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2-[(SUBSTITUTED)PHENYL]-5-[1-(2-PHENYLAZACYCLOHEPTYL)METHYL]-1*H*-PYRROLES WITH HIGH AFFINITY AND SELECTIVITY FOR THE DOPAMINE D_3 RECEPTOR

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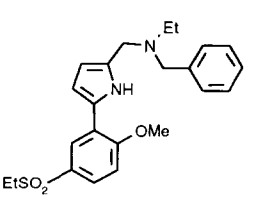
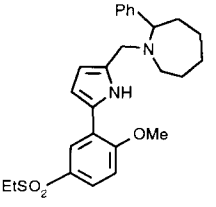
Abstract: A series of 2-[(substituted)phenyl]-5-[1-(2-phenylazacycloheptyl)methyl]-1*H*-pyrroles (**8** - **15**) has been prepared to investigate the effect on affinity and selectivity for the dopamine D_3 receptor of modifying the substituent in the phenyl ring at the 2-position of the pyrrole. Sulfonate **7** and sulfonamides **12**, **14**, **15** were shown to have high affinities (pKi's 8.0 - 8.7) and selectivities (100 - 150-fold) for the D_3 over the D_2 receptor.

Recent advances in the molecular biology of dopamine receptors have resulted in their classification into $D_{1\text{-}5}$ subtypes.[1-3] In particular, the D_2-like receptors, D_2, D_3, and D_4, have received much attention since existing drugs for the treatment of schizophrenia are believed to exert at least some of their antipsychotic effects through blockade of these receptors.[4] It has been proposed that the extra-pyramidal side-effects associated with currently available drugs result from blockade of D_2 receptors and that selective D_3 antagonists would offer the potential for antipsychotic therapy free of such side-effects.[2]

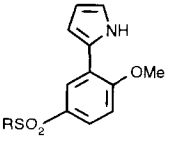
Recently we have described[5,6] the discovery of a series of 2,5-disubstituted pyrroles as dopamine D_3 receptor antagonists and shown how optimal conformational restraint of the high affinity (pKi 9.5) N-ethyl, N-benzyl side-chain of **1** gave 2-phenylazacycloheptane **2** with D_3 pKi 8.9 and 30-fold selectivity over the D_2 receptor. In this *Letter* we detail our investigations into the effect on D_3 affinity and selectivity of modification of the ethylsulfone substituent of **2** and describe the results with the single enantiomers of the 2-phenylazacycloheptane side-chain (Table 1).



1



2



3

Compounds **5** - **15** were prepared by reaction of the appropriate 2-[(substituted)phenyl]-1*H*-pyrroles **3** with the

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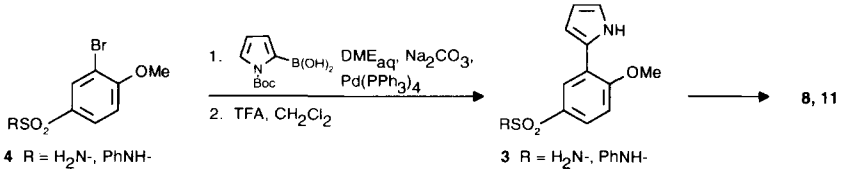
Vilsmeier reagent derived from 1-formyl-2-phenylazacycloheptane, followed by *in situ* reduction with $NaBH_4$. All compounds were then purified by chromatography and isolated as their hydrochloride or oxalate salts. In most cases, intermediate pyrroles **3** were prepared as described previously[7] from the appropriately substituted benzoic acids. However, for the primary and secondary sulfonamides **8** and **11** a change in strategy was required (Scheme 1) as these groups were incompatible with the previous methodology. Chlorosulfonation of 2-bromoanisole, followed by reaction with ammonia or aniline gave sulfonamides **4**. Coupling of **4** with N-Boc-pyrrole-2-boronic acid in aqueous DME in the presence of $Pd(PPh_3)_4$ and Na_2CO_3, followed by deprotection with TFA in CH_2Cl_2 gave pyrroles **3**.

Scheme 1.

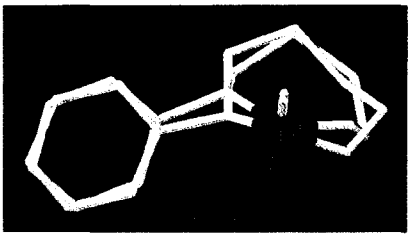


The single enantiomers of **2** and **12** were prepared using enantiomerically pure amines. 2-Phenylazacycloheptane was resolved *via* conversion to the amide with (S)-(+)-2-methoxy-2-phenylacetyl chloride and separation of the diastereoisomers by chromatography. Treatment of each diastereoisomer with methyllithium in THF gave the resolved amines, with the faster-eluting diastereoisomer providing the (R)-enantiomer.[8]

Compounds **2** and **5** - **15** were evaluated using displacement of ^{125}I-iodosulpride from human D_3 and D_2 receptors, expressed in CHO cells, and results are shown in Table 1.

Evaluation of the enantiomers of **2** showed that the (R)-enantiomer was only 5-fold higher in affinity, at both D_3 and D_2 receptors, than the (S)-enantiomer. Modelling of the protonated 2-phenylazacycloheptane side-chain demonstrated that this low eudismic ratio could be explained by the flexibility of the 7-membered ring (Figure 1). This allows the enantiomers to overlap, with the phenyl rings and azacycloheptane rings occupying similar regions of space, thus maintaining the relationship of these groups to the pyrrole ring.

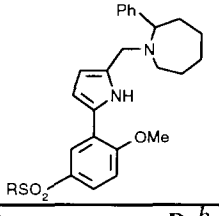
Figure 1. Overlap of the protonated enantiomers of 1-Methyl-2-Phenylazacycloheptane

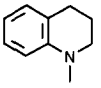
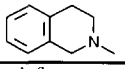


Increasing the size of the sulfone alkyl group from ethyl to either isopropyl **5** or benzyl **6** reduced affinity slightly at both D_3 and D_2 compared to **2**, leading to compounds of similar selectivity. Interestingly, replacement of the benzylic CH_2 of **6** by O, to give phenylsulfonate **7**, significantly reduced D_2 affinity, resulting in a compound with 100-fold selectivity for D_3 over D_2 receptors. This result suggested that the D_2 receptor was less able to

tolerate a heteroatom adjacent to the SO_2 moiety in this series and we therefore investigated a range of sulfonamides at this position. Although primary sulfonamide **8** had disappointingly low affinity at both D_3 and D_2 receptors, dimethylsulfonamide **9**, restored D_3 affinity and selectivity. Cyclic sulfonamides, illustrated by morpholine **10**, were also well tolerated at the D_3 receptor and maintained similar selectivity to the simple dimethylsulfonamide **9**. Introduction of a phenyl group to give secondary sulfonamide **11** reduced D_3 affinity by approximately 10-fold compared to sulfone **6** and sulfonate **7**. Together with the result for the primary sulfonamide **8**, this suggests that the D_3 receptor is unable to accommodate an acidic NH at this point in the molecule. The high D_3 affinity (pKi 8.2) and 100-fold selectivity of N-methyl, N-phenylsulfonamide **12** confirmed this hypothesis. As observed with **2**, the enantiomers of **12** had a low eudismic ratio with the (R)-enantiomer being slightly higher in affinity at both D_3 and D_2 receptors.

Table 1. Affinities of 2,5-Disubstituted-1*H*-Pyrroles at Human Cloned D_3 and D_2 Receptors



Compound[a]	R	D_3[b]	D_2[b]	Selectivity
2	Et-	8.9	7.4	30
(R)-2	Et-	9.1	7.6	30
(S)-2	Et-	8.4	7.0	25
5	^{i}Pr-	8.3	6.7	40
6	$PhCH_2$-	8.4	6.9	30
7	PhO-	8.0	6.0	100
8	H_2N-	7.4	6.4	10
9	Me_2N-	8.7	7.0	50
10		8.8	7.0	60
11	PhNH-	7.1	6.2	8
12	PhN(Me)-	8.2	6.2	100
(R)-12	PhN(Me)-	8.4	6.3	125
(S)-12	PhN(Me)-	7.8	5.8	100
13	$PhCH_2N(Et)$-	8.2	6.3	80
14		8.2	6.0	150
15		8.7	6.7	100

[a] All new compounds gave satisfactory analytical and/or mass spectral data.[9] [b]Affinities are pKi values. All values represent the mean of at least 2 experiments, each within 0.2 of the mean.

Further extension of both substituents on the sulfonamide could be tolerated with N-benzyl, N-ethylsulfonamide **13** having a similar binding profile to **12**. Introduction of conformational restraint to give tetrahydroquinoline **14** and tetrahydroisoquinoline **15** also gave compounds with high selectivity for the D_3 receptor. In particular, **15** showed an improvement in affinity at both D_3 and D_2 receptors compared to **13** and this may reflect the preferred conformation of **13** when bound to these receptors.

In conclusion, modification of the ethylsulfone substituent of **2** to either phenylsulfonate **7** or sulfonamides **12**, **14**, and **15** has given compounds with high affinities (pKi's 8.0-8.7) and selectivities (100-150-fold) for the dopamine D_3 receptor over the D_2 receptor. These compounds therefore represent valuable pharmacological tools for the characterisation of the role of the dopamine D_3 receptor in the central nervous system.

References and Notes

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8. Absolute stereochemistry was determined by X-ray crystallography on the HBr salts of the resolved 2-phenylazacycloheptanes. Egglestone D. Personal Communication.
9. ^{1}H NMR spectra were recorded at 250 MHz in d_6-DMSO as solvent. Compound (R)-**12** (oxalate), mpt 95-97 ^{o}C; $[\alpha]_D$ +19.3^o (c, 0.86%, MeOH); ^{1}H: δ 1.45 - 2.14 (m, 8H), 2.93 - 3.31 (m, 2H), 3.12 (s, 3H), 3.79 (br s, 2H), 3.95 (s, 3H), 4.12 (br s, 1H), 6.10 (br s, 1H), 6.45 (br s, 1H), 7.08 - 7.46 (m, 10H), 7.52 (d, 2H), 7.62 (br s, 1H), 10.94 (br s, 1H). Compound (S)-**12** (oxalate), mpt 96-98 ^{o}C; $[\alpha]_D$ -20.1^o (c, 0.72%, MeOH); ^{1}H: δ 1.46 - 2.18 (m, 8H), 2.96 - 3.34 (m, 2H), 3.12 (s, 3H), 3.81 (br s, 2H), 3.95 (s, 3H), 4.16 (br s, 1H), 6.12 (br s, 1H), 6.45 (br s, 1H), 7.10 - 7.48 (m, 10H), 7.53 (d, 2H), 7.63 (br s, 1H), 11.0 (br s, 1H).

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