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4-HETEROCYCLYL TETRAHYDROPYRIDINES AS SELECTIVE LIGANDS FOR THE HUMAN DOPAMINE D_4 RECEPTOR.

K. E. Haworth,* T. Harrison, J. J. Kulagowski, P. D. Leeson, A. P. Owens, M. P. Ridgill, M. R. Teall, M. Fielding, K. Chapman, F. Emms, R. Marwood, S. Patel, and K.L. Moss.

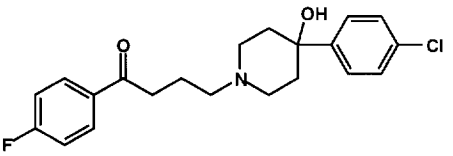
Departments of Medicinal Chemistry and Biochemistry, Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.

Abstract: A series of 1,2,3,6-tetrahydropyridines **3** were synthesised, which resulted in selective high affinity dopamine D_4 ligands. The SAR of heterocyclic replacements and aromatic substitution was investigated, leading to compounds of nanomolar binding affinity with excellent selectivity over both D_2 and D_3 receptors.

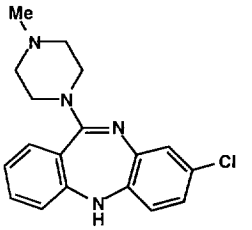
Schizophrenia is a serious and debilitating mental illness for which there is still a great need for a superior drug therapy. Classical neuroleptics, such as haloperidol **1**, are currently used for the treatment of schizophrenia, but their use is associated with severe mechanism-related side effects, including induction of acute extrapyramidal symptoms (EPS).[1] The atypical antipsychotic agent clozapine **2** does not induce EPS and may also be used to treat the more resistant negative symptoms of schizophrenia,[2] however its use is limited due to a 1-2% incidence of agranulocytosis,[3] a potentially fatal blood disorder, thus necessitating close monitoring of patient drug plasma levels. Classical neuroleptics are believed to act primarily as antagonists at the dopamine D_2 receptor;[4] however, clozapine has higher affinity for the D_4 receptor than for the D_2 receptor.[5] An association between the D_4 receptor and schizophrenia was also suggested by Seeman,[6] thus highlighting the need for selective D_4 antagonists to investigate their potential in the treatment of schizophrenia.

Recent work in this laboratory[7] led to the identification of L-745,870, an antagonist with high selectivity and affinity for the human dopamine D_4 receptor. On the basis of this lead, a series of novel 1,2,3,6-tetrahydropyridines **3** were prepared as potential D_4 antagonists.

Fax: +44 1279 440390; e-mail: janusz_kulagowski@merck.com



1



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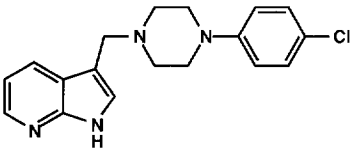
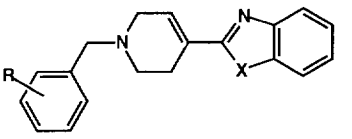


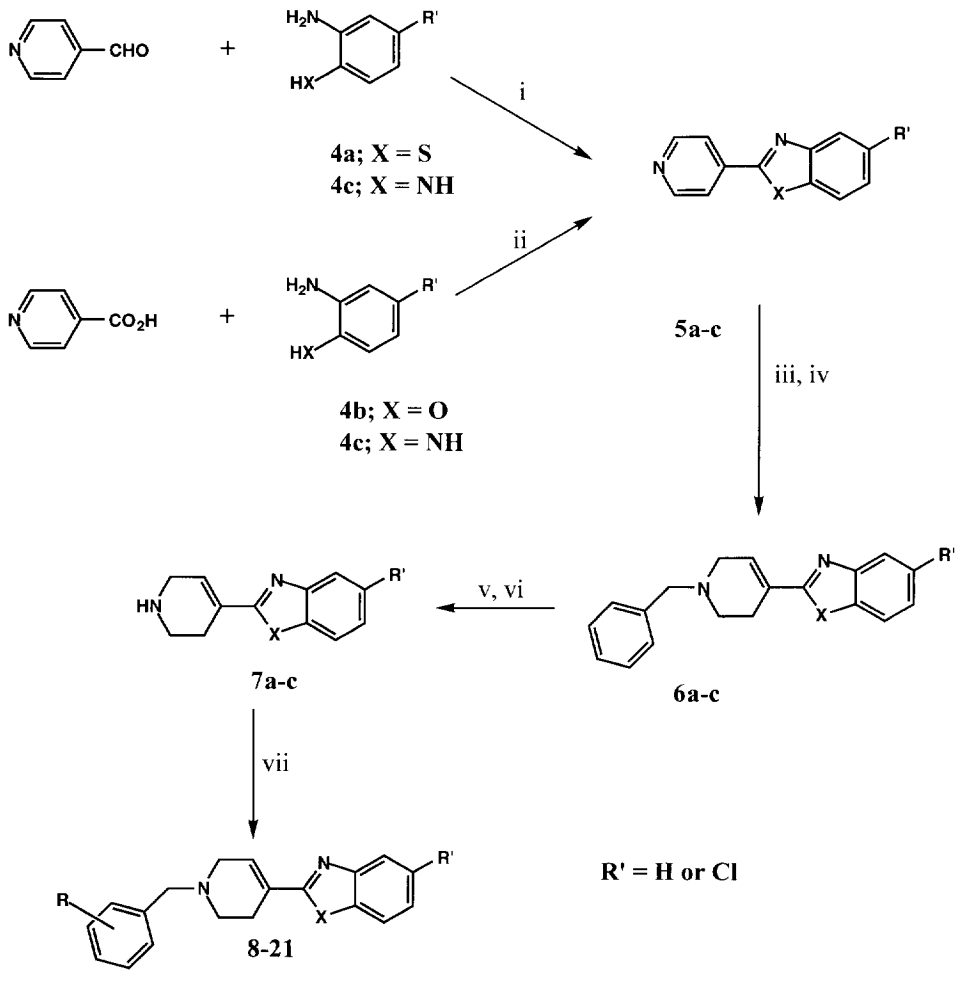
L-745,870



3a; X = S
3b; X = O
3c; X = NH

Synthesis

The required heterocycles were synthesised by one of two methods, employing either 4-pyridinecarboxaldehyde or 4-pyridinecarboxylic acid, to give the intermediates **5a-c** (Scheme 1). 2-(Pyridin-4-yl)benzothiazole **5a** was synthesised by reaction of 2-aminothiophenol with 4-pyridinecarboxaldehyde in DMSO at 200°C.[8] 2-Hydroxyaniline and isonicotinic acid in 1,2-dichlorobenzene were treated with trimethylsilyl polyphosphate (TMSPP) at 190°C for 2 hours to give 2-(pyridin-4-yl)benzoxazole **5b**.[9] 2-(Pyridin-4-yl)benzimidazole **5c** was synthesised using either route, starting from 1,2-diphenylenediamine. Quaternisation of the pyridines (**5a-c**) with benzyl bromide in DMF at reflux followed by reduction with sodium borohydride in ethanol at room temperature afforded **6a-c**. Debenzylation was achieved using 1-chloroethyl chloroformate in dichloromethane followed by hydrolysis of the intermediate chloroethyl carbamate in refluxing methanol.[10] The resulting tetrahydropyridines (**7a-c**) were then alkylated with a variety of benzyl bromides or benzyl chlorides to give the compounds (**8-21**) listed in Table 1. Compounds which are substituted on the phenyl ring were synthesised in an analogous manner, starting from the appropriate substituted aniline.



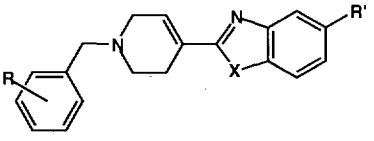
Reagents and conditions: i) DMSO, 200°C (85%); ii) TMSPP, 1,2-dichlorobenzene, 170°C (75%); iii) DMF, reflux, benzyl bromide; iv) $NaBH_4$, EtOH (70%); v) $CH_3CH(Cl)OCOCl$, CH_2Cl_2, 0°C; vi) MeOH, reflux (84%); vii) K_2CO_3, DMF, substituted benzyl bromide

Scheme 1

Discussion

For the novel 1,2,3,6-tetrahydropyridines of this study, receptor binding was determined by displacement of [^{3}H]spiperone from cloned human receptors, D_2 and D_3 being stably expressed in CHO cells[11] and D_4 in HEK293 cells[12]. In the benzimidazole series, substitution on the benzyl ring (**9**) had a marginal effect on both

Table 1: Dopamine Receptor Subtype Affinity of 1,2,3,6-tetrahydropyridines.



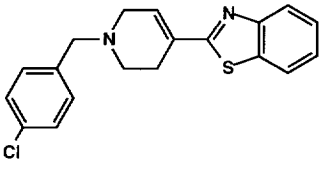
Compound[b]	X	R	R'	Ki(nM)[a] hD_2	hD_3	hD_4	D_2/D_4
8	NH	H	H	1400	4400	94	15
9	NH	4-Cl	H	670	1600	68	10
10	NH	H	Cl	590	2900	26	23
11	NH	4-Cl	Cl	330	900	10	33
12	O	H	H	240	4500	97	3
13	O	H	Cl	>1800	1600	17	>100
14	O	4-Cl	Cl	>1700	>4500	8.4	>200
15	S	H	H	600	560	5.0	120
16	S	H	Cl	>1600	1800	44	>36
17	S	4-Cl	Cl	2000	660	21	97
18	S	2-Cl	H	>2000	1400	87	23
19	S	3-Cl	H	340	630	8.1	42
20	**S**	**4-Cl**	**H**	**>1600**	**>4400**	**1.3**	**>1000**

[a] Data are the mean of two to four independent determinations.
[b] All new compounds were characterized by ^1H NMR and mass spectroscopy and gave satisfactory elemental analyses.

D_4 affinity and D_2/D_4 selectivity compared to the parent compound **8**. Substitution in the benzimidazole phenyl ring (**10**) however, leads to a 4-fold increase in D_4 affinity, and combining the two substitutions affords a compound (**11**) with moderate D_4 affinity (*Ki* 10nM) and good D_2/D_4 selectivity. The same trend in D_4 affinity is observed in the benzoxazole series (**12-14**). In this case, however, a significant loss in D_2 affinity is observed, which results in much improved D_2/D_4 receptor selectivity.

The unsubstituted compound in the benzothiazole series **15** was more active and selective than the corresponding compounds in either of the other two series. However, in contrast with the benzimidazole and benzoxazole series, substitution in the phenyl ring in the benzothiazole series (**16**) was detrimental to affinity at all the receptor subtypes, and when coupled with substitution of the benzyl group (**17**) gave no significant improvement in D_4 affinity (*Ki* 21nM) over(**15**). The influence of aromatic substitution in the pendant benzyl group on receptor affinity and selectivity of **15** was further probed by the introduction of chlorine atoms in the *ortho*, *meta* and *para* positions . Thus, *ortho* substitution resulted in reduced binding affinities at all three receptors (**18**), while *meta* substitution was tolerated (**19**), but afforded no advantage over the parent compound **15**. *Para* substitution however resulted in a compound (**20**) with a 4-fold increase in D_4 affinity over **15** (*Ki* 1.3nM) and remarkable selectivity (>1000) over both the D_2 and D_3 receptors. These excellent *in vitro* properties of **20** prompted the evaluation of its pharmacokinetic profile in rat and rhesus monkey (Table 2).

Table 2: Pharmacokinetic profile of **20** in rat and rhesus monkey.



	Rat	**Rhesus**
Dose i.v.	3 mg/kg	1 mg/kg
p.o	5 mg/kg	1 mg/kg
Bioavailability (F)	17 %	9 %
Plasma clearance (Clp)	39 ml/min/kg	
Half life ($T_{1/2}$)	3.1 hr	4.7 hr
Volume of distribution (Vss)	3.8 l/kg	2.5 l/kg
Maximum conc. in plasma (Cmax)	97 ng/ml	23 ng/ml

In conclusion, a series of 4-heterocyclyl tetrahydropyridines have been shown to be high affinity, selective ligands for the dopamine D_4 receptor subtype. In particular, 4-(benzothiazol-2-yl)-1-(4-chlorobenzyl)-1,2,3,6-tetrahydropyridine (**20**) with a *Ki* of 1.3nM at the D_4 receptor, >1000 fold selectivity over hD_2 and hD_3, and with an acceptable pharmacokinetic profile (Table 2) in both rat and rhesus monkey, represents an excellent pharmacological tool for evaluating the outcome of D_4 antagonism *in vivo*.

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