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NOVEL 1,2,3,4-TETRAHYDROISOQUINOLINES WITH HIGH AFFINITY AND SELECTIVITY FOR THE DOPAMINE D_3 RECEPTOR

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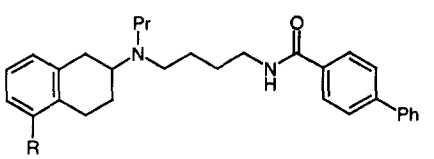
Abstract: Using clearance and brain penetration studies as a screen, tetrahydroisoquinoline **3** was identified as a lead having low clearance in rats (CLb 20 ml/min/kg). Introduction of a 7-CF_3SO_2O- substituent into the tetrahydroisoquinoline, followed by replacement of the biphenylamido group of **3** by a 3-indolylpropenamido group gave **31**, having high D_3 receptor affinity (pKi 8.4) and 150 fold selectivity over the D_2 receptor.

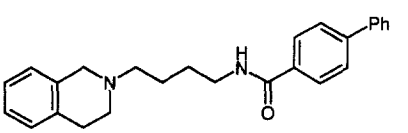
All clinically effective antipsychotic agents share the property of dopamine D_2 and D_3 receptor antagonism. At clinical doses these drugs occupy D_3 as well as D_2 receptors and their antipsychotic effects could therefore be mediated *via* D_2 and/or D_3 receptors. Blockade of D_2 receptors in the striatum leads to serious extrapyramidal side-effects, which result in poor patient compliance and consequently poor control of the disease. Dopamine D_3 receptors are preferentially located in limbic brain regions, such as the nucleus accumbens, where dopamine receptor blockade has been associated with antipsychotic activity. A selective dopamine D_3 receptor antagonist therefore offers the potential for an effective antipsychotic therapy, free of the serious side-effects of currently available drugs.[1-3]

Recently, we described a novel series of 5-substituted-*N*-propyl-2-aminotetralins, exemplified by compounds **1** and **2**, which had high affinity, pKi 8.8 (Ki 2 nM), for the dopamine D_3 receptor and over 200 fold selectivity against the D_2 receptor.[4,5] Further studies in the rat demonstrated that these compounds, such as **1**, were metabolised *via* *N*-depropylation and rapidly cleared (CLb 80 ml/min/kg). Using blood clearance and brain penetration studies as a screen,[6] tetrahydroisoquinoline **3**, D_3 pKi 7.6, was identified as a new lead having low clearance (CLb 20 ml/min/kg).



(**1**) R = Cl; D_3 pKi 8.8; D_2 pKi 6.4

(**2**) R = CF_3SO_2O-; D_3 pKi 8.8; D_2 pKi 6.4



(**3**) D_3 pKi 7.6; D_2 pKi 6.3

In this *Letter* we report some of our initial investigations into the optimisation of the D_3 affinity and selectivity of tetrahydroisoquinolines related to **3**.

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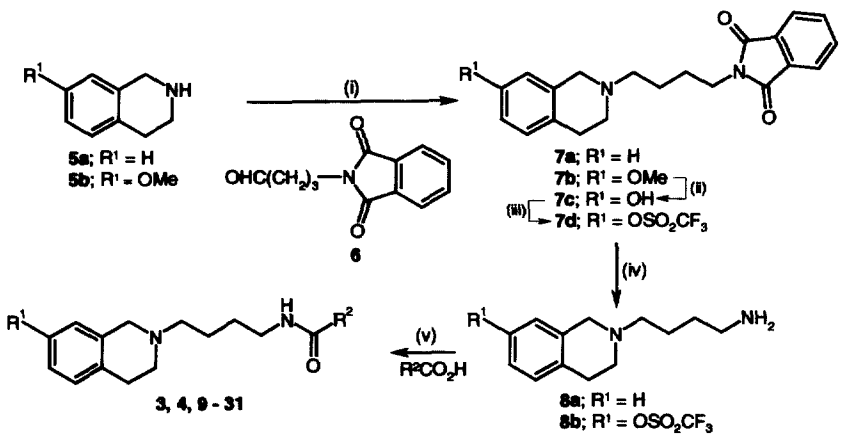
Compounds **3, 4 and 9 - 31** were prepared from the tetrahydroisoquinolines **5a** or **5b** as shown in Scheme 1.

Scheme 1.



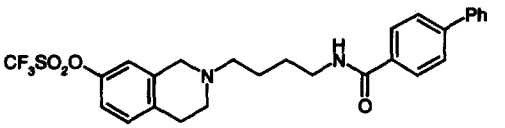
Reagents: (i) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (ii) (a) 1M HCl, Et_2O, (b) BBr_3, CH_2Cl_2; (iii) $(CF_3SO_2O)_2O$, pyridine; (iv) $NH_2NH_2.H_2O$, EtOH; (v) EDC, HOBT, CH_2Cl_2.

Reductive amination of **5a,b** with 4-phthalimidobutyraldehyde **6** in the presence of $NaBH(OAc)_3$ gave the 4-phthalimidobutyltetrahydroisoquinolines **7a,b**. In the case of the 7-methoxytetrahydroisoquinoline **7b**, *O*-demethylation was accomplished by conversion to the HCl salt, followed by treatment with BBr_3 in CH_2Cl_2. Reaction of the resulting 7-hydroxy derivative **7c** with trifluoromethanesulfonic anhydride in anhydrous pyridine gave the 7-trifluoromethylsulfonyloxy intermediate **7d**. Treatment of **7a,d** with hydrazine monohydrate in ethanol removed the phthalimido group to give the aminobutyltetrahydroisoquinolines **8a,b**. Coupling of **8a,b** to an appropriate acid, in the presence of EDC and HOBT in CH_2Cl_2 gave final compounds **3, 4, 9 – 31**. All new compounds were purified by chromatography and isolated as their hydrochloride salts.

Inspection of molecular models suggested that a 7-substituted tetrahydroisoquinoline would give the best overlap with the 5-substituted-2-aminotetralins (Figure 1).

Figure 1. Overlap of a 7-Substituted Tetrahydroisoquinoline (cyan) with a 5-Substituted-2-Aminotetralin (magenta).

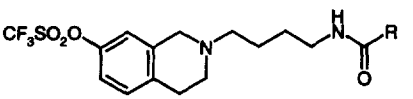
This rationale led to the synthesis of the 7-CF_3SO_2O- derivative **4**, which had improved D_3 affinity compared to the unsubstituted compound **3**.

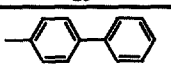
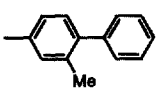
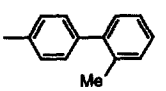
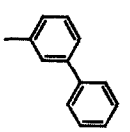
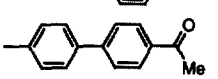
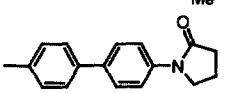
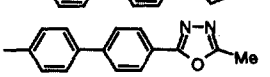
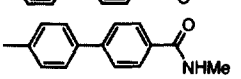
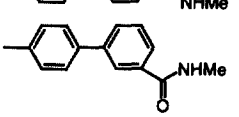


(**4**) D_3 pKi 8.1; D_2 pKi 6.3

By maintaining the 7-CF_3SO_2O- substituent in the tetrahydroisoquinoline ring, the effect of modifications to the biphenyl portion of the molecule was investigated (Table 1). Incorporation of *ortho*-methyl substituents (compounds **9** and **10**) resulted in a reduction in D_3 affinity compared to **4**, and highlighted the need for a coplanar conformation of the biphenyl moiety. Furthermore, the 3-phenyl derivative **11** was significantly lower in affinity than **4**, indicating the importance of the shape of the biphenyl group for high D_3 affinity.

Table 1. Affinities (pKi) of Biaryl Derivatives at Dopamine D_3 & D_2 Receptors



Compound[a]	R	D_3[b]	D_2[b]
4		8.1	6.3
9		7.3	6.0
10		7.3	5.8
11		6.9	6.3
12		8.6	6.7
13		8.6	6.9
14		8.7	7.0
15		8.6	7.0
16		8.7	6.9

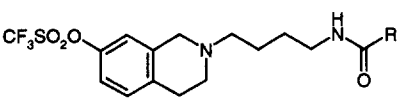
[a] All new compounds gave satisfactory analytical and/or mass spectral data.[7]

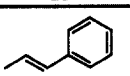
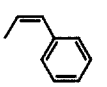
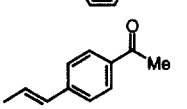
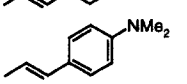
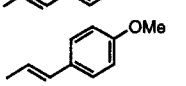
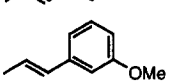
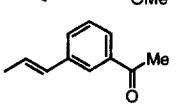
[b] All values represent the mean of at least 3 experiments, each within 0.3 of the mean.

In the 4-phenyl series (compounds **12** – **16**), a range of substituents at the 3′ and 4′-positions which were capable of hydrogen-bonding produced an increase in D_3 affinity compared to **4**. Interestingly, the 4′-acetyl derivative (compound **12**) had the highest selectivity over the D_2 receptor. Replacement of the 4'-acetyl substituent by the more sterically-demanding 2-oxo-pyrrolidine or 1,3,4-oxadiazole groups (compounds **13** and **14**) also gave compounds with high D_3 affinity, although their selectivities were marginally reduced. The 4'- and 3'-carboxamides **15** and **16** had similar D_3 affinities and selectivities, suggesting that these groups could be oriented so as to hydrogen-bond to the same region of the receptor.

Significantly, replacement of the biphenyl group of compound **4** by a *trans*-cinnamide moiety gave compound **17** which retained D_3 affinity and selectivity (Table 2). In contrast, the *cis*-cinnamide **18** had reduced D_3 affinity compared to the *trans*-isomer **17**. Comparison of molecular models for the biphenyl region of compound **4** with those of the *trans*- and *cis*-cinnamides **17** and **18** suggested that the *trans*-cinnamide could be more easily accommodated inside the volume occupied by the biphenyl group. Introduction of small electron-withdrawing or electron-donating substituents (compounds **19** – **23**) into the *meta* or *para*-positions of the *trans*-cinnamide was well tolerated. In particular, these modifications to the structure gave compounds **20**, **22**, and **23** which had 100 fold selectivity over the D_2 receptor.

Table 2. Affinities (pKi) of Cinnamide Derivatives at Dopamine D_3 & D_2 Receptors



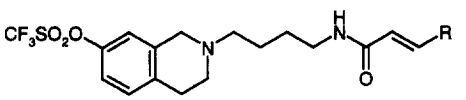
Compound[a]	R	D_3[b]	D_2[b]
17		8.3	6.5
18		7.4	6.5
19		8.4	6.6
20		8.4	6.3
21		8.4	6.5
22		8.5	6.5
23		8.4	6.4

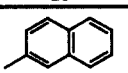
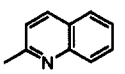
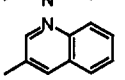
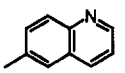
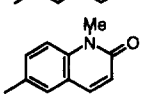
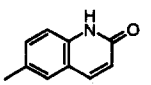
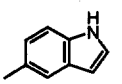
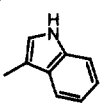
[a] All new compounds gave satisfactory analytical and/or mass spectral data.[7]

[b] All values represent the mean of at least 3 experiments, each within 0.3 of the mean.

Structural comparison of the cinnamide derivatives with the biphenyl series suggested that the 2-naphthylpropenamide **24** should be prepared. The encouraging profile of this compound (D_3 pKi 8.3, selectivity 200 fold *vs* D_2) prompted the synthesis of a range of bicyclic arylpropenamides (Table 3).[8] A particular concern in this series was the high cLogP (6.8) of compound **24**, which resulted in an effort to produce less lipophilic compounds.

Table 3. Affinities (pKi) of Arylpropenamide Derivatives at Dopamine D_3 & D_2 Receptors



Compound[a]	R	D_3[b]	D_2[b]
24		8.3	6.0
25		8.4	6.4
26		8.4	6.5
27		8.5	6.6
28		8.0	6.5
29		8.6	6.8
30		8.7	6.7
31[7]		8.4	6.2

[a] All new compounds gave satisfactory analytical and/or mass spectral data.[7]

[b] All values represent the mean of at least 3 experiments, each within 0.3 of the mean.

Replacement of the 2-naphthyl moiety of **24** by a 2-, 3-, or 6-quinolinyl group gave compounds **25** – **27**, which retained similar D_3 receptor affinity and selectivity. The *N*-methyl carbostyril derivative **28** also retained D_3 affinity, which was increased for the NH carbostyril **29**. This improvement in D_3 affinity was similar to that observed for hydrogen-bonding substituents in the biphenyl series, and led to the preparation of 5-indolylpropenamide **30** (D_3 pKi 8.7). Finally, replacement of the 2-naphthyl group by 3-indolyl moiety gave **31**. Compound **31** had high D_3 affinity, (pKi 8.4) and 150 fold selectivity over the D_2 receptor. Further studies in the *in vitro* functional assay[5] showed **31** to be a potent and selective antagonist (D_3 pKb 8.9) with similar selectivity over the D_2 receptor (pKb 6.6) to that observed in the binding assay.

CONCLUSIONS

Using clearance and brain penetration studies in the rat, tetrahydroisoquinoline **3** (D_3 pKi 7.6) was identified as a new lead with improved metabolic stability compared to the *N*-propyl-2-aminotetralins such as **1**. Further structural modifications led to the design of the 3-indolylpropenamide **31** with high D_3 receptor affinity and 150 fold selectivity over the D_2 receptor. Studies in the rat showed that compound **31** had a low blood clearance of 27 ml/min/kg, similar to that of the lead tetrahydroisoquinoline **3**. Furthermore, compound **31** was shown to be centrally penetrating following i.v. infusion, and in additional studies in the rat had a plasma half-life of 2.5 h.

REFERENCES AND FOOTNOTES

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3. Shafer, R.A.; Levant, B. *Psychopharmacology* **1998**, *135*, 1-16.

4. Boyfield, I.; Coldwell, M.C.; Hadley, M.S.; Johnson, C.N.; Riley, G.J.; Scott, E.E.; Stacey, R.; Stemp, G. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1995 - 1998.

5. Compounds were evaluated in binding assays using displacement of ^{125}I-iodosulpride from human D_3 and D_2 receptors, expressed in CHO cells. Functional activity of the compounds was determined *in vitro* using microphysiometry (for details 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**, *39*, 1946 - 1948.

6. CNS penetration at steady-state was investigated in the rat. Compounds were dissolved in 2% (v/v) DMSO in 5% (w/v) dextrose *aq* and administered at a constant infusion rate over 12 h at a target dose rate of 0.3 mg free base/kg/h. Blood samples were removed during the latter part of the infusion to confirm steady-state blood concentrations. Blood and brain samples were analysed by LC/MS/MS. Values for blood clearance (CLb) were determined according to the relationship CLb = infusion rate/steady-state blood concentration (Css).

7. ^{1}H NMR spectra were recorded at 250 MHz in $CDCl_3$ as solvent.
Compound **31**, mpt 177-180 °C (HCl salt); Mass spectrum (EI^+): Found 521.159986 (M^+). $C_{25}H_{26}F_3N_3O_4S$ requires 521.159613. ^{1}H (free base): δ 1.65 (m, 4H), 2.51 (m, 2H), 2.69 (t, J = 7 Hz, 2H), 2.89 (t, J = 7 Hz, 2H), 3.45 (m, 2H), 3.58 (s, 2H), 6.35 (d, J = 16 Hz, 1H), 6.36 (m, 1H), 6.90 (d, J = 16 Hz, 1H), 7.00 (dd, J = 9, 2 Hz, 1H), 7.05 – 7.46 (m, 5H), 7.85 (m, 2H), 9.20 (br s 1H).

8. Arylpropenamides **24**, **25** and **31** were conveniently prepared from commercially available arylpropenoic acids; **26** and **30** were prepared from known acids. The arylpropenoic acids required for compounds **27** - **29** were readily prepared by Heck reaction of the appropriate aryl bromide with ethyl acrylate, under standard conditions, followed by hydrolysis of the resulting ester.