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NOVEL 6-SUBSTITUTED 2-AMINOTETRALINS WITH POTENT AND SELECTIVE AFFINITY FOR THE DOPAMINE D_3 RECEPTOR

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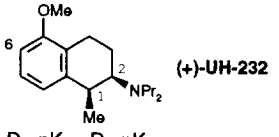
Abstract: Starting from (1S,2R)-5-methoxy-1-methyl-2-*N*,*N*-dipropylaminotetralin [(+)-UH-232] as a lead structure, a series of novel 6-substituted 2-aminotetralins have been discovered which show high affinity for dopamine D_3 receptors. One compound, GR218231, exhibits *ca.* 400 fold selectivity for the dopamine D_3 receptor over the D_2 receptor and *ca.* 10,000 fold selectivity with respect to D_1 and D_4 receptors.

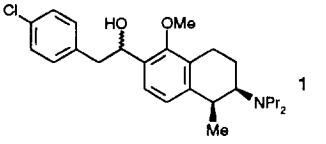
The discovery of the dopamine D_3 receptor has provoked much interest since it shows high affinity for many antipsychotics.[2,3] Of particular interest is that *in situ* hybridisation studies indicate its selective localisation in limbic areas of the brain[4,5] with the significance that a selective antagonist for the dopamine D_3 receptor might provide an effective antipsychotic free from the extrapyramidal side-effects which haunt the typical D_2 antagonists.[5,6] In their initial paper on the cloning of the D_3 receptor, Sokoloff et al.[3] identified one D_2 antagonist, (1S,2R)-5-methoxy-1-methyl-2-*N*,*N*-dipropylaminotetralin [(+)-UH-232][4], which actually showed greater affinity for the D_3 receptor. Although (+)-UH-232 shows only modest selectivity and potency for the D_3 receptor, its lack of affinity for non-dopaminergic receptors made it an attractive starting point for a chemical programme aimed at seeking potent and selective antagonists for the D_3 receptor.

Since substitution at the 6-position of the 5-methoxy-2-aminotetralin nucleus was readily achieved *via* directed metallation, this was one of the sites selected for modification. In particular, it allowed access to a range of phenethyl alcohols and related derivatives. The 4-chlorophenyl alcohol **1** (as an epimeric mixture) was an early compound that showed a distinct improvement in selectivity and was of sufficient interest to pursue further, although its affinity for the D_3 receptor was still modest.



(+)-UH-232

D_3 pK_i	D_2 pK_i
7.9	7.2

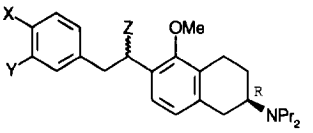


1

D_3 pK_i	D_2 pK_i
7.6	6.2

Since the three stereocentres present in **1** hindered a rapid exploitation of this new lead, a strategy of seeking structurally simplified analogues was adopted and key results are summarised in Tables 1 and 2. Removal of the C-1 methyl group from **1** gave **2** of which one of the diastereomeric alcohols (stereochemistry not known) showed higher D_3 affinity compared with **1** and displayed ~50 fold selectivity with respect to the D_2 receptor (Table 1). Compound **2** also maintained good selectivity over those receptors which have traditionally displayed significant affinity for 2-aminotetralin systems [e.g. α_1 (pKi = 6.0) and 5-HT_{1A} (pKi = 6.3) receptors]. Still further simplification through removal of the benzylic hydroxyl group, giving the (2R)-5-methoxy-6-arylethyl-2-aminotetralins **6-9**, resulted in some loss of selectivity but retention of D_3 affinity (e.g. **6**).

Table 1 Receptor affinities and selectivity of 6-arylethyl-5-methoxy-2-aminotetralins

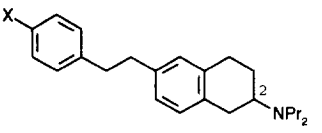


Compd	X	Y	Z	Receptor Affinity (pKi)[a]	
				D_3[b]	D_2[c]
2 (isomer i)	Cl	H	OH	8.2	6.5
2 (isomer ii)	Cl	H	OH	7.3	5.9
3[d]	H	H	OH	7.2	6.0
4[d]	Cl	Cl	OH	7.7	NT
5[d]	MeO	H	OH	7.3	NT
6	Cl	H	H	8.3	6.9
7	CF_3	H	H	8.2	7.0
8	H	H	H	7.7	NT
9	$MeSO_2NH$	H	H	6.3	NT

[a] Figures quoted are the mean of two independent determinations, each within 0.2 log units of the mean.
[b] Binding affinity, Chinese hamster ovary cells transfected with human D_3 receptor using [^{3}H]-spiperone.
[c] Binding affinity, mouse Ltk$^-$ cells transfected with human D_2 receptor (short form) using [^{3}H]-spiperone.
[d] Mixture of diastereomeric alcohols

The most dramatic improvements in profile were observed with the simple 6-arylethyl-2-aminotetralins **10-21** (Table 2). Initially, D_3 receptor affinity was rapidly assessed in the *racemic series* for a range of compounds bearing different aryl ring substituents. This provided a number of analogues which showed D_3 affinities >8.5 and selectivities of >100 fold with respect to the D_2 receptor. For selected structures these affinities and selectivities were subsequently confirmed for the (R)-configuration enantiomers (e.g. **10**,**12** & **13**). Polar substitutions on the aryl ring, such as carboxylic acid **20**, carboxamide **21** and sulphone **22**, were poorly tolerated.

Table 2[a] Dopamine binding affinities and selectivities of 6-arylethyl-2-aminotetralins

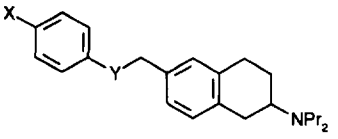


Compd	C-2 Stereochem.	X	Receptor Affinity (pKi) D_3	D_2
10	R	Cl	8.4	6.4
11	S	Cl	8.0	6.9
12	R	MeC(=O)-	8.5	6.1
13	R	MeC(N=OH)-	9.0	6.5
14	RS	MeC(=O)-	8.4	6.0
15	RS	MeC(N=OH)-	8.7	6.1
16	RS	H	8.4	6.4
17	RS	MeO	8.5	6.6
18	RS	HO	7.9	6.5
19	RS	EtO_2C	8.7	6.6
20	RS	HO_2C	5.5	NT
21	RS	H_2NOC	6.2	NT
22	RS	$MeSO_2$	5.8	NT

[a] Footnotes as for Table 1

A significant drawback of structures such as those summarised in Table 2 is their high lipophilicity and consequent rapid clearance *in vivo*. This led us to extend our programme of modifications to discover compounds of lower lipophilicity which still retained a high D_3 potency and selectivity profile. One approach to this objective was to introduce polar substitutions into the 6-arylethyl side-chain (Table 3). While incorporation of carbamate, amide, urea and sulphone functions (e.g. **23-26**) all markedly reduced lipophilicity, this strategy was also consistent with the retention of high D_3 potency and selectivity. Of particular note is the sulphone **26** which possesses a high D_3 affinity and shows enhanced selectivity. The active enantiomer, **27** (GR218231), is ~400 fold selective for the D_3 receptor and ~10,000 fold selective with respect to D_1 and D_4 receptors. It also only binds weakly to α_1, α_2 and 5-HT_{1A} receptors (pKi values < 6.0). GR218231 was tested for D_2 functional activity at presynaptic D_2 receptors in rat striatal slices using fast cyclic voltammetry: in this preparation[7] quinpirole inhibits the electrically-evoked release of dopamine and this is blocked by D_2 antagonists. Compound **27** shows no detectable agonist activity up to 1μM concentration in this test and its low D_2 antagonist potency (pKi = 5.8) correlates well with its D_2 binding affinity. The exceptionally high affinity and selectivity of the iodo derivative **29** suggests its potential utility, as a radioligand, for determining central D_3 receptor distribution and function.

Table 3[a] 6-Phenethyl-2-aminotetralins incorporating polar substitutions

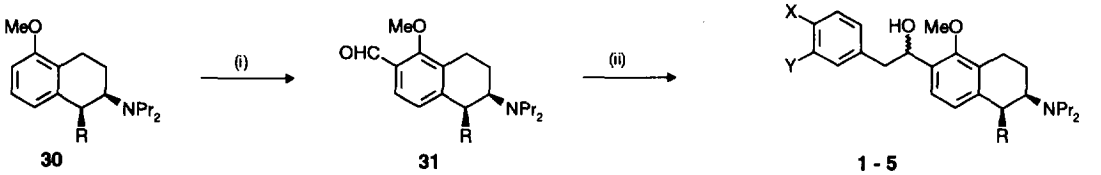


Compd	C-2 Stereochem	X	Y	mlogD	Receptor Affinity (pKi) D3	D2
17	RS	MeO	CH_2	>4.0	8.5	6.6
23	RS	MeO	NCO_2Me	2.9	8.2	6.1
24	RS	MeO	NCOMe	2.6	8.1	6.2
25	RS	MeO	$NCONH_2$	1.9	7.6	5.2
26	RS	MeO	SO_2	2.2	8.8	6.2
27	R	MeO	SO_2	2.2	8.9	6.3
28	RS	MeO	S	4.3	8.9	6.7
29	R	I	SO_2	3.4	9.8	6.7

[a] Footnotes as for Table 1

Chemical synthesis: The 6-phenethyl analogues **2-5** were synthesized *via* a directed metallation of enantiomerically pure 5-methoxy-2-aminotetralins **30** (R = H, Me) followed by quenching with DMF and subsequent reaction with the appropriate benzyl Grignard reagent (Scheme 1).

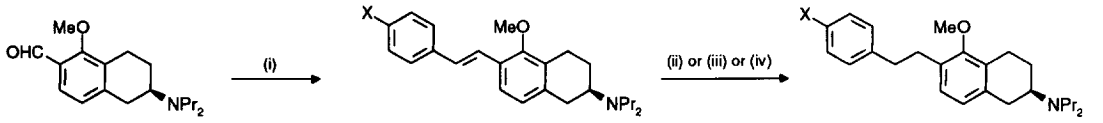
Scheme 1



(i) a) n-BuLi, TMEDA, Et_2O, 0°C b) DMF, -78°C (R = H, 71%; R = Me, 61%) (ii) $ArCH_2MgCl$, THF or Et_2O (X = Cl, Y =H, R = Me, 38%; X = Cl, Y = R = H, 24%; X = Y = Cl, R = H, 34%; X = Y = R = H, 39%)

The 6-carboxaldehyde **31** also served as the key intermediate for the synthesis of the 6-arylethyl-5-methoxy-2-aminotetralin analogues **6-9**. Thus, reaction of **31** with the appropriate Wittig reagent followed by hydrogenation and further elaboration, as necessary, afforded the desired compounds (Scheme 2). In the case of the unsubstituted analogue (X = H), hydrogenation/hydrogenolysis of the corresponding 4-chorophenyl intermediate afforded **8** directly.

Scheme 2

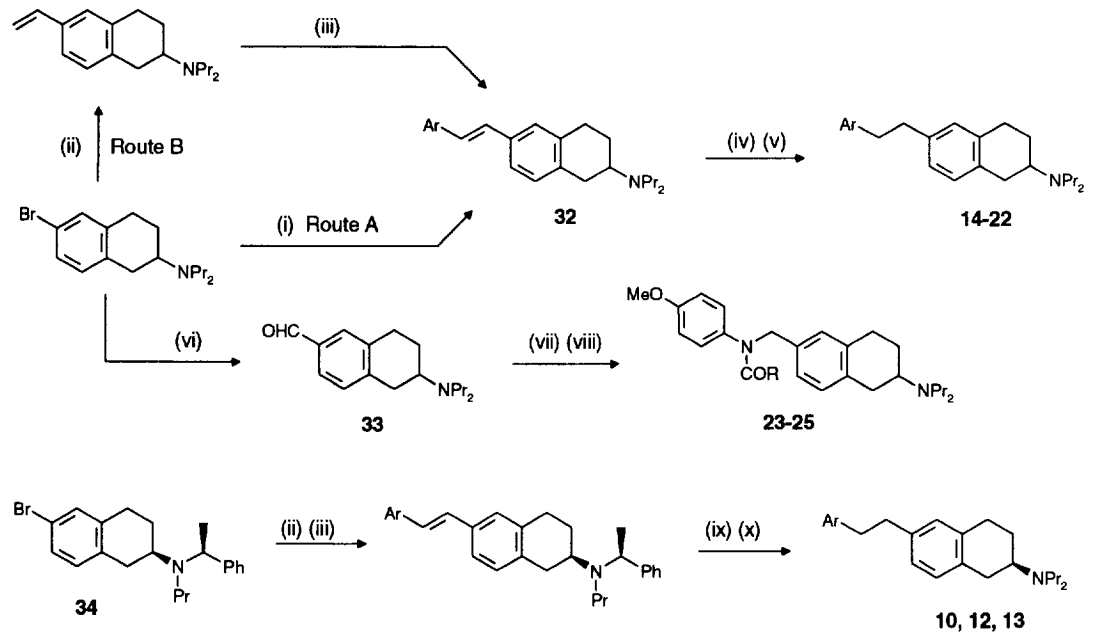


31 (R = H) **6 - 9**

(i) ArCH=PPh_3, THF (X = Cl, 34%; X = NO_2, 92%; X = CF_3, 50%) (ii) H_2/Pd-C, EtOH (X = CF_3, 44%; X = H, 89%) (iii) H_2/Pt-C, EtOH (X = Cl, 81%) (iv) a) H_2/Pd-C, EtOH b) $MeSO_2Cl$, Et_3N, CH_2Cl_2 (X = $MeSO_2NH$; 42%)

6-Bromo-2-(*N,N*-dipropylamino)tetralin provides a straightforward entry to the synthesis of the racemic 6-arylethyl-2-aminotetralins **14-22** and 6-arylaminomethyl-2-aminotetralin derivatives **23-25** (Scheme 3). Where appropriate, Heck reactions using styrenes (route A) or Stille coupling using vinylstannanes (route B) followed by Heck reactions on the 6-vinyl intermediate gave the stilbenes **32**. Reduction of the olefinic bond and, for certain examples, minor functional group modifications gave the desired products. The (2R) enantiomers **10**, **12** and **13** were obtained in high optical purity *via* the same methodology but employing the resolved bromotetralin **34** (see also Scheme 4).

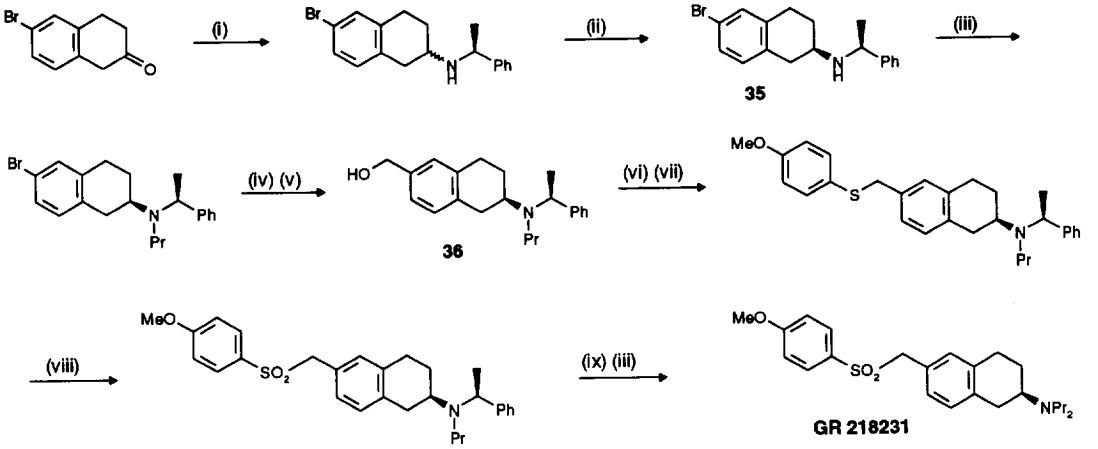
Scheme 3



(i) ArCH=CH_2, $Pd(OAc)_2$, P(o-tolyl)$_3$, Et_3N, DMF; 60-80% (ii) $Bu_3SnCH=CH_2$, $Pd(PPh_3)_4$, toluene, Δ; 80% (iii) As for (i) but + ArBr 51% (iv) H_2/Pd-C, EtOH 61% (v) functional group modifications (vi) a) n-BuLi, THF, -78°C b) DMF, -78°C; 96% (vii) 4-$MeOC_6H_4NH_2$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; 57% (viii) a) $ClCO_2Me$, Et_3N; 54% or b) MeCOCl, pyridine; 62% or c) KOCN, AcOH, then NH_3, EtOH; 87% (ix) HCO_2NH_4, Pd-C, MeOH; 80-90% (x) EtCHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; 55%

The synthesis of the sulphone GR218231 is outlined in Scheme 4. A key aspect of this route is the expeditious preparation of the 6-bromo-2-aminotetralin **35** in high optical purity (de 99.2%). Subsequent metallation, formylation and reduction gave the benzyl alcohol **36,** appropriately functionalised at the C-6 position for elaboration to GR218231. Similar chemistry but using 4-iodobenzyl mercaptan led to the corresponding iodo derivative **29.**[8]

Scheme 4



(i) (S)-PhCH(Me)NH_2, $NaBH(OAc)_3$, AcOH, CH_2Cl_2. 85% (ii) a) HCl, Et_2O b) recryst.; 33%, 99% de
(iii) EtCHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; 100% (iv) a) n-BuLi, THF, -78° b) DMF; 81% (v) $NaBH_4$, 81% (vi) $SOCl_2$, CH_2Cl_2, DMF, 0° (vii) p-$MeOC_6H_4SH$, Na_2CO_3, CH_2Cl_2; 77% for two steps (viii) Oxone, i-PrOH, H_2O, 0°; 93%
(ix) HCO_2NH_4, Pd/C, MeOH, 67%

In summary, through successive modification of a novel series of 2-aminotetralins we have obtained compounds which have high affinity for the dopamine D_3 receptor and high selectivity over dopamine D_1, D_2 and D_4 receptors.

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1. Author to whom correspondence should be addressed. Present address: GlaxoWellcome Cambridge Chemistry Laboratory, University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW, U.K.
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8. All new compounds exhibited satisfactory spectral and elemental analysis data.

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