Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 223–226

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Dopaminergic Properties of the Two Enantiomers of 3-(3,4-Dimethylphenyl)-1-propylpiperidine, a Potent and Selective Dopamine D4 Receptor Ligand

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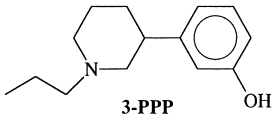
Received 1 August 2000; revised 17 October 2000; accepted 6 November 2000

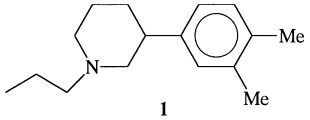
Abstract—The synthesis of the two enantiomers of 3-(3,4-dimethylphenyl)-1-propylpiperidine **1**, a potent and selective D4 dopaminergic ligand, was performed. The 3-(3,4-dimethylphenyl)-1-propylpiperidine with the *R* configuration showed an affinity for the D4 receptors 6-fold higher than the corresponding enantiomer with the *S* configuration. Furthermore, the (*R*)-**1** enantiomer proved to be highly selective for D4 receptors with respect to D2–D3 receptors, with a K_i ratio higher than 25,000, while the (*S*)-**1** enantiomer was about 100-fold less selective than the (*R*)-**1** one

Cerebral dopaminergic receptors have been classified into D1-like and D2-like subtypes according to biochemical criteria.[1] D2-like receptors are the target of classic antipsychotics, which are used in the therapy of schizophrenic syndromes. However, serious adverse effects are associated with antipsychotic therapy, including extrapyramidal Parkinson-like syndromes.[2] Several isoforms of D2-like receptors, which are the D2, D3 and D4 subtypes, have been identified by means of cloning techniques.[3] The D2 isoform is predominant in most brain areas. At the level of the striatum (believed to be the origin of extrapyramidal disturbances), the D3 isoform is also expressed, whereas D4 receptors are present in significant quantities in the cortex and other areas that control emotional and cognitive functions.[4] Therefore, it has been hypothesised that D4 selectivity might be a pharmacological requisite in order to obtain antipsychotic drugs devoid of side-effects, or at least possessing limited side-effects, as observed for clozapine.[5] Furthermore, recent neurophysiological studies have revealed a possible correlation between a decrease, due to ageing, in the density of cerebral dopaminergic receptors (D2-like?) and a loss of the capacity for coordination and for mental agility, which is typical of various neurodegenerative syndromes.[6] The possibility of making use of drugs with a high degree of selectivity at the level of the dopamine D4 receptor subtype might thus be extremely useful in the study of the physiology and pathology of important higher brain functions.

3-Phenylpiperidines (PPEs) have been studied for several years in view of their dopaminergic properties and preclamol (3-PPP), a 3-(3-hydroxyphenyl)-1-propylpiperidine, has been reported to be the first autoreceptor-selective agonist.[7] It has recently been discovered by us that a dimethyl substitution on the phenyl ring of PPEs affords compounds with a marked affinity towards D4 receptors,[8] particularly in the case of **1**, which proved to be the most potent and selective compound for D4 receptors.[8]



3-PPP



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In order to verify whether the chirality present in PPE **1** could be a prerequisite for its biological activity, the synthesis of the two enantiomers of PPE **1** [(*S*)-**1**, (*R*)-**1**]

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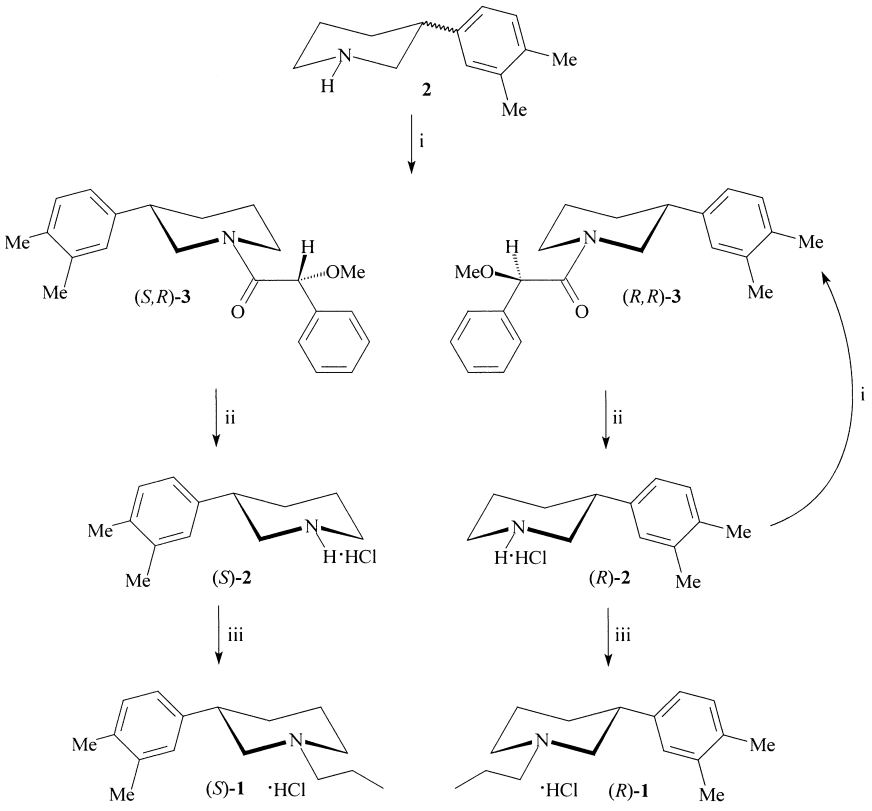

Scheme 1. Reagents and conditions: (i) (*R*)-(−)-α-methoxyphenylacetic acid (1 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.2 equiv), 1-hydroxybenzotriazole (1.5 equiv), anhyd THF, rt, 24 h; (ii) potassium *tert*-butoxide (5 equiv), THF, H_2O, rt, 24 h; (iii) propionaldehyde (2.4 equiv), sodium cyanoborohydride (2.1 equiv), MeOH, rt, 24 h.

was performed. The affinities of enantiomers (*S*)-**1** and (*R*)-**1** towards dopamine receptor subtypes is discussed and compared with those shown by chiral (*S*)- and (*R*)-3-PPP.

Chemistry

Racemic 3-(3,4-dimethylphenyl)piperidine **2**[8] (Scheme 1) was treated with (*R*)-(−)-α-methoxyphenylacetic acid, in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole, to give a diastereoisomeric mixture of amides (*S*,*R*)-**3** and (*R*,*R*)-**3**; diastereoisomers (*S*,*R*)-**3** and (*R*,*R*)-**3** were separated by column chromatography[9] and then hydrolysed to the corresponding enantiomerically pure 3-(3,4-dimethylphenyl)piperidines (*S*)-**2** and (*R*)-**2**, by reaction with potassium *tert*-butoxide.[10] Reductive alkylation of piperidines (*S*)-**2** and (*R*)-**2** with propionaldehyde and sodium cyanoborohydride yielded enantiomerically pure 3-(3,4-dimethylphenyl)-1-propylpiperidines (*S*)-**1** and (*R*)-**1**.[11]

The structures and configurations of the intermediate compounds (*S*,*R*)-**3**, (*R*,*R*)-**3**, (*S*)-**2**, (*R*)-**2** and of the final products (*S*)-**1** and (*R*)-**1** were assigned on the basis of a comparison of the ^{1}H NMR spectral data of all compounds[9–11] and a crystallographic analysis of one of the diastereoisomeric amides [(*R*,*R*)-**3**].[12] An ORTEP plot of the X-ray structure of (*R*,*R*)-**3** (see Figure 1), reporting the crystallographic atom numbering scheme,

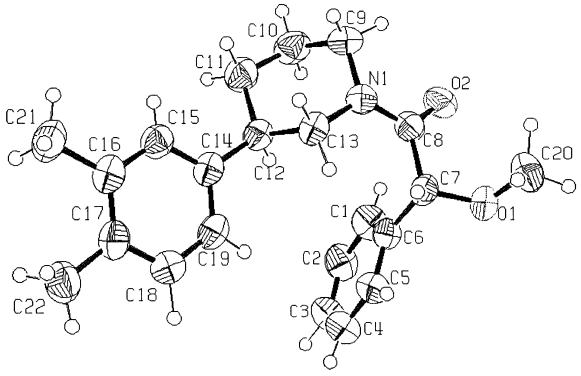

Figure 1. ORTEP 2 plot (50% probability level for thermal ellipsoids) of the X-ray structure of (*R*,*R*)-**3**, showing the crystallographic atom numbering scheme.

showed that the two chiral centres both possess an *R* configuration. On this basis, it was then possible to assign the proper stereochemistry of the diastereoisomeric amide (*S*,*R*)-**3** and also of piperidines (*S*)-**2**, (*R*)-**2** and (*S*)-**1**, (*R*)-**1**, bearing in mind that in the synthetic sequence leading from (*S*,*R*)-**3** and (*R*,*R*)-**3** to (*S*)-**1** and (*R*)-**1**, the chiral centres were not involved.

However, in order to confirm unequivocally the lack of racemisation during the hydrolysis reaction of amides (*S*,*R*)-**3** and (*R*,*R*)-**3** to give, respectively, the 3-(3,4-dimethylphenyl)piperidines (*S*)-**2** and (*R*)-**2**, the piperidine (*R*)-**2** was treated with (*R*)-(−)-α-methoxyphenylacetic acid following the same procedure used in

Table 1. Binding affinities for D1-like and D2-like dopamine receptors

Compound	K_i±SEM (nM)[a]			
	D1 (retina)[b]	D2–D3 (striatum)[c]	D4 (retina)[c]	(D2–D3)/D4
(*R*)-**1**	>100,000	>100,000	4±2	>25,000
(*S*)-**1**	>100,000	5000±2000	23±5	217
1	>100,000	11,000±4000	10±2	1100
(*R*)-3-PPP	nd	404±188	397±201	1.02
(*S*)-3-PPP	nd	8±2	187±88	0.06
Dopamine	4 300±1200	130±25	15±6	9
(−)-Quinpirole	nd[d]	241±17	59±11	5
PD 168,077	nd	18,300±3600[e]	25±8[e]	732

[a]Values represent the means of three to five experiments for each compound±standard error.
[b]D1-like receptors labelled with [^{3}H]SCH23390.
[c]D2–D3 and D4 receptors labelled with [^{3}H]YM-09-151-2.
[d]Not determined.
[e]PD 168,077 affinity for cloned human D2 and D4 receptors were 3740 and 9 nM, respectively.[13]

the case of the racemate **2** (see above). ^{1}H NMR analysis of the resulting product showed the presence only of the corresponding diastereoisomer (*R*,*R*)-**3** (GC, 99%), without any appreciable quantity of (*S*,*R*)-**3**.

Results and Discussion

The affinities of enantiomers (*R*)-**1** and (*S*)-**1** for D1, and D2–D3 and D4 isoforms of D2-like receptors were investigated by binding experiments which were performed as previously described.[8] The results are summarised in Table 1, together with those obtained for (*R*)- and (*S*)-3-PPP, the endogenous agonist dopamine, the D2-like selective agonist (−)-quinpirole and the D4-selective agonist PD 168,077, taken as reference drugs. Data are expressed as inhibition constant (K_i) values (nM).

Both enantiomeric 3-(3,4-dimethylphenyl)-1-propylpiperidines (*R*)-**1** and (*S*)-**1** possessed a low affinity for D1 receptors. As regards D4 receptors, the 3-(3,4-dimethylphenyl)-1-propylpiperidine with the *R* configuration, (*R*)-**1**, showed an affinity for D4 receptors 6-fold higher than the corresponding enantiomer with the *S* configuration, (*S*)-**1**. As for D2–D3 receptors, the (*R*)-**1** and (*S*)-**1** enantiomers showed decidedly lower affinities than for D4 receptors and, in this case, (*S*)-**1** proved to be the preferred one, with a K_i value of 5 μM against a K_i value higher than 100 μM for (*R*)-**1**.

These results show that the (*R*)-**1** enantiomer proved to be highly selective for D4 receptors with respect to D2–D3 receptors, with a K_i ratio higher than 25,000, while the (*S*)-**1** enantiomer showed an approximately 100-fold lower selectivity than (*R*)-**1**.

In contrast, it is interesting to note that the *R* enantiomer of 3-PPP appeared to lack any selectivity between D4 and D2–D3 receptor isoforms, similar to the *S* enantiomer, whose selectivity was modest.

Conclusions

The chirality present in PPE **1** does not represent an essential prerequisite for its interaction with the D4 receptor, as indicated by the fact that both enantiomers proved to possess a significant affinity for this receptor, even if the (*R*) enantiomer was slightly better than the (*S*) one. On the contrary, the different chirality seems to play an important role in determining a marked value of selectivity for D4 over D2–D3 receptors, as shown by the K_i ratio values which are >25,000 and 217, respectively for the (*R*) and (*S*) enantiomers.

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9. The resulting diastereoisomeric mixture was purified by column chromatography (230–400 mesh silica gel, Merck), eluting with Et_2O to give diastereoisomers (*S*,*R*)-**3** and (*R*,*R*)-**3** with a purity, respectively, of 80% and 86% (GC). The diastereoisomer (*S*,*R*)-**3** was further purified (99%, GC) by column chromatography (230–400 mesh silica gel, Merck), eluting with diisopropyl ether (180 mg, yield 12%). The diastereoisomer (*R*,*R*)-**3** was obtained practically pure (98%, GC) by further crystallisation with hexane (440 mg, yield 29%). (*S*,*R*)-**3**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.18–1.81 (m, 4H), 2.14–2.18 (m, 6H), 3.18–3.41 (m, 3H), 3.82–4.11 (m, 1H), 4.28–4.57 (m, 1H), 5.13–5.19 (m, 1H), 6.60–6.73 (m, 1H), 6.88–7.03 (m, 2H), 7.28–7.45 (m, 5H). Anal. ($C_{22}H_{27}NO_2$) C, H, N. MS *m*/*e* 337 (M^+). (*R*,*R*)-**3**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.11–1.98 (m, 4H), 2.14–2.18 (m, 6H), 2.38–2.97 (m, 3H), 3.21–3.40 (m, 3H), 3.75–4.18 (m, 1H), 4.29–4.57 (m, 1H), 5.15–5.22 (m, 1H), 6.57–6.70 (m, 1H), 6.88–7.10 (m, 2H), 7.23–7.44 (m, 5H). Anal. ($C_{22}H_{27}NO_2$) C, H, N. MS *m*/*e* 337 (M^+).

10. The solvent was evaporated and the resulting residue was extracted with Et_2O. The organic phase was evaporated to give a crude residue which was dissolved in EtOH and then acidified to pH 3 at 0 °C by addition of a saturated Et_2O/HCl solution. Evaporation of the organic solvent gave the appropriate crude (*S*)-**2** and (*R*)-**2** as hydrochloride salts which were purified by crystallisation with EtOH/Et_2O. (*S*)-**2**·HCl: yield 40%, $[\alpha]_D = +10.5$ (c = 0.90, MeOH). (*R*)-**2**·HCl: yield 32%, $[\alpha]_D = -9.9$ (c = 0.91, MeOH). ^{1}H NMR spectral data for (*S*)-**2**·HCl and (*R*)-**2**·HCl were practically identical to their corresponding racemate **2**·HCl.[8]

11. The work up was the same as in the case of racemate **1**·HCl.[8] (*S*)-**1**·HCl: yield 39%, $[\alpha]_D = -9.7$ (c = 0.94, MeOH). (*R*)-**1**·HCl: yield 32%, $[\alpha]_D = +10.0$ (c = 0.96, MeOH). ^{1}H NMR spectral data for (*S*)-**1**·HCl and (*R*)-**1**·HCl were practically identical to their corresponding racemate **1**·HCl.[8]

12. Crystals of the title compound suitable for X-ray analysis were obtained by slow evaporation of a hexane solution. A Siemens AED diffractometer, equipped with a Mo K_α source (using $\theta/2\theta$ scan mode, scan speed 3/12 deg min^{-1}, scan width $1.20 + 0.34 \tan\theta$, θ in the range 3–30 deg) was used to obtain intensity data and orthorhombic cell parameters: $a = 10.477(4)$ Å, $b = 21.844(3)$ Å, $c = 8.297(2)$ Å $\alpha = \beta = \gamma = 90.0(0)$ deg, $Z = 4$, $V = 1898.9(9)$ Å^3, $d_c = 1.18$ g cm^{-3}, space group $P2_12_12_1$. The structure was solved by direct methods using SIR97 and refined using SHELX97 by full matrix least squares on *F*o with anisotropic thermal parameters (isotropic for the hydrogens). The final *R* indexes were, respectively: $R^1 = 0.0495$ for 1045 reflections with $Fo > 4\sigma$ (*F*o), $R^2 = 0.1304$ for all the 3145 reflections, $wR^2 = 0.1240$. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 150952.

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