Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 5253–5256
Bioorganic & Medicinal Chemistry Letters

N-[(3*S*)-1-Benzylpyrrolidin-3-yl]-(2-thienyl)benzamides: Human dopamine D_4 ligands with high affinity for the 5-HT_{2A} receptor

Jalaj Arora, Michel Bordeleau, Laurence Dube, Keith Jarvie, Lucy Mazzocco, Jack Peragine, Ashok Tehim† and Ian Egle*

NPS Pharmaceuticals, 6850 Goreway Dr., Mississauga, Ont., Canada L4V 1V7

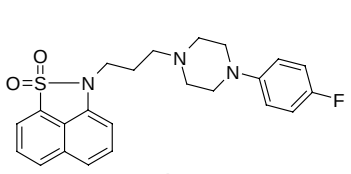
Received 27 July 2005; revised 15 August 2005; accepted 15 August 2005
Available online 15 September 2005

Abstract—A series of *N*-[(3*S*)-1-benzylpyrrolidin-3-yl]-(2-thienyl)benzamides **8** has been prepared and found to bind with high affinity to the human D_4 (hD_4) and 5-HT_{2A} receptors. Several compounds displayed selectivity for these receptors versus hD_2 and α_1 adrenergic receptors of over 500-fold.

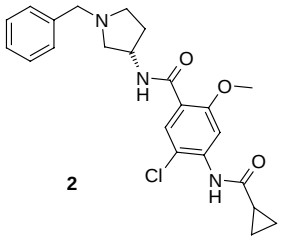
The diverse pharmacology of the atypical antipsychotic clozapine[1] has complicated the search for newer agents with more tolerable side-effect profiles. The efforts to dissect the pharmacology required for novel antipsychotics have led to the conclusion that D_4 antagonism alone may not be sufficient for clinical efficacy[2] however, such compounds might yet find use in the treatment of attention deficit hyperactivity disorder or mood disorders.[3,4] There is evidence that a D_4 antagonist that also possesses serotonergic activity (i.e., 5-HT_{2A} antagonism) might function as a useful antipsychotic.[5] There has been considerable interest in the development of tool compounds with the appropriate pharmacology to yield answers to this question.[6–9]

The combination of D_4 and 5-HT_{2A} receptor blockade is attractive for a number of reasons. A favourable 5-HT_2/D_2 ratio may limit the propensity of a compound to induce extrapyramidal symptoms (EPS).[10] 5-HT_{2A} antagonists are also known to be efficacious in the treatment of negative symptoms of schizophrenia.[11] In addition, cortical dopaminergic systems are regulated by 5-HT indirectly via glutamatergic and GABAergic systems,[12,13] suggesting a synergistic relationship between the dopaminergic and serotonergic systems.

Fananserin **1** was the first selective D_4/5-HT_{2A} antagonist to undergo clinical trials for schizophrenia. It has high affinity for D_4 (K_i 2.9 nM) and 5-HT_{2A} (K_i 0.37 nM) receptors, and is over 100-fold selective versus H_1, α_1 adrenergic, 5-HT_{1A} and D_2 dopamine receptors.[14] Development of this compound was halted following phase II clinical trials due to lack of efficacy.[15] The extent to which this result precludes the use of a D_4/5-HT_{2A} antagonist is difficult to discern because D_4 receptor blockade in vivo was not demonstrated at clinically relevant doses.[16]



1



2

Herein we wish to report the discovery of a novel class of compounds with D_4/5-HT_{2A} activity that is an extension of previous work.[17] The broad-spectrum dopamine ligand YM-43611 **2** from Yamanouchi Pharmaceuticals[18] was used as the starting point for the design of compounds for this study. YM-43611 has affinities for the D_2, D_3 and D_4 receptors of 220, 21 and 2.1 nM,

Keywords: Dopamine; Serotonin; Schizophrenia; D4; 5-HT2A.
* Corresponding author. Tel.: +1 90 56 7 70 831; fax: +1 90 56 77 95 95; e-mail: iegle@npsp.com
† Present address: Memory Pharmaceuticals Corp., 100 Philips Parkway, Montvale, NJ 07645, USA.

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.08.051

respectively. The compounds for this study were prepared as illustrated in Scheme 1, starting from commercially available (3*S*)-3-amino-1-benzylpyrrolidine **3**. Compound **3** was acylated with either 3- or 4-iodo benzoyl chloride, followed by a Suzuki coupling with thiophene-2-boronic acid under typical conditions to provide **5a** (*meta* isomer) or **5b** (*para* isomer). N-debenzylation was best accomplished in a two-step procedure using 2,2,2-trichloroethyl chloroformate, followed by zinc reduction to provide the key intermediates **7a**, **b**.[19] Hydrogenolysis of the *N*-benzyl protecting group failed, presumably due to the thiophene moiety present in the compounds, and other chloroformate deprotections provided less satisfactory chemical yields. Finally, **7a**, **b** were alkylated with the various benzylic halides under typical basic conditions in parallel to provide the compounds for this study, **8a**–**o** (see Table 1). Following column chromatography, they were determined to be of sufficient purity (by ^{1}H NMR) for pharmacological assessment. For the purposes of this study enantiomeric purity was not assessed, as retention of chirality was expected under the reaction conditions employed.

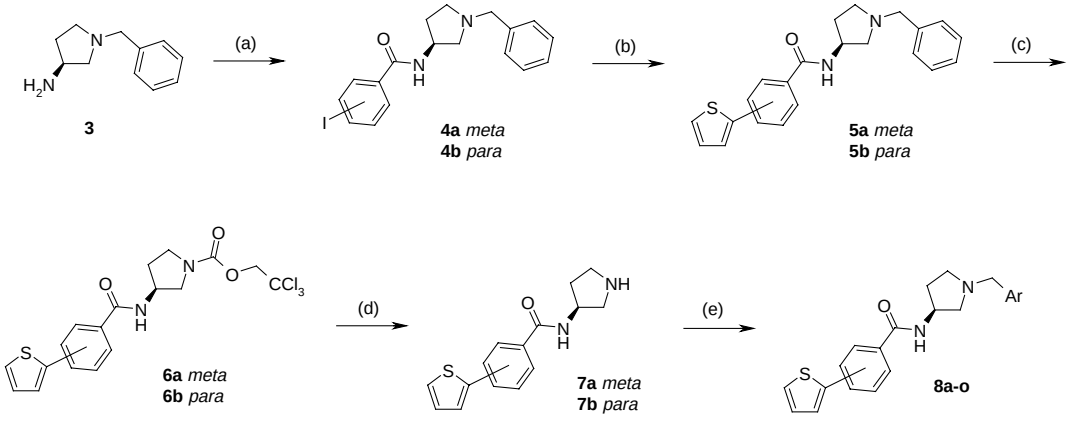
The hD_2, hD_4 and $h5HT_{2A}$ receptor binding profiles of compounds **8a** to **8o** were evaluated by their ability to displace [^{3}H]spiperone (dopamine receptors) or [^{3}H]ketanserin ($h5HT_{2A}$ receptor) binding to heterologous cells expressing the cloned receptors. Non-specific binding was determined using 30 μM methysergide. For the purposes of this assay, human embryonic kidney 298 cells were stably transfected with hD_4 ($D_{4.2}$ subtype) and $h5HT_{2A}$ receptor, and GH_4C_1 (rat pituitary) cells were stably transfected with hD_2 (short isoform) receptor. Rat frontal cortex tissue was used for the α_1 adrenergic receptor assay, using 7-methoxy-[^{3}H]prazosin as the radioligand. Clozapine was used as a reference in all of the assays. Non-specific binding was determined using 30 μM methysergide. K_i values for each compound were calculated by the Cheng and Prusoff transformation.[20]

The affinities of these compounds for the 5-HT_{2A} receptor have a clear dependence on the point of attachment of the 2-thiophene ring (see pairs **8a** and **8b**, **8c** and **8d**, and **8e** and **8f**). There is a strong preference for the *para* isomer of these pairs over the *meta* isomer. In the case of the positional isomers **8a** and **8b**, the ratio of affinities for the 5-HT_{2A} receptor is 256-fold in favour of the *para* isomer. The *para* isomer also exhibits lower affinity for the dopamine D_2 and α_1 adrenergic receptors, while dopamine D_4 receptor affinity remains unaffected. This results in ligands with high affinity for D_4/5-HT_{2A} receptors with good selectivity over dopamine D_2 and α_1 adrenergic receptors (e.g., **8a**, **8k**). The nature and position of the substituent on the benzyl group had a less dramatic effect on the affinity. There was a slight preference for *para* substitution over *meta* or *ortho* (compare **8c** to **8g**, and **8j** to **8k**), but in all cases the unsubstituted derivative **8a** had the highest affinity. In our previous paper in this area, we have shown that there is a preference for the *S* enantiomer over the *R*, and that methylation of the amide nitrogen or replacement of the amide with a sulfonamide was not tolerated.[17]

Previous work has demonstrated that a similar compound was a dopamine D_4 antagonist;[17,21] however, we do not have knowledge of the functional role of the compounds disclosed herein on either the D_4 or 5-HT_{2A} receptors.

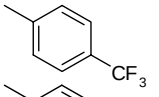
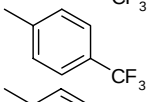
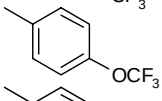
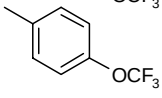
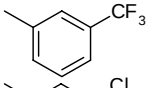
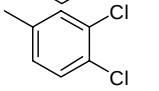
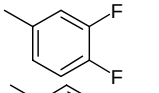
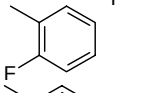
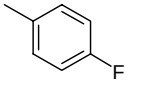
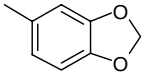
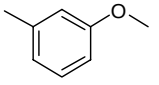
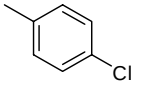
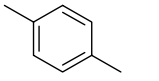
These compounds display a favourable selectivity profile for further development as antipsychotics. Their lack of affinity for the α_1 adrenergic receptor suggests that they may be free of undesirable cardiovascular effects such as orthostatic hypotension; however, it is possible that there are beneficial effects of α_1 antagonism in an antipsychotic medication.[16] The large D_4/D_2 and 5-HT_{2A}/D_2 ratios indicate that these compounds are likely to be free of EPS.[10]

This study has successfully identified a novel class of highly potent dopamine D_4 ligands that also display high affinity for the serotonin 5-HT_{2A} receptor. They are selective over the dopamine D_2 and α_1 adrenergic receptors. The utility of such compounds for the treatment of schizophrenia remains to be determined.



Scheme 1. Reagents and conditions: (a) 3- or 4-iodobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C; (b) thiophene-2-boronic acid, $Pd(PPh_3)_4$, DME, 2 M Na_2CO_3; (c) 2,2,2-trichloroethyl chloroformate, MeCN; (d) Zn, AcOH; (e) $ArCH_2Cl$, K_2CO_3, KI, MeCN, 90 °C.

Table 1. Binding profile of series **8** at the serotonin 5-HT_{2A}, dopamine hD_4 and hD_2, and α_1 adrenergic receptors

Compound	Biaryl isomer	Ar	D_4 K_i (nM)[a]	5-HT_{2A} K_i (nM)[a]	D_2 K_i (nM)	α_1 K_i (nM)[a]
1			2.9	0.37		
8a	*para*	Ph	3.0	1.8	980	1200
8b	*meta*	Ph	1.5 ± 0.3	460	60 ± 20	160 ± 50
8c	*para*		14	130	7% at 100 nM	2% at 1 μM
8d	*meta*		21 ± 3	740	1300 ± 100	360 ± 6
8e	*para*		78	140	7% at 100 nM	16,000
8f	*meta*		52 ± 6	5600	500 ± 100	1200 ± 300
8g	*para*		22	76% at 100 nM	0% at 100 nM	0% at 100 nM
8h	*para*		15 ± 6	22	29,000	5000 ± 2000
8i	*para*		14 ± 4	16	18,000	10,000 ± 2000
8j	*para*		33	89% at 100 nM	38,000	6900
8k	*para*		5 ± 3	14	1500 ± 400	420
8l	*para*		7 ± 0	89% at 100 nM	1800 ± 400	400 ± 30
8m	*para*		14 ± 2	22	4460 ± 30	920 ± 70
8n	*meta*		16 ± 2	1100	230 ± 70	220 ± 60
8o	*meta*		4 ± 2	610	60 ± 6	80 ± 10

[a] K_i values are reported as means of at least two independent determinations ± SEM. Where no SEM is reported, only a single determination was made.

References and notes

1. Tamminga, C. A. *Can. J. Psychiatry* **1997**, *42*, 265.
2. Kramer, M. S.; Last, B.; Getson, A.; Reines, S. A. *Arch. Gen. Psychiatry* **1997**, *54*, 567.
3. Zhang, K.; Baldessarini, R. J.; Tarazi, F. I.; Neumeyer, J. L. *Curr. Med. Chem.-Cent. Nerv. Syst. Agents* **2002**, *2*, 259.
4. Hrib, N. J. *Drugs Future* **2000**, *25*, 587.
5. Capuano, B.; Crosby, I. T.; Lloyd, E. J.; Podlouka, A.; Taylor, D. A. *Aust. J. Chem.* **2003**, *56*, 875.
6. Capuano, B.; Crosby, I. T.; Lloyd, E. J.; Taylor, D. A. *Aust. J. Chem.* **2002**, *55*, 565.
7. Chaki, S.; Nakazato, A.; Okuyama, S. *CNS Drug Rev.* **2000**, *6*, 95.
8. Steiner, G.; Bach, A.; Bialojan, S.; Greger, G.; Hege, H.-G.; Hoger, T.; Jochims, K.; Munschauer, R.; Neumann, B.; Teschendorf, H.-J.; Traut, M.; Unger, L.; Gross, G. *Drugs Future* **1998**, *23*, 191.
9. Bolos, J. *Mini-Rev. Med. Chem.* **2003**, *3*, 239.
10. Meltzer, H. Y.; Matsubara, S.; Lee, J. C. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238.
11. Schmidt, C. J.; Sorensen, S. M.; Kehne, J. H.; Carr, A. A.; Palfreyman, M. G. *Life Sci.* **1995**, *56*, 2209.
12. Mrzljak, L.; Bergson, C.; Pappy, M.; Huff, R.; Levenson, R.; Goldman-Rakic, P. S. *Nature* **1996**, *381*, 245.
13. Schmidt, C. J.; Fadayel, G. M. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 1541.
14. Heuillet, E.; Petitet, F.; Mignani, S.; Malleron, J. L.; Lavayre, J.; Neliat, G.; Doble, A.; Blanchard, J. C. *Eur. J. Pharmacol.* **1996**, *314*, 229.
15. Truffinet, P.; Tamminga, C. A.; Fabre, L. F.; Meltzer, H. Y.; Riviere, M.-E.; Papillon-Downey, C. *Am. J. Psychiatry* **1999**, *156*, 419.

16. Ellenbroek, B. A.; Liegeois, J.-F. *CNS Drug Rev.* **2003**, *9*, 41.
17. Egle, I.; Barriault, N.; Bordeleau, M.; Drage, J.; Dube, L.; Peragine, J.; Mazzocco, L.; Arora, J.; Jarvie, K.; Tehim, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4847.
18. Ohmori, J.; Maeno, K.; Hidaka, K.; Nakato, K.; Matsumoto, M.; Tada, S.; Hattori, H.; Sakamoto, S.; Tsukamoto, S.; Usada, S.; Mase, T. *J. Med. Chem.* **1996**, *39*, 2764.
19. As a representative procedure, to a suspension of **5** (1.97 g, 5.43 mmol) in EtOAc (40 mL) was added 2,2,2-trichloroethyl chloroformate (11.5 g, 54.3 mmol). After 1 h, the mixture was poured into water and extracted three times with EtOAc, dried ($MgSO_4$), filtered and concentrated. Column chromatography (50% EtOAc/hexanes) provided carbamate **6** as a colourless solid. To a solution of **6** (100 mg, 0.223 mmol) in MeOH (3 mL) were added AcOH (10 drops) and Zn dust (500 mg). After 1 h, the reaction mixture was filtered and concentrated to provide **7**, suitable for use in the next step.
20. Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
21. Tehim, A.; Wang, X.; Arora, J.; Treasurywala, A. WO Patent 9837064, 1998.