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Design and Synthesis of Novel 2,3-Dihydro-1*H*-isoindoles with High Affinity and Selectivity for the Dopamine D_3 Receptor

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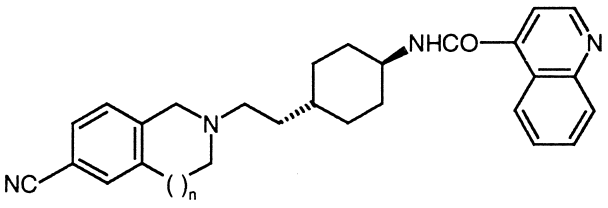
Abstract—Starting from the tetrahydroisoquinoline SB-277011 **1,** a novel series of 5-substituted-2,3-dihydro-1*H*-isoindoles has been designed. Subsequent optimisation resulted in identification of **19**, which has high affinity for the dopamine D_3 receptor (pK_i 8.3) and $\geq$100-fold selectivity over other aminergic receptors. In rat studies **19** was brain penetrant with an excellent pharmacokinetic profile (oral bioavailability 77%, $t_{1/2}$ 5.2 h).

All clinically effective antipsychotic agents share the property of dopamine D_2 and D_3 receptor antagonism. Since these drugs occupy both D_3 and D_2 receptors at clinical doses, their antipsychotic effects could be mediated via D_2 and/or D_3 receptors. Blockade of D_2 receptors in the striatum leads to serious extrapyramidal side-effects, resulting in poor patient compliance and therefore poor control of the disease. Interestingly, 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. Consequently, a selective dopamine D_3 receptor antagonist offers the potential for an effective antipsychotic therapy, free of the serious side-effects of currently available drugs.[1–4] The presence of the dopamine D_3 receptor in projection regions of the mesocorticolimbic system also suggests a potential therapeutic role in reinforcement processes and drug abuse.[5]

Recent reports from these laboratories have described the design and synthesis of SB-277011 **1**, a potent and selective dopamine D_3 antagonist.[6] As part of our continuing studies around SB-277011 **1**, it was important to establish the effect on D_3 affinity and selectivity of replacing the tetrahydroisoquinoline with a 2,3-dihydro-1*H*-isoindole. Examination of molecular models suggested a good overlap between the 6-substituted-tetrahydroisoquinoline of **1** and 5-substituted-2,3-dihydro-1*H*-isoindoles, such as **2** (Fig. 1). However, the modelling study also indicated the different spatial requirements of the 2,3-dihydro-1*H*-isoindole, which might adversely affect dopamine D_3 affinity. Accordingly, a series of 5-substituted-2,3-dihydro-1*H*-isoindoles, related to **1**, has been synthesised and the structure–activity relationship investigated, the results of which are disclosed in this paper.

The synthesis of the starting 5-substituted-2,3-dihydro-1*H*-isoindoles **3b–e** is outlined in Scheme 1. Preparation of 5-methanesulfonyloxy- and 5-cyano-2,3-dihydro-1*H*-isoindoles **3b**,**c** was accomplished via the key 5-hydroxy intermediate **4**, derived from 5-methoxy-2,3-dihydro-1*H*-isoindole **3a**[7] by sequential *O*-demethylation and *N*-protection. Reaction of **4** with methanesulfonyl chlo-



1 n=1 SB-277011 D_3 pKi 8.0; D_2 pKi 6.0

2 n=0

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ride or trifluoromethanesulfonic anhydride gave the sulfonates **5** and **6**, respectively. Palladium catalysed reaction of **6** with $Zn(CN)_2$ furnished the 5-cyano derivative **7**. Deprotection of **5** and **7** then afforded the required 2,3-dihydro-1*H*-isoindoles **3b**,**c**. The 5-trifluoromethyl-2,3-dihydro-1*H*-isoindole **3e** was obtained from the 5-bromo intermediate **8**[7] by reaction with potassium trifluoroacetate in DMF, followed by *N*-detosylation of **9** with 48% hydrobromic acid in the presence of phenol and propionic acid. Similarly, **8** afforded the 5-bromo analogue **3d**.[7]

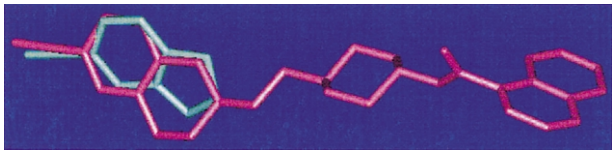
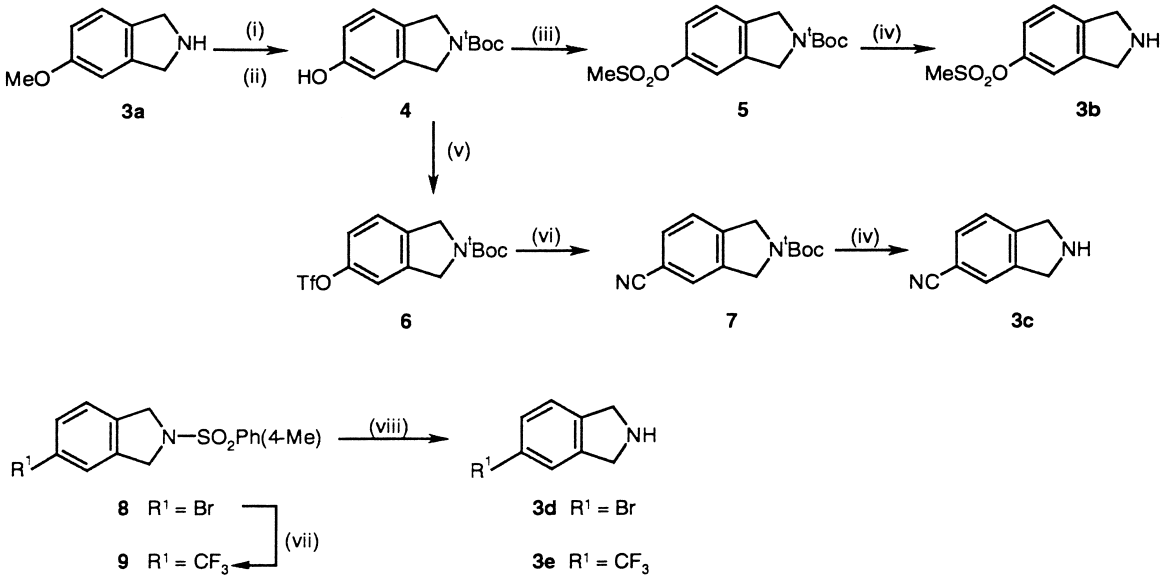


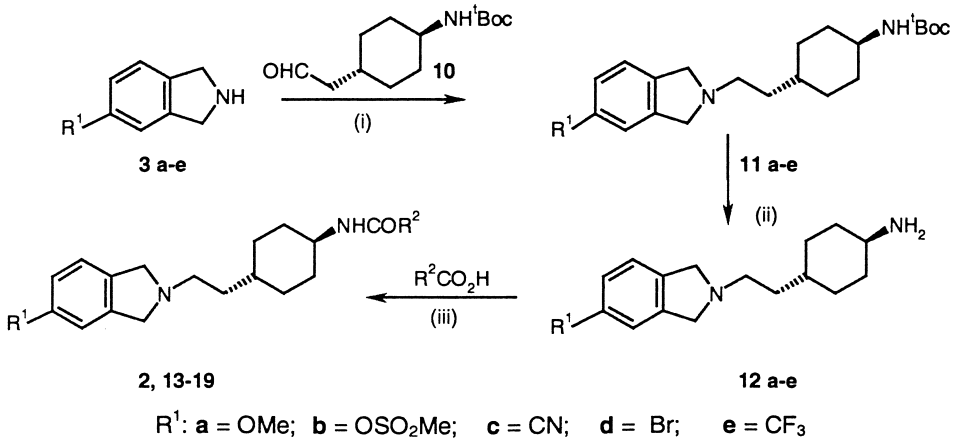
Figure 1. Overlap of 5-cyano-2,3-dihydro-1*H*-isoindole (cyan) with SB-277011 (magenta).

Transformation of the 2,3-dihydro-1*H*-isoindoles **3a–e** into the final compounds **2** and **13–19** is outlined in Scheme 2. Thus, reductive amination of the aldehyde **10**[6] with the requisite 5-substituted-2,3-dihydro-1*H*-isoindole **3a–e** in the presence of $NaBH(OAc)_3$ afforded the corresponding protected amines **11a–e**. *N*-Deprotection with TFA, followed by EDC-HOBt mediated coupling of the resulting amines **12a–e** with an appropriate acid provided the amides **2** and **13–19**. All compounds were purified by chromatography and isolated as their hydrochloride salts.

For direct comparison with the tetrahydroisoquinoline, the first derivative prepared and evaluated was the 5-cyano-2,3-dihydro-1*H*-isoindole **2**. Albeit less potent than the corresponding tetrahydroisoquinoline SB-277011 **1**, the 5-cyano-2,3-dihydro-1*H*-isoindole analogue **2** had encouraging affinity for the D_3 receptor (pK_i 7.2) with 40-fold selectivity over the D_2 receptor (Table 1). By replacement of the 4-quinolinyl group by a 2-indolyl



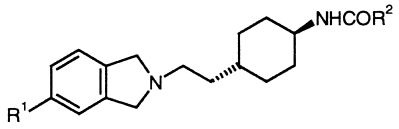
Scheme 1. Reagents: (i) 48% HBr, 100 °C, 2 h, 80%; (ii) $(Boc)_2O$, NEt_3, CH_2Cl_2, rt, 16 h, 40%; (iii) $MeSO_2Cl$, NEt_3, CH_2Cl_2, rt, 16 h, 70%; (iv) TFA, CH_2Cl_2, 40 °C, 0.5 h, 90%; (v) $(CF_3SO_2)_2O$, NEt_3, CH_2Cl_2, −20 °C–rt, 6 h, 70%; (vi) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 100 °C, 4 h, 90%; (vii) CF_3CO_2K, CuI, DMF–PhMe, 110 °C, 1.5 h, 90%; (viii) 48% HBr, PhOH, $EtCO_2H$, 150 °C, 6 h, 65%.

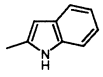
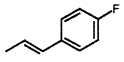
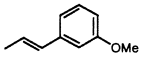
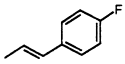
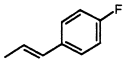
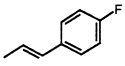
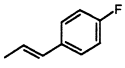


Scheme 2. Reagents: (i) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 16 h, 55–85%; (ii) TFA, CH_2Cl_2, 40 °C, 0.5 h, 90%; (iii) EDC, HOBt, CH_2Cl_2, rt, 16 h, 50–90%.

group, as in compound **13**, D_3 affinity was slightly increased and 100-fold selectivity over the D_2 receptor was demonstrated. It had previously been observed in the 6-cyano-tetrahydroisoquinoline series that a 4-fluorocinnamide moiety gave higher dopamine D_3 receptor affinity than the 4-quinolinylcarboxamide group.[6,10] This modification to the acylamino moiety identified the *trans*-cinnamide **14**, which had high affinity for the D_3 receptor with a pK_i of 7.9. Unfortunately, D_2 receptor affinity also increased, with a slight reduction in selectivity to 50-fold. Variation of the phenyl substituent identified the 3-methoxycinnamide **15**, which firmly established that both high affinity (pK_i 8.0) for the D_3 receptor and 100-fold selectivity over the D_2 receptor was achievable in this series. On cross-screening against other aminergic receptors, cinnamide **15** was shown to be only 50-fold selective over the 5-HT_{1D} receptor. The reduced selectivity over the 5-HT_{1D} receptor observed in the 5-cyano-2,3-dihydro-1*H*-isoindole series was in contrast to the 6-cyano-tetrahydroisoquinoline series[6] and may result from the subtly different spatial requirements of the 2,3-dihydro-1*H*-isoindole and tetrahydroisoquinoline rings (see Fig. 1). With the aim of maintaining D_3 affinity and improving the overall selectivity, alternative 5-substituted-2,3-dihydro-1*H*-isoindole derivatives were investigated in the 4-fluorocinnamide series. While the 5-trifluoromethyl- and 5-methoxy-analogues, **16** and **18** respectively, had similar D_3 affinity to the 5-cyano analogue **14**, the 5-bromo analogue **17** had increased D_3 affinity with a pK_i of 8.5. These modifications however, resulted in a similar enhancement of D_2 receptor affinity and therefore only 25–40-fold selectivity over D_2. In previous studies on a series of 2-aminotetralin derivatives, replacement of methoxy by methanesulfonyloxy had maintained D_3 affinity and enhanced D_2 selectivity.[11] In agreement with this observation **19** demonstrated excellent affinity (pK_i 8.3) for the D_3 receptor, and 100-fold selectivity over the D_2 receptor. Furthermore, **19** had an excellent cross-screening profile, being 270-fold selective over the 5-HT_{1D} receptor (pK_i 5.9) and $\geq$200-fold selective over other aminergic receptors (pK_i 5-HT_{1A} 5.5, 5-HT_{1B} 5.3, 5-HT_{2A} <5.3, 5-HT_{2B} <6.0, 5-HT_{2C} <5.1, 5-HT_6 <5.0, 5-HT_7 <5.4, α_{1B} <5.3). Studies in the in vitro functional assay[9] showed **19** to be a potent antagonist at the D_3 receptor with a pK_b of 8.3. In vivo evaluation in the rat demonstrated that **19** was centrally penetrant (brain:blood 0.5:1) and had an excellent pharmacokinetic profile, with high oral bioavailability (77%), low clearance (CL_b 14 mL/min/kg) and long terminal half-life ($t_{1/2}$ 5.2 h).[12]

Table 1. Affinities (pK_i) of substituted 2,3-dihydro-1*H*-isoindole derivatives at dopamine D_3 and D_2 receptors



Compound[a]	R^1	R^2	D_3[b]	D_2[b]	Selectivity[c]
SB-277011	—	—	8.0	6.0	100
2	NC–		7.2	5.6	40
13	NC–		7.6	5.6	100
14	NC–		7.9	6.2	50
15	NC–		8.0	6.0	100
16	F_3C–		8.0	6.4	40
17	Br–		8.5	7.0	35
18	MeO–		8.1	6.7	25
19	$MeSO_2O$–		8.3	6.3	100

[a]All new compounds gave satisfactory analytical and/or mass spectral data.[8]
[b]All values represent the mean of at least 3 experiments, each within 0.3 of the mean.[9]
[c]Selectivity is defined as the antilogarithm of the difference between D_3 and D_2 pK_i values.

Conclusions

Based on the tetrahydroisoquinoline SB-277011 **1**, a novel series of 5-substituted-2,3-dihydro-1*H*-isoindoles has been designed and structure–activity relationships investigated. From this study, the 5-methanesulfonyloxy derivative **19**, with a binding affinity (pK_i 8.3) for the D_3 receptor 2-fold higher than SB-277011 **1** and with similar 100-fold selectivity over the D_2 receptor, was identified. Furthermore it has been shown that **19** was $\geq$200-fold selective over a package of 63 receptors and ion channels. Additional studies established that **19** had an exceptional pharmacokinetic profile and was also brain penetrant, and therefore represents an excellent pharmacological tool for the further characterisation of the role of the dopamine D_3 receptor in the central nervous system.

References and Notes

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8. ^{1}H NMR spectra were recorded at 250 MHz in $CDCl_3$ as solvent. Compound **19** mp 264–266 °C (HCl salt); (Found: C, 59.6; H, 6.1; N, 5.3; *m*/*z* 487 (MH^+). $C_{26}H_{31}FN_2O_4S$ requires C, 59.7; H, 6.2; N, 5.4%, M 486); ^{1}H NMR (free base): δ 1.05–1.30 (m, 5H), 1.40–1.54 (m, 2H), 1.80–1.90 (m, 2H), 2.00–2.15 (m, 2H), 2.74 (t, J = 7 Hz, 2H), 3.12 (s, 3H), 3.86 (m, 1H), 3.90 (m, 4H), 5.45 (d, J = 8 Hz, 1H), 6.27 (d, J = 16 Hz, 1H), 7.00–7.20 (m, 5H), 7.47 (m, 2H), 7.57 (d, J = 16 Hz, 1H).
9. 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 compound **19** was determined in vitro using microphysiometry. Apparent pK_b values were D_3 (8.3) and D_2 (6.7). 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.; Stemp, G. *J. Med. Chem.* **1996**, *39*, 1946.
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12. CNS penetration at steady-state was investigated in the rat. The compound was 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).