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SYNTHESIS AND SAR OF 2- AND 3-SUBSTITUTED 7-AZAINDOLES AS POTENTIAL DOPAMINE D_4 LIGANDS

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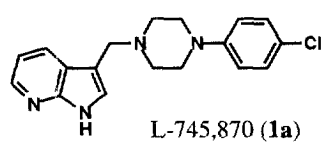
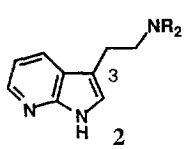
Abstract: 7-azaindole compounds bearing a cyclic amine moiety linked by a one or two carbon chain attached at the 2- or 3-position were synthesised and evaluated as potential dopamine D_4 ligands. Highest affinity and selectivity for the D_4 receptor resided in the 3-aminomethyl-7-azaindole series.

The dopaminergic system is thought to play a key role in the manifestation of schizophrenic illness,[1] a belief supported by the observation that clinically effective antipsychotic agents act as antagonists at the dopamine D_2 receptor.[2] The discovery of two new dopamine receptor subtypes with close homology to the D_2 receptor, designated D_3 and D_4,[3] and the disclosure of preferential binding of the atypical antipsychotic drug clozapine to the D_4 receptor[4] has elicited considerable interest.[5] These intriguing findings prompted us to initiate a programme to identify a selective D_4 antagonist for evaluation in the clinic, leading to the discovery of the pyrrolo[2,3-b]pyridine (7-azaindole) L-745,870 (**1a**).[6-10]

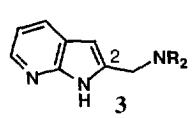
As a continuation of our study of 7-azaindole compounds as potential D_4 ligands we sought to investigate variation of the length (one or two carbon atoms) and position of attachment (C-2 or C-3) of the chain linking the heterocycle and the cyclic amine moiety. In this letter we describe the synthesis and dopamine receptor subtype binding affinities of examples of alternative 7-azaindole structures **2**, **3** and **4**.



L-745,870 (**1a**)



2



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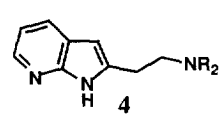

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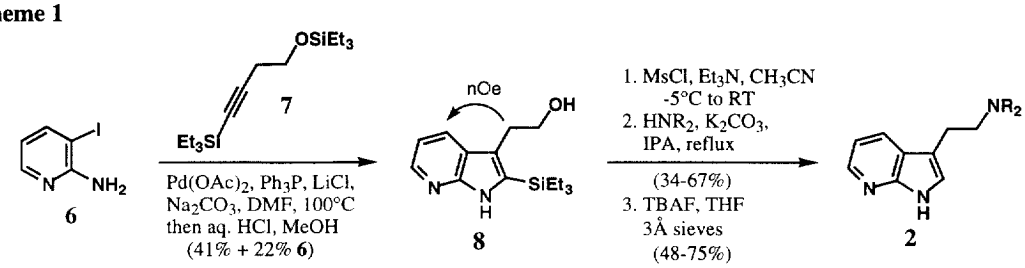
Chemistry

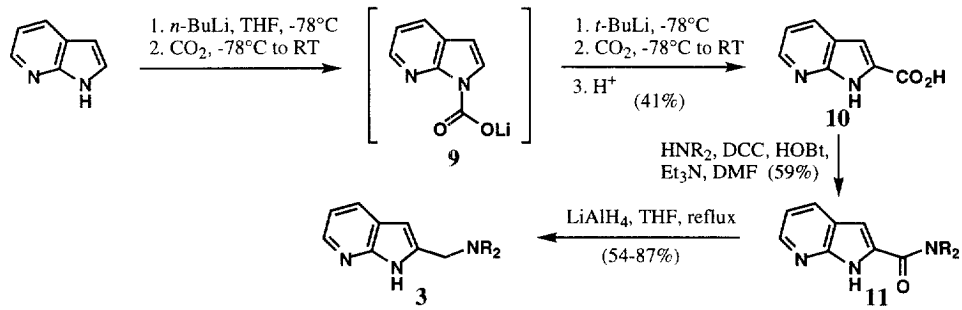
L-745,870 (**1a**) and analogues (**1b-d**) were readily prepared by Mannich reaction or displacement of 7-azagramine (**5**).[6] We envisaged that the homologated C-3 linked compounds **2** would be available by extension of the Larock indole methodology,[11] recently used for synthesis of the 5-HT_{1D} receptor agonist MK-0462,[12] to 7-azaindole preparation.[13] Thus, 2-amino-3-iodopyridine (**6**)[14] was reacted with protected acetylene **7**[12] to afford a modest yield of azatryptol **8**, as the only regioisomer observed (**Scheme 1**). The expected regiochemistry[11,12] was confirmed by nOe experiment. The alcohol **8** was activated as the mesylate, displaced by the appropriate cyclic amine and the azaindole desilylated to give **2**. It is noteworthy that the C-2 triethylsilyl group was stable to HCl-MeOH conditions, in contrast to related indole compounds.[12]

Scheme 1



Synthesis of the 2-aminomethyl compounds **3** was accomplished by amine coupling of 7-azaindole-2-carboxylic acid (**10**) and subsequent reduction of amide **11** (**Scheme 2**). The acid **10** was prepared from 7-azaindole *via* directed lithiation of the 1-carboxylate protected intermediate **9**.[15]

Scheme 2



The 2-aminoethyl-7-azaindoles **4** were prepared by reaction of the dilithio species derived from 2-*tert*-butylcarbonylamino-3-methylpyridine (**12**) with an amino ester **13**, followed by treatment with hydrochloric acid, in a modification of a recently published method (**Scheme 3**).[16] The yields for this procedure were low due to competing side reactions and were not optimised, although replacing amino ester **13** with the corresponding Weinreb amide was unsuccessful.[16]

Scheme 3

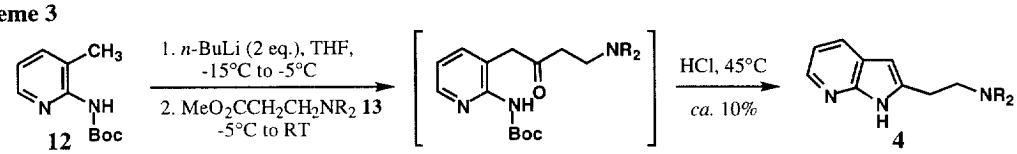
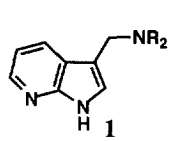
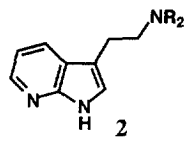


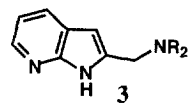
Table - Human dopamine D_2, D_3 and D_4 receptor binding affinities of 7-azaindole compounds



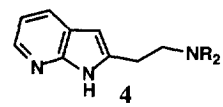
1



2



3



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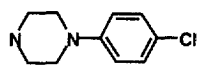
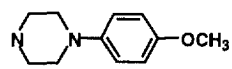
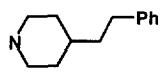
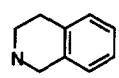
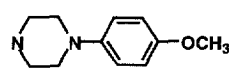
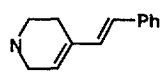
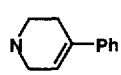
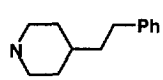
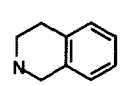
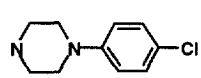
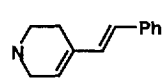
Compound[§]	NR_2	K_i (nM)[#] hD_2	hD_3	hD_4
1a (L-745,870)		960	2300	0.43
1b		>1500	3900	1.3
1c		1100	1300	1.8
1d		640	170	7.0
2a		900	530	26
2b		280	180	6.5
2c[†]		21	10	34
3a		200	250	2.0
3b		600	1100	59
4a		800	50	11.7
4b		1300	25	30

[#] Data are the mean of two to four independent determinations

[§] All new compounds were characterised by ^1H NMR and mass spectroscopy and gave satisfactory CHN analysis

[†] Single determination

Results and Discussion

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 and D_4 in HEK293 cells.[7] Data on L-745,870 (**1a**)[6] and analogues (**1b-d**) are shown to exemplify the D_4 selectivity achieved in this (3-aminomethyl-7-azaindole) series with a range of cyclic amine side chains (see **Table**).

Homologation of **1** to give the corresponding 3-aminoethyl-7-azaindoles **2** gave reduced hD_4 binding affinity, whilst retaining modest selectivity over hD_2 and hD_3 in the case of **2a** and **2b** (*c.f.* **1b** and **1c**). The phenyltetrahydropyridine **2c** was non-selective as a consequence of increased hD_2 and hD_3 affinity.

The 2-substituted 7-azaindole **3a** displayed comparable hD_4 binding to the corresponding 3-substituted analogue **1c**, although lower selectivity, whereas the tetrahydroisoquinoline **3b** showed reduced hD_4 affinity compared to **1d**. An arylpiperazine side chain was not evaluated in this series.

The 2-aminoethyl compounds **4a** and **4b** had reduced hD_4 affinity compared to **1a** and **1c** (in common with the analogous 3-aminoethyl analogues **2a** and **2b** described above). However, hD_3 affinity was improved some 50-fold in each case, an interesting finding given the poor D_3 activity shown by most of the other 7-azaindole compounds prepared.

Conclusion

The alternative 7-azaindole compounds **2-4** investigated generally gave poorer human dopamine D_4 receptor affinity than the corresponding 3-aminomethyl-7-azaindoles **1** (exemplified by L-745,870, **1a**), although some degree of selectivity over hD_2 was retained in many of the compounds disclosed here.

Acknowledgements: We are indebted to Paul Mitchell for the synthesis of compound **2a** (by an alternative route to that described here) and to Steve Thomas for conducting the nOe experiment.

References and Notes

1. Seeman, P. *Synapse* **1987**, *1*, 133.
2. Seeman, P. *Neuropsychopharmacology* **1992**, *7*, 261.
3. (a) Sibley, D.R.; Monsma F.J., Jr. *TiPS* **1992**, *13*, 61; (b) Grandy, D.K.; Civelli, O. *Curr. Opin. Neurobiol.* **1992**, *2*, 275; (c) Seeman, P.; Van Tol, H.H.M. *TiPS* **1994**, *15*, 264.
4. Van Tol, H.H.M.; Bunzow, J.R.; Guan, H-C.; Sunahara, R.K.; Seeman, P.; Niznik, H.B.; Civelli, O. *Nature* **1991**, *350*, 610.
5. (a) Kulagowski, J.J.; Patel, S. *Curr. Pharm. Design* **1997**, *3*, 355; (b) Liegeois, J.-F.; Eyrolles, L.; Bruhwyler, J.; Delarge, J. *Curr. Med. Chem.* **1998**, *5*, 77.
6. Kulagowski, J.J.; Broughton, H.B.; Curtis, N.R.; Mawer, I.M.; Ridgill, M.P.; Baker, R.; Emms, F.; Freedman, S.B.; Marwood, R.; Patel, Shil; Patel, Smita; Ragan, C.I.; Leeson, P.D. *J. Med. Chem.* **1996**, *39*, 1941.
7. Patel, S.; Freedman, S.; Chapman, K.L.; Emms, F.; Fletcher, A.E.; Knowles, M.; Marwood, R.; McAllister, G.; Myers, J.; Patel, S.; Curtis, N.; Kulagowski, J.J.; Leeson, P.D.; Ridgill, M.; Graham, M.; Matheson, S.; Rathbone, D.; Watt, A.P.; Bristow, L.J.; Rupniak, N.M.; Baskin, E.; Lynch, J.J.; Ragan, C.I. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 636.
8. Bristow, L.J.; Collinson, N.; Cook, G.P.; Curtis, N.; Freedman, S.B.; Kulagowski, J.J.; Leeson, P.D.; Patel, S.; Ragan, C.I.; Ridgill, M.; Saywell, K.L.; Tricklebank, M.D. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1256.
9. Kramer, M.; Last, B.; Zimbroff, D.; Hafez, H.; Alpert, M.; Allan, E.; Rotrosen, J.; McEvoy, J.; Kane, J.; Kronig, M.; Merideth, C.; Silva, J.A.; Ereshefsky, L.; Marder, S.; Wirshing, W.; Conley, R.; Getson, A.; Chavez-Eng, C.; Cheng, H.; Reines, S. *Arch. Gen. Psychiatry* **1997**, *54*, 567.
10. Bristow, L.J.; Kramer, M.S.; Kulagowski, J.; Patel, S.; Ragan, C.I.; Seabrook, G.R. *TiPS* **1997**, *18*, 186.
11. Larock, R.C.; Yum, E.K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
12. Chen, C.; Lieberman, D.R.; Larsen, R.D.; Reamer, R.A.; Verhoeven, T.R.; Reider, P.J.; Cottrell, I.F.; Houghton, P.G. *Tetrahedron Lett.* **1994**, *35*, 6981.
13. Such methodology has been applied to the synthesis of 5- and 6-azaindoles; Wensbo, D.; Eriksson, A.; Jeschke, T.; Gronowitz, S.; Cohen, L.A. *Tetrahedron Lett.* **1993**, *34*, 2823.
14. Estel, L.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.
15. Romero, D.L.; Mitchell, M.A.; Thomas, R.C.; Palmer, J.R.; Tarpley, W.G.; Aristoff, P.A.; Smith, H.W. *US Patent Appl.* 491782, 28 Dec 1989.
16. Hands, D.; Bishop, B.; Cameron, M.; Edwards, J.S.; Cottrell, I.F.; Wright, S.H.B. *Synthesis* **1996**, 877.