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NOVEL CYCLOHEXYL AMIDES AS POTENT AND SELECTIVE D_3 DOPAMINE RECEPTOR LIGANDS

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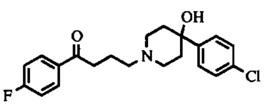
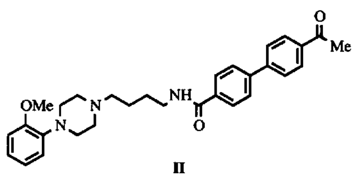
Abstract: The dopamine D_3 receptor is an attractive target for the treatment of schizophrenia. We identified PD137557 (**V**) as a ligand for the D_2 receptor and desired to prepare a selective D_3 compound. SAR studies involving different amides and different phenyl piperazines have led to the discovery of **8a** and **8c** as selective D_3 receptor ligands. © 1997 Elsevier Science Ltd.

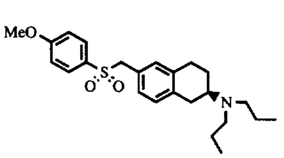
It is generally accepted that schizophrenia arises from overactivity of the brain dopamine (DA) system.[1–4] Current therapy for schizophrenia relies on neuroleptics which block dopamine receptors.[5–7] The typical antipsychotic agents on the market today, such as haloperidol (I), are D_2 antagonists and most have extrapyramidal side effects (EPS).[8]



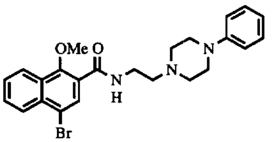
I
Haloperidol



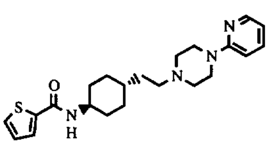
II
GR103691



III
GR218231



IV

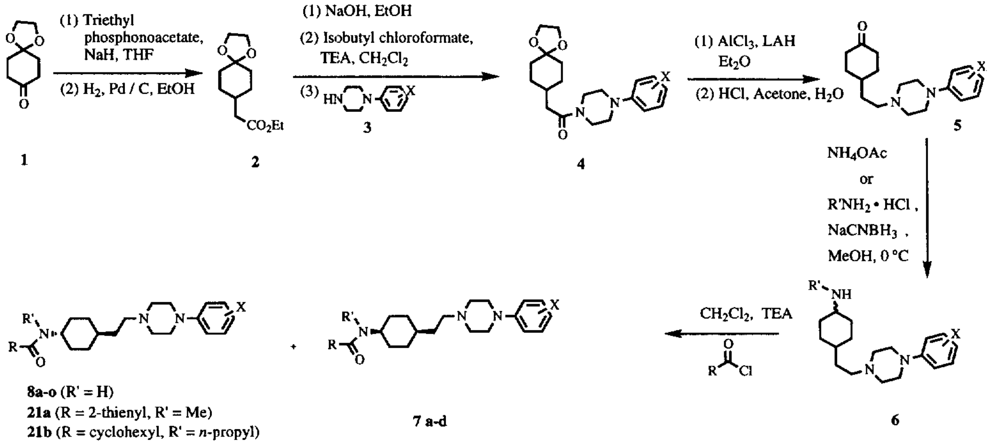


V
PD 137557

It has been shown by selective binding experiments that D_2 receptors are more concentrated in the striatal regions of the brain, which are responsible for locomotor control than in the limbic regions which are responsible for thought processes.[9–12] D_3 receptors are more concentrated in the limbic regions than the striatal regions. It is therefore believed that selective D_3 ligands may relieve symptoms of schizophrenia without causing the EPS associated with blockade of D_2 receptors.[13] Attempts by various groups to prepare such ligands have led to the synthesis of GR103691 (**II**),[14] GR218231 (**III**),[15] and the phenylpiperazine (**IV**).[16]

Our mass screening efforts have uncovered another class of phenylpiperazines (e.g., PD 137557 (**V**)) (D_3 k_i = 4.3 nM, D_2 k_i= 71 nM), which we previously disclosed (U.S. Patent 5047406), as D_2 ligands. In this paper, we describe our efforts to prepare analogs of PD 137557 that are selective for the D_3 receptor.

Compounds **7**, **21**, and **8 a–o** were prepared by the route shown in Scheme 1. The commercially available cyclohexanedione mono ethylene ketal **1** was converted to the ethyl ester **2**, which was hydrolysed and coupled with various phenyl piperidines to give amides **4**. Reduction with allane followed by deprotection of the ketone gave the amines **5**. The cyclohexylamines **6** were obtained by reductive amination with NH_4OAc as the aminating agent for R′ = H or with the corresponding primary amine hydrochloride for R′ = alkyl. Acylation of **6** with acid chlorides in CH_2Cl_2 gave mixtures of *cis* and *trans* amides which were separated by medium pressure chromatography on silica gel with mixtures of methanol (2–5%) in chloroform as the eluants.



Scheme 1

In order to assign the *cis/trans* stereochemistry, an X-ray crystal structure was done on compound **8a** (Figure 1). The rest of the compounds were assigned by comparison of the chemical shift ([1]H NMR, 400 MHz, $CDCl_3$) of the cyclohexyl proton on the carbon alpha to the amide nitrogen to the chemical shift of the same proton in **8a**. In the *trans* isomer this proton is 0.2-0.3 ppm upfield from the same proton in the *cis* isomer.

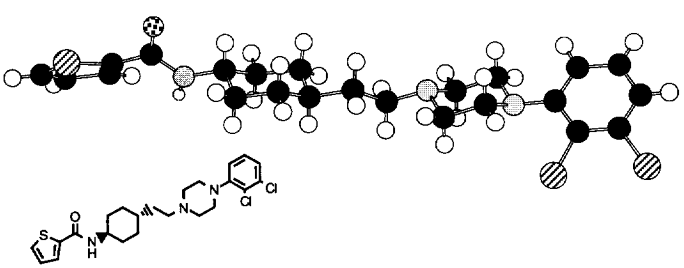
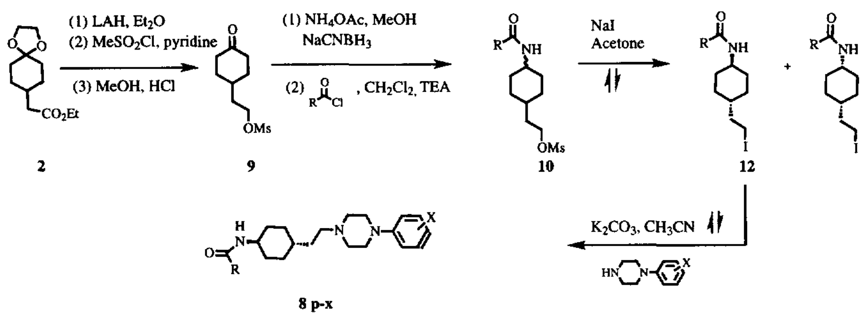


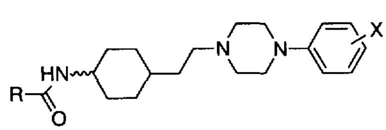
FIGURE 1

The route in Scheme 2 provided a more convergent synthesis for compounds **8 p–x** in which the phenyl piperazine ring substitution was varied. Reduction of **2** with LAH followed by mesylation of the alcohol and removal of the ketal gave **9** in 70% overall yield. Reductive amination followed by acylation gave **10** as a *cis /trans* mixture in 65% yield. Interestingly, the mesyl group survived reductive amination. This was advantageous since attempts to carry out the reductive amination with unprotected alcohol were unsuccessful. The mesylate was converted to its iodide and the *cis/trans* isomers were separated by MPLC (5% $Et_2O/CHCl_3$, silica gel). The *trans* isomers **12** were converted to the desired products, **8 p–x** in 60-70% yield.



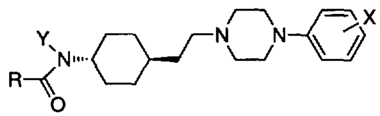
Scheme 2

Table 1



Compound	R	X	Cyclohexyl Stereochemistry	D2	D3 (ki nM)	D2/D3 (ki nM)
7a	2-thienyl	2,3 - di Cl	*cis*	18.0	1.8	10
7b	phenyl	2,3 - di Cl	*cis*	41.5	19.0	2
7c	cyclohexyl	H	*cis*	100	2.0	50
7d	2-thienyl	H	*cis*	40	25	1.6
8a	2-thienyl	2,3 - di Cl	*trans*	0.6	0.02	30
8b	phenyl	2,3 - di Cl	*trans*	4.5	4.7	1
8c	cyclohexyl	H	*trans*	38	0.14	270
8d	2-thienyl	H	*trans*	3.4	0.8	4
	R(+) 7-OH-DPAT (Standard)			0.5	0.6	1

Table 2



Compound	R	X	Y	D_2 (Ki nM)	D_3 (Ki nM)	D_2/D_3
8a	2-thienyl	2,3 - di Cl	H	0.6	0.02	30
8b	phenyl	2,3 - di Cl	H	4.5	4.7	1
8c	cyclohexyl	H	H	38	0.14	270
8d	2-thienyl	H	H	3.4	0.8	4
8e	cyclohexyl	2,3 - di Cl	H	7.4	4.5	2
8f	2-furanyl	2,3 - di Cl	H	3.0	1.4	2
8g	3-thienyl	2,3 - di Cl	H	5.0	4.7	1
8i	cyclopentyl	2,3 - di Cl	H	1.7	4.0	0.4
8j	2-(3-methylthienyl)	2,3 - di Cl	H	11.4	19.7	0.5
8k	2-(4-methylthienyl)	2,3 - di Cl	H	19.0	32.0	0.6
8l	2-(5-methylthienyl)	2,3 - di Cl	H	10.0	24.0	0.4
8m	adamantyl	2,3 - di Cl	H	339	22	15
8n	cycloheptyl	2,3 - di Cl	H	12	4.8	2.5
8o	Me	H	H	10	2.5	4
8p	2-thienyl	2 - OMe	H	1.4	0.6	2
8q	2-thienyl	3 - OMe	H	12.0	1.4	2
8r	2-thienyl	4 - OMe	H	177	12.4	14
8s	2-thienyl	2 - Cl	H	1.0	0.5	2
8t	2-thienyl	3 - Cl	H	6.5	2.0	3
8u	2-thienyl	4 -Cl	H	34	8.0	4
8v	2-thienyl	2 - Me	H	5.0	3.2	2
8w	2-thienyl	3 - Me	H	6.3	2.4	3
8x	2-thienyl	4 - Me	H	16.5	4.3	4
8y	cyclohexyl	3,4 - di Me	H	5.6	5.2	1
8z	cyclohexyl	2 - Cl	H	15	5	3
8aa	cyclohexyl	4 - Cl	H	81	15	5
8bb	cyclohexyl	3 - Cl	H	37.5	6	6
21a	2-thienyl	2,3 - di Cl	Me	16.5	4.2	3.9
21b	cyclohexyl	2,3 - di Cl	*n*-Propyl	182	85	2.1

The target compounds were tested for DA D_2 and D_3 receptor binding affinity by measuring their ability to displace radioligand from human DA D_2 and D_3 receptor transfected Chinese hamster ovary cell membranes.[17] The radioligand used for the D_2 assay was [^{3}H]-N-0437, which labels the high affinity agonist state of the receptor. Since the D_3 receptor exists predominantly in a high affinity state,[18] [^{3}H]spiperone was used for the D_3 binding assay. With the exception of **7b** and **8b** (Table 1), those with *trans* substitution on the cyclohexyl ring (**8a–8d**) were more selective for the D_3 receptor than their *cis* (**7a–7d**) counterparts.

In order to study the effects of substituents at the amide and phenyl piperazine ends of the molecule, the series of alkyl and aryl amides shown in Table 2 were prepared. Among the alkyl amides with a 2,3-di-chloro-phenylpiperazine, the cyclohexyl amide (**8e**) and the cycloheptyl amide (**8n**) had the same D_3 receptor affinity and selectivity. When the amide ring is made smaller, as in the cyclopentyl case (**8i**), the D_3 selectivity is lost due to greater affinity for the D_2 receptor. The adamantyl group (**8m**) diminishes affinity at both receptors. The cyclohexyl amide with an unsubstituted phenyl piperazine (**8c**) was the most D_3 potent and selective alkyl amide that we prepared.

The SAR of the aryl amides did not follow that of the alkyl amides. Of the aryl amides containing a 2,3-di-chloro-phenylpiperazine (**8a**, **8b**, and **8e–8n**) the most D_3 selective compound was **8a**, containing a 2-thienyl amide. Changing the thienyl ring to a 2-furanyl (**8f**) caused a loss of D_3 potency, as did changing the point of attachment to the thienyl ring (**8g**). Compounds with a methyl substituent anywhere on the 2-thienyl ring (**8j–8l**) were less potent at the D_3 receptor and therefore less D_3 selective. Substituting a phenyl ring for the 2-thienyl group (**8b**) also lowered the D_3 affinity.

In order to see if improvements could be made by changing the phenylpiperazine substituents, the series of 2-thienyl amides (**8p–8x**) was prepared. These nine compounds contain either a methoxy, chloro, or methyl group in each position (*o*, *m*, *p*) on the phenylpiperazine ring. In all three cases, the most selective compound for the D_3 receptor is the one containing the 4-substituent (**8r**, 4OMe; **8u**, 4-Cl; **8x**, 4-Me), although the effect is not as pronounced for the methyl group. Unfortunately, we were not able to prepare any aryl amide with better D_3 selectivity and affinity than **8a**.

In the case of amides **8a** and **8e** substitution at the amide nitrogen (**21a** vs **8a** and **21b** vs **8e**) greatly decreases affinity at both receptors.

Of all the compounds prepared, **8c** was the most selective for the D_3 receptor, although **8a** had the best affinity. These two compounds were found to have Ki's greater than 140 nm in adrenergic, (alpha1, alpha2) and seretonergic (5HT1a, 5HT2) binding assays. They were also tested for their ability to stimulate [^{3}H]thymidine uptake in D_3 human receptor transfected chinese hamster ovary cells.[18,19] The thienyl amide **8a** did not stimulate uptake. Compound **8c** stimulated uptake at 44% of the level of quinpirole, a known full DA agonist, indicating that it is a partial agonist. Because **8a** blocks the stimulation of **8c** it is an antagonist at the DA receptor. Because of their selectivity for the DA D_3 receptor, these two compounds are good tools for studying its function.

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