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4-N-*linked*-Heterocyclic Piperidine Derivatives with High Affinity and Selectivity for Human Dopamine D_4 Receptors

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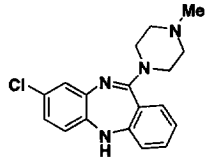
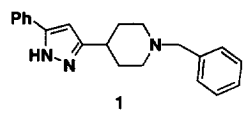
Abstract: The syntheses of a number of different N-linked heterocyclic pyrazole replacements based on the structure **1** are described (compounds **3-12**) as hD4 ligands. After further optimisation the best compound identified was **13** which has high affinity for hD4 (5.2 nM) and >300-fold selectivity for hD4 receptors over hD2 and hD3 receptors.

The current treatment of choice for schizophrenia is the chronic administration of neuroleptics or antipsychotic drugs but these compounds can be poorly tolerated due to extrapyramidal motor side effects.[1] The recent discovery that the atypical antipsychotic clozapine, which does not induce extrapyramidal motor side effects,[2] has higher affinity for human dopamine D_4 (hD_4) receptors than human dopamine D_2 (hD_2) receptors together with reports that hD_4 receptor density is apparently elevated in postmortem schizophrenic brain,[3] has driven the search for selective hD_4 antagonists.[4]



Clozapine



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Our group recently described the synthesis and biological activity of a series of carbon linked heterocyclic 4-piperidinyl derivatives as potent and selective ligands for the human dopamine D_4 receptors.[5] The carbon linked pyrazole derivative **1**[5] was demonstrated to have good affinity for hD4 receptors (11 nM, Table 1) with six fold selectivity for hD4 over hD2. In an attempt to improve hD4 affinity and selectivity, a series of nitrogen linked heterocycles have been synthesized and evaluated for human dopamine subtype selectivity and affinity.

The starting material for the preparation of the pyrazole derivatives **3,4**, and **13-16** was N-^{t}butyloxycarbonyl 4-hydroxypiperidine (**17**) which was converted to the mesylate (**18**) and the leaving group was displaced using the anion of 3-methyl-4-phenylpyrazole to give a mixture of regioisomers in the ratio of 1:1.3 (**19** and **20**, Scheme 1). The isomers were separated using flash chromatography and independently treated with hydrogen chloride in diethyl ether to yield the versatile intermediates **21** and **22** whose respective regiochemistry was determined by NOE experiments.[6] These intermediates were then alkylated with the appropriate alkyl halide to give the required compounds. The imidazole derivative (**7**) and tetrazole derivative (**12**) were prepared in a similar manner, except reacting 5-phenyl imidazole and 5-phenyl tetrazole respectively with **18** in the second step.[7]

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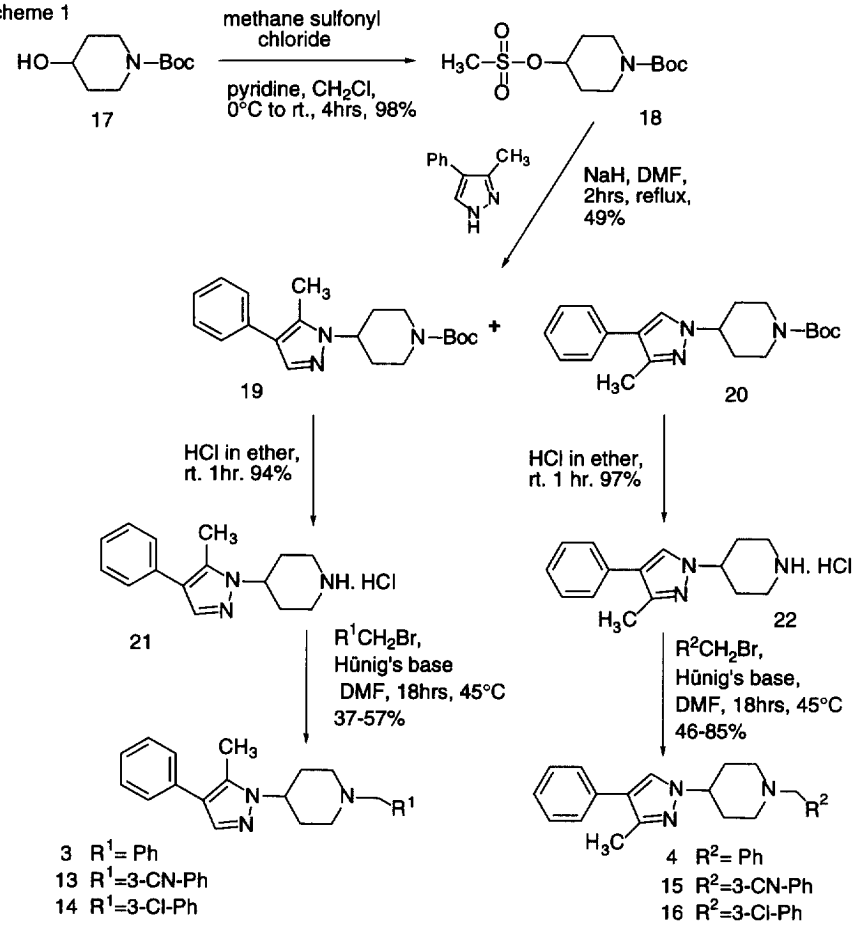
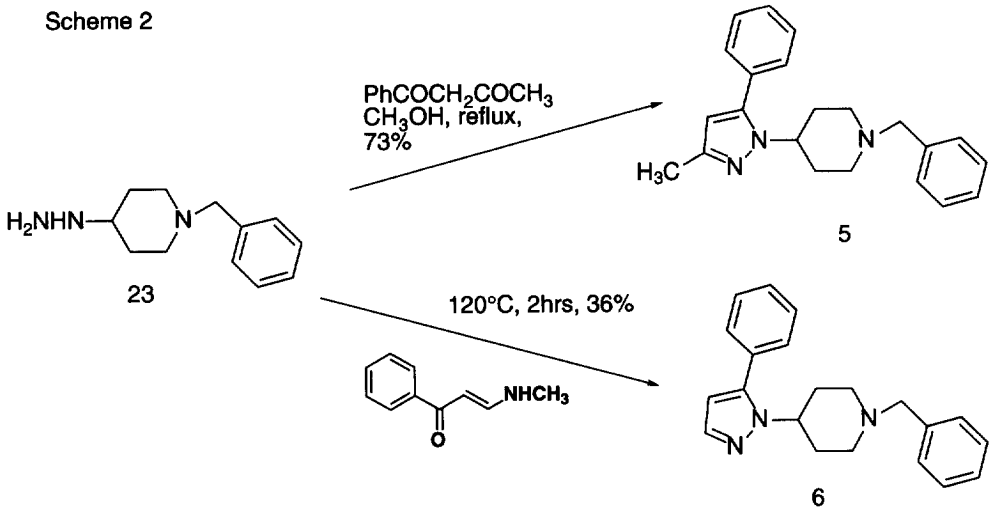
To prepare the pyrazole derivatives **5** and **6** N-benzyl-4-hydrazinopiperidine (**23**) was condensed with either benzoylacetone or 3-(methylamino)acrylophenone (Scheme 2). The 1,2,3-triazole derivatives **8** and **9** were prepared as outlined in Scheme 3. Triazole ring construction was achieved by a cycloaddition reaction between the azide **25** and phenyl propyne at high temperature to yield a 2:1 mixture of regioisomers. These compounds were inseparable by chromatography so the mixture was treated with hydrogen chloride in diethyl ether to remove the amine protecting group and then alkylated with benzyl bromide. The regioisomers were then separated using chromatography to give the required compounds **8** and **9** whose structures were assigned by NOE experiments. Compound **10** was prepared in an analogous way except using phenylacetylene in the cycloaddition step.

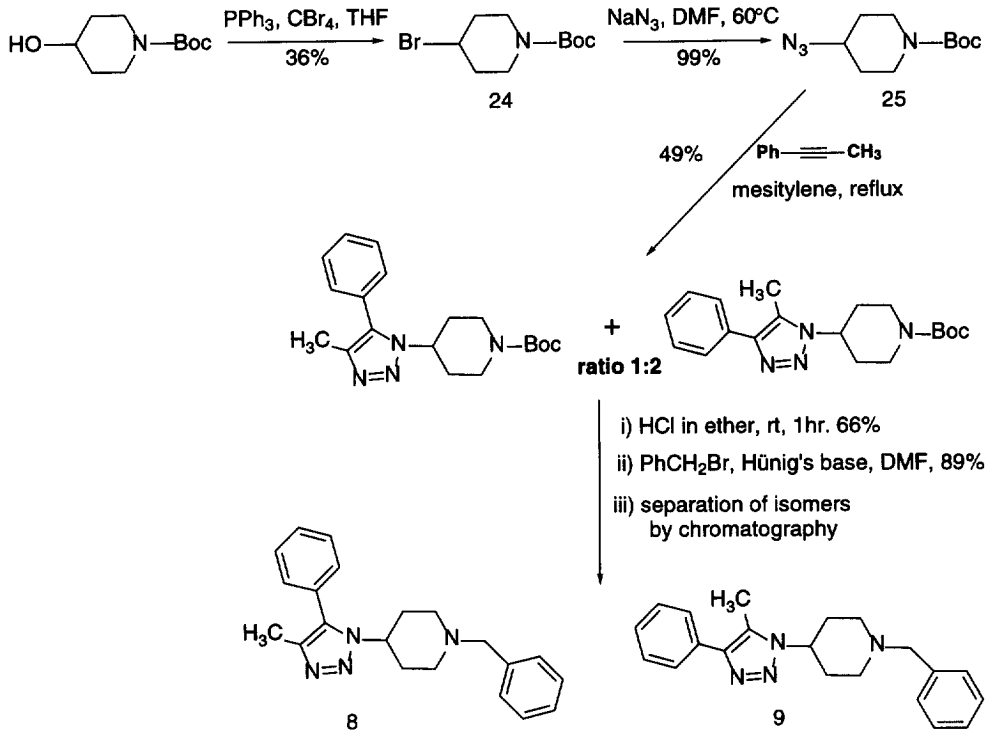
Scheme 1



Scheme 2

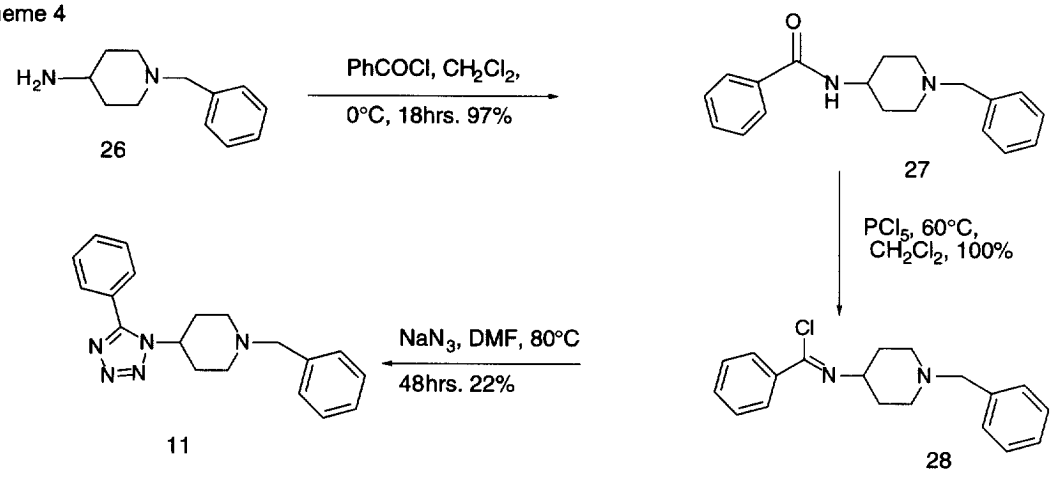


Scheme 3



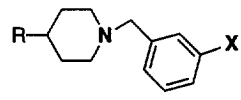
The tetrazole **11** was prepared from 4-amino-N-benzyl-piperidine (**26**) by acylation with benzoyl chloride to give the benzamide **27**, followed by conversion to the chloroimidate **28** with phosphorus pentachloride (Scheme 4). Treatment with sodium azide at 80°C in dimethylformamide caused displacement of chloride followed by ring closure to give the required product.

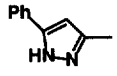
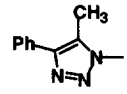
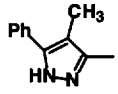
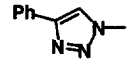
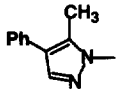
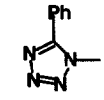
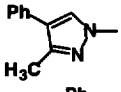
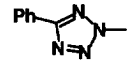
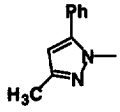
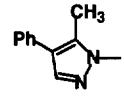
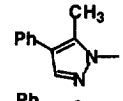
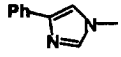
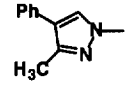
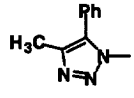
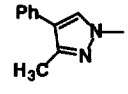
Scheme 4



The compounds were evaluated for their ability to displace [^{3}H]spiperone from human cloned receptors, hD2 stable expressed in CHO cell[8], hD3 and hD4 in HEK-293 cells.[9] As observed previously with close analogues,[5] the introduction of a methyl group to the 4-position of the pyrazole ring of **1** to give **2** results in improved affinity (Ki 4.7 nM) and selectivity (~20 fold) for hD4. The corresponding N-linked pyrazole **3** also has high affinity for hD4 (Ki 2.5 nM) and has good selectivity for hD4 over hD2 (56-fold). On transposing the methyl group from the 5- to the 3-position of the pyrazole to give compound **4**, affinity is increased to give a highly potent hD4 ligand (Ki 0.39 nM) but selectivity over hD2 is only 16-fold. Moving the 4-phenyl group in compound **4** to the 5-position (**5**) results in 350-fold loss of hD4 affinity but deletion of the 3-methyl group to give **6** regains some hD4 affinity (~10-fold, Ki 15 nM) and produces >30-fold selectivity over hD2. The N-linked imidazole **7** is 4-fold lower in affinity at hD4 than the lead pyrazole **1** and shows comparable selectivity. On addition of a nitrogen atom to the pyrazole **3** (Ki 2.5 nM), to give the 1,2,3-triazole **9**, decreased hD4 affinity is observed (Ki 17 nM) but comparable selectivity over hD2 is retained. The regioisomer **8** shows no significant difference in its human dopamine binding profile and even deletion of the 5-methyl group of **9** to give **10** has only a marginal effect on hD4 affinity and selectivity. The 2-linked-5-phenyl tetrazole 12 (Ki 27 nM) also has a comparable binding profile to the triazoles **9** and **10**.

Table 1

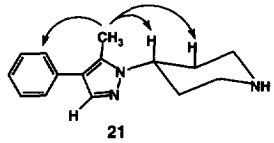


No	R	X	Ki (nM) hD_2	hD_3	hD_4	No	R	X	Ki (nM) hD_2	hD_3	hD_4
	Clozapine		74	200	10						
1		H	66	1400	11	9		H	1600	2500	17
2		H	90	450	4.7	10		H	460	1300	32
3		H	140	450	2.5	11		H	>1800	>4400	1200
4		H	6.1	28	0.39	12		H	1100	1400	27
5		H	310	3000	140	13		CN	>1700	4400	5.2
6		H	510	810	15	14		Cl	370	820	3.1
7		H	450	740	40	15		CN	15	260	1.2
8		H	1200	2200	18	16		Cl	15	120	3.1

Of all the different N-linked heterocycles investigated (compounds **3-12**) the highest affinity compounds were the N-linked pyrazoles **3** and **4**, and these were chosen for further optimisation studies. By analogy with SAR uncovered in an analogous series of compounds,[10] *meta*-cyano and *meta*-chloro substitution improved selectivity in the 5-methyl-4-phenyl pyrazole cases (**13** and **14**) but had no effect in the 3-methyl-4-phenyl pyrazoles (**15** and **16**, Table 1).

In conclusion, we have described the syntheses of a number of different N-linked heterocylic piperidine derivatives, the best compound being **13** which has high affinity for hD4 (5.2nM) and >300 selectivity for human dopamine D4 receptors over human dopamine D2 & D3 receptors.

References

1. Baldessarini, R.J.; Tarsey, D. Dopamine and the pathophysiology of dyskinesias induced by antipsychotic drugs. *Annu.Rev. Neurosci.* **1980**, *3*, 23.
2. Ashby, C.R.; Wang, R. Y. Pharmacological action of the atypical antipsychotic drug clozapine. *Synapse,* **1996**, *24,* 349-394.
3. (a) Seeman, P.; Guan, H. C.; Van Tol, H. M. Dopamine D4 receptors elevated in schizophrenia. *Nature,*.**1993**, *365,* 441-445.
   (b) Reynolds, G. P.; Mason, S. L. Are striatal dopamine D4 receptors increased in schizophrenia?*J. Neurochem.* **1994**, *63*, 1576-1577.
   (c) Stefanis, N. C.; Bresnick, J. N.; Kerwin, R. W.; Schofield, W.N.; McAllister, G. Elevation of D4 dopamine receptor mRNA in postmortem schizophrenic brain. *Mol. Brain Res.*, **1998**, *53*, 112-119.
4. (a) Hadley, M. S. D4 Receptors and their antagonists. *Med. Res. Rev.*, **1996**, *16*, 507-526.
   (b) Kulagowski, J. J.; Patel, S. *Current Pharm. Des.* **1997**, *3*, 355-366.
   (c) Liegeois, J. F.; Eyrolles, L.; Bruhwyler, J.; Delarge, J. Dopamine D4 receptors: A new opportunity for research on schizophrenia. *Current Med. Chem.* **1998**, *5*, 77-100.
5. Rowley, M.; Collins, I. Broughton, H. B.; Davey, W.D.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Freedman, S.; Leeson, P. D. 4-Heterocyclylpiperidines as selective high-affinity ligands at the Human Dopamine D4 Receptor. *J. Med. Chem.* **1996**, *39,* 2374-2385.
6. 

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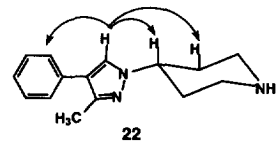

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7. Carling, R.W.; Leeson, P. D.; Moore, K. W. 5-Membered heteroaromatic compounds as dopamine antagonists. WO 9621660 (1996).
8. Freedman, S.B.; Patel, S.; Marwood, R.; Emms, F.; Seabrook, G.R.; Knowles, M.R.; McAllister, G. Expression and pharmacological characterisation of the human D3 dopamine receptor. *J. Pharmacol. Exp. Ther.* **1994,** *286,* 417-426. Marwood, R.; Emms, F.; Patel, S.; Smith, G.R.; Seabrook, G.R.; Freedman, S.B. Functional coupling of human D2, D3, and D4 dopamine receptors in HEK293 cells. *J. Recep. Sig. Trans. Res.* **1995**, *15*, 267-281.
9. McAllister, G.; Knowles, M. R.; Wrad-Booth, S. M.; Sinclair, H. A.; Patel, S. Marwood, R.; Emms, F.; Patel, S.; Smith, G. R.; Seabrook, G. R.; Freedman, S. B. Functional coupling of human D2, D3, and D4 dopamine receptors in HEK293 cells. *J. Recept. Sig. Trans. Res.* **1995**, *15*, 267-281.
10. Carling, R.W.; Moore, K. W.; Moyes, C. R.; Jones, E. A.; Bonner, K.; Emms, F.; Marwood, R.; Patel, S.; Patel,; S.; Beer, M.; Sohal, B.; Pike, A.; and Leeson, P. D. 1-(3-Cyanobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydro-imidazol-2-one: A Selective High Affinity Antagonist for the Human Dopamine D4 Receptor with Improved Selectivity over Ion Channels. *J. Med. Chem. (submitted).*