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

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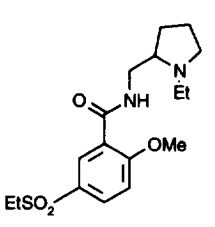
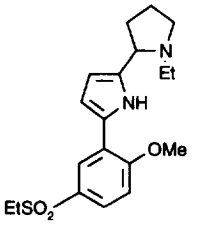
Abstract: A series of 2,5-disubstituted-1*H*-pyrroles (**4**-**18**) has been prepared based on replacement of the amide of sultopride **1** by a pyrrole ring. Subsequent modification of the basic side chain gave compounds with high affinity for the dopamine D_3 receptor. In addition, **12** and **17** were shown to be D_3 antagonists with 30-fold selectivity for the D_3 receptor over the D_2 receptor.

Schizophrenia is a devastating psychotic disorder which affects approximately 0.5% of the World's population. The majority of drugs currently used to control the symptoms of the disease have poor side-effect profiles, which in many cases leads to low patient compliance and costly hospitalization. Schizophrenia has been associated with up-regulation of the dopaminergic system and existing drugs are believed to exert at least some of their antipsychotic effects through blockade of D_2-like receptors.[1] Recent advances in the molecular biology of dopamine receptors have allowed these D_2-like receptors to be classified as D_2, D_3 and D_4.[2-4] It has been proposed that some of the side-effects associated with currently available drugs, such as Parkinsonism, tardive dyskinesia and hyperprolactinaemia, result from blockade of D_2 receptors and that compounds with selectivity for D_3 receptors would offer the potential for antipsychotic therapy free of side-effects.[3]

Following on from the original observation[3] that substituted benzamides exhibited high D_3 affinity, we investigated a range of structural modifications of **1**. In the course of these investigations we discovered that replacement of the amide of **1** by a pyrrole ring (**2**; DU 122290)[5] maintained affinity for the D_3 receptor and introduced modest selectivity over D_2 (see Table 1). This *Letter* describes our initial modifications of the basic side chain of **2**, leading to a further improvement in D_3 selectivity.



1 sultopride

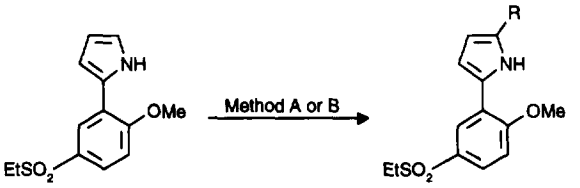


2 DU 122290

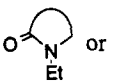
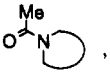
Compounds **4** - **18** were readily prepared from the known 2-[(5-ethylsulfonyl-2-methoxy)phenyl]-1H-pyrrole **3**[5] either by Mannich reaction with the appropriate amine (method A) or by reaction with the Vilsmeier reagent

derived from the appropriate amide, followed by *in situ* reduction with $NaBH_4$ (method B) as shown in Scheme 1. All compounds were then purified and isolated as their hydrochloride salts.

Scheme 1



3 **6 - 10, 14 - 18** (Method A)
2, 4, 5, 11 - 13 (Method B)

Reagents: Method A: CH_2O, EtOH, AcOH, R^1R^2NH; Method B: $POCl_3$,  or  , then $NaBH_4$.

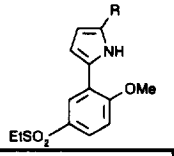
The D_3 and D_2 affinities of compounds **1**, **2** and **4** - **18** were evaluated using displacement of ^{125}I-iodosulpride from human D_3 and D_2 receptors, expressed in CHO cells, and results are shown in Table 1.

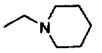
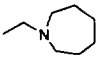
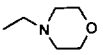
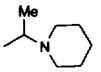
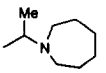
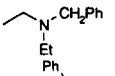
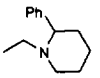
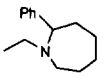
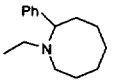
As noted above, replacement of the amide moiety of **1** by a pyrrole ring **2** maintained high affinity at D_3 receptors and, interestingly, resulted in a 4-fold decrease in affinity at D_2 receptors. Modification of the N-ethylpyrrolidine of **2** to N-ethylpiperidine **4** or azacycloheptane **5** increased affinity slightly at both D_3 and D_2 receptors. Introduction of the more flexible N, N-diethylaminomethyl side-chain **6** reduced both D_3 and D_2 affinity, but maintained D_3 selectivity. Constraining the N, N-diethyl groups of **6** into pyrrolidine **7** or piperidine **8** maintained D_3 affinity. Azacycloheptane **9** gave a slight improvement in D_3 affinity compared to **6**. However, replacement of piperidine by morpholine **10** dramatically reduced D_3 and D_2 affinity, presumably due to a reduction in pKa of the basic nitrogen.

The introduction of further conformational restraint into the side-chain *via* a methyl group α- to the pyrrole ring gave compounds **11** - **13**. For the pyrrolidine **11** and piperidine **12**, this modification improved D_3 affinity compared to **7** and **8**, respectively, with **12** having 30-fold selectivity over the D_2 receptor. Interestingly, further increase in ring size to the azacycloheptane **13** resulted in an increase in D_2 affinity compared to **12**.

A more dramatic improvement in D_3 affinity (pKi 9.5) was observed on introduction of an N-benzyl substituent, as in **14**, although a similar increase in D_2 affinity resulted in only a 3-fold selectivity. These data suggest the presence of an aromatic binding region in both receptors. A combination of this structural motif with pyrrolidine **7**, piperidine **8** and azacycloheptane **9** led us to prepare the 2-phenylazacycloalkanes **14** - **18**, where the N-benzyl group was conformationally restricted. Although all of these compounds showed a slight decrease in D_3 affinity compared to **14**, the 2-phenylazacycloheptane **17** showed a greater reduction in D_2 affinity to give a compound with a D_3 pKi of 8.9 and 30-fold selectivity. The selectivity of this compound may reflect a more advantageous orientation of the 2-phenyl group for interaction with the D_3 receptor, or may arise from unfavourable steric interactions of the azacycloheptane ring with the D_2 receptor. It is interesting to note that further increase in ring size to the azacyclooctane **18** resulted in a similar loss of both D_3 and D_2 affinity compared to **17**.

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
1 sultopride	-	8.2	8.2	-
2 DU 122290		8.3	7.6	5
4		8.7	8.1	4
5		8.7	8.1	4
6		7.4	6.5	8
7		7.2	6.6	4
8		7.6	6.8	6
9		7.8	6.8	10
10		6.1	5.5	4
11		7.7	6.4	20
12		8.0	6.5	30
13		7.7	7.1	4
14		9.5	9.1	3
15		9.0	7.8	15
16		8.9	7.9	10
17		8.9	7.4	30
18		7.7	6.5	15

[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 0.2 of the mean.

Studies with **12** and **17** have shown that these compounds are able to antagonise the effects of the D_3 selective agonist quinpirole on acidification changes observed using a microphysiometer.[7]

In conclusion, replacement of the amide of **1** by a pyrrole ring **2**, followed by modification of the basic side chain has given **12** and **17** as D_3 antagonists with D_3 affinities of 8.0 and 8.9, respectively, and 30-fold selectivity over the D_2 receptor. As such, these compounds will be useful pharmacological tools for further characterising the role of this receptor in the central nervous system.

Acknowledgement

We thank Stephen Ginn for his enthusiastic technical assistance.

References and Notes

1. Seeman, P. *Synapse.* **1987**, *1*, 133-152.
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3. Sokoloff, P.; Giros, B.; Martres, M-P.; Bouthenet, M-L.; Schwartz, J-C. *Nature.* **1990**, *347*, 146-151.
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5. van Wijngaarden, I.; Kruse, C. G.; van Hes, R.; van der Heyden, J. A. M.; Tulp, M. T. M. *J. Med. Chem.* **1987**, *30*, 2099-2104.
6. ^{1}H NMR spectra were recorded at 250 MHz in $CDCl_3$ as solvent. Compound **12**, mpt 125-129 °C; ^{1}H: δ 1.27 (t, J=7Hz, 3H), 1.40 (m, 1H), 1.79 (d, J=7Hz, 3H), 1.55-1.96 (m, 6H), 2.08 (m, 1H), 2.36 (m, 1H), 2.46-2.80 (m, 2H), 3.17 (q, J=7Hz, 2H), 3.40 (m, 2H), 4.16 (s, 3H), 4.53 (m, 1H), 6.25 (m, 1H), 6.62 (m, 1H), 7.08 d, J=9Hz, 1H), 7.70 (dd, J=9, 1Hz, 1H), 8.12 (d, J=1Hz, 1H), 11.65 (br m, 2H). Compound **17**, mpt 142-144 °C; ^{1}H (free base): δ 1.19 (t, J=7Hz, 3H), 1.40-1.90 (m, 8H), 2.72 (m, 1H), 2.91 (m, 1H), 3.02 (q, J=7Hz, 2H), 3.43 (d, J=14Hz, 1H), 3.53 (d, J=14Hz, 1H), 3.66 (m, 1H), 4.00 (s, 3H), 5.93 (t, J=3Hz, 1H), 6.52 (m, 1H), 7.01 (d, J=9Hz, 1H), 7.24 (m, 1H), 7.26 (m, 2H), 7.38 (m, 2H), 7.55 (m, 1H), 7.99 (d, J=2Hz, 1H), 9.6 (br s, 1H).
7. For details of the microphysiometer method see Boyfield, I., Brown, T.H., Coldwell, M.C., Cooper, D.G., Hadley, M.S., Hagan, J.J., Healy, M.A., Johns, A.J., King, R.J., Middlemiss, D.N., Nash, D.J., Riley, G.J., Scott, E.E., Smith, S.A., and Stemp, G. *J. Med. Chem.* **1996**, in press. In antagonist experiments, compounds **12** and **17** had apparent pKb's at the D_3 receptor of 7.7 and 9.7, respectively.

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