33 (m, 8H); MS m/z 340 [M$^+$]. Anal. $C_{19}H_{21}ClN_4$ (340.86) C, H, N.

4.30. 4-[4-(3-Chlorophenyl)piperazin-1-yl]-2,3-dihydro-1*H*-1,5-benzodiazepine (6e)

Preparation and purification (CH_2Cl_2/MeOH = 95:5) according to **5a** from **15** (81 mg, 0.5 mmol) and *N*-(3-chlorophenyl)piperazine (**35e**) (0.5 g) gave **4h** (78 mg, 46%) as light yellow powder. Mp 173–175 °C; ^{1}H NMR ([d_6]DMSO) 2.59 (t, 2H, $J = 6.0$ Hz), 3.24 (t, 4H, $J = 5.2$ Hz), 3.56 (t, 2H, $J = 6.0$ Hz), 3.64 (t, 4H, $J = 5.2$ Hz), 4.91 (s, br, 1H, exchangeable with D_2O), 6.65–7.27 (m, 8H); MS m/z 340 [M$^+$]. Anal. $C_{19}H_{21}N_4O$ (340.86) C, H, N.

4.31. 4-[4-(2-Chlorophenyl)piperazin-1-yl]-2,3-dihydro-1*H*-1,5-benzodiazepine (6f)

Preparation and purification (CH_2Cl_2/MeOH = 97:3) according to **5a** from **15** (81 mg, 0.5 mmol) and *N*-(2-chlorophenyl)piperazine (**35f**) (0.5 g) gave **6f** (8 5 mg, 50%) as light yellow powder. Mp 148–149 °C; ^{1}H NMR ([d_6]DMSO) 2.61 (t, 2H, $J = 5.8$ Hz), 3.03 (t, 4H, $J = 4.8$ Hz), 3.57 (t, 2H, $J = 2.7$, 5.8 Hz), 3.68 (t, 4H, $J = 4.8$ Hz), 4.94 (s, br, 1H, $J = 2.7$ Hz, exchangeable with D_2O), 6.65–7.48 (m, 8H); MS m/z 340 [M$^+$]. Anal. $C_{19}H_{21}ClN_4$ (340.86) C, H, N.

4.32. 4-(4-Benzylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (6g)

Preparation and purification (CH_2Cl_2/MeOH = 97:3) according to **5a** from **15** (81 mg, 0.5 mmol) and *N*-benzylpiperazine (**35g**) (0.6 g) gave **6g** (75 mg, 44%) as light yellow powder. Mp 162–164 °C; ^{1}H NMR ([d_6]DMSO) 2.20–2.57 (m, 8H), 2.75 (t, 2H, $J = 7.6$ Hz), 2.95 (t, 2H, $J = 7.6$ Hz), 3.44 (s, 2H), 4.91 (s, br, 1H, exchangeable with D_2O), 7.06–7.14 (m, 2H), 7.20–7.36 (m, 5H), 7.39–7.51 (m, 2H); MS m/z 320 [M$^+$]. Anal. $C_{20}H_{24}N_4$ (320.44) C, H, N.

4.33. 4-(4-Pyridin-2-ylpiperazin-1-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (6h)

Preparation and purification (CH_2Cl_2/MeOH = 95:5) according to **5a** from **15** (81 mg, 0.5 mmol) and *N*-(pyridin-2-yl)piperazine (**35h**) (0.5 g) gave **6h** (85 mg, 50%) as light yellow powder. Mp 148–149 °C; ^{1}H NMR

([d_6]DMSO) 2.61 (t, 2H, $J = 6.0$ Hz), 3.53–3.60 (m, 6H), 3.64 (m, 4H), 4.92 (t, br, $J = 2.9$ Hz, exchangeable with D_2O), 6.63–6.77 (m, 4H), 6.80 (m, 1H), 6.86 (d, 1H, $J = 8.5$ Hz), 7.56 (m, 1H), 8.14 (dd, 1H, $J = 4.6$, 1.1 Hz); MS m/z 307 [M^+]. Anal. $C_{18}H_{21}N_5$ (307.40) C, H, N.

4.34. 2-(4-Phenylpiperazin-1-yl)-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepine (7a)

A mixture of **26a** (82 mg, 0.5 mmol), PCl_5 (105 mg, 0.5 mmol), $POCl_3$ (5 mL) and pyridine (two drops) was heated to 135 °C under a nitrogen atmosphere for 4 h. After cooling to room temperature volatile components were evaporated. The residue was dried in vacuum over night and refluxed in EtOH. Without further purification 1-phenylpiperazine (**35a**) (0.5 g) was added and the resulting mixture was refluxed in dry EtOH (10 mL) for another 4 h. The solvent was removed in vacuum. The residue was purified by column chromatography (CH_2Cl_2/MeOH = 94:6) to obtain **7a** (74 mg, 48%). Mp 176–178 °C. ^{1}H NMR ([d_6]DMSO) 2.61 (t, 4H, $J = 4.6$ Hz), 2.86 (t, 2H, $J = 7.5$ Hz), 3.05 (t, 2H, $J = 7.5$ Hz), 3.12 (t, 4H, $J = 4.6$ Hz), 6.76 (m, 1H, H-8), 6.89–6.95 (m, 2H), 7.13–7.23 (m, 3H), 7.88 (d, 1H, $J = 7.4$ Hz), 8.25 (d, 1H), 12.76 (s, br, 1H, exchangeable with D_2O); MS m/z 307 [M^+]. Anal. $C_{18}H_{21}N_5$ (307.40) C, H, N.

4.35. 8-Chloro-2-(4-phenylpiperazin-1-yl)-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepine (7b)

Preparation and purification (CH_2Cl_2/MeOH = 97:3) according to **7a** from **26b** (99 mg, 0.5 mmol) and 1-phenylpiperazine (**35a**) (0.5 g) gave **7b** (70 mg, 41%). Mp 153–155 °C; ^{1}H NMR ([d_6]DMSO) 2.56 (t, 2H, $J = 6.8$ Hz,), 2.72 (t, 4H, $J = 5.0$ Hz), 3.16 (t, 2H, $J = 6.8$ Hz), 3.28 (t, 4H, $J = 5.0$ Hz), 6.56 (s, br, 1H), 6.83–7.00 (m, 2H), 7.14 (s, 1H), 7.23–7.52 (m, 3H), 7.64 (s, 1H, exchangeable with D_2O); MS m/z 341 [M^+]. Anal. $C_{18}H_{20}ClN_5$ (341.85) C, H, N.

4.36. 2-[(4-(4-Chlorophenyl)piperazin-1-yl]-4,5-dihydro-3*H*-pyrido[2,3-*b*][1, 4]diazepine (7c)

Preparation and purification (CH_2Cl_2/MeOH = 96:4) according to **5a** from **26a** (82 mg, 0.5 mmol) and 1-(4-chlorophenyl)piperazine (**35d**) (0.5 g) gave **7c** (70 mg, 41%). Mp 196–198 °C; ^{1}H NMR 2.59 (t, 4H, $J = 4.5$ Hz), 2.85 (t, 2H, $J = 7.5$ Hz), 3.04 (t, 2H, $J = 7.5$ Hz), 3.12 (t, 4H, $J = 4.5$ Hz), 6.93 (d, 2H), 7.14–7.23 (m, 3H), 7.88 (d, 1H, $J = 7.6$ Hz), 8.24 (d, 1H, $J = 3.3$ Hz), 12.78 (s, br, 1H, exchangeable with D_2O); MS m/z 341 [M^+]. Anal. $C_{18}H_{20}ClN_5$ (341.85) C, H, N.

4.37. 4-(4-Phenylpiperazin-1-yl-)-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]diazepine (8)

Preparation and purification (CH_2Cl_2/MeOH = 95:5) according to **7a** from **30** (82 mg, 0.5 mmol) and 1-phenylpiperazine (**35a**) (0.5 g) gave **8** (60 mg, 39%). Mp 193–194 °C; ^{1}H NMR ([d_6]DMSO) 2.61 (t, 4H, $J = 4.8$ Hz), 2.81 (d, 2H, $J = 6.9$ Hz), 3.03 (t, 2H, $J = 6.9$ Hz), 3.19 (t, 4H, $J = 4.8$ Hz), 6.73 (s, br, 1H, exchangeable with D_2O), 6.93–6.99 (m, 2H), 7.11–7.21 (m, 3H), 7.66 (d, 1H, $J = 6.2$ Hz), 8.83 (d, 1H, $J = 6.2$ Hz), 9.02 (s, 1H); MS m/z 307 [M^+]. Anal. $C_{18}H_{21}N_5$ (307.40) C, H, N.

4.38. 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-one (34)

3,4-Dihydro-1*H*-1,4-benzodiazepin-2,5-dione (**33**) (8.8 g, 50 mmol) was added in small portions to a slurry of $LiAlH_4$ (3.91 g, 115 mmol) in dry THF (100 mL) at a rate, which causes mild reflux. Refluxing was continued for 14 h, and then kept at room temperature over night. The mixture was treated carefully with water (20 mL), 2 N NaOH (15%, 10 mL) and finally with water (50 mL). The formed slurry was filtered through a Celite pad and washed with hot THF several times. The filtrate and washings were combined and extracted with $CHCl_3$. Combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography (CH_2Cl_2/MeOH = 97:3) to yield **34** (2.98 g, 37%) as colorless powder. Mp 143–145 °C.; IR 2924, 2852, 1660, 1631, 1599, 1495 cm^{-1}; ^{1}H NMR ([d_6]DMSO) 3.27–3.43 (m, 4H), 6.39–6.58 (m, 2H), 6.66 (d, 1H, $J = 8.4$ Hz), 7.09–7.17 (m, 1H), 7.68–7.75 (m, 1H), 7.93 (t, br, 1H, $J = 5.2$ Hz, exchangeable with D_2O); MS m/z 162 [M^+]. Anal. $C_9H_{10}N_2O$ (162.19) C, H, N.

4.39. 1-Allyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (36)

To a solution of **34** (2.43 g, 15 mmol) in dry benzene (10 mL), allyl bromide (1.82, 15 mmol) and triethylamine (0.2 mL) were added and the mixture was refluxed with stirring for 2 h and allowed to stand over night at room temperature. The solvent and excess of allyl bromide was removed in vacuum. The residue was treated with ice water (20 mL) and extracted three times with diethyl ether (50 mL). Combined ether layers were dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash chromatography (cyclohexane/EtOAc = 6:4) to yield **36** (1.61 g, 53%) as colorless powder. Mp 92–94 °C; ^{1}H NMR ([d_6]DMSO) 3.20 (m, 4H), 3.80 (d, 2H, $J = 5.7$ Hz), 5.14–5.27 (m, 2H), 5.77–5.90 (m, 1H), 6.90 (m, 1H), 7.33 (m, 1H), 7.47 (m, 1H), 8.15 (s, br, 1H, exchangeable with D_2O); MS m/z 202 [M^+]. Anal. $C_{12}H_{14}N_2O$ (202.26) C, H, N.

4.40. 1-Allyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-5-thione (37)

Compound **36** (1.52 g, 7.5 mmol) and P_2S_5 (2.22 g, 10 mmol) were refluxed for 2.5 h in dry pyridine. The solvent was removed in vacuum. The brown, resinous residue was suspended in a Na_2CO_3 solution (10%, 50 mL) and extracted with CH_2Cl_2. Combined organic

layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by flash chromatography (cyclohexane/EtOAc = 7:3) to obtain **37** (1.37 g, 84%) as yellow oil; ^{1}H NMR ([d_6]DMSO) 3.21–3.30 (m, 4H), 3.75 (d, 2H, J = 5.8 Hz), 5.13–5.29 (m, 2H), 5.73–5.86 (m, 1H), 6.92–7.01 (m, 2H), 7.35 (t, 1H, J = 7.8 Hz), 7.69 (d, 1H), J = 3.9 Hz), 10.68 (s, br, 1H). MS m/z 218 [M$^+$]. Anal. $C_{12}H_{14}N_2S$ (218.32) C, H, N.

4.41. 1-Allyl-5-methylsulfanyl-2,3-dihydro-1*H*-1,4-benzodiazepine (38)

Compound **37** (1.31 g, 6 mmol) was dissolved in a solution of sodium ethoxide (408 mg, 6 mmol) in ethanol (20 mL). MeI (851 mg, 6 mmol) was added. The reaction mixture was heated under reflux for 2 h. After cooling, water (40 mL) was added. The mixture was extracted with $CHCl_3$. Combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by flash chromatography (cyclohexane/EtOAc = 9:1) to yield **38** (909 mg, 65%) as light yellow oil. ^{1}H NMR ([d_6]DMSO) 2.35 (s, 3H), 3.43 (t, 2H, J = 5.8 Hz), 3.73 (d, 2H, J = 3.0 Hz), 5.14–5.25 (m, 2H), 5.73–5.87 (m, 1H), 6.90–6.96 (m, 2H), 7.30–7.41 (m, 2H); MS m/z 232 [M$^+$]. Anal. $C_{13}H_{16}N_2S$ (232.35) C, H, N.

4.42. 1-Allyl-5-(4-phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,4-benzodiazepine (9a)

A stirred mixture of **38** (232 mg, 1 mmol), 1-phenylpiperazine (**35a**) (810 mg, 5 mmol), and acetic acid (two drops) was heated to 120 °C for 12 h. Excess of amine was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc/TEA = 50:47:3) to yield **9a** (164 mg, 48%) as light yellow oil. ^{1}H NMR ($CDCl_3$) 3.20 (m, 4H), 3.39 (m, 8H), 3.72 (d, 2H, J = 5.7 Hz), 5.09–5.29 (m, 2H), 5.73–5.88 (m, 1H), 6.81–7.04 (m, 5H), 7.21–7.39 (m, 4H); MS m/z 346 [M$^+$]. Anal. $C_{22}H_{26}N_4$ (346.48) C, H, N.

4.43. 1-Allyl-5-[4-(4-fluorophenyl)piperazin-1-yl]-2,3-dihydro-1*H*-1,4-benzodiazepine (9b)

Preparation and purification (cyclohexane/EtOAc/TEA = 50:47:3) according to **9a** from **38** (232 mg, 1 mmol) and 1-(4-fluorophenyl)piperazine (**35b**) (900 mg, 5 mmol) gave **9b** (154 mg, 43%) as light yellow oil. ^{1}H NMR ($CDCl_3$) 3.12–3.53 (m, 12H), 3.86 (d, 2H, J = 5.2 Hz), 5,16–5.29 (m, 2H), 5.68–5.83 (m, 1H), 6.83–6.93 (m, 3H), 6.95–7.03 (m, 4H), 7.11–7.20 (m, 1H); MS m/z 364 [M$^+$]. Anal. $C_{22}H_{25}FN_4$ (364.47) C, H, N.

4.44. 1-Allyl-5-[4-(2-methoxyphenyl)piperazin-1-yl]-2,3-di-hydro-1*H*-1,4-benzodiazepine (9c)

Preparation and purification (cyclohexane/EtOAc/TEA = 50:47:3) according to **9a** from **38** (232 mg, 1 mmol) and 1-(2-methoxyphenyl)piperazine (**35c**) (960 mg, 5 mmol) gave **9c** (140 mg, 37%) as light yellow oil. ^{1}H NMR ($CDCl_3$) 3.10 (s, 3H), 3.22–3.56 (m, 6H), 3.73 (d, 2H, J = 5.1 Hz), 3.80–3.91 (m,, 4H), 5.10–5.28 (m, 2H), 5.74–5.84 (m, 1H), 6.83–7.07 (m, 5H), 7.24–7.40 (m, 3H); MS m/z 376 [M$^+$]. Anal. $C_{23}H_{28}N_4O$ (376.51) C, H, N.

4.45. 5-(4-Phenylpiperazin-1-yl)-2,3-dihydro-1*H*-1,4-benzodiazepine (10a)

A mixture of **9a** (104 mg, 0.3 mmol), Pd/C (10%, 55 mg) and methanesulfonic acid (29 mg, 0.3 mmol) in dry ethanol (5 mL) was refluxed for 2 h under a nitrogen atmosphere. The reaction mixture was filtered through a Celite pad. The residue was washed with ethanol and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (cyclohexane/EtOAc/TEA = 50:45:5) to obtain **10a** (74 mg, 71%) as light yellow powder. Mp 129–131 °C. ^{1}H NMR ($CDCl_3$) 3.22 (t, 4H, J = 4.8 Hz), 3.37 (t, 4H, J = 4.8 Hz), 3.56 (t, 2H, J = 5.2 Hz), 3.68 (t, 2H, J = 5.2 Hz), 6.68–6.74 (m, 1H), 6.82–6.99 (m, 4H), 7.18–7.38 (m, 5H); MS m/z 306 [M$^+$]. Anal. $C_{19}H_{22}N_4$ (306.41) C, H, N.

4.46. 5-[4-(4-Fluorophenyl)piperazin-1-yl]-2,3-dihydro-1*H*-1,4-benzodiazepine (10b)

Preparation and purification (cyclohexane/EtOAc/TEA = 50:45:5) according to **10a** from **9b** (107 mg, 0.3 mmol) gave **10b** (67 mg, 69%) as light yellow powder. Mp 150–151 °C. ^{1}H NMR ($CDCl_3$) 3.16 (t, 4H, J = 4.6 Hz), 3.41 (t, 4H, J = 4.6 Hz), 3.58 (t, 2H, J = 4.8 Hz), 3.71 (t, 2H, J = 4.8 Hz), 6.70–6.76 (m, 1H), 6.83–7.01 (m, 5H), 7.20–7.36 (m, 3H); MS m/z 324 [M$^+$]. Anal. $C_{19}H_{21}FN_4$ (324.40) C, H, N.

4.47. 5-[4-(2-Methoxyphenyl)piperazin-1-yl]-2,3-dihydro-1*H*-1,4-benzodiazepine (10c)

Preparation and purification (cyclohexane/EtOAc/TEA = 50:45:5) according to **10a** from **9c** (112 mg, 0.3 mmol) gave **10c** (75 mg, 75%) as light yellow powder. Mp 191–193 °C. ^{1}H NMR ($CDCl_3$) 3.14 (t, 4H, J = 4.8 Hz), 3.48 (t, 4H, J = 4.8 Hz), 3.58 (t, 2H, J = 5.3 Hz), 3.70 (t, 2H, J = 5.3 Hz), 3.84 (s, 3H) 6.70–6.76 (m, 1H), 6.83–7.01 (m, 5H), 7.20–7.36 (m, 3H); MS m/z 336 [M$^+$]. Anal. $C_{20}H_{24}N_4O$ (336.44) C, H, N.

5. Receptor binding studies

Receptor binding assays at the dopamine D1 receptor were carried out using porcine 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.[32] Preparations of membranes from CHO cells expressing human dopamine $D2_{long}$, $D2_{short}$, D3, and D4.4 receptors were employed for competition binding analysis displacing

the radioligand [^{3}H]spiperone according to literature.[32] The assays were run with a protein concentration of 5–20 μg/assay tube, with K_d values being 0.10–0.20, 0.10, 0.20, and 0.10–0.30 nM for the $D2_{long}$, $D2_{short}$, D3, and D4.4 receptors, respectively. Protein concentration was established by the method of Lowry using bovine serum albumin as standard.[41] Screening of receptor binding to the different dopamine receptors was achieved by measuring the displacement of radio ligands by the test compounds of representative concentrations of 10, 100 μM, and 1 nM. Compounds reflecting interesting binding affinities have been further investigated. Receptor binding studies were carried out as described in literature.[35] Mitogenesis experiments were done employing CHO 10001 stably expressing the human dopamine D4.2 receptor as described previously.[37,42] In brief, the 5-$HT1_A$ and 5-HT2 receptor assays were done with porcine cortical membranes at a final protein concentration of 400 mg/assay tube and 200 μg/assay tube, respectively. The radioligand [^{3}H]8-OH–DPAT was used for experiments with 5-$HT1_A$ receptors ($K_d = 2.2$ nM) and [3H]ketanserin was established for the 5-HT2 receptor experiments ($K_d = 2.7$ nM). Both assays were run with the radioligands at a final concentration of 0.5 nM.

6. Data analysis

The resulting competition curves of the receptor binding experiments were analyzed by nonlinear regression using the algorithms in PRISM (Graph Pad Software, San Diego, CA). 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.[43]

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