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**Short communication**

# 3-Phenylpyrrolidines: synthesis and evaluation of the *in vitro* binding affinity at D1 and D2 receptors

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**Summary** — A variety of 3-phenylpyrrolidines were synthesized and evaluated for their dopamine binding affinity in rat striatal tissue *in vitro* using [$^3$H] SCH 23390 and [$^3$H] spiperone as the D1 and D2 selective radioligands, respectively. Maximal D1 and D2 receptor binding affinity occurs with a *n*-pentyl group on the pyrrolidine ring nitrogen. Introduction of a *trans* methyl group at the 4-position of the ring decreases both D1 and D2 binding affinity. However, a *cis* 4-methyl group increases D1 receptor selectivity when the pyrrolidine ring is substituted with a *n*-propyl group. 3-Phenylpyrrolidines having a catechol nucleus exhibit greater affinity at both D1 and D2 receptors than *meta*-hydroxyphenyl derivatives

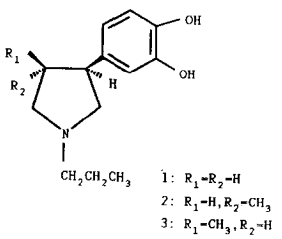
**dopamine / 3-phenylpyrrolidines / 4-methyl-3-phenyl-pyrrolidines / D1 and D2 receptor binding affinity**

## Introduction

The synthesis and dopaminergic activity of the 3-phenylpyrrolidine **1** was reported previously [1]. A subsequent study showed that *trans*-3-(3,4-dihydroxyphenyl)-4-methyl-1-*n*-propylpyrrolidine (**2**) was virtually inactive as a dopamine agonist [2]. In contrast, the *cis* isomer **3** exhibited dopamine agonist activity in behavioral assays [3].

The effect of *N*-substitution on a variety of compounds having dopaminergic activity has been extensively investigated [4, 5]. Wikström *et al* have proposed a receptor model in which two directions of the *N*-alkyl group are possible [4]. According to this model when the nitrogen substituent is directed downward, a steric demand exists that limits maximal interaction of either an *n*-propyl group or a piperidine ring with the receptor. However, the upward direction is sterically much less restricted. Similarly, the rotamer-based dopamine receptor model developed by Seiler [5] defines both small and large *N*-alkyl binding sites. Invoking either of these receptor models gives rise to the '*n*-butyl phenomenon' [5] in the ergolines [4], aporphines [6], *trans*-9-hydroxybenzo[f]quinolines [4], and oxaergolines [7]. In each of these classes of dopaminergic agonists the *n*-butyl group is directed downwards toward the sterically restricted *N*-alkyl binding site. Thus, these compounds are apparently unable to properly bind to dopamine receptors leading to a decrease or loss of biological activity. However, in the *trans*-7-hydroxybenzo[f]quinolines replacement of the *n*-propyl group by a *n*-butyl group leads to a compound with increased dopaminergic activity [4].

Since previous studies [1–3] on 3-phenylpyrrolidines have demonstrated dopaminergic activity in both behavioral and biochemical tests, the purpose of this investigation was to determine the effect of increased *N*-alkyl chain length on dopamine D1 and D2 receptor binding affinity. Decreased binding at D1 and D2 receptors, when nitrogen is substituted with *n*-butyl and higher homologues, may suggest that the *N*-substituent is directed downwards toward the sterically restricted *N*-alkyl binding site (*n*-butyl phenomenon) [5]. However, an increase in dopamine receptor binding affinity may indicate that the *N*-substituent is directed in the upward, sterically less restricted direction [4, 5].



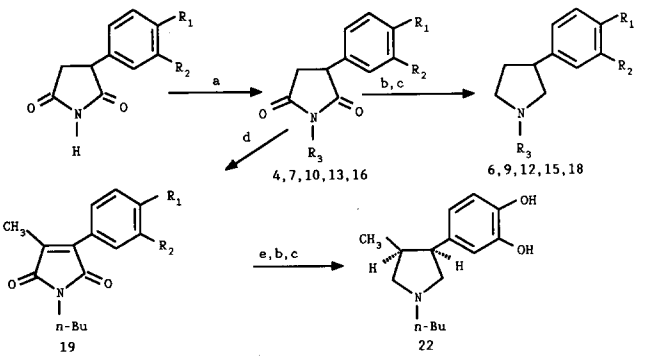
## Results and discussion

### *Chemistry*

Compounds evaluated for *in vitro* dopamine receptor binding were synthesized using general methods A–E [1–3] as described in *Experimental protocols* and shown in scheme 1. The physicochemical data for all novel compounds are given in table I. The NMR spectra of all intermediates and final products were consistent with the assigned structures.

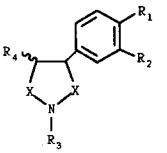
### *Pharmacology*

The *in vitro* binding affinity of the 3-phenylpyrrolidines at dopamine D1 and D2 receptors was evaluated in rat striatal tissue using [$^3$H] SCH 23390




**Scheme 1.** a = RX/NaH-DMF, b = LAH/THF, c = 48% HBr, d = EtOCOCOOEt/NaH-THF, $CH_2O/Et_3N$, e = $H_2$/Pd-C.

**Table I.** 3-Phenylpyrrolidine derivatives.



| *Compd* | *X* | *R¹* | *R²* | *R³* | *R⁴* | *mp, °C (bp, °C, mm)* | *Yield %* | *Recryst Solvent* [a] | *Formula* [b] |
|---|---|---|---|---|---|---|---|---|---|
| **1** | $CH_2$ | OH | OH | *n*-Pr | H[c] | | | | |
| **2** | $CH_2$ | OH | OH | *n*-Pr | $CH_3$[d,e] | | | | |
| **3** | $CH_2$ | OH | OH | *n*-Pr | $CH_3$[f,g] | | | | |
| **4** | CO | OMe | OMe | *i*-Pr | H | 72–74 | 38 | A | $C_{15}H_{19}NO_4$ |
| **5** | $CH_2$ | OMe | OMe | *i*-Pr | H | 164–165[h] | 38 | B | $C_{15}H_{24}ClNO_2$[i] |
| **6** | $CH_2$ | OH | OH | *i*-Pr | H | 138.5–139.5 | 53 | B | $C_{13}H_{20}BrNO_2$ |
| **7** | CO | OMe | OMe | *n*-Bu | H | 58–59 | 42 | C | $C_{16}H_{21}NO_4$ |
| **8** | $CH_2$ | OMe | OMe | *n*-Bu | H | (155–160, 1.3) | 63 | | $C_{16}H_{25}NO_2$ |
| **9** | $CH_2$ | OH | OH | *n*-Bu | H | 126–128 | 23 | B | $C_{14}H_{22}BrNO_2$ |
| **10** | CO | H | OMe | *n*-Bu | H | (186–187, 0.8) | 43 | | $C_{15}H_{19}NO_3$ |
| **11** | $CH_2$ | H | OMe | *n*-Bu | H | (140–143, 0.8) | 57 | D | $C_{15}H_{23}NO$ |
| **12** | $CH_2$ | H | OH | *n*-Bu | H | 117–119 | 61 | B | $C_{14}H_{22}BrNO$ |
| **13** | CO | OMe | OMe | *n*-Pt | H | 46–48 | 54 | E | $C_{17}H_{23}NO_4$ |
| **14** | $CH_2$ | OMe | OMe | *n*-Pt | H | 134–135[j] | 59 | F | $C_{17}H_{28}ClNO_2$[i] |
| **15** | $CH_2$ | OH | OH | *n*-Pt | H | 119–121 | 62 | B | $C_{15}H_{24}BrNO_2$ |
| **16** | CO | OMe | OMe | *n*-Hx | H | 55–57[k] | 50 | E | $C_{18}H_{25}NO_4$ |
| **17** | $CH_2$ | OMe | OMe | *n*-Hx | H | (155–160, 0.1) | 78 | | $C_{18}H_{19}NO_2$ |
| **18** | $CH_2$ | OH | OH | *n*-Hx | H | 108–110 | 59 | G | $C_{16}H_{26}BrNO_2$ |
| **19** | CO | OMe | OMe | *n*-Bu | $CH_3$[l] | 61–62 | 33 | H | $C_{17}H_{21}NO_4$ |
| **20** | CO | OMe | OMe | *n*-Bu | $CH_3$[f] | 119–121 | 65 | H | $C_{17}H_{23}NO_4$ |
| **21** | $CH_2$ | OMe | OMe | *n*-Bu | $CH_3$[f] | 147–148[m] | 52 | B | $C_{17}H_{28}ClNO_6$ |
| **22** | $CH_2$ | OH | OH | *n*-Bu | $CH_3$[f] | 153–154 | 56 | B | $C_{17}H_{24}BrNO_2$ |

[a]A = $CHCl_3$/hexane, B = EtOH/$Et_2O$, C = hexane, D = EtOAc/$Et_2O$, E = $Et_2O$/petroleum ether, F = *i*-PrOH/$Et_2O$, G = EtOAc, H = *i*-PrOH/$H_2O$. [b]All compounds gave acceptable C, H, N analyses, ± 0.4% of the calculated values. [c][1], [d]*trans*, [e][2], [f]*cis*, [g][3]. [h]bp of the free base (139–143°C, 0.5 mm). [i]Hydrochloride. [j]bp of the free base (132–141°C, 0.5 mm). [k]Purified by silica gel flash chromatography using Hx:EtOAc 5:5. [l]3,4-Dehydro. [m]bp of the free base (156–158°C, 0.4 mm).

and [$^3$H] spiperone as the selective D1 and D2 radioligands, respectively (table II) [8, 9]. The effect of *N*-alkyl substitution on dopaminergic activity has been examined in several series of compounds. In a recent report [10] on *N*-substituted norapomorphines, maximal D2 agonist affinity was demonstrated with a nitrogen substituent of cyclopropylmethyl, allyl, *n*-propyl, or ethyl. Extension of the chain length to four carbons (*n*-butyl) or branching of the *N*-substituent, dramatically decreased D2 binding affinity. Similar results have also been found with 6-substituted ergolines [4]. In contrast, 7-hydroxybenzo[f]quinolines show an increase in activity when *n*-propyl is replaced by *n*-butyl. Likewise, replacement of the *n*-propyl group of (±)-3-PPP with *n*-butyl, *n*-pentyl, or phenethyl enhances affinity for dopamine autoreceptors [11].

Affinity for both D1 and D2 receptors can be increased by lengthening the *N*-alkyl chain on the pyrrolidine ring. The *n*-pentyl derivative **15** has about ten and fifteen times the affinity at D1 and D2 binding sites than the *n*-propyl derivative **1**. However, no selectivity at dopamine receptors is seen with any of the *N*-alkyl pyrrolidines. The *n*-hexyl derivative **18** is slightly less effective in displacing [$^3$H] spiperone at D2 sites than **15**. Apparently, the D1 receptor has a sterically-restricted lipophilic pocket. This appears to be supported by results obtained by a number of authors. Neumeyer *et al* [10] found that *N*-alkylation of norapomorphine produced compounds with decreased affinity for D1 receptors in comparison with apomorphine. Similar results were also obtained at D1 and $DA_1$ binding sites for 1,2,3,4-tetrahydroisoquinolines and the related thienyl isosteres [12].

Branching of the *N*-alkyl group on the 3-phenylpyrrolidine ring (*N* = *i*Pr, **9**) dramatically decreases affinity for both D1 and D2 binding sites. Neumeyer [10] also found markedly decreased D2 binding affinity with *N*-isopropylnorapomorphine. However, the *N*-*i*Pr derivative of (±)3-PPP was more potent than the parent compound in terms of dopamine autoreceptor activity [11].

Introduction of a 4-methyl group on the pyrrolidine ring alters both D1 and D2 receptor binding. A *trans* 4-methyl group **2** essentially eliminates D1 and D2 receptor affinity. However, introduction of a *cis* 4-methyl group **3** produces enhanced binding at D1 receptors while D2 affinity is decreased approximately three-fold. Replacement of the *N*-*n*-propyl group of the **3** with a *n*-butyl **22** dramatically decreases D1 binding while D2 receptor affinity remains unaltered. These results appear to be in contrast with a report that *trans* 4-arylpyrrolidines gave $DA_1$ selective compounds while the *cis* compounds were inactive [13].

A catechol nucleus is not a requirement for D1 and D2 binding in the 3-phenylpyrrolidines. The *n*-butyl monohydroxy derivative **12** has greater affinity than the *n*-propyl catechol **1** at both D1 and D2 receptors. However, **12** is slightly less active at D1 and D2 receptors than the *n*-butyl catechol **9**. Thus, it appears that the presence of an *n*-butyl group on the pyrrolidine ring nitrogen has a greater influence on binding at both D1 and D2 receptors than the presence of a catechol group. Seiler [14] also found that in the benzergolines a catechol was not a requirement for potent D1 binding affinity.

Based on results obtained with the structurally simple 3-phenylpyrrolidines, additional work is in progress to develop compounds with greater selectivity and affinity at dopamine receptors. Although several 3-phenylpyrrolidines have shown potent affinity for D1 and D2 binding sites, behavioral and biochemical studies are necessary to completely describe the pharmacological activity of these derivatives.

**Table II.** *in vitro* binding of 3-phenylpyrrolidines at D1 and D2 receptors[a].

| *Compd* | *D1* $K_I$ *(nM)* [b] | *D2* $K_I$ *(nM)* [b] |
|---|---|---|
| **1** | 765 | 450 |
| **2** | 4120 | 6700 |
| **3** | 503 | 1250 |
| **6** | 4495 | 3126 |
| **9** | 362 | 95 |
| **12** | 540 | 241 |
| **15** | 73 | 31 |
| **18** | 1700 | 70 |
| **22** | 4890 | 1249 |

[a][$^3$H] SCH 23390 and [$^3$H] spiperone were used as the D1 and D2 ligands, respectively. The results are the means of 2–3 experiments using 3–6 concentrations in each assay. [b]$K_I$ values were calculated from the expression $K_I = IC_{50}/(1 + [L]/K_D)$ where $IC_{50}$ is the concentration of agonist causing 50% inhibition of specific binding, L is the concentration of radioligand used and $K_D$ is the dissociation constant of the radioligand ([$^3$H] SCH 23390: 0.14 nM; [$^3$H] spiperone: 0.08 nM [8]). Both D1 and D2 assays were performed without inclusion of GTP or ATP.

## Experimental protocols

*Chemistry*

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The IR spectra were recorded as potassium bromide pellets or as liquid films with a Nicolet 5MX FT spectrometer. The NMR spectra were recorded on a JEOL FX 90Q spectrometer. Chemical shifts are

reported in parts per million (δ) relative to tetramethylsilane (1%) or in the case of deuterium oxide sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Mass spectra were recorded on a Finnigan MAT TQS 4510 spectrometer. Analytical data were obtained from Oneida Research Services, Inc, Whitesboro, New York and are within ± 0.4% of the calculated values.

*3-(3,4-Dimethoxyphenyl)-1-(2-propyl)pyrrolidine-2,5-dione* ***4***
*Method A.* Sodium hydride (6.12 g, 128 mmol) as a 50% mineral oil dispersion was washed with hexane (3 x 20 ml), suspended in DMF (50 ml), and charged into a reaction flask under nitrogen. The stirred suspension was treated dropwise with a solution of 3-(3,4-dimethoxyphenyl)pyrrolidine-2,5-dione (30.0 g, 128 mmol) [1] in DMF (100 ml). After the addition has been completed, the reaction mixture was heated at 80°C for 2 h, cooled, and treated with 2-bromopropane (15.7 g, 128 mmol) in DMF (50 ml) and heated at 80°C for 24 h. The reaction mixture was cooled, treated with 10 ml of absolute ethanol, and evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (250 ml) and water (100 ml). The $CHCl_3$ layer was separated, dried ($Na_2SO_4$), filtered, and evaporated to give a yellow oil. Flash chromatography of the oil on silica gel using an EtOAc (5):hexane (5) solvent system gave after evaporation of the solvents a white solid. Recrystallization yielded 13.3 g of **4**. IR (KBr): 1785 and 1725 (C=O, imide) $cm^{-1}$. NMR ($CDCl_3$): δ 1.55 (d, 6H, $J$ = 7 Hz, $CH(CH_3)_2$), 2.93 (m, 2H, $C_4$-H), 3.87 (br s, 7H, $OCH_3$'s and NCH), 4.53 (m, 1H, $C_3$-H), 6.80 (m, 3H, ArH). Compounds **7**, **10**, **13** and **16** were also prepared by this method.

*1-(n-Butyl)-3-(3,4-dimethoxy)phenylpyrrolidine* ***8***
*Method B.* A solution of **7** (16.3 g, 56 mmol) in THF (100 ml) was added dropwise under nitrogen to a stirred suspension of LAH (12.8 g, 33.8 mmol) in THF (200 ml). After the addition had been completed, the reaction mixture was refluxed for 18 h. The mixture was cooled, and water was carefully added to decompose the excess LAH. The reaction mixture was filtered, evaporated under reduced pressure, and the resulting residue partitioned between $CH_2Cl_2$ (300 ml) and water (100 ml). The $CH_2Cl_2$ layer was separated, dried ($Na_2SO_4$), filtered, and evaporated to yield an oil. Vacuum distillation afforded 9.3 g (63%) of **8** as a clear, colorless oil. NMR ($CDCl_3$): δ 0.95 (t, 3H, $CH_3$), 1.1–3.5 (m, 13H), 3.77 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 6.80 (m, 3H, ArH). This method was also used to prepare compounds **5**, **8**, **11**, **14**, **17** and **21**.

*3-(3,4-Dihydroxy)phenyl-1-(n-hexyl)pyrrolidine hydrobromide* ***18***
*Method C.* A solution of **17** (1.0 g, 3.4 mmol) in 48% HBr (30 ml) was refluxed under a nitrogen atmosphere for 2 h. The solution was cooled and evaporated under reduced pressure to yield a dark brown oil. Azeotropic distillation with absolute ethanol followed by trituration of the oil with diethyl ether gave a solid. Recrystallization gave 0.7 g of a beige solid. NMR (DMSO–$d_6$): δ 0.87 (br t, 3H, $CH_3$), 1.10–3.95 (m, 17H), 6.71 (m, 3H, ArH), 8.85 (br s, 2H, OH), 10.0 (br s, 1H, $NH^+$). Compounds **6**, **9**, **12**, **15**, and **22** were also synthesized by this method.

*1-n-Butyl-3-(3,4-dimethoxyphenyl)-4-methyl-3-pyrrolidine-2,5-dione* ***19***
*Method D.* A mixture of **7** (7.0 g, 24 mmol), 60% NaH (2.2 g, 55 mmol) previously washed with hexane (3 x 30 ml), and diethyl oxalate (7.8 g, 53 mmol) in THF (200 ml) was refluxed under nitrogen for 48 h. The dark red solution was cooled, acidified with glacial acetic acid, and evaporated under reduced pressure to afford an oil. Flash chromatography on silica gel using ethyl acetate as the solvent gave 1.8 g of a yellow solid. [TLC (silica gel) $R_f$ = 0.33, ethyl acetate-2 drops of glacial acetic acid]. The solid was dissolved in a dioxane (25 ml)-water (25 ml) mixture and treated with 40% aqueous formaldehyde (2 ml) and triethylamine (2 ml) using a previously reported method [3]. After stirring overnight, the reaction mixture was acidified with 6 N HCl and the dioxane was removed under reduced pressure. The remaining water phase was extracted with diethyl ether (3 x 100 ml). The ether layer was washed with saturated sodium bicarbonate solution (3 x 25 ml) followed by water (100 ml), separated, and dried (sodium sulfate). Evaporation of the solvent gave a yellow solid. Flash chromatography on silica gel using EtOAc:hexane (5:5) as the solvent gave analytically pure **19** as fluorescent green crystals. NMR ($CDCl_3$): δ 0.95 (t, 3H, $CH_3$), 1.1–2.7 (m, 4H, $CH_2CH_2$), 2.31 (s, 3H, $C_4$-$CH_3$), 3.55 (t, 2H, $NCH_2$), 3.93 (s, 6H, $OCH_3$), 7.1 (m, 3H, ArH).

*cis-1-(n-Butyl)-3-(3,4-dihydroxyphenyl)-4-(methyl)pyrrolidine-2,5-dione* ***20***
*Method E.* A mixture of **19** (3.60 g, 11.9 mmol) and 0.5 g of 10% palladium on carbon was shaken on a Parr hydrogenator at an initial pressure of 46 psi. After the theoretical amount of hydrogen had been absorbed, the catalyst was filtered and the solvent was removed under reduced pressure to yield 3.0 g of **20**. An analytical sample was prepared by recrystallization from isopropanol-water. NMR ($CDCl_3$): δ 0.92 (br t, 6H, $C_4$-$CH_3$ and $CH_2CH_3$), 1.50 (m, 4H, $CH_2CH_2$), 3.13 (m, 1H, $C_4$-H), 3.62 (t, 3H, $NCH_2$), 3.70 (d, 6H, $OCH_3$), 4.11 (d, 1H, $C_3$-H), 6.75 (m, 3H, ArH).

*Pharmacology*

Male Wistar rats weighing 130–200 g (Møllegaards Breeding Labs, Lille Skensved, Denmark) were used for all *in vitro* binding studies. [$^3$H] SCH 23390 (73.4 Ci/mmol) was obtained from Amersham, UK and [$^3$H] spiperone (29.6 Ci/mmol) was obtained from NEN, Boston, MA USA.

*[$^3$H]SCH 23390 binding*
Rat striatal tissue was processed as previously described by Andersen [8, 9]. Briefly, the tissue was homogenized gently by hand using a glass-teflon homogenizer (10 strokes) in 100 vol of 10 mM imidazole hydrochloride (pH 7.4 at 25°C) containing 2 mM EDTA and centrifuged at 25 000 *g* for 20 min at 4°C. The pellet was resuspended in 100 vol of the same buffer and the homogenization-centrifugation step was repeated three times. The final pellet was resuspended in 100 vol of 2 mM imidazole hydrochloride (pH 7.4 at 25°C) containing 2 mM EDTA, and used immediately for the binding assays. A mixture of 100 µl of the rat striatal tissue suspension; 600 µl of 16.67 mM imidazole hydrochloride (pH 7.4 at 25°C) containing 16.67 mM theophylline, 1 mM EGTA and 10 mM $MgSO_4$; 100 µl [$^3$H]SCH 23390 (final concentration 0.2 mM); and 200 µl of water/test compound/1 µM *cis*-flupentixol (control/compound testing/nonspecific binding) were incubated at 30°C for 60 min followed by rapid filtration through Whatman GF/B filters under vacuum. The filters were washed with 2 x 10 ml 0.9% NaCl and the radioactivity was determined in 4 ml scintillation fluid and counted in a conventional counter. Binding data were fitted using EBDA-scarfit software package obtained from Elsevier Biosoft.

*[$^3$H]Spiperone binding*
As previously described [8, 9], rat striatal tissue was homogenized in 2 x 10 ml 50 mM Tris hydrochloride (pH 7.4 at 30°C) containing 120 mM NaCl and 4 mM $MgCl_2$ using a polytron homogenizer and centrifuged for 10 min at 40 000 *g*. The pellet was resuspended in 1000 vol (original wet weight) and used immediately for the D2 binding assay. The assay mixture consisted of 2.5 ml tissue suspension, 25 µl [$^3$H] spiperone (final concentration 0.05 nM) and 25 µl $H_2O$/test compound/100 nM domperidone (control/compound testing/ non-specific binding). Incubation was carried out at 30°C for 20 min followed by 10 min on ice. The reaction was terminated by rapid filtration through Whatman GF/B filters followed by a 2 x 10 ml wash with 0.9% NaCl. Radioactivity trapped on the filters was measured by conventional scintillation counting.

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