Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 271–274

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

New Generation Dopaminergic Agents. Part 8: Heterocyclic Bioisosteres that Exploit the 7-OH-2-(Aminomethyl)chroman D_2 Template

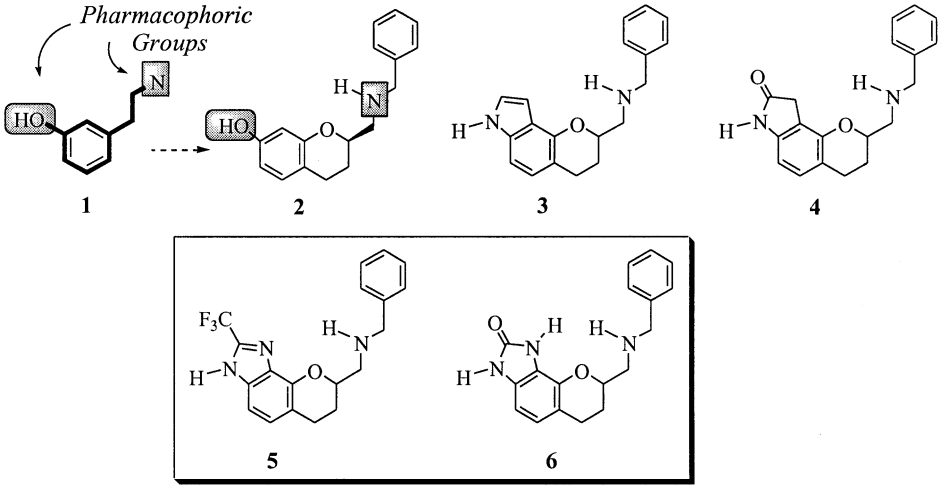
Richard E. Mewshaw,* Rulin Zhao, Xiaojie Shi, Karen Marquis, Julie A. Brennan, Hossein Mazandarani, Joseph Coupet and Terrance H. Andree

Global Chemical Sciences and CNS Disorders Departments, Wyeth-Ayerst Research Laboratories, PO Box 42528, Philadelphia, PA 19101-2528, USA

Received 11 September 2001; accepted 23 October 2001

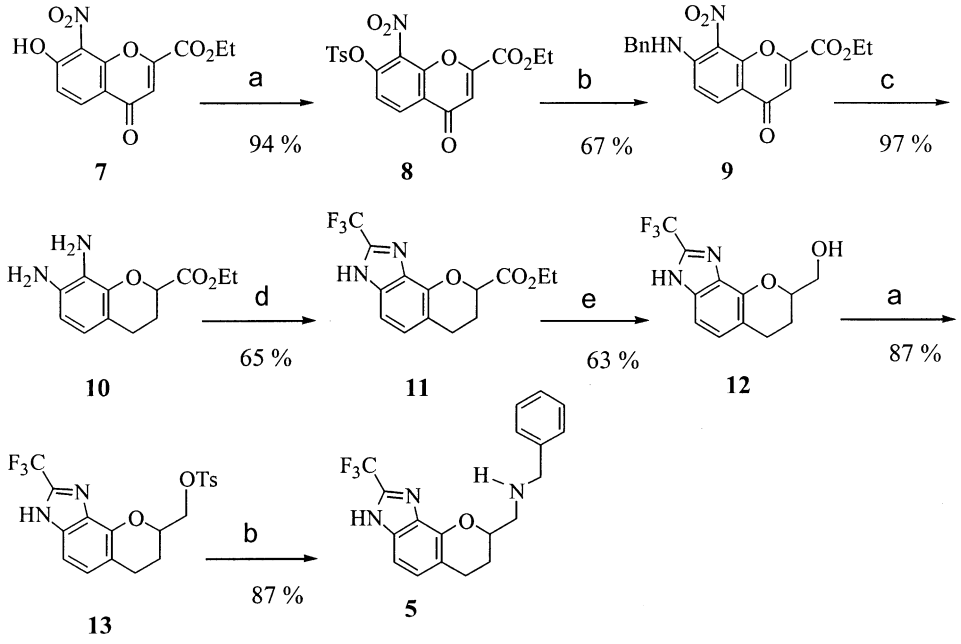
Abstract—Based on the 7-OH-2-(aminomethyl)chroman dopamine D_2 template (**2**) is described the preparation and resolution of two bioisosteric analogues. The benzimidazol-2-one derivative (**6**) had similar affinity to the known indolone derivative (**4**).

Recent studies from our laboratories have focused on discovering novel dopamine (DA) D_2 partial agonists potentially useful for the treatment of schizophrenia. By selectively acting on the D_2 autoreceptors, partial agonists may offer an alternative therapeutic strategy devoid of the extrapyramidal side effects, commonly associated with the currently marketed D_2 antagonists.[1] In our previous studies (Parts 1–7), we have reported on the discovery of several phenolic prototypes which have since led to numerous heterocyclic analogues embracing the D_2 agonist pharmacophore.[2] Compounds discovered from our studies are unique in that they are no longer based on the '3-OH-phenethylamine' framework (i.e., **1**), a feature commonly exploited in most traditional dopamine D_2 drug design strategies.[3] These unique scaffolds allow for the alignment of the crucial pharmacophoric groups (i.e., basic nitrogen and phenolic OH groups) to fulfill most of the D_2 pharmacophoric requirements represented by the McDermed DA D_2 model.[4]

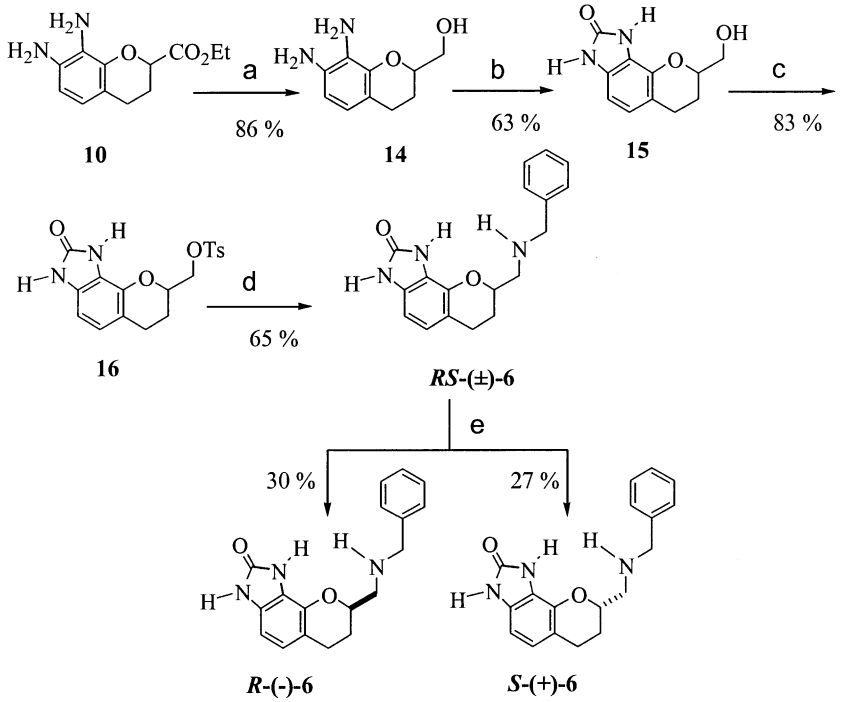


*Corresponding author. Fax: +1-484-865-9399; e-mail: mewshar@war.wyeth.com

0960-894X/02/$ - see front matter
PII: S0960-894X(01)00778-8



Scheme 1. Reagents and conditions: (a) TsCI, C_5H_5N; (b) $BnNH_2$, *o*-$C1_2C_6H_4$, 180 °C; (c) 10% Pd/C, 12 N HC1, EtOH; (d) CF_3COOH, reflux; (e) $LiBH_4$, THF.



Scheme 2. Reagents and conditions: (a) $LiBH_4$, THF; (b) CDI, THF; (c) TsC1, C_5H_5N; (d) $BnNH_2$, DMSO; (e) resolution by chromatography.

In our first paper, we reported a systematic structure–activity relationship (SAR) study which led us to the potent D_2 partial agonist **2**.[5] The benzyl group was discovered to be the best side chain to achieve selectivity over the $5HT_{1A}$ and α_1 adrenergic receptors and maintained throughout subsequent investigations. The bioisosteric analogues (**3** and **4**) were prepared later and observed to be potent D_2 partial agonists.[6] In this report we will describe the synthesis and activities of two related heterocyclic analogues (**5** and **6**) which are also based around the 7-OH-2-(aminomethyl)chroman template (**2**).

Shown in Schemes 1 and 2 are the syntheses of target molecules **5** and **6**. Using previously reported chromene **7**[7] as a starting point allowed us to successfully build both requisite tricyclic frameworks. Tosylation (TsCl, K_2CO_3, THF, rt) of **7** led to **8** in excellent yield. Displacement of the tosylate by benzylamine (2 equiv) was best achieved by heating to 170 °C for 1 h in *o*-dichlorobenzene to afford **9**. Exhaustive reduction using 10% Pd on carbon (1:5, 12 N HCl/EtOH) for 12 h produced **10**. Heating **10** at reflux in the presence of trifluoroacetic acid led to **11**. Reduction of **11** with lithium borohydride,

Table 1. Affinity of target molecules (**5** and **6**) and reference molecules for D_2–D_4 receptors

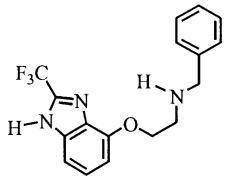
No.	K_i (nM)[10]					
	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
R-(−)-**2**[5]	0.2	3.3	42	10.4	2.4	116
R-(−)-**3**[6]	1.9	35.9	24	107	34	2174
R-(−)-**4**[6]	0.14	5.9	42	9.3	2.4	359
(±)-**5**	5.75	65.1	11	132	263	37
(±)-**6**	0.14	7.01	50	5.0	1.0	10
(−)-**6**	0.07	4.81	69	3.0	0.4	7.0
(+)-**6**	5.45	67.5	12	67.0	81.0	313

followed by tosylation provided **13**. Heating **13** in the presence of excess benzylamine in DMSO (80 °C) led to our final target molecule (**5**).

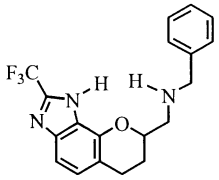
The synthesis of **6** can be achieved in four steps by utilizing intermediate **10**. Reduction of **10** using lithium borohydride led to **14**. Treatment of **14** with 1,1′-carbonyldiimidazole (1.5 equiv) at room temperature followed by tosylation afforded **16**. Heating **16** in the presence of benzylamine (5 equiv) at 80 °C led to target molecule (±)-**6**. Resolution of (±)-**6** into its respective enantiomers using a chiral column provided (+)-**6** and (−)-**6** in 99 and 98% ee, respectively {optical rotations were performed on the oxalate salts: (+)-**6**·$C_2H_2O_4$; $[\alpha]_D^{25}+82$ (c = 1.0, DMSO): (−)-**6**·$C_2H_2O_4$; $[\alpha]_D^{25}-81$ (c = 1.0, DMSO)}.

Shown in Table 1 are the affinities of the target compounds [(±)-**5**, (±)-**6**, (−)-**6**, (+)-**6**] for the $D_{2\text{-like}}$ receptors. The affinities of compounds for the D_2 receptors in rat striatal membranes were determined for both the agonist state (high affinity state, D_2^{High}) and the antagonist state (low affinity state, D_2^{Low}). The D_2^{High} state was labeled with [^{3}H]quinpirole (in the absence of GTP and sodium) and the D_2^{Low} state was labeled with [^{3}H]spiperone (using ketanserin to exclude 5-HT_2 receptor binding) in the presence of GTP and sodium. The ratio $K_i(D_2^{Low})/K_i(D_2^{High})$ was used as a preliminary and reliable estimate of the compounds' intrinsic activity as determined by other assays described by Lahti[8] and Wasik.[9] The D_2 partial agonist, (*S*)-3-PPP [$(K_i(D_2^{Low})/K_i(D_2^{High}) = 33$[5,8]], was used as a benchmark to compare a compound's estimated intrinsic activity. Affinity for the human cloned receptors was determined using membranes from CHO cells labeled with [^{3}H]spiperone.

Though (±)-**5** was observed to have good affinity for the D_2^{High} receptors ($K_i = 5.75$ nM), it was surprisingly 41-fold less potent than (±)-**6** and 32-fold less potent than previously prepared **17**[2] ($K_i = 0.18$ nM, shown below). In Part 7[2] we had observed that the 2-trifluoromethyl-benzimidazole (e.g., **17**) and benzimidazol-2-one moieties were of equal effectiveness when used as phenolic replacements, even though the benzimidazole moiety may exist in two tautomeric forms. One possible explanation for this unexpected contrast in D_2^{High} affinity between (±)-**5** and **17** is the subtle differences in the electronic effects and/or the constraining effects induced by the pyran ring. The lower affinity of (±)-**5** suggests that the predominant tautomer (±)-**5** does not correspond to the predominant tautomer of **17**.[2] This suggests the pyran ring maybe shifting the tautomeric equilibrium such that the crucial hydrogen bond donating directionality requirements of the D_2 agonist pharmacophore are no longer as effectively being met (as indicated in **5** below).



17



5

Upon resolution of (±)-**6** it was learned that (−)-**6** had 78-fold higher affinity than (+)-**6**. From our earlier reported resolutions within the chroman series, the *R* configuration was consistently found to be associated with the eutomer. Even though we have not determined the absolute stereochemistry of the enantiomers of **6**, the similarity of the eudismic ratio, the affinities for the D_2–D_4 receptors, the optical rotations of our four previously resolved racemates within the chroman framework (see Parts 1 and 4), as well as the results discussed below, strongly suggest that the eutomer has the *R* configuration [i.e., *R*-(−)-**6**]. Interestingly, even though (−)-**6** was observed to have similar predicted intrinsic activity and affinity for the D_2^{High} receptor as its indolone analogue[6] [*R*-(−)-**4**, see Table 1], it had significantly higher affinity for the human cloned D_2–D_4 receptors.

Dopamine agonists are known to reduce locomotor activity by stimulation of presynaptic receptors while dopamine antagonists reduce locomotor activity by antagonism of dopamine at postsynaptic receptors. Dopamine partial agonists show a mixture of effects with a reduction in locomotor activity occurring at low doses which stimulate presynaptic receptors followed by a return to baseline levels of activity or hyperactivity as the dose is increased.

Consistent with the estimated intrinsic activity predicted from binding and with the results previously reported for *R*-(−)-**2**,[5] in vivo studies showed both (±)-**6** and (−)-**6** to reduce spontaneous locomotor activity in mice [($ED_{50} = 0.04$ (0.02–0.07) mg/kg sc and 0.03 (0.01–0.11) mg/kg sc, respectively)], while (+)-**6** did not alter locomotor activity significantly at doses up to 3 mg/kg sc.

In conclusion we have identified two novel D_2 partial agonists which are heterocyclic bioisosteric analogues of the recently discovered DA D_2 template (**2**). Resolution of (±)-**6** resulted in finding the eutomer to be (−)-**6**, with an eudismic ratio of similar magnitude to compounds previously resolved in the chroman series (i.e., 50–80). Studies in our laboratories are continuing to further understand the D_2 agonist pharmacophoric criteria and ultimately to identify novel antipsychotic agents belonging to this new generation of dopaminergic agents.

References and Notes

1. Meltzer, H. Y.; Stahl, S. M. *Schizophr. Bull.* **1979**, *2*, 19.
2. For previous work see Part 7, Mewshaw, R. E.; Nelson, J. A.; Shah, U. S.; Shi, X.; Mazandarani, H.; Coupet, J.; Marquis, K.; Brennan, J. A.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2593 and references therein..
3. Kaiser, C.; Jain, T. *Med. Res. Rev.* **1985**, *5*, 145.
4. Freeman, H. S.; McDermed, J. D. In *Chemical Regulation of Biological Mechanisms*; Crieghton, A. M., Turner, S., Ed.; Royal Society of Chemistry: London, 1982; p. 154.
5. Mewshaw, R. E.; Kavanagh, J.; Stack, G.; Marquis, K.; Shi, X.; Kagan, M. Z.; Webb, M. B.; Katz, A. H.; Park, A.; Kang, Y. H.; Abou-Gharbia, M.; Wasik, T.; Cortes-Burgos, L.; Scerni, R.; Spangler, T.; Brennan, J. A.; Piesla, M.; Mazandarani, H.; Coupet, J.; Andree, T. H. *J. Med. Chem.* **1997**, *40*, 4235.
6. Mewshaw, R. E.; Marquis, K.; Shi, X.; McGaughey, G.; Stack, G.; Webb, M. B.; Abou-Gharbia, M.; Wasik, T.; Scerni, R.; Spangler, T.; Brennan, J. A.; Mazandarani, H.; Coupet, J.; Andree, T. H. *Tetrahedron* **1998**, *54*, 7081.
7. Ellis, G. P.; Barker, G. *J. Chem. Soc. C* **1970**, *18*, 2609.
8. Lahti, R. A.; Figur, L. M.; Peircey, M. F.; Ruppel, P. L.; Evans, D. L. *Mol. Pharm.* **1992**, *42*, 432.
9. Wasik, T.; Cockett, M.; Andree, T. H. *Soc. Neurosci. Abst.* **1996**, *22*, 831.
10. K_i values are the means of $n = 2$–3 experiments run at six different concentrations. Each experiment was carried out in triplicate. 95% confidence limits were generally +15% of the mean value.