SYNTHESIS, SAR AND PHARMACOLOGY OF CP-293,019:

A POTENT, SELECTIVE DOPAMINE D_4 RECEPTOR ANTAGONIST

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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. © 1998 Elsevier Science Ltd. All rights reserved.

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.

(±)-**3a** (CP-88,703)
D_4 K_i = 4.1 nM
D_2 K_i = 66 nM

10j (CP-293,019)
D_4 K_i = 3.4 nM
D_2 K_i > 3,310 nM
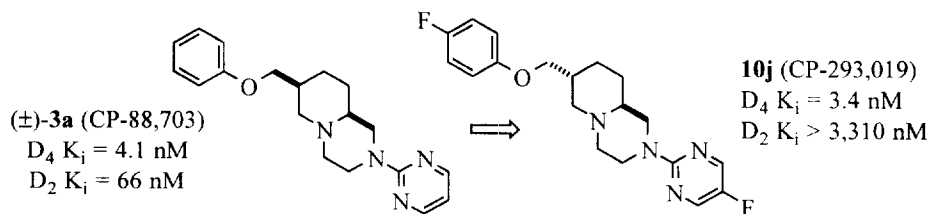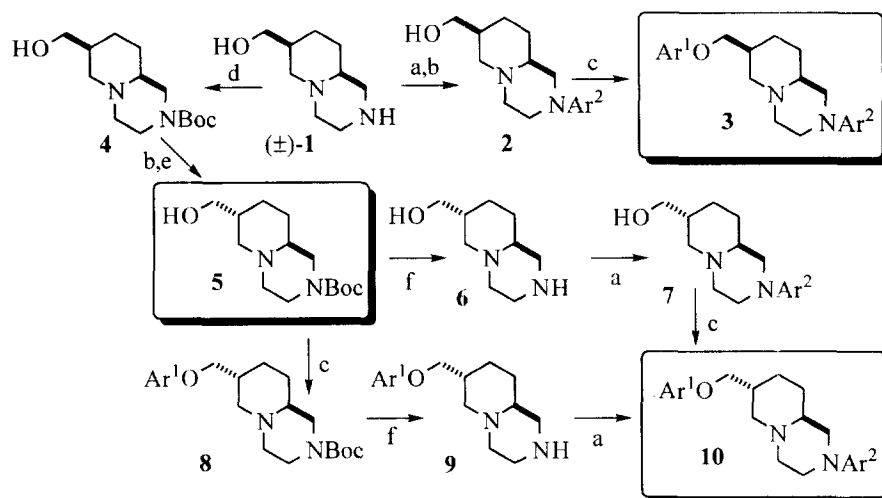
Scheme 1. Refs 5 and 6. (a) 2-Cl-pyrimidine, Na_2CO_3, water, reflux or 2-Br-pyridine, Na_2CO_3, *i*-amyl alcohol, reflux; (b) (-)-tartaric acid, MeOH; (c) Ar^1OH, Ph_3P, DEAD, THF; (d) Boc_2O, CH_2Cl_2; (e) i. SO_3/pyr, ii. Na_2CO_3, MeOH, iii. $NaBH_4$, MeOH; (f) HCl, $CHCl_3$.

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 (7S,9aS)-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 (7R,9aS)-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 9aS 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,

Figure 1.

buspirone *in vivo:*
X =H→OH

BMY 14802

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).

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 <u>and</u> *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
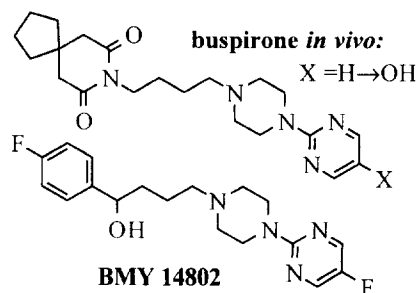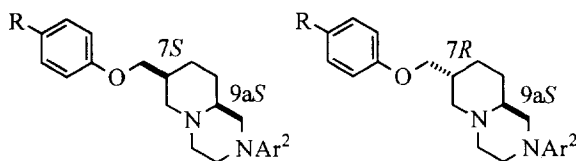
Table 1. In vitro dopamine receptor binding.

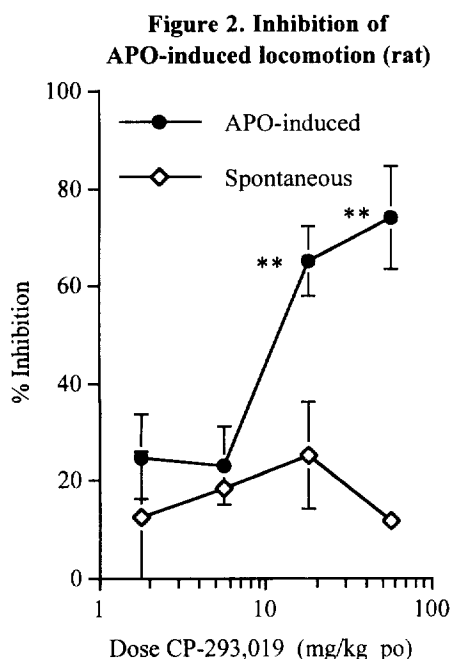| Compound	R	Ar²	7,9a-Stereo	$D_2 K_i$ (nM)[a]	$D_4 K_i$ (nM)[b]	D_2/D_4
3 a (CP-88,703)	H		(±)-*cis*	66	4.1	16
10 a	H	"	(±)-*trans*	185	3.8	49
3 b	H	"	*S,S*	38	1.7	22
10 b	H	"	*R,S*	1,140	3.5	326
10 c	F	"	*R,S*	1,196	2.8	427
10 d	OMe	"	*R,S*	918	18	51
10 e	*t*-Bu	"	*R,S*	1,720	20	86
10 f	CO2Me	"	*R,S*	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]

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

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

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

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.