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# Stereocontrolled Dopamine Receptor Binding and Subtype Selectivity of Clebopride Analogues Synthesized from Aspartic Acid

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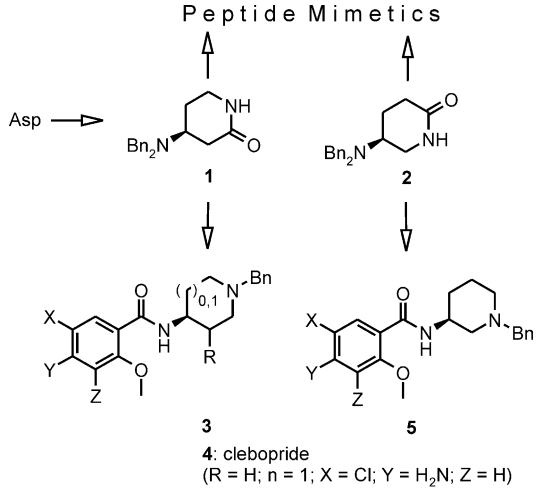
**Abstract**—Employing the achiral 4-aminopiperidine derivative clebopride as a lead compound, chiral analogues were developed displaying dopamine receptor binding profiles that proved to be strongly dependent on the stereochemistry. Compared to the D1 receptor, the test compounds showed high selectivity for the D2-like subtypes including $D2_{long}$, $D2_{short}$, D3 and D4. The highest D4 and D3 affinities were observed for the *cis*-3-amino-4-methylpyrrolidines **3e** and the enantiomer **ent3e** resulting in $K_i$ values of 0.23 and 1.8 nM, respectively. The benzamides of type **3** and **5** were synthesized in enantiopure form starting from (*S*)-aspartic acid and its unnatural optical antipode.


In connection with our program on peptide promoted receptor modulation, we reported on a practical synthesis of the enantiopure aminolactams **1** and **2**, which proved to be valuable scaffolds for the design of biologically active peptide mimetics. Compounds of this type, which were accessible from (*S*)-aspartic acid, proved to adopt β-turn like conformations and exhibited pharmacological effects comparable to the genuine dopamine receptor modulating peptide PLG.[1] As a consequence of our very recent findings indicating that a modification of the relative topicity of the pharmacophoric benzamide and the basic amine function of nemonapride derivatives strongly influences the binding preferences towards the subtypes of the D2 receptor family,[2] we were intrigued by the question, whether the building blocks **1** and **2** could also give access to novel chiral dopamine receptor ligands to serve as new atypical neuroleptics. Thus, we chose the 4-aminopiperidine clebopride (**4**) as a further pharmacological lead.[3] Clebopride displays a dual D2 and D4 affinity.[4] On the other hand, benzamide derivatives such as sulpiride[5] and amisulpride,[6] being therapeutically used as antipsychotic drugs, additionally exhibit a significant D3 affinity. In order to design pharmacological tools that might help to figure out the in vivo consequences of the fine tuning of subtype profiles, clebopride analogues of type **3** and the regioisomeric 3-aminopiperidines of type **5** should be investigated. Systematic SAR studies involving the modification of the heterocyclic core structure and the benzamide unit should help to find a potentially antipsychotic drug candidate with a well-balanced dopamine receptor binding profile. Modifications of the piperidine should be realized by the introduction of a methyl group into the position 3 or by formally rearranging an endocyclic $sp^3$-carbon into an exocyclic position leading to a methylpyrrolidine substructure. SAR studies in the benzamide moiety should involve suitably substituted methoxybenzene and methoxynaphthalene derivatives. The synthesis of the clebopride regioisomer of type **5** should proceed through the key intermediate **2**. To study whether the receptor binding and selectivity proceeds in a stereocontrolled way, the stereoisomers of the target

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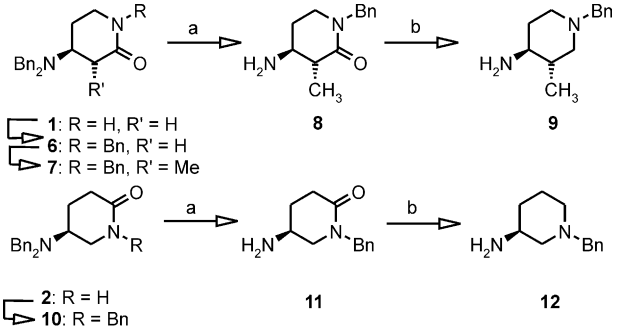
compounds should be prepared in both enantiomeric forms starting from (*S*)-aspartic acid and its unnatural antipode as the respective precursors.

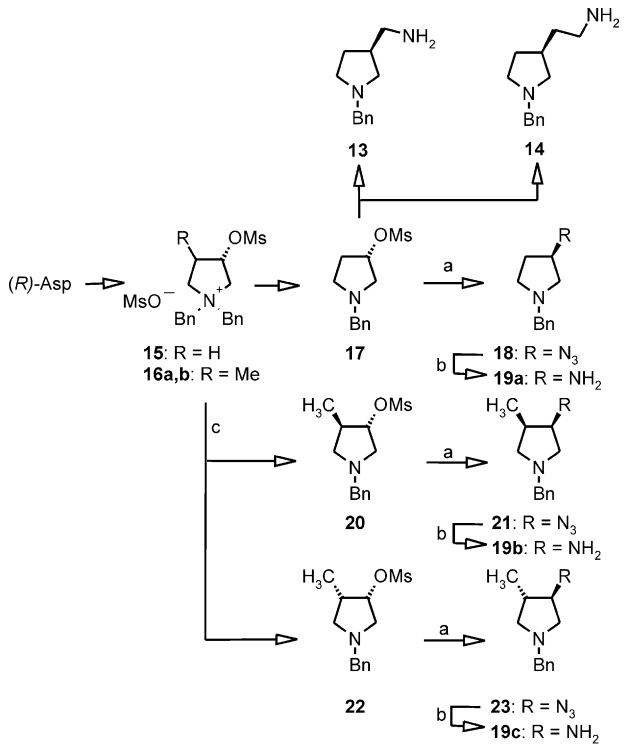
Starting from the chiral building blocks **1** and **2** being readily available by chemo- and regioselective transformations of natural aspartic acid, efficient *N*- and *C*-alkylations gave the chiral intermediates **7** (via **6**) and **10**, according to our previously reported protocol (Scheme 1).[1] The preparation of the aminopiperidine building blocks **9** and **12** was planned by hydrogenolytic debenzylation of the tertiary amine and reduction of the lactam functionality. Applying Perlman's catalyst and an atmospheric pressure of hydrogen, we were able to perform a chemoselective deprotection of the exocyclic nitrogen to give the primary amine derivative **8** in 97% yield. Subsequently, $LiAlH_4$ promoted reduction was performed to furnish the diamine **9** as an acylation precursor. Starting from the regioisomer **10**, hydrogenolytic deprotection gave access to the primary amine **11**. Subsequent hydride mediated reduction of the lactame functionality afforded the regioisomeric piperidine derivative **12**. The enantiomers **ent9** and **ent12** were prepared analogously starting from (*R*)-aspartic acid.




**Scheme 1.** (a) $H_2$, $Pd(OH)_2/C$, MeOH, rt, 15 h (**8**: 97%, **11**: 96%); (b) $LiAlH_4$, THF, reflux, 15 min, then, rt, 12 h (**9**: 88%, **12**: 61%).

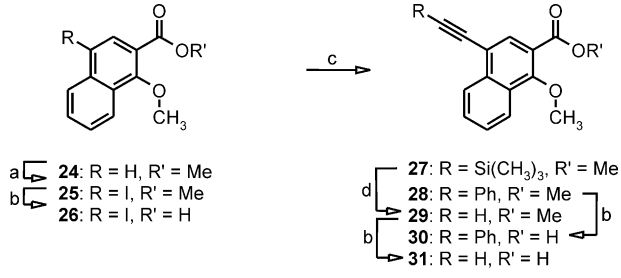
The 3-amino-4-methyl-pyrrolidines **19b**,**c** were synthesized by exploiting a short and effective reaction sequence, that has been developed in our laboratories giving access to the enantiopure mesyloxypyrrolidinium methanesulfonates **16a**,**b** starting from (*R*)-aspartic acid (Scheme 2). In contrast to our previously reported protocol,[2] we conveniently prepared **16a**,**b** as a mixture of diastereomers, which was subjected to a reductive debenzylation, neutralized with $NEt_3$ and subsequently separated by flash chromatography to give the pure mesyloxypyrrolidines **20** and **22** in acceptable overall yields. $S_N2$ reaction using $NaN_3$/DMSO proceeded under complete inversion giving access to the diastereomers **21** and **23**, respectively.[7] Subsequent $LiAlH_4$ reduction furnished the corresponding primary amine derivatives **19b**,**c**. Starting from the mesyloxypyrrolidinium salt **15**, which was hydrogenated to give the monobenzyl derivative **17**, the diamines **13**, **14** and **19a** (via **18**) were prepared as described recently.[2,8–10] The corresponding enantiomers **ent19a**,**b**,**c** were synthesized starting from (*S*)-aspartic acid.

Considering the 4-cyanonaphthamide nafadotride[11] and bromonaphthamide analogues[12] as promising pharmacological leads for the development of D3 active drugs, we decided to synthesize the corresponding 4-ethynyl and 4-phenylethynyl surrogates as well as iodo-substituted naphthoic acid derivatives **30** and **31** as promising building blocks.



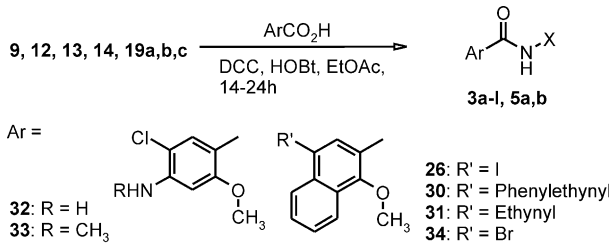

**Scheme 2.** (a) $NaN_3$, DMSO, 60 °C, **18**: 5 h, **21** and **23**: 14 h (**18**: 78%, **21**: 78%, **23**: 81%); (b) $LiAlH_4$, $Et_2O$, 0 °C to rt, **19a**: 0.5 h, **19b**,**c**: 3 h (**19a**: 92%; **19b**,**c**: crude); (c) (1) $H_2$, $Pd(OH)_2/C$, EtOH, rt, $H_2$-consumption monitored; (2) $NEt_3$, $CHCl_3$, rt (**20**: 38%, **22**: 18%).

Starting from the readily available 1-methoxy-2-naphthoic acid methyl ester **24**,[13] the 4-iodo derivative **25** was accessible in 83% yield by the reaction with ICl (Scheme 3). Sonogashira-reaction[14] allowed the introduction of TMS-acetylene and phenylacetylene to afford the respective ethynyl derivatives **27** and **28** in high yield. Desilylation of **27** by $NBu_4F$ furnished the corresponding ethynyl derivative **29**. Finally, we performed a smooth saponification of the carboxylic esters **25**, **28** and **29** using $KHCO_3$/MeOH to give the carboxylic acid derivatives **26**, **30** and **31**.




**Scheme 3.** (a) ICl, HOAc, rt, 1 h, 80 °C, 2 h (83%); (b) $KHCO_3$, MeOH, reflux, 3 h (**26**: 89%, **30**: 98%, **31**: 99%); (c) **25**, TMS-acetylene or phenylacetylene, $PdCl_2(PPh_3)_2$ 2 mol%, CuI 4 mol%, THF, rt, 18 h (**27**: 83%, **28**: 84%); (d) $Bu_4NF$, THF, rt, 30 min (94%).

The chiral diamines **9**,**12**,**13**,**14**,**19a**,**b**,**c** and their enantiomers were acylated using the aminobenzoic acid **32** and its *N*-methyl derivative **33** as well as the naphthoic acids **26**,**30**,**31** and the 4-bromo analogue **34**[15] applying DCC/HOBt as the coupling reagent to give the corresponding amides **3a**–**l**, **5a**,**b** and the optical antipodes **ent3a-l**, **ent5a**,**b** (Scheme 4, Table 1).[16–18]

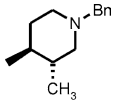
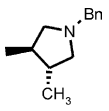
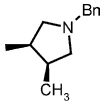
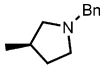
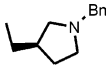
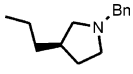
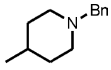
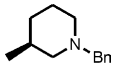



**Scheme 4.**

The test compounds **3a**–**l**, clebopride (**4**) and **5a**,**b** and the optical antipodes **ent3a-l** and **ent5a**,**b** as well as *N*-methyl-clebopride[18] were evaluated in vitro for their abilities to displace [$^3$H]spiperone from the cloned human dopamine receptors D2$_{long}$, D2$_{short}$,[19] D3[20] and D4.4[21] being stably expressed in CHO cells (Table 1).[22] D1 affinity was determined by employing bovine striatal membrane preparations and the D1 selective antagonist [$^3$H]SCH 23390.[22]

Generally the test compounds showed weak D1 binding. Compared to clebopride (**4**) and *N*-methylclebopride, the formal migration of the basic nitrogen within the chiral regioisomers **5a**,**b** and **ent5a**,**b** led to a significant decrease of the dopamine receptor recognition. On the other hand, the *trans*-configured 3-methyl-4-aminopiperidine derivatives **ent3a** and **ent3b** showed substantial D2, D3 and D4 affinities resulting in $K_i$ values of 20 and 13 nM, respectively, for D3 as well as 7.4 and 1.6 nM, respectively, for D4. Thus, the introduction of the methyl substituent resulted in a significant increase of D3 affinity for the (3*R*,4*R*)-isomers **ent3a**,**b** and in a decrease of D3 binding for the (3*S*,4*S*)-enantiomers **3a**,**b**. Investigating the methylpyrrolidine derivative **ent3c** with the same spatial orientation of the substituents as for **ent3a**,**b**, substantial D3 affinity could be observed as well ($K_i = 27$). For the enantiomer **3c**, strong and selective D4 binding was observed ($K_i = 0.77$ nM). For the *cis*-isomer **ent3e**, the highest D3 affinity was measured ($K_i = 1.8$ nM), leading to the observation, that both the absolute configuration at the attachment posi-

**Table 1.** Chemical reaction and receptor binding data [$K_i$ values [a] (nM) based on the means of 2–4 experiments performed in triplicate at eight concentrations]

| Product | –X | $ArCO_2H$ | R | R′ | Yield (%) | D1 | D2$_{long}$ | D2$_{short}$ | D3 | D4 |
|---|---|---|---|---|---|---|---|---|---|---|
| **3a** |  | 32 | H | — | 94 | 19,000 | 470 | 340 | 2200 | 35 |
| **ent3a** | | 32 | H | — | | 7100 | 8.6 | 7.4 | 20 | 7.4 |
| **3b** | | 33 | Me | — | 94 | 8200 | 54 | 39 | 510 | 4.7 |
| **ent3b** | | 33 | Me | — | | 4400 | 8 | 6.4 | 13 | 1.6 |
| **3c** |  | 33 | Me | — | 63 (two steps) | 12,000 | 21 | 19 | 220 | 0.77 |
| **ent3c** | | 33 | Me | — | | 5300 | 15 | 11 | 27 | 4.3 |
| **3d** | | 34 | — | Br | 66 (two steps) | 8400 | 1000 | 700 | 740 | 17 |
| **ent3d** | | 34 | — | Br | | 4200 | 490 | 260 | 140 | 59 |
| **3e** |  | 33 | Me | — | 64 (two steps) | 4100 | 3.7 | 3 | 100 | 0.23 |
| **ent3e** | | 33 | Me | — | | 4700 | 2.3 | 2 | 1.8 | 0.84 |
| **3f** | | 34 | — | Br | 69 (two steps) | 4700 | 200 | 135 | 390 | 2.7 |
| **ent3f** | | 34 | — | Br | | 4000 | 290 | 170 | 130 | 27 |
| **3g** | | 34 | — | Br | 80 | 7200 | 180 | 130 | 250 | 5 |
| **ent3g** | | 34 | — | Br | | 7400 | 150 | 150 | 84 | 21 |
| **3h** |  | 26 | — | I | 70 | 3000 | 60 | 23 | 34 | 1.2 |
| **ent3 h** | | 26 | — | I | | 6100 | 190 | 70 | 33 | 3.3 |
| **3i** | | 31 | — | Ethynyl | 85 | 3300 | 190 | 82 | 86 | 2.5 |
| **ent3i** | | 31 | — | Ethynyl | | 6100 | 500 | 250 | 79 | 7 |
| **3j** | | 30 | — | Phenylethynyl | 77 | 2800 | 6400 | 4000 | 1000 | 500 |
| **ent3j** | | 30 | — | Phenylethynyl | | 3300 | 7700 | 5500 | 1000 | 1500 |
| **3k** |  | 34 | — | Br | 69 | 2100 | 640 | 420 | 410 | 130 |
| **ent3k** | | 34 | — | Br | | 2900 | 1300 | 870 | 1000 | 78 |
| **3l** |  | 34 | — | Br | 89 | 1700 | 2000 | 1900 | 580 | 500 |
| **ent3l** | | 34 | — | Br | | 2100 | 2500 | 2800 | 1000 | 610 |
| Clebopride (**4**) |  | 32 | H | — | — | 6000 | 18 | 12 | 170 | 3.2 |
| *N*-Methyl-clebopride | | 33 | Me | — | 95 | 6800 | 24 | 15 | 160 | 8.3 |
| **5a** |  | 32 | H | — | 85 | 17,000 | 1600 | 1100 | 2900 | 200 |
| **ent5a** | | 32 | H | — | | 13,000 | 7900 | 4200 | 8700 | 530 |
| **5b** | | 33 | Me | — | 86 | 10,000 | 170 | 130 | 560 | 25 |
| **ent5b** | | 33 | Me | — | | 5600 | 250 | 210 | 1500 | 64 |

[a]D1 binding was determined with the radioligand [$^3$H]SCH23390 ($K_D = 0.35$ nM) at 0.3 nM; D2, D3 and D4 data were derived from experiments employing [$^3$H]spiperone at a concentration of 0.5 nM and were calculated with $K_D$ values of 0.1 nM, 0.2–0.45 nM and 0.1–0.45 nM, respectively.

tion of the amine and the spatial disposition of the methyl substituent strongly controls D3 binding. On the other hand, comparable D2 and D4 affinities were observed for **3e** and **ent3e**. Interestingly, **3e** turned out to be one of the most potent D4 ligands reported ($K_i = 0.23$ nM). The 4-bromonaphthamide analogues **3d, ent3d** and **ent3f** exhibited significantly diminished dopamine receptor affinities. On the other hand, **3f** displayed a strong and quite selective D4 binding ($K_i = 2.7$ nM; $D2_{long}/D4 = 74$, $D2_{short}/D4 = 50$, $D3/D4 = 144$). Within our assay, the binding profiles of the recently described aminopyrrolidines **3g** and **ent3g**[12] renouncing the C-methyl substitution were comparable to those of **3f** and **ent3f**. Interestingly, the 4-iodo and 4-ethynyl derivatives **3h,i**/**ent3h,i** displayed only poor stereodifferentiation. The phenylethynyl derivatives **3j**, **ent3j** only exhibited weak receptor recognition, obviously due to unfavorable interactions in the binding pocket of the receptor. This effect could also be observed, when we investigated the homologous pyrrolidine derivatives **3k,l** and **ent3k,l**.

In conclusion, SAR studies on novel chiral benzamide derivatives revealed insights into the three-dimensional structural requirements of subtype specific binding. Within future studies, a series of pharmacological tools with graduated receptor binding profiles might help to establish relationships between the balance of subtype recognition and atypical antipsychotic properties.

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16. **3b**: $\alpha_D^{20} = +17.3°$ (*c* 1.0, $CHCl_3$); **ent3b**: $\alpha_D^{20} = -17.5°$ (*c* 1.0, $CHCl_3$); mp: 184 °C; $^1$H NMR ($CDCl_3$, 360 MHz): $\delta = 0.92$ (d, $J = 6.4$ Hz, 3H, CH−C$H_3$), 1.50 (dddd, $J = 12.0$, 12.0, 11.4, 3.6 Hz, 1H, H-5a), 1.60–1.72 (m, 1H, H-5b), 1.78–1.88 (m, 1H, H-3), 2.01–2.18 (m, 2H, 2-Ha, 6-Ha); 2.84–2.93 (m, 2H, 2-Hb, 6-Hb); 2.95 (d, $J = 5.3$ Hz, 3H, NHC$H_3$); 3.50 (s, 2H, NC$H_2$Ph); 3.72 (dddd, $J = 11.4$, 10.8, 8.7, 3.9 Hz, 1H, H-4), 3.93 (s, 3H, $OCH_3$), 4.65–4.75 (m, 1H, N*H*$CH_3$), 6.10 (s, 1H, Ar), 7.16–7.37 (m, 5H, Ph), 7.51 (d, $J = 8.7$ Hz, 1H, NHCO), 8.10 (s, 1H, Ar). IR (KBr) 3390, 2935, 2800, 1640, 1600, 1520, 1280, 1245, 755, 700 cm$^{-1}$; Analysis calcd for $C_{22}H_{28}ClN_3O_2$: C, 65.74H, 7.02 N, 10.45. Found: C, 65.74H, 7.08 N, 10.30. EIMS (*m*/*z*): 401 ($M^+$).
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