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FUSED AMINOTETRALINS: NOVEL ANTAGONISTS WITH HIGH SELECTIVITY FOR THE DOPAMINE D_3 RECEPTOR

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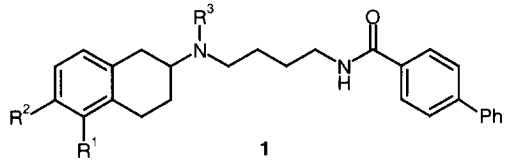
Abstract: Starting from a series of 2-aminotetralins **1**, a novel series of N-[4-(4-phenylbenzoylamino)butyl]-octahydrobenzoquinolines and hexahydrobenzoindoles with high potency and selectivity for the dopamine D_3 receptor has been designed. The effect of ligand chirality on binding affinity has been established. Selected derivatives (e.g. **2o**, **2p**) show high functional selectivity and enhanced *in vivo* properties compared to **1**.

The current treatment of schizophrenia relies heavily on drugs which block up-regulation of the dopaminergic system (in particular *via* blockade of D_2-like receptors).[1] Advances in the molecular biology of dopamine receptors have shown that D_2-like receptors may be divided into D_2, D_3 and D_4 subtypes.[2-4] The localisation of these receptor subtypes supports the hypothesis that the extra-pyramidal side-effects associated with currently available drugs result from blockade of the dopamine D_2 receptor subtype and that selective dopamine D_3 receptor antagonists would offer the potential for antipsychotic therapy free of such side-effects.[3]

In a recent report,[5] we described the discovery and initial evaluation of a series of 2-aminotetralins **1** (R^2=H) as selective dopamine D_3 receptor ligands. In that report, we showed that for optimal potency and selectivity, the N-substituent R^3 should be an n-propyl group. However, further evaluation indicated that these aminotetralins were metabolised *via* N-depropylation and rapidly cleared. Based on these results, we speculated that affinity for the dopamine D_3 receptor might be maintained and metabolic stability improved if, formally, the propyl group was fused to the tetralin nucleus as in **2**. This communication describes some of our studies to investigate the effect of such conformational constraint on dopamine D_3 affinity and selectivity and on metabolic stability.



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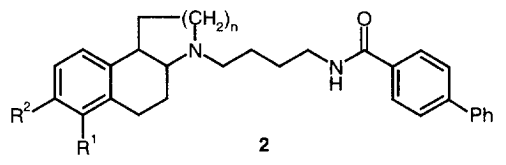

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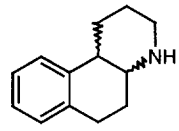
We initially turned our attention to the synthesis of octahydrobenzoquinolines **2** (n=2). The unsubstituted *trans* and *cis* analogues **2a** and **2b** were prepared from the previously reported *trans* and *cis* amines **3**.[6,7] 7- and 8-Substituted racemic octahydroisoquinolines (**2c, 2d, 2p** and **2q**) were prepared by a similar route. Methanesulfonyloxy derivatives were prepared from the related methoxy derivatives by treatment with boron tribromide followed by reaction with methanesulfonyl chloride in the presence of triethylamine.



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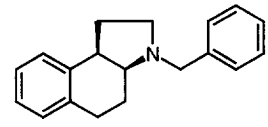

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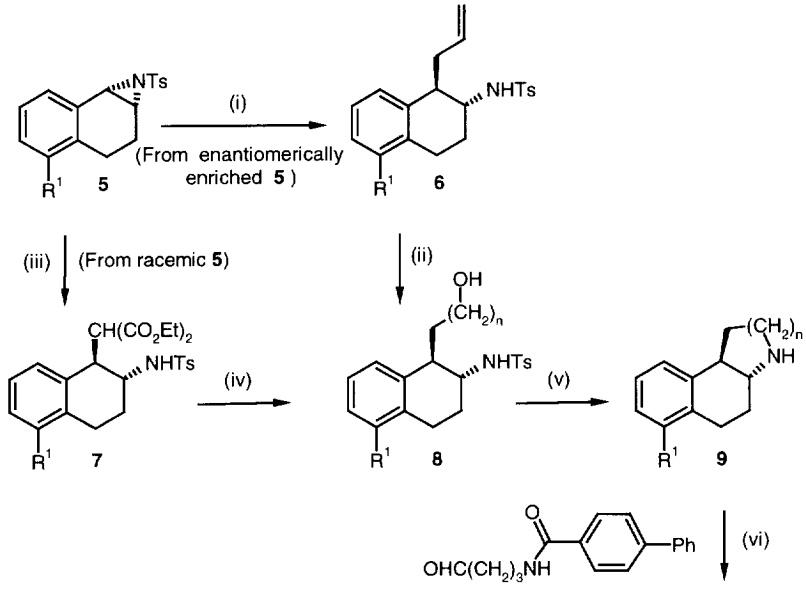
The enantiomers of *trans* derivative **2c** were prepared *via* the opening of aziridine **5** (prepared in enantiomerically enriched form from the corresponding dihydronaphthalene)[8a] with allyl magnesium bromide (Scheme 1). Subsequent transformations gave the required single enantiomers **2** (n=2).[9]

Scheme 1



(±) **2** (n=1) or
(R,R) or (S,S) **2** (n=2)

Reagents: (i) CH_2=$CHCH_2MgBr$, Et_2O; (ii) BH_3.THF then NaOH, H_2O_2; (iii) $CH_2(CO_2Et)_2$, NaOEt, EtOH; (iv) (a) KOH, EtOH/H_2O then HCl, (b) Reflux in xylene, (c) $LiAlH_4$, THF; (v) (a) MsCl, Et_3N, (b) K_2CO_3, MeOH, (c) $LiAlH_4$, THF; (vi) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$.

In the corresponding hexahydrobenzoindole series **2** (n=1), the benzyl derivative **4** was prepared using a reported method[10] and elaborated to the racemic *cis* isomer **2l**. The related racemic *trans* isomers **2k**, **2m-2o**, **2r** and **2s** were prepared (Scheme 1) *via* malonate opening of aziridine **5** (prepared in racemic form).[8b]

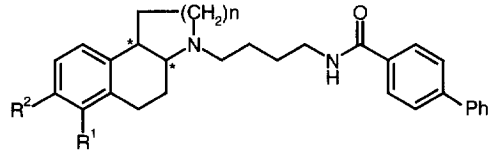
Compounds **2a** to **2s** were evaluated using displacement of ^{125}I-iodosulpride from human D_3 and D_2 receptors, expressed in CHO cells, and results are shown in Table 1. The dopamine D_3 receptor has been shown to be weakly coupled to adenylate cyclase in CHO cells.[11] The functional activity of selected compounds at both the D_3 and D_2 receptor was therefore determined *in vitro* using microphysiometry.[12]

From the initial results (Table 1), we were encouraged that the unsubstituted racemic *trans* derivative **2a** maintained good affinity for, and was a functional antagonist at, the D_3 receptor. Furthermore, a level of stereochemical recogition was apparent as the related racemic *cis* isomer **2b** proved a much less potent ligand at this receptor. A similar trend was observed with the corresponding racemic methanesulfonyloxy derivatives **2c** and **2d**. (The introduction of the methanesulfonyloxy group shows particularly beneficial effects on lipophilicity). The level of stereochemical recognition proved even greater within the enantiomerically pure *trans* series (compounds **2e** - **2j**) with virtually all recognition for the D_3 receptor residing within the (S,S) enantiomers **2e** - **2g**. This result is in stark contrast with that of the corresponding aminotetralins **1** in which there is little preference for either enantiomer at the D_3 receptor[14] and is clearly a consequence of increased rigidity of the tricyclic system. Some equivalence with the aminotetralin series was seen however, with the hydroxy derivative **2f** proving of higher affinity but of lower selectivity than methansufonyloxy analogue **2g**.

Broadly similar results were found in the hexahydrobenzoindole system (**2**, n=1) with *trans* stereochemistry around the ring junction preferred over *cis* (cf. **2k** vs. **2l**). The methanesulfonyloxy derivative **2o** is particularly worthy of note for potency at the D_3 receptor and selectivity over the D_2 receptor both in binding and functional studies.

Within the aminotetralin series **1**, there is only a small preference for 5-substitution over 6-substitution.[14] In our constrained tricyclic series **2**, however, there is a clear preference for the equivalent of the former (cf. **2c** vs. **2q** and **2o** vs. **2s**) with both ring systems (n = 1 or 2). The effects of constraint on the hydroxy derivative **2p** are even more pronounced - in contrast with results from the aminotetralin work,[5] compound **2p** is an antagonist at the D_3 receptor. Indeed, **2p** shows over 100 fold selectivity for the dopamine D_3 receptor over the D_2 receptor in functional experiments. A likely explanation of this change in functional activity is that the hydroxyl group in compound **2p** can no longer interact with one of the key serine residues on trans-membrane helix 5 implicated[15] in receptor activation.

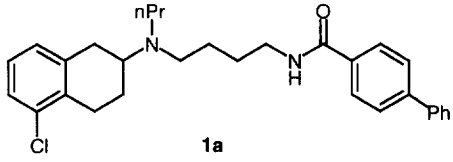
Table 1. Affinities of Tricyclic derivatives at Dopamine D_3 and D_2 receptors



Compound[a]	R^1	R^2	n	Stereochem at * *	D_3[b]	D_2[b]	Selectivity	D_3 Function[c, d]
2a	H	H	2	(±) *trans*	7.8	6.3	38	Antagonist
2b	H	H	2	(±) *cis*	6.6	6.1	3	
2c	MsO	H	2	(±) *trans*	8.0	6.5	30	Antagonist
2d	MsO	H	2	(±) *cis*	6.6	6.4	2	
2e	MeO	H	2	(S,S) *trans*	8.1	6.3	65	
2f	HO	H	2	(S,S) *trans*	9.0	7.6	22	
2g	MsO	H	2	(S,S) *trans*	8.2	6.6	45	
2h	MeO	H	2	(R,R) *trans*	6.1	6.1	1	
2i	HO	H	2	(R,R) *trans*	6.2	6.2	1	
2j	MsO	H	2	(R,R) *trans*	5.9	5.9	1	
2k	H	H	1	(±) *trans*	7.8	6.3	33	
2l	H	H	1	(±) *cis*	7.3	6.3	12	
2m	MeO	H	1	(±) *trans*	7.8	6.2	40	
2n	HO	H	1	(±) *trans*	8.7	7.2	26	
2o	MsO	H	1	(±) *trans*	8.3	6.5	65	Antagonist
2p	H	HO	2	(±) *trans*	8.1	6.3	72	Antagonist
2q	H	MsO	2	(±) *trans*	6.7	5.7	10	
2r	H	HO	1	(±) *trans*	7.9	6.5	27	
2s	H	MsO	1	(±) *trans*	7.3	6.0	22	

[a] All new compounds gave satisfactory analytical/spectral data.[13] [b] Affinities are pKi values. All values represent the mean of at least 2 experiments, each within 0.2 of the mean. [c] Microphysiometer.[12] [d] Selected compounds were evaluated.

Alongside these binding and functional studies, the rate of clearance from the rat following *iv* administration was measured for a representative group of compounds (Table 2).[16] These data, when compared with those obtained from our original lead (compound **1a**) in the aminotetralin series, indicate that the tricyclic derivatives are indeed cleared more slowly than their N-propyl predecessors, vindicating our original conjecture.



1a

Table 2. Clearance data

Compound No.	Clearance (ml/min/kg)
2a	46
2c	61
2l	59
1a	96

In conclusion, we have identified two related novel series of tricyclic derivatives **2**, which not only show high potency and selectivity for the dopamine D_3 receptor over the D_2 receptor, but also show the promise of considerable improvement in their *in vivo* stabilities when compared with the parent aminotetralins. These improved *in vivo* characteristics should facilitate their use as tools for the evaluation of the role of D_3 receptors in schizophrenia.

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13. ^{1}H NMR spectra were recorded at 250 MHz in $CDCl_3$ as solvent. Compound **2g**, ^{1}H: δ 1.25 (1H,m), 1.55 (1H,m), 1.56-1.89 (6H,m), 2.06-2.37 (3H,m), 2.38-2.67 (3H,m), 2.69-3.13 (4H, m), 3.17 (3H,s), 3.52 (2H,m), 6.60 (1H,m), 7.09-7.27 (3H,m), 7.44 (3H,m), 7.62 (4H,m), 7.85 (2H, d, J = 9 Hz). Mass spectrum (API^+):Found 533 (MH^+). $C_{31}H_{36}N_2O_4S$ requires 532. Compound **2g** was assigned the (S,S) configuration following x-ray analysis of the allyl precursor **6**.
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16. The relative blood clearance values were determined for each compound under steady-state conditions. Each compound was dissolved in 5% (w/v) glucose *aq* containing 2% (v/v) DMSO and 10% EncapsinTM HPB at a target concentration of 0.2 mg free base/ml and administered as a constant rate intravenous infusion to rats (n = 3 per compound) over 12 h at a target dose rate of 1 mg free base/kg/h. Serial blood samples were obtained during the latter part (2 h) of the infusion period to confirm steady-state blood concentrations. At the end of the infusion, the animals were killed and exsanguinated. Parent compound concentrations in blood were determined using appropriate LC/MS/MS methodologies. Blood clearance (CLb) was calculated according to the relationship; CLb = R/Css where R = the infusion rate and Css = the steady-state blood concentrations.