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LETTERS

## ISOINDOLINONE ENANTIOMERS HAVING AFFINITY FOR THE DOPAMINE D<sub>4</sub> RECEPTOR

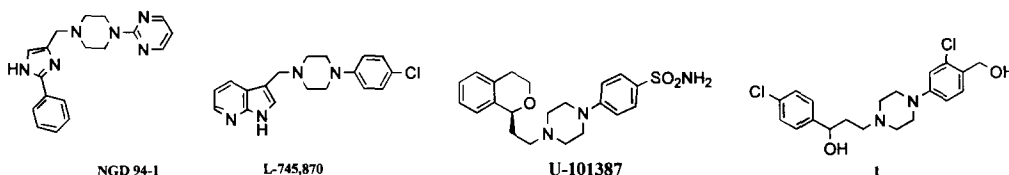
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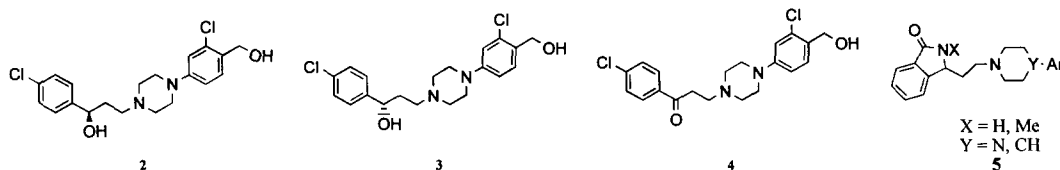
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**Abstract:** PD 108635 (**1**) was identified as a potent dopamine D<sub>4</sub> ligand and we wanted to replace the benzylic alcohol with a metabolically more stable moiety. Investigations led to the discovery of a series of isoindolinones having D<sub>4</sub> affinity. © 1998 Elsevier Science Ltd. All rights reserved.

The dopamine theory of schizophrenia states that the disorder is caused by hyperactivity of the brain dopamine (DA) system.<sup>1–4</sup> Earlier studies showed a correlation between DA D<sub>2</sub> receptor affinity and the efficacy of antipsychotic drugs.<sup>5</sup> Through cloning studies, it has now been shown that the D<sub>2</sub> receptor family consists of D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> subtypes.<sup>6</sup> The highest concentration of D<sub>4</sub> receptors has been found in the limbic regions of the brain such as the amygdala, thalamus, hypothalamus, and cerebellum.<sup>7</sup> Also, the atypical antipsychotic clozapine, which lacks the extrapyramidal side effects associated with most other antipsychotics, has a higher affinity for D<sub>4</sub> receptors than for D<sub>2</sub> receptors.<sup>8</sup> These facts suggest that the D<sub>4</sub> receptor is a good target for drug treatment of schizophrenia. Recent research has led to D<sub>4</sub> antagonists such as NGD 94-1,<sup>9</sup> L-745,870,<sup>10</sup> U-101387,<sup>11</sup> and others.<sup>12–17</sup> Mass screening efforts in our laboratories uncovered **1** (D<sub>4</sub> K<sub>i</sub> = 11.0 nM) as a potent D<sub>4</sub> ligand.



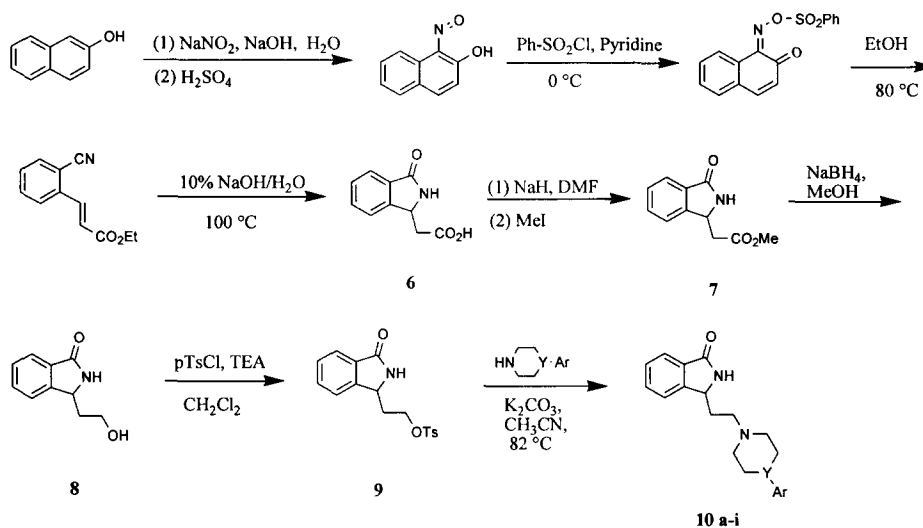
The enantiomers **2** (D<sub>4</sub> K<sub>i</sub> = 81.4 nM) and **3** (D<sub>4</sub> K<sub>i</sub> = 8.6 nM) were prepared by chiral reduction of the corresponding ketone **4** (D<sub>4</sub> K<sub>i</sub> = 60.0 nM) with DIP chloride in THF at 25 °C.<sup>18</sup> We found the *S*-isomer **3** to have the highest D<sub>4</sub> affinity.



Because benzylic alcohols are known to undergo metabolic oxidation,<sup>19</sup> 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<sub>4</sub> affinity.

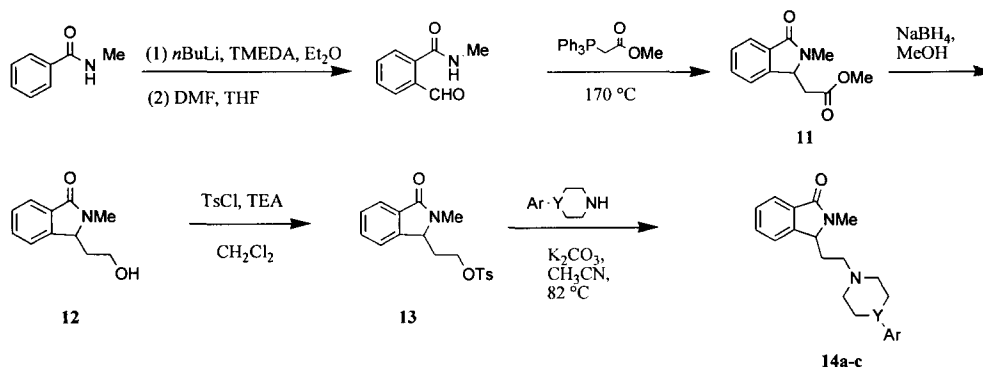
A series of 2-H isoindolinones (**10a–i**) was prepared from the known isoindolinone acetic acid **6**<sup>20</sup> as shown in Scheme 1. Satisfactory conditions to reduce the acid directly to the alcohol **8** were not found, so the methyl

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<sub>4</sub> in methanol proceeded at room temperature. Care was taken to remove any trace of acid from the methanol to prevent decomposition of the NaBH<sub>4</sub>. 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

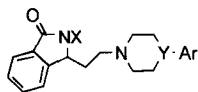
The N-methyl derivatives (**14a–c**) were prepared as shown in Scheme 2. Reduction of the ester **11**<sup>21</sup> followed by tosylation gave **13** in 70% yield. The tosyl group was displaced with phenylpiperazines to give **14a–c**.



Scheme 2

The compounds **10a–i**, and **14a–c** were tested for their ability to displace [<sup>3</sup>H]spiperone from human DA D<sub>2</sub> and D<sub>4</sub> receptor transfected Chinese hamster ovary cells (Table 1).<sup>22</sup> Compounds containing substituents in the 3- and 4-positions of the phenyl ring (**10a–d**) have the highest D<sub>4</sub> receptor affinity. The 4-methoxy and 4-chloro compounds (**10h,i**) have only moderate affinity for the D<sub>4</sub> receptor.

Table 1

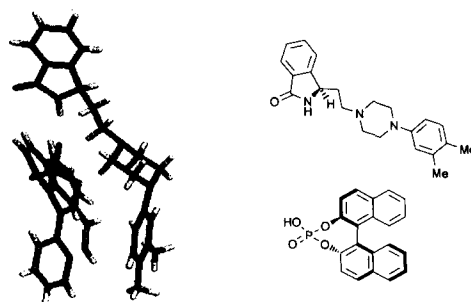


Compound	X	Y	Ar	D <sub>2</sub> (k <sub>i</sub> , nM)	D <sub>3</sub> (k <sub>i</sub> , nM)	D <sub>4</sub> (k <sub>i</sub> , nM)
10a	H	N	3,4-dimethylphenyl	1842	2682	8.8
10b	H	CH	3,4-dimethylphenyl	1209	>3000	9.3
10c	H	N	2-naphthyl	>5000	>3000	10.0
10d	H	N	4-methylphenyl	>5000	>3000	12.4
10e	H	N	4,5-dimethyl-2-thiazolyl	>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<sub>4</sub> 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. 14b, and 10i vs. 14c), the N-methyl derivative has lower affinity for the D<sub>4</sub> 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<sub>4</sub> 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, [α]<sup>20</sup> –31.3), or CH<sub>3</sub>CN (PD 172939, D-malic acid salt, [α]<sup>20</sup> +32).<sup>23</sup>

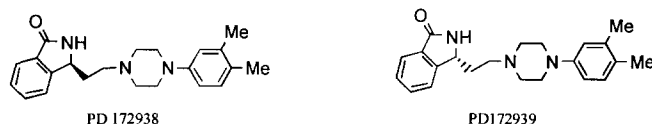
The absolute configuration of PD 172939 was determined to be *R* from the X-ray structure of its *S*-1,1'-binaphthyl-2,2'-diyl-hydrogen phosphate salt shown in Figure 1.

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<sub>4</sub> receptor suggesting that the isoindolinone N-H mimics the OH in the original PD 108635 series. Note that both enantiomers have affinity for the 5HT-2 receptor. Both of the enantiomers have k<sub>i</sub> values > 3000 nM at the D<sub>3</sub> receptor.

Table 2



	PD 168568 [R/S]	PD 172938 [S-(-)]	PD 172939 [R-(+)]
D <sub>2</sub> (k <sub>i</sub> , nM)	1842	5882	2748
D <sub>4</sub> (k <sub>i</sub> , nM)	8.8	7.8	42
Alpha 1 (k <sub>i</sub> , nM)	NT	343	127
Alpha2 (k <sub>i</sub> , nM)	NT	1708	1023
5HT-1A (k <sub>i</sub> , nM)	NT	991	525
5HT-2(k <sub>i</sub> , 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<sup>24</sup> (Table 2). The enantiomer with the highest D<sub>4</sub> and 5HT-2 affinity (PD 172938) was the more effective in this test.

In summary, a series of D<sub>4</sub> 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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