Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 725–730

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS, SAR AND PHARMACOLOGY OF CP-293,019: A POTENT, SELECTIVE DOPAMINE D_4 RECEPTOR ANTAGONIST

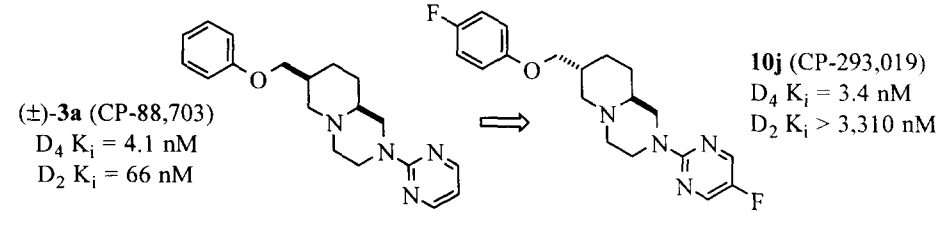
Mark A. Sanner,* Thomas A. Chappie, Audrey R. Dunaiskis, Anton F. Fliri, Kishor A. Desai, Stevin H. Zorn, Elisa R. Jackson, Celeste G. Johnson, Jean M. Morrone, Patricia A. Seymour, Mark J. Majchrzak, W. Stephen Faraci, Judith L. Collins, David B. Duignan, Cecilia C. Di Prete, Jae S. Lee, and Angela Trozzi

Pfizer Central Research, Eastern Point Road, Groton, CT 06340, U.S.A.

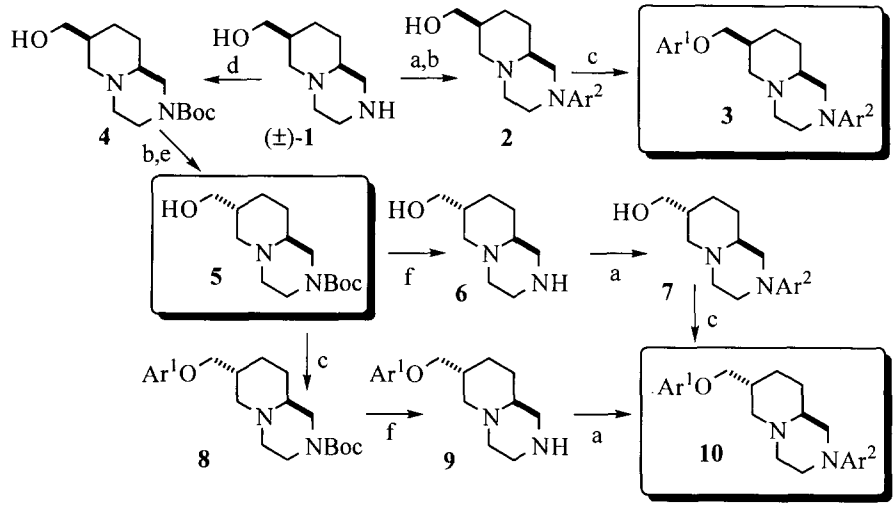
Received 12 January 1998; accepted 5 February 1998

Abstract: A series of novel, potent and selective pyrido[1,2-*a*]pyrazine dopamine D_4 receptor antagonists are reported including CP-293,019 (D_4 K_i = 3.4 nM, D_2 K_i > 3,310 nM), which also inhibits apomorphine-induced hyperlocomotion in rats after oral dosing.

The discovery of the dopamine D_4 receptor subtype in 1991 and the higher affinity of the atypical antipsychotic clozapine for D_4 relative to D_2 sparked a flurry of interest in developing a new class of antipsychotic agents.[1-4] Using structural elements common to known neuroleptics, a subset of 4,500 compounds was culled from a much larger compound library, and screening this subset for D_2 and D_4 receptor binding uncovered several distinct yet related series with potency and selectivity for the D_4 receptor. The lead compound in one family, **3a** ((±)-CP-88,703), had been prepared several years earlier as a buspirone-haloperidol hybrid, and was an attractive lead structure for the D_4 receptor antagonist program with D_4 K_i = 4.1 nM and D_2 K_i = 66 nM. Although **3a** had minimal D_4 selectivity, the conformationally rigid pyrido[1,2-*a*]pyrazine template offered unique possibilities for manipulating the receptor binding profile through stereocontrol and substituent manipulation. Building on previous experience with the synthesis, pharmacology, and pharmacokinetics of **3a**-related compounds led to **10j** (CP-293,019) as a potential new therapy for the treatment of schizophrenia.



0960-894X/98/$19.00
PII: S0960-894X(98)00108-5



Scheme 1. Refs 5 and 6. (a) 2-Cl-pyrimidine, Na_2CO_3, water, reflux or 2-Br-pyridine, Na_2CO_3, *i*-amyl alcohol, reflux; (b) (-)-tartaric acid, MeOH; (c) Ar^1OH, Ph_3P, DEAD, THF; (d) Boc_2O, CH_2Cl_2; (e) i. SO_3/pyr, ii. Na_2CO_3, MeOH, iii. $NaBH_4$, MeOH; (f) HCl, $CHCl_3$.

Target compounds *cis*-**3** and *trans*-**10** are all prepared from racemic intermediate diamine (±)-**1**, which is in turn derived from pyridine 2,5-dicarboxylic acid in five steps.[5] N-Arylation with 2-chloropyrimidine gives racemic **2a**, which is resolved with (-)-tartaric acid to (7*S*,9a*S*)-**2a** in 99% ee (Scheme 1). Mitsunobu coupling with phenols (Ar^1-OH) then gives target compounds **3**. Because the racemic *trans* isomer of **2** can not be efficiently resolved, *cis*-N-Boc derivative **4** is resolved instead followed by inversion of C7 oxidation to the aldehyde, equilibration to the thermodyamically favored *trans* isomer, and reduction to optically active *trans*-N-Boc-**5** in 27% overall yield. Though somewhat inelegant in derivation, the versatile key intermediate (7*R*,9a*S*)-**5** commands a pivotal position in the synthetic development of this series.[6] That is, deprotection of **5** and N-arylation allows for easy Ar^1 analoging, again using standard Mitsunobu conditions, or conversely, initial O-arylation of **5** followed by deprotection to **9** enables flexible analoging at N-Ar^2. N-Pyrimidyl and N-pyridyl analogs are available by heating the appropriate aryl halide with base, N-phenyl analogs require a three-step process of nucleophilic aromatic substitution with 2- or 4-fluoro-nitrobenzene, reduction to the aniline and diazo de-amination with amyl nitrite. During the course of this work, direct nickel-catalyzed N-arylation methods became available which condensed preparation of N-phenyl analogs into a single step.[7] Thus, the two-pronged synthetic sequence from **5** facilitates rapid construction of an Ar^1/Ar^2 structure-activity matrix.

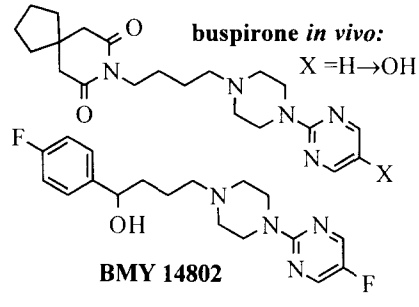
Comparing binding affinities for the unsubstituted racemic *cis* and *trans* compounds **3a** and **10a** indicates that both isomers maintain equally high affinity for D_4, but *trans*-**10a** is significantly weaker at D_2 resulting in greater selectivity (D_2/D_4 = 49, Table 1). Similarly, the resolved isomer *trans*-**10b** with 9a*S* absolute

configuration has superior selectivity relative to *cis*-**3b** except that **10b** has an unexpectedly high D_2 K_i = 1,140 nM resulting in a dramatic improvement in selectivity (D_2/D_4 = 326). In fact, *trans*-(7*R*,9a*S*) configuration is the key factor inducing D_4 potency and selectivity in this series.

Probing phenyl ether SAR with a range of *para*-PhO substituents proved quite narrow in scope. For example, 4-F analog **10c** is equivalent to the parent **10b**, but nearly all other analogs have higher D_4 K_i or lower selectivity or both (Table 1). Compounds **10d-g** are a representative sample exhibiting no discernible trend based on lipophilic, electronic, or H-bonding properties, suggesting a restrictive steric constraint at the 4-X-(C_6H_4)-O position of the D_4 receptor pharmacophore allowing for only very small groups such as H and F. Intermediate **7**, lacking the phenyl ether, is inactive at D_2 and D_4 receptors. As for the N-aryl substituent, the parent 2-pyrimidyl **10b**, 2-pyridyl **10h** and phenyl **10i** all have high D_4 affinity, but there is a consistent downward trend in D_2 K_i and a corresponding erosion in D_2/D_4 selectivity for this trio. Thus, this phase of SAR investigation shows that the original phenyl ether and 2-pyrimidyl appendages are nearly optimum, and identifies the superior D_2/D_4 selectivity of the 7*R*,9a*S* configuration.

As for metabolic stability, the 2-pyrimidyl-piperazine of buspirone is metabolized into the 5-hydroxy-pyrimidine in vivo (Figure 1),[8] and blocking this metabolic pathway with 5-F-pyrimidyl improves the in vivo performance of BMY 14802 relative to its unsubstituted counterpart.[9,10] Similarly, 5-F-pyrimidyl also improves the in vitro metabolic stability of D_4 antagonists: the unsubstituted **10b** and mono-fluoro **10c** are rapidly metabolized in human liver microsomes ($T_{1/2}$ = 3 min and 3.6 min, respectively) whereas di-fluoro **10j** has in vitro half-life of 12.2 min. Furthermore, **10j** displays very good in vivo pharmacokinetics: mean plasma $T_{1/2}$ = 4.5 h, mean Cmax = 0.73 μg/mL at about 1 h, and 93% mean absolute bioavailability after oral dosing in rat (10 mg/kg in water, N = 4).

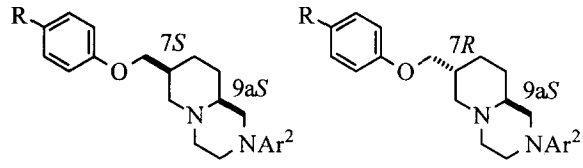
Figure 1.

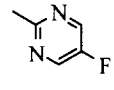
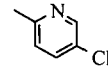
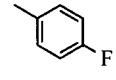
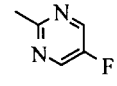


BMY 14802

The N-(5-F-pyrimidyl) substituent not only improves metabolic stability, but it also decreases D_2 affinity while maintaining D_4 potency (compare D_2 Ki for **10c** and **10j**). In fact, decreasing D_2 affinity and improving D_2/D_4 selectivity by N-aryl halogenation is a trend that applies to all three N-aryl groups: compare D_2 K_i's for pyrimidines **10b** and **10j**, pyridines **10h** and **10k**, and phenyls **10i** to **10l**. In other words, the high D_4 potency and selectivity arising from the *trans*-7R,9aS configuration is enhanced by 2-pyrimidyl and *para*-F as independent variables. The additive combination of these features in **10j** (CP-293,019) produces high D_4 potency, 1000-fold D2/D4 selectivity (D_2 K_i > 3,310 nM, D_4 K_i = 3.4 nM), and functional antagonist activity in D_4 receptor-transfected CHO cells in vitro (K_i = 2.4 nM vs. agonist quinpirole when measuring inhibition of

Table 1. In vitro dopamine receptor binding.



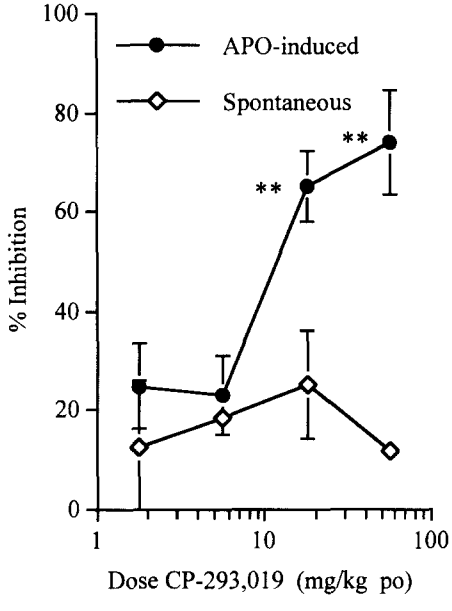
Compound	R	Ar^2	7,9a-Stereo	D_2 K_i (nM)[a]	D_4 K_i (nM)[b]	D_2/D_4
3 a (CP-88,703)	H		(±)-*cis*	66	4.1	16
10 a	H	"	(±)-*trans*	185	3.8	49
3 b	H	"	*S,S*	38	1.7	22
10 b	H	"	*R,S*	1,140	3.5	326
10 c	F	"	*R,S*	1,196	2.8	427
10 d	OMe	"	*R,S*	918	18	51
10 e	*t*-Bu	"	*R,S*	1,720	20	86
10 f	CO_2Me	"	*R,S*	254	127	2
10 g	NHAc	"	*R,S*	948	316	3
10 h	H		*R,S*	187	1.7	110
10 i	H		*R,S*	44	1.6	28
10 j (CP-293,019)	**F**		***R,S***	**> 3,310**	**3.4**	**> 1,000**
10 k	F		*R,S*	1,880	3.2	588
10 l	F		*R,S*	206	5.3	39
10 m	F		*S,R*	195	106	1.8
3 c	F	"	*S,S*	68	2.0	34
3 d	F	"	*R,R*	980	39	26
L-745,870 [11]				1,210	3.4	356
PNU-101,387 [12]				1,820	29	63
clozapine				155	47	3.3
haloperidol				0.84	3.3	0.25

[a] CHO cells expressing D_{2S} receptor vs. ^{3}H-spiperone.
[b] CHO cells expressing $D_{4.4}$ receptor vs. ^{3}H-spiperone.

forskolin-stimulated adenylate cyclase activity). CP-293,019 is also selective relative to D_3 (K_i > 2,000 nM) as well as a variety of adrenergic, histamine, and serotonin receptors (all IC_{50} > 1,000 nM), and has weak affinity for $5HT_{1A}$ (IC_{50} = 180 nM) and $5HT_{2A}$ (IC_{50} = 500 nM).

In vivo, **10j** inhibits the hyperactivity produced by apomorphine (APO) in habituated rats with ID_{50} = 10 mg/kg sc and 13.3 mg/kg po (vs. 1.78 mg/kg APO sc), but has no significant effect on spontaneous locomotor activity when given alone to nonhabituated rats (ID_{50} > 56 mg/kg po, Figure 2). D_2 antagonists such as haloperidol also inhibit APO-induced hyperactivity, but display a markedly different profile than D_4 antagonists such as **10j**.[13] The selective D_4 antagonists L-745,870 and PNU-101,387 are inactive at lower doses in similar behavioral models of schizophrenia.[12,14] Compound **10j** also inhibits APO-induced blockade of prepulse inhibition at 17.8 mg/kg sc.[15] Finally, **10j** resembles the atypical antipsychotic clozapine in that it fails to antagonize APO-induced stereotypy and does not produce catalepsy (ID_{50} > 56 mg/kg po), two endpoints that may be predictive of extrapyramidal side effects (EPS).[16]

Figure 2. Inhibition of APO-induced locomotion (rat)



Starting from lead compound CP-88,703 (**3a**), a combination of design, diligence, fortuitous events and seemingly small structural changes led to CP-293,019 (**10j**), a potent, selective, D_4 receptor antagonist with excellent pharmacokinetic properties and activity in an in vivo model responsive to antipsychotic drugs, yet lacking activity in two measures of EPS. How well this exceptional preclinical profile translates into clinical efficacy is not known, but another D_4 antagonist (L-745,870) had no effect on the symptoms of schizophrenia in one clinical trial.[17,18] Be that as it may, the results of pending clinical trials with other selective D_4 receptor antagonists should help clarify the role of the D_4 receptor in the etiology of schizophrenia and related disorders.

Acknowledgments

The generous contributions of Phil Hammen, Alex Grodski, Richard Watrous, Robert Dugger, Greg Young, Tom Staigers, and Cliff Meltz are gratefully acknowledged.

References and Notes

1. Van Tol, H. H. M.; Bunzow, J. R.; Guan, H.-C.; Sunahara, J. R.; Seeman, P.; Niznik, H. B.; Civelli, O. *Nature* **1991**, *350*, 610.
2. Seeman, P.; Van Tol, H. H. M. *Curr. Opinion Neurol. Neurosurg.* **1993**, *6*, 602.
3. Seeman, P.; Guan, G.-C.; Van Tol, H. H. M. *Nature* **1993**, *365*, 441.
4. Kulagowski, J. J.; Patel, S. *Curr. Pharm. Design* **1997**, *3*, 355.
5. Urban, F. J. PCT Int. Appl. WO 9325552.
6. Desai, K. A.; Fliri, A. F.; Sanner, M. A. PCT Int. Appl. WO 9610571.
7. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.
8. Temple, D. L.; Yevich, J. P.; New, J. P. *J. Clin. Psychiatry* **1982**, *43*, 4.
9. Yevich, J. P.; New, J. S.; Lobeck, W. G.; Dextraze, P.; Bernstein, E.; Taylor, D. P.; Yocca, F. D.; Eison, M. S.; Temple, D. L. J. *J. Med. Chem.* **1992**, *35*, 4516.
10. Dunaiskis, A.; Staigers, T.; Keltonic, T.; Chappie, T.; Meltz, C.; Dugger, R.; Sanner, M. A. *Org. Prep. Proc. Int.* **1995**, *5*, 600.
11. 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, S.; Patel, S.; Ragan, C. I.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1941.
12. Merchant, K. M.; Gill, G. S.; Harris, D. W.; Huff, R. M.; Eaton, M. J.; Lookingland, K.; Lutzke, B. S.; McCall, R. B.; Piercey, M. F.; Schreur, P. J. K. D.; Sethy, V. H.; Smith, M. W.; Svensson, K. A.; Tang, A. H.; VonVoigtlander, P. F.; Tenbrink, R. E. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 1392.
13. Majchrzak, M. J.; Zorn, S. H.; Sanner, M. A.; Seymour, P. A. *Abstract of Papers,* 27th Annual Meeting of the Society for Neuroscience, New Orleans, LA; Society for Neuroscience: Washington, DC, 1997; 165.8.
14. Patel, S.; Freedman, S.; Chapman, K. L.; Emms, F.; Fletcher, A. E.; Knowles, M.; Markwood, 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.
15. Mansbach, R. S.; Brooks, E. W.; Sanner, M. A.; Zorn, S. H. *Psychopharmacol.* **1998**, *135*, 194.
16. Zorn, S. H.; Johnson, C. G.; Jackson, E. R.; Seymour, P. A.; Majchrzak, M.; Mansbach, R. S.; Winston, E. N.; DeWet, J. R.; Dunaiskis, A.; Chappie, T.; Sanner, M. A. *Abstract of Papers,* 26th Annual Meeting of the Society for Neuroscience, Washington, DC; Society for Neuroscience: Washington, DC, 1996; 697.1.
17. Bristow, L. J.; Kramer, M. S.; Kulagowski, J.; Patel, S.; Ragan, C. I.; Seabrook, G. R. *Trends Pharmacol. Sci.* **1997**, *18*, 186.
18. Kramer, M. S.; Last, B.; Getson, A.; Reines, S. A. *Arch. Gen. Psych.* **1997**, *54*, 567.