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NOVEL 2,5-DISUBSTITUTED-1*H*-PYRROLES WITH HIGH AFFINITY FOR THE DOPAMINE D_3 RECEPTOR: N-BENZYL MODIFICATIONS

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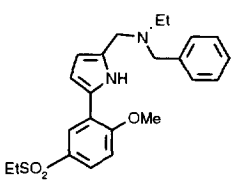
Abstract: A series of 2,5-disubstituted-1*H*-pyrroles (**4** - **26**) has been prepared where the conformational requirements of the N-ethyl, N-benzyl side-chain of **1** and the effect of introducing substituents into the benzyl group have been investigated. The (R)-α-methylbenzyl **6** and aminoindane **10** side-chains retained high affinity for the dopamine D_3 receptor, although neither showed the selectivity of 2-phenylazacycloheptane **2**.

The majority of drugs currently used to control the symptoms of schizophrenia have poor side-effect profiles, which in many cases leads to low patient compliance and costly re-hospitalization. The recent classification[1-3] of dopamine D_2-like receptors into the D_2, D_3 and D_4 subtypes, together with receptor distribution studies, has given rise to the proposal that the extra-pyramidal side-effects associated with currently available drugs result from blockade of dopamine D_2 receptors and that selective dopamine D_3 antagonists would offer the potential for antipsychotic therapy free of such side-effects.[2]

In a recent publication[4], we described the discovery of the novel 2,5-disubstituted pyrrole **1** with an N-ethyl, N-benzyl side chain as a high affinity (pKi 9.5) ligand at the dopamine D_3 receptor. We also demonstrated that conformational restriction of this side chain to give the 2-phenylazacycloheptane **2** maintained high affinity (pKi 8.9) at the dopamine D_3 receptor and improved selectivity over the D_2 receptor. This *Letter* describes our investigations into the effect on D_3 affinity and selectivity of alternative modes of conformational restraint of the N-ethyl, N-benzyl side chain of **1** (Table 1) and the effect of introducing substituents into the side-chain phenyl groups of **1** and **2** (Tables 2 and 3).



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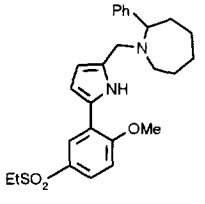

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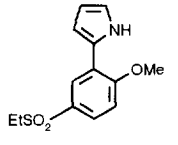

3

Novel compounds **4** - **26** were readily prepared, as described previously,[4] from the known 2-[(5-ethylsulfonyl-2-methoxy)phenyl]-1*H*-pyrrole **3**[5] either by Mannich reaction with the appropriate amine or by reaction with the Vilsmeier reagent derived from the appropriate amide, followed by *in situ* reduction with $NaBH_4$. All compounds were then purified by chromatography and isolated as their hydrochloride salts.

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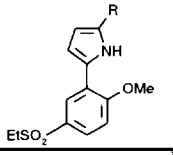
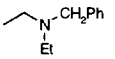
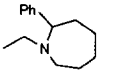
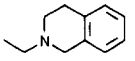
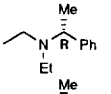
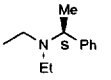
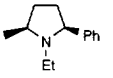
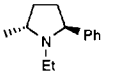
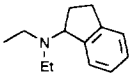
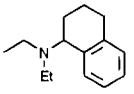
Compounds **1**, **2** and **4** - **26** were evaluated using displacement of ^{125}I-iodosulpride from human D_3 and D_2 receptors, expressed in CHO cells, and results are shown in Tables 1-3.

Table 1. Effects of Side Chain Modification on Affinities at Human Cloned D_3 and D_2 Receptors



Compound[a]	R	D_3[b]	D_2[b]	Selectivity
1		9.5	9.1	3
2		8.9	7.4	30
4		7.5	7.0	3
5		8.0	7.4	4
6		9.1	8.1	10
7		8.6	7.6	10
8		7.0	6.8	-
9		8.0	7.4	4
10		9.1	9.1	-
11		8.3	7.9	3

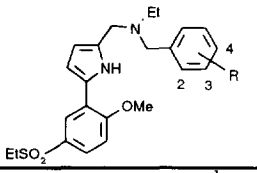
[a] All new compounds gave satisfactory analytical and/or mass spectral data.[6] [b]Affinities are pKi values. All values represent the mean of at least 3 experiments, each within 0.3 of the mean.

Initially, cyclisation of the N-ethyl chain onto the phenyl ring of the N-benzyl to give tetrahydroisoquinoline **4** was investigated, but this mode of conformational restraint reduced both D_3 and D_2 affinity by approximately 100-fold. Cyclisation of the N-ethyl group onto the carbon α- to the pyrrole ring to give N-benzyl pyrrolidine **5** also resulted in a marked reduction in D_3 and D_2 affinity compared to **1**. However, introduction of conformational restraint into the N-benzyl side chain *via* a methyl group at the benzylic position gave the (R)- and (S)-enantiomers, **6** and **7** respectively, which proved more interesting. (R)-enantiomer **6** maintained the high affinity of **1** at the D_3 receptor and had slightly reduced D_2 affinity to give a compound with 10-fold selectivity. A similar change in selectivity was also found with the (S)-enantiomer **7**, although affinity at both D_3 and D_2

receptors was reduced compared to **6**. The improved selectivity observed with **6** and **7** prompted the synthesis of 2,5-disubstituted pyrrolidines **8** and **9**, where the benzylic methyl is cyclised onto the carbon α- to the pyrrole ring. However, both the *cis*- and *trans*-isomers, **8** and **9** respectively, showed marked reductions in D_3 affinity compared to **6** and **7**, with only the *trans*-isomer **9** retaining respectable D_3 affinity and 4-fold selectivity over D_2. Finally in this series, the effect of cyclisation of the benzylic methyl to the *ortho*-position of the phenyl ring to give 1-aminoindane **10** and 1-aminotetralin **11** was investigated. The results with these two compounds highlighted the sensitivity of D_3 and D_2 affinity to subtle changes in the orientation of the phenyl ring compared to the basic nitrogen. Aminoindane **10** retained the high D_3 affinity associated with **1**, but was non-selective; on the other hand, aminotetralin **11** showed reduced D_3 and D_2 affinity compared to **1**.

These studies on conformational restriction of the high affinity N-ethyl, N-benzyl side chain of **1** demonstrated that some modes of constraint, such as introduction of a benzylic methyl group **6** or cyclisation to aminoindane **10**, could be tolerated. They also confirmed the 2-phenylazacycloheptane **2** as the optimum side chain in this series in terms of D_3 affinity and selectivity over the D_2 receptor. We therefore turned our attention to investigating the influence on D_3 affinity of substituents in the phenyl ring of both the N-ethyl, N-benzyl and 2-phenylazacycloheptane side chains (Tables 2 and 3).

Table 2. Effects of Benzyl Substitution on Affinities at Human Cloned D_3 and D_2 Receptors



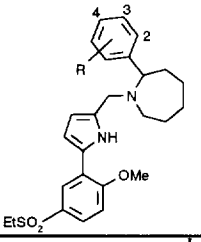
Compound[a]	R	D_3[b]	D_2[b]	Selectivity
1	H	9.5	9.1	3
12	2-Cl	8.2	7.7	3
13	2-Me	8.5	8.2	2
14	2-OMe	8.0	7.8	-
15	3-Cl	8.6	8.0	4
16	3-Me	8.8	8.1	5
17	3-OMe	8.1	7.1	10
18	4-Cl	9.4	9.0	3
19	4-Me	9.7	9.4	2
20	4-OMe	9.6	8.7	8
21	3,4-diOMe	7.9	7.5	3
22	3,4-methylenedioxy	9.2	8.5	5

Footnotes: See Table 1.

In general, substitution at the 2- or 3- positions resulted in a reduction in D_3 affinity compared to **1**. However, a 3-OMe substituent, as in **17**, produced a larger reduction in D_2 affinity to give a compound with 10-fold selectivity. At the 4-position, both electron-withdrawing and donating groups were tolerated, with a 4-OMe substituent **20** giving a slight enhancement in selectivity. These results prompted the synthesis of the 3,4-diOMe analogue **21**, which was significantly lower in affinity than **20**. However, cyclisation of the methoxy groups of **21** to a 3,4-methylenedioxy group **22** restored D_3 affinity, suggesting that in **21** the methoxy groups have an

adverse conformational effect on one another. Following these results, a limited range of substituents was investigated in the phenylazacycloheptane series (Table 3). The results broadly paralleled those in the N-ethyl, N-benzyl series with the 4-OMe and 4-Me analogues **25** and **26** having similar D_3 affinities and selectivities to **2**.

Table 3. Effects of Phenyl Substitution on Affinities at Human Cloned D_3 and D_2 Receptors



Compound[a]	R	D_3[b]	D_2[b]	Selectivity
2	H	8.9	7.4	30
23	2-Me	7.0	5.9	10
24	3-OMe	7.3	6.1	15
25	4-OMe	8.8	7.6	15
26	4-Me	9.1	7.6	30

Footnotes: See Table 1.

In conclusion, investigation of alternative modes of conformational restriction of the high affinity N-ethyl, N-benzyl side-chain of **1** resulted in (R)-α-methylbenzyl **6** and aminoindane **10** which retained high D_3 affinity, although neither showed the selectivity of 2-phenylazacycloheptane **2**. Comparison of substituent effects between the N-ethyl, N-benzyl and 2-phenylazacycloheptane series indicates that the phenyl rings of each series probably interact with the same region of the D_3 receptor. This suggests that the enhanced selectivity of **2** may arise from an unfavourable steric interaction of the azacycloheptane ring with the D_2 receptor, although the possibility cannot be ruled out that the selectivity of **2** reflects a more advantageous orientation of the 2-phenyl group for interaction with the D_3 receptor.

References and Notes

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6. ^1H NMR spectra were recorded at 250 MHz in $CDCl_3$ as solvent. Compound **6**, mpt 143-145 °C; ^1H: δ 1.20 (t, 3H), 1.25 (t, 3H), 1.90 (m, 3H), 2.65-3.30 (m, 4H), 3.95-4.50 (m, 2H), 4.20 (s, 3H), 4.60-4.80 (m, 1H), 6.25 (m, 1H), 6.60 (m, 1H), 7.10 (d, 1H), 7.40-7.55 (m, 3H), 7.60-7.80 (m, 3H), 8.15 (d, 1H), 11.80 (br m, 1H), 12.10 (br s, 1H). Compound **10**, mpt 151-155 °C; ^1H (mixture of protomers): δ 1.30 (m, 6H), 2.30-2.65 (m, 2H), 2.70-3.20 (m, 6H), 4.10-4.55 (m, 2H), 4.20 (s, 3H), 4.95 and 5.05 (2 x t, 1H), 6.30 and 6.35 (2 x m, 1H), 6.55 (m, 1H), 7.10 (d, 1H), 7.30 (m, 3H), 7.70 and 7.85 (2 x dd, 1H), 8.15 (m, 1H), 11.70 and 11.95 (2 x br s, 1H), 12.30 and 12.55 (2 x br s, 1H).

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