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ISOINDOLINONE ENANTIOMERS HAVING AFFINITY FOR THE DOPAMINE D_4 RECEPTOR

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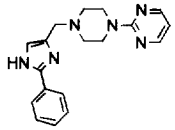
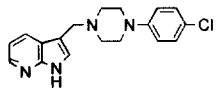
Abstract: PD 108635 (**1**) was identified as a potent dopamine D_4 ligand and we wanted to replace the benzylic alcohol with a metabolically more stable moiety. Investigations led to the discovery of a series of isoindolinones having D_4 affinity.

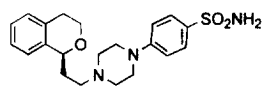
The dopamine theory of schizophrenia states that the disorder is caused by hyperactivity of the brain dopamine (DA) system.[1-4] Earlier studies showed a correlation between DA D_2 receptor affinity and the efficacy of antipsychotic drugs.[5] Through cloning studies, it has now been shown that the D_2 receptor family consists of D_2, D_3, and D_4 subtypes.[6] The highest concentration of D_4 receptors has been found in the limbic regions of the brain such as the amygdala, thalamus, hypothalamus, and cerebellum.[7] Also, the atypical antipsychotic clozapine, which lacks the extrapyramidal side effects associated with most other antipsychotics, has a higher affinity for D_4 receptors than for D_2 receptors.[8] These facts suggest that the D_4 receptor is a good target for drug treatment of schizophrenia. Recent research has led to D_4 antagonists such as NGD 94-1,[9] L-745,870,[10] U-101387,[11] and others.[12-17] Mass screening efforts in our laboratories uncovered **1** (D_4 k_i = 11.0 nM) as a potent D_4 ligand.



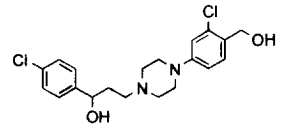
NGD 94-1



L-745,870

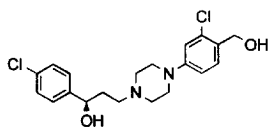


U-101387



1

The enantiomers **2** (D_4 k_i = 81.4 nM) and **3** (D_4 k_i = 8.6 nM) were prepared by chiral reduction of the corresponding ketone **4** (D_4 k_i = 60.0 nM) with DIP chloride in THF at 25 °C.[18] We found the *S*-isomer **3** to have the highest D_4 affinity.



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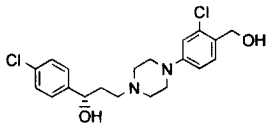

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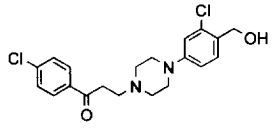

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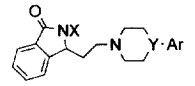

X = H, Me
Y = N, CH

5

Because benzylic alcohols are known to undergo metabolic oxidation,[19] we wanted to explore the use of the isoindolinone ring as a benzylic alcohol bioisostere. Isoindolinones **5** in which we felt the NH of the isoindolinone ring would mimic the benzylic OH of **1** were prepared. We also investigated the effect of methyl substitution on the isoindole nitrogen atom, and the effect of the stereochemistry of the isoindolinone ring on D_4 affinity.

A series of 2-H isoindolinones (**10a–i**) was prepared from the known isoindolinone acetic acid **6**[20] as shown in Scheme 1. Satisfactory conditions to reduce the acid directly to the alcohol **8** were not found, so the methyl

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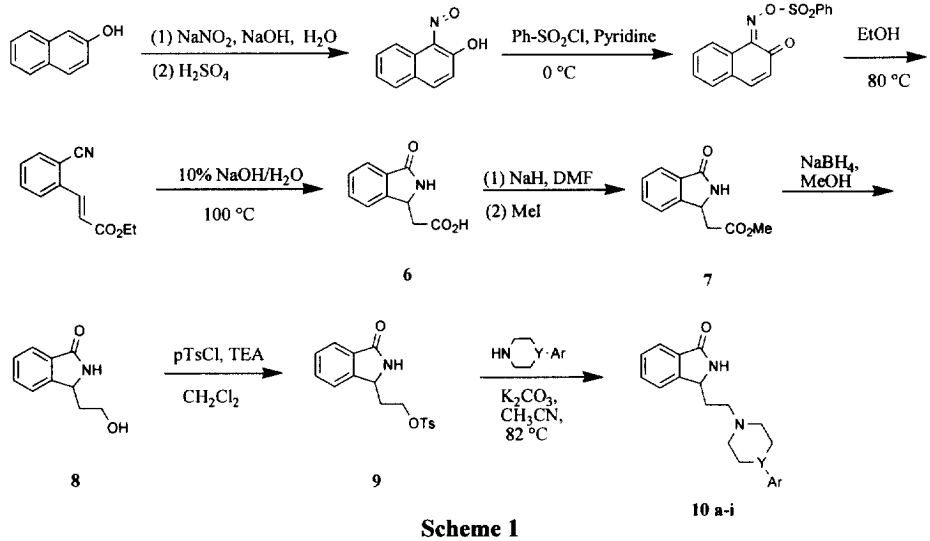
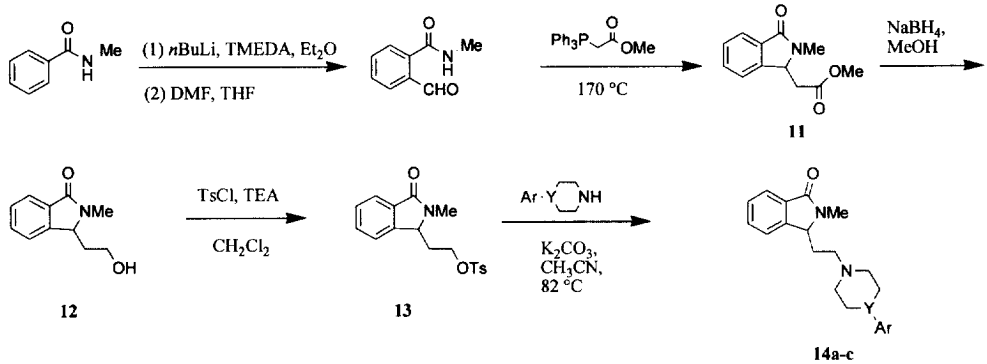
ester was prepared for reduction to the alcohol. Attempts to carry out esterification under acidic conditions led to decomposition of the ring, but basic conditions gave ester **7** in 56% yield. Reduction of **7** with $NaBH_4$ in methanol proceeded at room temperature. Care was taken to remove any trace of acid from the methanol to prevent decomposition of the $NaBH_4$. We found that stirring with 1–2 pellets of NaOH for a minute at room temperature followed by removal of the solid NaOH was satisfactory. The alcohol **8** was tosylated to give **9**, and the tosyl group was readily displaced by various phenylpiperidines and phenylpiperazines to give compounds **10a–i**.



Scheme 1

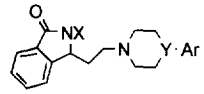
The N-methyl derivatives (**14a–c**) were prepared as shown in Scheme 2. Reduction of the ester **11**[21] followed by tosylation gave **13** in 70% yield. The tosyl group was displaced with phenylpiperazines to give **14a–c**.



Scheme 2

The compounds **10a–i**, and **14a–c** were tested for their ability to displace [^{3}H]spiperone from human DA D_2 and D_4 receptor transfected Chinese hamster ovary cells (Table 1).[22] Compounds containing substituents in the 3- and 4-positions of the phenyl ring (**10a–d**) have the highest D_4 receptor affinity. The 4-methoxy and 4-chloro compounds (**10h,i**) have only moderate affinity for the D_4 receptor.

Table 1

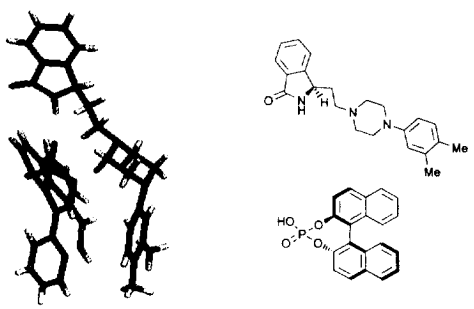


Compound	X	Y	Ar	D_2 (k_i, nM)	D_3 (k_i, nM)	D_4 (k_i, nM)
10a	H	N	3,4-dimethylphenyl	1842	2682	8.8
10b	H	CH	3,4-dimethylphenyl	1209	>3000	9.3
10c	H	N	2-naphthyl	>5000	>3000	10.0
10d	H	N	4-methylphenyl	>5000	>3000	12.4
10e	H	N	4,5-dimethyl-2-thiazolyl	>5000	>3000	20.8
10f	H	N	4-methyl-2-pyridyl	>5000	>3000	22.6
10g	H	N	phenyl	NT	2682	24.5
10h	H	N	4-chlorophenyl	>5000	>3000	27.8
10i	H	N	4-methoxyphenyl	>5000	>3000	37.3
14a	Me	N	3,4-dimethylphenyl	>5000	>3000	35.1
14b	Me	N	4-chlorophenyl	>5000	>3000	78.6
14c	Me	N	4-methoxyphenyl	>5000	>3000	333.0
		L-754870		908	>3030	0.91

Attempts to increase selectivity by substitution of a thiazolyl ring (**10e**) for the phenyl ring in **10a** decreases D_4 affinity, as does substitution of a pyridyl ring (**10f**) for the phenyl ring in **5d**. To test the theory that the N-H bond of the isoindolinone ring provides a hydrogen bond donor, we prepared three N-methyl isoindolinones (**14a–c**). In all three cases (**10a** vs. **14a**, **10h** vs. **14h**, and **10i** vs. **14c**), the N-methyl derivative has lower affinity for the D_4 receptor than the N-H derivative. This suggests that the N-H is binding to a hydrogen bonding site just as the O-H in the original PD 108635 series. Because **10a** has the greatest affinity for the D_4 receptor, we chose to separate its enantiomers. This was accomplished by fractional crystallization (2×) of the mono malic acid salts from either isopropyl alcohol (PD 172938 L-malic acid salt, $[\alpha]^{20}$ –31.3), or CH_3CN (PD 172939, D-malic acid salt, $[\alpha]^{20}$ +32).[23]

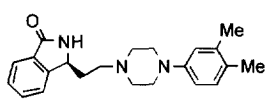
The absolute configuration of PD 172939 was determined to be *R* from the X-ray structure of its *S*-1,1′-binaphthyl-2,2′-diyl-hydrogen phosphate salt shown in Figure 1.

Figure 1. X-ray structure of PD 172939

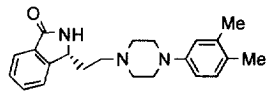


The separated enantiomers were converted to their free bases and tested for affinity at the DA, adrenergic, and serotonergic receptors (Table 2). Note that PD 172938, the *S*-enantiomer, is more potent at the D_4 receptor suggesting that the isoindolinone N-H mimics the OH in the original PD 108635 series. Note that both enatiomers have affinity for the 5HT-2 receptor. Both of the enantiomers have k_i values > 3000 nM at the D_3 receptor.

Table 2



PD 172938



PD172939

	PD 168568 [*R/S*]	PD 172938 [*S*-(–)]	PD 172939 [*R*-(+)]
D_2 (k_i, nM)	1842	5882	2748
D_4 (k_i, nM)	8.8	7.8	42
Alpha 1 (k_i, nM)	NT	343	127
Alpha2 (k_i, nM)	NT	1708	1023
5HT-1A (k_i, nM)	NT	991	525
5HT-2(k_i, nM)	NT	14.6	36.4
LMA*	49%	70%	8%

*Reversal of amphetamine (0.5 mg/kg, ip) stimulated locomotor activity at 3 mg/kg po in the rat.

The enantiomers were also tested in vivo (po administration) for their ability to inhibit amphetamine-stimulated locomotor activity in the rat[24] (Table 2). The enantiomer with the highest D_4 and 5HT-2 affinity (PD 172938) was the more effective in this test.

In summary, a series of D_4 ligands in which an isoindolinone ring has been used as a bioisostere for the benzylic alcohol moiety in the mass screen hit **1** was prepared. Our most potent compound PD 172938 inhibits amphetamine-stimulated locomotor activity in the rat, indicating possible antipsychotic activity.

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