Chapter 6

Derivatives of Nemonapride (YM-09151-2). Attempts to Develop a Selective Dopamine D₄ Antagonist

L. Alexander van Vliet and Håkan Wikström
Department of Medicinal Chemistry, University Centre for Pharmacy, University of Groningen, Antonius Deusinglaan 1, NL-9713 AV Groningen, The Netherlands

Thomas A. Pugsley, Thomas G. Heffner, and Lawrence D. Wise
Departments of Chemistry and Neuroscience Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105, USA

Abstract

Nemonapride (3, YM-09151-2) is a well-known dopamine (DA) receptor antagonist, with high affinity for DA D₂, D₃, and D₄ receptors. By synthesizing derivatives (substituted cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides) that are different from nemonapride in the substitution pattern on the benzamide phenyl moiety, we have tried to eliminate affinity for the DA D₂ and D₃ receptors, in order to obtain a selective DA D₄ antagonist. The new compounds were evaluated in binding assays for human DA D₂, D₃, and D₄ receptors. The structure affinity relationships that were found for the series of benzamides in Chapter 5, turned out to be applicable to this series of nemonapride derivatives only to a limited extent. Although some of the derivatives have high affinity for DA receptors, most of them are non-selective.

6.1 Introduction

In 1981 the Yamanouchi Pharmaceutical Company undertook a large SAR study with the aim to develop a highly potent dopamine antagonist of the benzamide type.¹ Starting from metoclopramide (1, Fig. 6.1) and sulpiride (2), benzamides that were known for their neuroleptic activity, nemonapride (3, YM-09151-2, formerly also known as emonapride) was developed. Nemonapride was the most potent dopamine antagonist from the series that was studied, displaying higher affinity for dopamine receptors in canine caudate nucleus than chlorpromazine and haloperidol (30 times and 3 times, respectively).² The compound is studied in its racemic form. Nemonapride has proven its value in numerous studies, both as a dopamine antagonist in
pharmacological studies, and as a dopamine receptor radioligand.\textsuperscript{3-5} Initially, nemonapride was characterized as a potent neuroleptic, showing higher potency than haloperidol in inhibiting apomorphine induced stereotypy in rats,\textsuperscript{1} but with a weaker cataleptogenic effect in the rat than the classic neuroleptics haloperidol and chlorpromazine.\textsuperscript{6} Later, when cloned DA receptor subtypes became available, nemonapride was found to be a non-selective dopamine antagonist with sub-nanomolar affinity for DA D\textsubscript{2}, D\textsubscript{3} and D\textsubscript{4} receptor subtypes.\textsuperscript{7,8}

Nemonapride has a particular chloro-methoxy-methylamino substitution pattern on the benzamide aromatic ring, which is also found in drugs like metoclopramide (\textbf{1}). Furthermore, it has a pyrrolidine ring with a methyl group attached in a \textit{cis}-orientation with respect to the benzamide attachment. The structure of the compound was studied with single crystal X-ray spectroscopy, which revealed an intramolecular hydrogen bond between the amide hydrogen and the methoxyl oxygen atom,\textsuperscript{2} which is a common feature for ortho-methoxy benzamides. This hydrogen bond forms a virtual six-membered ring fused with the benzene ring, which has been speculated to function as a pseudo-aromatic ring forming the phenyl ring of the DA pharmacophore.\textsuperscript{9,10}

![Chemical structures of metoclopramide (1), sulpiride (2), and nemonapride (3).]

In the previously studied series of \textit{N}-\textit{(1-benzyl-piperidin-4-yl)}benzamides (Chapter 5) we found that the affinity for the DA D\textsubscript{2} receptor subtype of compounds without ortho-methoxy group, was decreased as compared to analogous benzamides with an \textit{ortho}-methoxy group. The intramolecular hydrogen bond between amide -NH- and the \textit{ortho}-methoxy group leads to a coplanar arrangement of the amide carbonyl with respect to the aromatic ring plane.\textsuperscript{11} We concluded that this conformation is probably required for DA D\textsubscript{2} affinity, but does not appear to be essential for DA D\textsubscript{4} affinity. In order to develop an antagonist with high affinity and selectivity for the DA D\textsubscript{4} receptor subtype, we decided to apply this finding to nemonapride. By removing the \textit{ortho}-methoxy group of this compound, we may be able to eliminate its affinity for the DA D\textsubscript{2} receptor subtype (and possibly also for the DA D\textsubscript{3} receptor subtype), thereby increasing its selectivity for the DA D\textsubscript{4} receptor. Therefore, we decided to synthesize the “des-methoxy” analogue of nemonapride, as well as several other analogues which are different from
nemonapride in their substitution pattern on the benzamide phenyl moiety. The new compounds were evaluated in binding assays for human DA D₂, D₃ and D₄ receptors.

6.2 Chemistry

“Des-chloro” nemonapride (5) was prepared by reducing nemonapride (3) catalytically with palladium on carbon, employing ammonium formate as a hydrogen donor, which gave 4 as the product (Scheme 6.1). However, this reduction not only removed the aromatic chlorine but also the benzyl group. Therefore, 4 was re-benzylated in a simple alkylation reaction with benzyl chloride, using cesium carbonate as a base.

Scheme 6.1 (a) HCO₂NH₄, 10% Pd/C, MeOH; (b) PhCH₂Cl, Cs₂CO₃, MeCN.

The “des-methoxy” derivative of nemonapride (8) was prepared as follows (Scheme 6.2). Nemonapride (3) was demethylated with boron tribromide to yield the corresponding hydroxy derivative (6).¹² Compound 6 was subsequently triflated with N-phenyltrifluoromethanesulfonylimide to give 7, which was subjected to a selective catalytic reduction to remove the triflate group without affecting the aromatic chlorine or the benzyl group, to yield derivative 8.¹³

Triflate 7 was also subjected to a non-selective catalytic reduction with palladium on carbon and ammonium formate (Scheme 6.2), which eliminated both the aromatic chlorine and the triflate group. Intermediate 9 was then re-benzylated to yield derivative 10.
Scheme 6.2 (a) BBr$_3$, HCl/Et$_2$O, CH$_2$Cl$_2$, 0 °C; (b) PhN(SO$_2$CF$_3$)$_2$, Et$_3$N, CH$_2$Cl$_2$; (c) Et$_3$N, HCO$_2$H, PPh$_3$, Pd(OAc)$_2$, 60 °C; (d) HCO$_2$NH$_4$, 10% Pd/C, MeOH; (e) PhCH$_2$Cl, C$_5$CO$_3$, MeCN.

6.3 Receptor Binding Studies

The cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides were tested for their \textit{in vitro} binding affinity for cloned human dopamine (DA) D$_{2L}$, D$_3$, or D$_{4.2}$ receptors, expressed in Chinese hamster ovary (CHO) K-1 cells. The affinities of the compounds were determined by their abilities to displace $^3$H-spiperone from human D$_{2L}$, D$_3$ or D$_{4.2}$ DA receptors. Receptor affinities are presented in Table 6.1. Nemonapride is included as a reference.
6.4 Discussion

In this study we have tried to apply the structure affinity relationships that were found for the series of benzamides in Chapter 5, to nemonapride, to increase its selectivity for the DA D₄ receptor subtype. However, as can be seen from the receptor binding data in Table 6.1, none of the derivatives that were synthesized has a reasonable selectivity for the DA D₄ receptor. Nevertheless, some interesting structure-affinity relationships can be observed from Table 6.1.

Elimination of the aromatic chlorine on the 5-position reduces the affinity for DA receptors slightly, resulting in the non-selective derivative 5 with high affinity for all three receptor subtypes. Manipulation of the other substituents has a more dramatic effect on the receptor binding profile. For example, when also the ortho-methoxy group is taken away (compound 10) the affinity for the DA D₂ receptor is reduced by about a factor 1000, whereas affinity for the DA D₄ receptor subtype is reduced by a factor 100, as compared to 5. This effect is comparable to the structure-affinity relationships found for the benzamides in Chapter 5, for which elimination of the ortho-methoxy group resulted in a larger reduction in affinity for the DA D₂ than for the DA D₄ receptor subtype. Thus, also for this series of cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides the ortho-methoxy group appears to be more important for DA D₂ binding than for DA D₄ binding.

The affinity of hydroxy derivative 6 is reduced by about a factor 100 for all three DA receptor subtypes, as compared to nemonapride. This ortho-hydroxy group may form an intramolecular hydrogen bond with the amide carbonyl oxygen, thereby rotating the entire compound.

### Table 6.1. DA receptor affinities of the cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides.

<table>
<thead>
<tr>
<th>compound</th>
<th>R₁</th>
<th>R₂</th>
<th>hD₂, nM</th>
<th>hD₃, nM</th>
<th>hD₄, nM</th>
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</thead>
<tbody>
<tr>
<td>3 (nemonapride)</td>
<td>OMe</td>
<td>Cl</td>
<td>0.09</td>
<td>0.30</td>
<td>0.15</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>H</td>
<td>0.22</td>
<td>0.40</td>
<td>0.56</td>
</tr>
<tr>
<td>6</td>
<td>OH</td>
<td>Cl</td>
<td>33</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>OSO₂CF₃</td>
<td>Cl</td>
<td>1370</td>
<td>570</td>
<td>350</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>Cl</td>
<td>22</td>
<td>8.4</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>Cl</td>
<td>200</td>
<td>60</td>
<td>59</td>
</tr>
</tbody>
</table>

*Kᵢ values were obtained from six concentrations of each drug, run in triplicate, by a non-linear regression analysis, which varied less than 30%.*
amide phenyl moiety by 180° (see section 5.4). It is easy to imagine that such a conformational change has a dramatic effect on the DA receptor binding profile.

The triflated compound 7 has a much reduced affinity for these DA receptors. Although the trifluoromethanesulfonyloxy group serves as a valuable bio-isoster of a methoxy and/or hydroxy group within other drug classes,\textsuperscript{16,17} the binding data show that this approach is not suitable for this series of nemonapride derivatives. The low affinity of 7 may be explained electronically, because of the strong electron withdrawing properties of the triflate substituent, but also sterically, because the size of this substituent may distort the coplanar arrangement of amide carbonyl and phenyl ring.

Compound 8, which has no methoxy group as compared to nemonapride, does not have the desired DA D\textsubscript{4} selectivity which we had expected on the basis of the structure affinity relationships found in Chapter 5. When compared to compound 10 the aromatic chlorine atom of 8 seems to eliminate the DA D\textsubscript{4} preferring properties of the des-methoxy derivatives.

In conclusion, eliminating the ortho-methoxy group to enhance DA D\textsubscript{4} selectivity within this series is only effective when no aromatic chlorine substituent is present on the 5 position. Compound 10 has some selectivity for the DA D\textsubscript{4} receptor (over the DA D\textsubscript{2} receptor), but its affinity as compared to nemonapride has been reduced dramatically.

Recently, the Yamanouchi Pharmaceutical Company developed a selective DA D\textsubscript{4} antagonist from a series of N-(1-benzylpyrrolidin-3-yl)benzamides, related to nemonapride.\textsuperscript{18,19} (S)-(++)-N-(1-benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (YM-43611, 11), showed high affinity for DA D\textsubscript{3} and D\textsubscript{4} receptors (K\textsubscript{i} values of 21 and 2.1 nM, respectively) with 110-fold DA D\textsubscript{4} selectivity over DA D\textsubscript{2} receptors. Apparently, for this series of compounds selectivity for the DA D\textsubscript{4} receptor is more effectively obtained by manipulating other structural features.

\[ C \backslash O \backslash \text{HCl} \backslash \text{N} \backslash \text{OMe} \]

11 (YM-43611)

6.5 Experimental Section

General. Physical and spectral data were obtained as described in section 5.5. In addition, 500 MHz spectra were obtained on a Varian Unity 500 spectrometer. MPLC and recrystallization procedures were also performed as described in Section 5.5.
**Materials.** Nemonapride was kindly provided by Parke Davis Pharmaceutical Research. Acetonitril was dried on molecular sieves 4Å. All other chemicals and solvents are commercially available, and were used without further purification.

**Nemonapride (3).** $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.12 (d, $J = 6.4$, 3H), 1.56-1.68 (m, 1H), 2.56-2.68 (m, 1H), 2.95 (d, $J = 5.1$, 3H), 2.92-3.02 (m, 1H), 3.17 (d, $J = 13.2$, 1H), 3.98 (s, 3H), 4.04 (d, $J = 13.2$, 1H), 4.59-4.75 (m, 2H), 6.12 (s, 1H), 7.22-7.38 (m, 5H), 8.01 (d, $J = 12.0$, 1H), 8.10 (s, 1H); $^{13}$C NMR $\delta$ 13.8, 29.9, 30.9, 51.5, 52.1, 55.9, 57.4, 61.5, 93.0, 110.5, 111.2, 126.7, 128.0 (2C), 128.5 (2C), 132.2, 147.9, 158.0, 164.0, 169.0.

**cis-N-(2-Methylpyrrolidin-3-yl)-2-methoxy-4-(methylamino)-benzamide (4).** Nemonapride 3 (0.17 g, 0.43 mmol) and ammonium formate (0.12 g, 1.9 mmol) were dissolved in 10 mL of methanol, and the solution was treated (under N$_2$) with 10% Pd/C (0.15 g). The reaction mixture was stirred at room temperature, while monitoring the reaction with TLC. After 40 min all starting material was consumed, and the Pd/C was removed by filtration over Celite, after which the solvent was evaporated under reduced pressure. Because the residue contained some ammonium formate, it was resuspended in acetonitril. The solids were filtered off, and the acetonitril was evaporated under reduced pressure which yielded 4 as a clear oil (0.11 g, 97 %). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.41 (d, $J = 6.6$, 3H), 2.12-2.18 (m, 1H), 2.44-2.51 (m, 1H), 2.82 (s, 3H), 3.19-3.26 (m, 1H), 3.50-3.58 (m, 1H), 3.68 (s, 1H), 3.72-3.78 (m, 1H), 4.62-4.70 (m, 1H), 6.05 (s, 1H), 6.21 (d, $J = 8.7$, 1H), 7.85 (d, $J = 8.7$, 1H), 8.20 (d, $J = 8.1$, 1H); $^{13}$C NMR $\delta$ 12.4, 30.0, 30.9, 43.4, 51.0, 55.8, 58.2, 63.7, 94.0, 104.7, 133.3, 153.9, 159.6, 166.5. HRMS calcd. (obsd.) for C$_{14}$H$_{21}$N$_3$O$_2$: 263.1634 (263.1651).

**cis-N-(1-Benzyl-2-methylpyrrolidin-3-yl)-2-methoxy-4-(methylamino)-benzamide (5).** Compound 4 (0.11 g, 0.43 mmol) and benzyl chloride (60 µL, 0.50 mmol) were dissolved in 5 mL of acetonitril. Cesium carbonate (0.27 g, 0.81 mmol) was added, and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residuals were fractionated between ethyl acetate and water, and the water layer was extracted once with ethyl acetate. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and the solvents were evaporated under reduced pressure. The residual oil was purified with MPLC on silica (initial eluent 100 % hexane, final eluent 100 % ethyl acetate), which yielded 5 as a clear oil (0.10 g, 66 %): MS (CI with NH$_3$) $m/e$ 354 (M$^+$). Part of the product was converted to the oxalate and recrystallized from 2-propanol, which yielded white crystals: mp 172-175 °C. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.12 (d, $J = 6.4$, 3H), 1.58-1.72 (m, 1H), 2.10-2.30 (m, 2H), 2.57-2.68 (m, 1H), 2.87 (d, $J = 3.4$, 3H), 2.92-3.01 (m, 1H), 3.17 (d, $J = 13.0$, 1H), 3.94 (s, 3H), 4.04 (d, $J = 13.0$, 1H), 4.10-4.24 (m, 1H), 4.60-4.74 (m, 1H), 6.09 (d, $J = 2.0$, 1H), 6.27 (dd, $J_1 = 8.6$, $J_2 = 2.2$, 1H), 7.24-7.38 (m, 5H), 8.04 (d, $J = 8.8$, 2H); $^{13}$C NMR $\delta$ 13.9, 30.1, 31.0, 51.5, 51.9, 55.4, 57.4, 61.5, 94.2, 104.8, 110.5, 126.7, 128.0 (2C), 128.5 (2C), 133.6, 139.5, 153.0, 159.2, 165.1. Anal. calcd. (obsd.) for C$_{21}$H$_{25}$N$_3$O$_2$·C$_2$H$_5$O$_4$·1/3H$_2$O: C: 61.40 (61.65), H: 6.60 (6.70), N: 9.34 (8.88).
cis-N-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-hydroxy-4-(methylamino)benzamide (6). A solution of nemonapride 3 (0.26 g, 0.68 mmol) in 5 mL of methylene chloride was treated with 1 N HCl-ether (1.35 mL, 1.35 mmol). The mixture was cooled on ice, and BBr₃ (0.68 mL of a 1 N solution in methylene chloride, diluted with 1 mL of methylene chloride, 0.68 mmol) was added dropwise, over a 1 h period. After the addition was completed, the reaction was stirred at 0 °C for 1 h. The mixture was basified with 5 % ammonia, and the layers were separated. The aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure, which yielded 6 as a white solid (0.26 g, 100 %). Part of the product was converted to the hydrochloride and recrystallized from ethanol/isopropylether, which yielded white crystals: mp 221-223 °C. ¹H NMR (200 MHz, CDCl₃) δ 1.17 (d, J = 6.4, 3H), 1.57-1.63 (m, 1H), 2.05-2.28 (m, 2H), 2.53-2.59 (m, 1H), 2.91 (d, J = 4.9, 3H), 2.94-3.01 (m, 1H), 3.13 (d, J = 12.8, 1H), 4.05 (d, J = 12.8, 1H), 4.62-4.72 (m, 2H), 6.16 (s, 1H), 6.41 (br d, J = 9.3, 1H), 7.26-7.35 (m, 7H); ¹³C NMR δ 13.3, 29.8, 30.3, 51.3, 51.6, 57.3, 62.1, 98.0, 103.2, 109.2, 125.4, 127.0, 128.2 (2C), 128.9 (2C), 138.2, 149.2, 162.6, 168.7; MS (CI with NH₃) m/e 374 (M⁺1). Anal. calcd. (obsd.) for C₂₀H₂₄ClN₃O₂·HCl: C: 58.54 (58.23), H: 6.14 (6.04), N: 10.24 (10.18).

cis-N-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-4-(methylamino)-2-[(trifluoromethyl)-sulfonyl]oxy]benzamide (7). Compound 6 (0.26 g, 0.68 mmol) was dissolved in methylene chloride (10 mL), and triethylamine (0.6 mL, 4.3 mmol) and N-phenyltrifluoromethanesulfonimide (0.78 g, 2.2 mmol) were added. The reaction mixture was stirred at room temperature for 24 h, after which extra triethylamine (0.6 mL, 4.3 mmol) and N-phenyltrifluoromethanesulfonimide (0.3 g, 0.85 mmol) were added. When all starting compound was consumed (TLC), the reaction mixture was washed with water (20 mL). The aqueous layer was extracted once with methylene chloride (20 mL), after which the combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residual oil contained a substantial amount of N-phenyltrifluoromethanesulfonamide, and the product was purified by MPLC on silica (initial eluent 100% hexane, final eluent 100% ethyl acetate) which yielded 7 as a clear oil (0.31 g, 90 %). Part of the product was converted to the oxalate and recrystallized from ethyl acetate/hexane yielding light-yellow crystals: mp 165.5-166.5 °C. ¹H NMR (500 MHz, CD₃OD, oxalate) δ 1.35 (d, J = 6.6, 3H), 2.09-2.17 (m, 1H), 2.49-2.56 (m, 1H), 2.88 (s, 3H), 3.19-3.25 (m, 1H), 3.31-3.32 (m, 1H), 3.51-3.57 (m, 1H), 3.80-3.84 (m, 1H), 4.25 (d, J = 12.9, 1H), 4.59 (d, J = 12.9, 1H), 4.68-4.73 (m, 1H), 6.48 (s, 1H), 7.46-7.48 (m, 3H), 7.55-7.57 (m, 2H), 7.69 (s, 1H); ¹³C NMR (125.7 MHz, CD₃OD, oxalate) δ 11.6, 28.8, 30.0, 49.3, 52.9, 57.6, 66.5, 104.0, 115.6, 118.4, 120.1 (q, J = 321 Hz, CF₃), 130.4 (2C), 131.0, 131.1, 131.5, 131.7 (2C), 148.9, 150.3, 166.6 (2C), 167.2; MS (CI with NH₃) m/e 506 (M⁺1). Anal. calcd. (obsd.) for C₂₁H₂₅ClF₃N₂O₄S·C₂H₅O₂: C: 46.35 (46.09), H: 4.23 (4.02), N: 7.05 (7.06).
cis-N-(1-Benzyl-2-methylpyrrolidin-3-yl)-3-chloro-4-(methylamino)-benzamide (8). Triflate 7 (0.11 g, 0.22 mmol) was dissolved in 3 mL of DMF, and triethylamine (120 µL, 0.87 mmol), formic acid (33 µL, 0.87 mmol), triphenylphosphine (12 mg, 0.043 mmol) and palladium acetate (7.3 mg, 0.033 mmol) were added. The reaction mixture was heated to 60 °C under a nitrogen atmosphere for 5 h. After cooling to room temperature, 5 % hydrochloric acid (3 mL) was added, and the mixture was stirred overnight. The mixture was basified with 10 % sodium hydroxide until pH = 10, and extracted with methylene chloride (3 × 10 mL). The combined organic layers were washed once with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residual oil was purified with MPLC on silica (initial eluent 99 % hexane + 1 % triethyl amine, final eluent 99 % ethyl acetate + 1 % triethyl amine) which yielded 8 as a clear oil (0.073 g, 93 %): ¹H NMR (200 MHz, CDCl₃) δ 1.15 (d, J = 6.3, 3H), 1.55-1.68 (m, 1H), 2.02-2.31 (m, 2H), 2.53-2.62 (m, 1H), 2.86-3.00 (m, 4H), 3.12 (d, J = 12.8, 1H), 4.03 (d, J = 12.8, 1H), 4.62-4.73 (m, 1H), 6.60 (d, J = 8.6, 1H), 7.22-7.51 (m, 7H), 7.63 (dd, J₁ = 8.6, J₂ = 2.2, 1H), 7.77 (d, J = 2.2, 1H); ¹³C NMR δ 13.4, 29.9, 30.5, 51.5, 51.9, 57.5, 62.3, 109.3, 118.4, 122.7, 126.8, 127.0, 128.2 (2C), 128.9 (2C), 131.9, 138.3, 147.2, 165.7; MS (CI with NH₃) m/e 358 (M+1). The product was converted to the oxalate but failed to crystallize, and was obtained as an off-white foam. Anal. calcd. (obsd.) for C₂₀H₂₄ClN₃O·C₂H₂O₄·¾H₂O: C: 57.21 (57.49), H: 5.96 (5.73), N: 9.10 (8.71).

cis-N-(2-Methylpyrrolidin-3-yl)-4-(methylamino)-benzamide (9). Triflate 7 (0.14 g, 0.28 mmol) was converted to 9, as described for the preparation of 4, and was isolated as a clear oil (0.05 g, 80 %). The intermediate was used without further purification.

cis-N-(1-Benzyl-2-methylpyrrolidin-3-yl)-4-(methylamino)-benzamide (10). Compound 9 (0.05 g, 0.23 mmol) was benzylated as described for the preparation of 5, which afforded 10 as a light-brown oil (0.027 g, 36 %): ¹H NMR (200 MHz, CDCl₃) δ 1.18 (d, J = 6.1, 3H), 1.60-1.67 (m, 1H), 2.02-2.29 (m, 2H), 2.59-2.65 (m, 1H), 2.92-3.07 (m, 1H), 3.09 (s, 3H), 3.18 (d, J = 11.5, 1H), 4.07 (d, J = 11.5, 1H), 4.60 (s, 1H), 4.69-4.76 (m, 1H), 6.71 (d, J = 8.8, 2H), 7.15-7.38 (m, 6H), 7.71 (d, J = 9.0, 2H); MS (CI with NH₃) m/e 324 (M⁺).

Pharmacology. Receptor Binding Assays. The receptor binding studies were performed at Parke Davis Pharmaceutical Research Division, by T.A. Pugsley, as described in section 5.5.

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6.6 References


