Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 3195–3199
Bioorganic & Medicinal Chemistry Letters

Benzimidazoles as new potent and selective DP antagonists for the treatment of allergic rhinitis

Christian Beaulieu,* Zhaoyin Wang, Danielle Denis, Gillian Greig, Sonia Lamontagne, Gary O'Neill, Deborah Slipetz and Jennifer Wang

Merck Frosst Centre for Therapeutic Research, PO Box 1005, Kirkland, QC, Canada H9R 4P8

Received 4 March 2004; revised 30 March 2004; accepted 1 April 2004

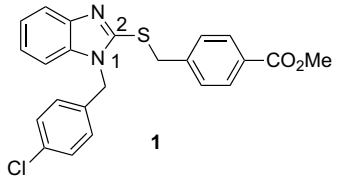
Abstract—A series of 2-substituted *N*-benzyl benzimidazole containing molecules has been synthesized and its structure–activity relationship for the human DP receptor has been evaluated. Selective DP antagonists with nanomolar potency for the DP receptor were identified in this novel series of benzimidazoles.

The symptoms of allergic rhinitis are multifactorial and induced by the action of a variety of lipid mediators, of which histamine, cysteinyl leukotrienes (cys-LTs) and prostaglandin D_2 (PGD_2) are considered as the most important.[1] Prostaglandin D_2 is the major cyclooxygenase metabolite produced by the immunologic stimulation of mast cells[2] and is found in nasal lavage fluid following allergen challenge of atopic individuals.[3] Nasal congestion in allergic rhinitis results from tissue edema and vasodilatation in the nasal mucosa. Comparative studies in humans have shown that the intranasal instillation of PGD_2 reproduces the airway obstruction experienced by seasonal allergic rhinitics with a potency 10 times greater than histamine.[4] Considering its various inflammatory effects, PGD_2 appears to be an important component in the pathogenesis of allergic diseases.[3–7] PGD_2 as a bioactive prostanoid interacts preferentially with DP receptor, which is one of eight known prostanoid receptors (DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP).[8] The role of the DP receptor in the regulation of mucous secretion[9] and the efficacy of DP receptor blockade in allergic disease models[10] supported the idea that a selective DP antagonist might be of therapeutic value for allergic rhinitis.

In this communication, we describe the discovery and detailed SAR studies of a novel series of potent and selective DP antagonists built on a 2-substituted *N*-benzyl benzimidazole scaffold.

Based on radioligand competition binding assays using recombinant human DP receptor, high throughput screening of our sample collection revealed that *N*-benzyl benzimidazole derivatives were potentially a new series of potent DP antagonists. In the design of the molecules to be synthesized, the selection of 4-chlorobenzyl substitution at position-1 of benzimidazole (Fig. 1) was derived from previous studies in this program based on a similar scaffold.[11] These SAR studies showed the superiority of 4-chlorobenzyl as substituent at position-1. To explore the structure–activity relationship in the series, 4-chlorobenzyl group was kept at position-1 of the benzimidazole template and various groups and linkers were introduced at position-2 to probe the requirements for both potency and selectivity.

The general synthetic routes to these benzimidazole derivatives are outlined in Schemes 1–5. The 2-benzylthio benzimidazoles (Scheme 1) were prepared from the commercially available 2-chloro benzimidazole **2**.

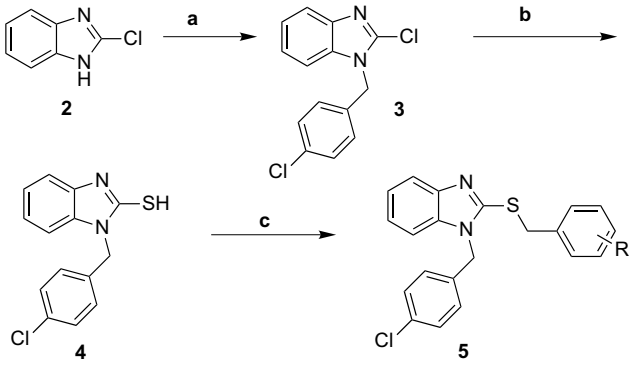


1

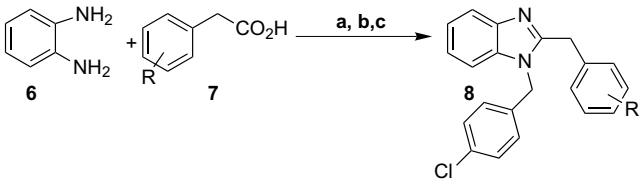
Figure 1.

Keywords: Benzimidazole; DP antagonist.
* Corresponding author. Tel.: +1-514-4283297; fax: +1-514-4284900; e-mail: christian_beaulieu@merck.com

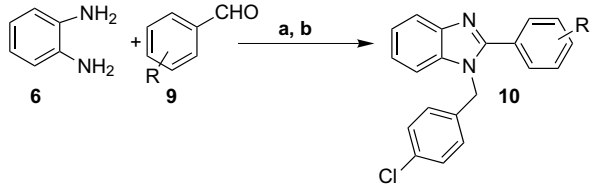
0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.04.005



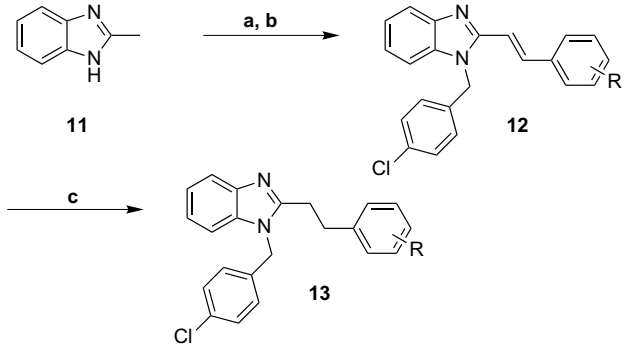
Scheme 1. Reagents and conditions: (a) NaH, DMF, 4-ClPhCH$_2$Br, 80%; (b) potassium thioacetate, EtOH, reflux, 80%; (c) Cs_2CO_3, CH_3CN, ArCH$_2$Br, 50–90%.



Scheme 2. Reagents and conditions: (a) CDI, CH_2Cl_2; (b) HCl (concd), MeOH, 80%; (c) K_2CO_3, DMF, 4-ClPhCH$_2$Br, 86%.

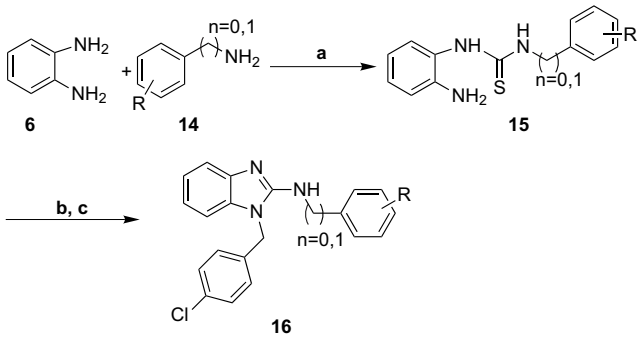


Scheme 3. Reagents and conditions: (a) $PhNO_2$, 120 °C, 50%; (b) NaH, DMF, 4-ClPhCH$_2$Br, 91%.



Scheme 4. Reagents and conditions: (a) K_2CO_3, DMF, 4-ClPhCH$_2$Br, 88%; (b) ArCHO, Ac_2O, xylene, reflux, 35%; (c) H_2, Pd/C, EtOH, 88%.

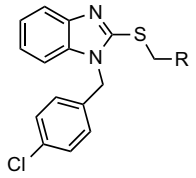
Deprotonation of **2** with NaH in DMF followed by reaction with 4-chlorobenzyl bromide afforded the intermediate **3**. The alkylation product was then converted to the 2-thio benzimidazole **4** by displacement of the chlorine atom with potassium thioacetate followed by hydrolysis catalyzed by the presence of a base in the reaction mixture. Alkylation of **4** with various substituted benzyl bromides in the presence of cesium carbonate in acetonitrile gave the final 2-benzylthio benzimidazoles **5**. 2-Alkyl benzimidazoles (Scheme 2) were prepared by a condensation reaction involving benzene-1,2-diamine **6** and the carboxylic acid **7** using carbonyl diimidazole as a coupling reagent and HCl as a catalyst for cyclization. The cyclization product was then alkylated with 4-chlorobenzyl bromide to give the 2-alkyl-1-(4-chlorobenzyl)-benzimidazoles **8**. The same starting material was used for the synthesis of 2-aryl benzimidazole **10** (Scheme 3). The diamine **6** was condensed with properly substituted benzaldehydes in nitrobenzene and the resulting benzimidazole intermediates were alkylated to give the product **10**. The 2-phenylethenyl benzimidazoles **12** and 2-phenethyl benzimidazoles **13** (Scheme 4) were prepared from the 2-methyl benzimidazole **11** by condensation with a substituted benzaldehyde in the presence of acetic anhydride. A simple hydrogenation of the double bond of **12** afforded **13**. For the synthesis of 2-alkylamino benzimidazoles **16** (Scheme 5), we used a procedure developed by Meissner[12] which consists of acylation of an alkylamine with thiocarbonyldiimidazole followed by the addition of 1,2-phenylenediamine to promote the formation of the unsymmetrical thiourea **15** which after cyclodesulfurization provided access to the 2-alkylamino benzimidazoles **16**.



Scheme 5. Reagents and conditions: (a) 1,1-Thiocarbonyldiimidazole, imidazole, CH_3CN, reflux, 55–80%; (b) HgO, S8, EtOH, 50–55%; (c) K_2CO_3, DMF, 4-Cl-PhCH$_2$Br, 35–63%.

The SAR studies were first initiated with the sulfur linker series due to the simplicity of synthesis and availability of a large variety of substituted benzyl halides. The SAR on the nature of the substitution pattern of the benzyl moiety is summarized in Table 1 and based on affinities measured in radioligand competition assays.[13] In general, compounds were screened for affinity against all eight human prostanoid receptors. The principal 'off-target' affinity of compounds in this series was at the thromboxane A_2 receptor (TP). In addition, in order to evaluate the effect of proteins on the affinity of compounds at DP receptor, binding assays in the presence of 0.5% human serum albumin (HSA) were performed. We were delighted to see that the first compound prepared in this series (**1**, Table 1) shows a K_i of 0.073 μM on human DP receptor and 9.1 μM on human TP receptor

Table 1. Dissociation equilibrium constant determination of selected analogs for the SAR on the aryl ring of the benzylic group



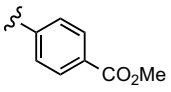
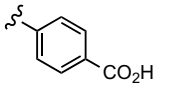
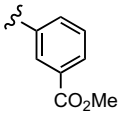
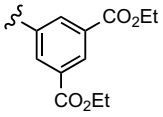
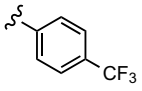
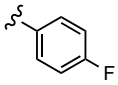
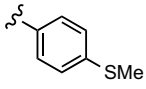
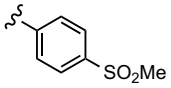
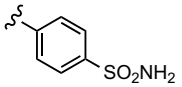
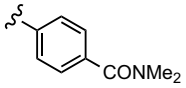
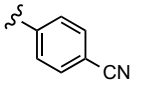
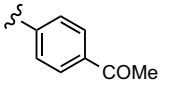
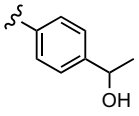
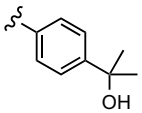
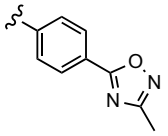
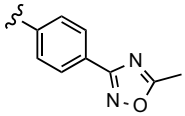
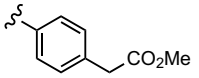
Compds	R	DP[a] K_i (μM)	TP[a] K_i (μM)
1		0.073	9.1
17		3.5	4.7
18		1.1	9.3
19		>43	>71
20		6.7	4.2
21		2.6	>73
22		>42	6.1
23		0.55	>73
24		1.1	2.0
25		1.2	>70
26		0.8	2.0
27		4.2	0.95
28		0.3	3.8
29		0.27	1.5
30		0.14	11.9

Table 1 (*continued*)

Compds	R	DP[a] K_i (μM)	TP[a] K_i (μM)
31		0.31	>74
32		0.096	>74
33		0.33	1.5

[a] Radioligand competition binding assays using recombinant human prostaglandin D_2 (DP) and recombinant human thromboxane receptor (TP).

in the radioligand competition assays. The selectivity of compound **1** on DP over TP is 125-fold based on K_i values. The hydrolysis of the methyl ester **1** to the corresponding carboxylic acid **17** resulted in the loss of potency by approximately 50-fold. Based on this observation we concentrated our efforts on non-acid groups at this position. The substitution at the *para* position of the phenyl ring appeared to be critical for the affinity on DP receptor. Thus the ester **18** and the diester **19** substituted in *meta* position are much less active than the corresponding *para* substituted compound and that was also true with the unsubstituted analog **20**. Once the *para* substitution on the phenyl ring was defined as optimal, we focused on finding groups that provide better potency than the methyl ester. Introduction of nonpolar electron-withdrawing groups such as CF_3 (**21**) and fluorine atom (**22**) significantly reduced the potency. Introduction of groups such as methylthioether (**23**), methylsulfone (**24**), sulfonamide (**25**), dimethyl carboxamide (**26**) and nitrile (**27**) resulted in compounds less active than **1**. The presence of methyl ketone (**28**), secondary alcohol (**29**) and tertiary alcohol (**30**) also diminished the activity to some extent. However, the potency of these analogs is approaching that of **1**. Of particular interest is the tertiary alcohol **30** with a K_i of 0.14 μM at DP. In addition, the affinity at DP receptor is minimally shifted (3.5-fold) in the presence of 0.5% HSA. The methyl ester group in **1** is metabolically labile, therefore it would be desirable to replace it with ester mimetics such as methyl oxadiazole ring. Among the two isomeric oxadiazole analogs prepared, **31** is less potent than **1**, whereas the other isomer **32** retains the potency of **1** and its potency is shifted only by 2-fold in the presence of 0.5% HSA with a K_i of 0.195 μM compared to a K_i of 0.297 μM for **1** in the same assay. We also observed loss of activity with **33** in which a methyl phenyl acetate group replaces the methyl benzoate group from **1**.

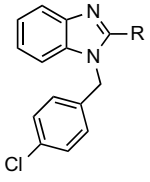
In summary, the SAR studies done on the phenyl ring of the benzyl group at position-2 on the benzimidazole core did not provide any improvement of potency compared

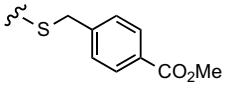
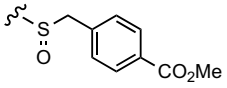
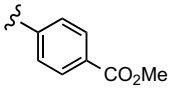
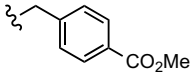
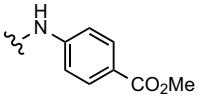
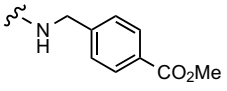
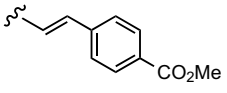
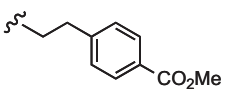
to that of **1**. It appeared that methyl ester group and methyl oxadiazole were the best substituents and we decided to investigate the impact of the spacer separating the benzimidazole ring and the *para* substituted phenyl ring on the activity and the results are summarized in Table 2.

The first modification to the spacer between the benzimidazole ring and the phenyl ring was the oxidation of the sulfide group from **1** to the sulfoxide **34** and that resulted in a 8-fold loss of activity. The need of a spacer is demonstrated by the low activity obtained with the 2-aryl benzimidazole **35**. Slightly better potency was observed for the 2-benzyl benzimidazole analog **36** that has a methylene group as the spacer. The replacement of the methylene group of **36** by a nitrogen atom in **37** increased the activity but was still 20-fold less than that for **1**. The addition of a methylene group between the nitrogen atom and the phenyl group of **37** did not improve dramatically the activity as observed for **38**. However the 2-phenylethenyl benzimidazole **39** and the 2-phenethyl benzimidazole **40** showed improved activity over **1**. These new spacers improved the activity on DP by 2- and 3-fold, respectively (**39**: DP $K_i = 0.038\,\mu M$, **40**: DP $K_i = 0.024\,\mu M$). The potency of **40** in the presence of 0.5% HSA is shifted to the same extent than **1**, and the potency of **39** is 2-fold less shifted than **1**. However, **39** and **40** are 4- and 2-fold more active than **1**, respectively, in the presence of 0.5% HSA, which is a significant improvement over **1**. The selectivity of **40** over the TP receptor is similar to **1**, however **39** is more selective than **1** and **40** by ~15-fold.

In conclusion, the SAR around the spacer between the benzimidazole ring and the phenyl group allowed design of compounds with improved activity and less protein

Table 2. Dissociation equilibrium constant determination for selected analogs with different spacers separating the benzimidazole ring and the phenyl ring



Compds	R	DP K_i (μM)	DP + 0.5% HSA K_i (μM)	TP K_i (μM)
1		0.073	0.297	9.1
34		0.55	1.5	3.1
35		8.0	0.8	7.0
36		6.2	>12	4.0
37		1.5	5.4	0.9
38		1.1	n.d.	6.0
39		0.038	0.067	>75
40		0.024	0.137	2.2

shift than the original lead compound **1**. The 2-phenylethylene and 2-phenethyl benzimidazoles **39** and **40** were identified as potent DP antagonists with improved selectivity at TP receptor, which are worthy of further investigations. Pharmacokinetics and in vivo studies will be the next step in evaluating the potential of these compounds.

References and notes

1. Howarth, P. H. *Allergy* **1997**, *52*, 12–18.
2. Naclerio, R. M.; Meier, H. L.; Kagey-Sobotka, A.; Norman, P. S.; Lichtenstein, L. M. *Am. Rev. Respir. Dis.* **1983**, *128*, 597.
3. Naclerio, R. M.; Proud, D.; Togias, A. G.; Adkinson, N. F., Jr.; Meyers, D. A.; Kagey-Sobotka, A.; Plaut, M.; Norman, P. S.; Lichtenstein, L. M. *N. Engl. J. Med.* **1985**, *313*, 65.
4. Doyle, W.; Boehm, S.; Skoner, D. P. *J. Allergy Clin. Immunol.* **1990**, *86*, 924.
5. Murray, J. J.; Tonnel, A. B.; Brash, A. R.; Roberts, L. J., II; Gosset, P.; Workman, R.; Capron, A.; Oates, J. A. *N. Engl. J. Med.* **1986**, *315*, 800.
6. Proud, D.; Sweet, J.; Stein, P.; Settipane, R. A.; Kagey-Sobotka, A.; Friedlaender, M. H.; Lichtenstein, L. M. *J. Allergy Clin. Immunol.* **1990**, *85*, 896.
7. Charlesworth, E. N.; Kagey-Sobotka, A.; Schleimer, R. P.; Norman, P. S.; Lichtenstein, L. M. *J. Immunol.* **1991**, *146*, 671.
8. Boie, Y.; Sawyer, N.; Slipetz, D. M.; Metters, K. M.; Abramovitz, M. *J. Biol. Chem.* **1995**, *270*, 18910.
9. Wright, D. H.; Ford-Hutchinson, A. W.; Chadee, K.; Metters, K. M. *Br. J. Pharmacol.* **2000**, *131*, 1537.
10. Arimura, A.; Yasui, K.; Kishino, J.; Asanuma, F.; Hasegawa, H.; Kakudo, S.; Ohtani, M.; Arita, H. *J. Pharm. Exp. Ther.* **2001**, *298*, 411.
11. Unpublished results.
12. Perkins, J. J.; Zartman, A. E.; Meissner, R. S. *Tetrahedron Lett.* **1999**, *40*, 1103.
13. Abramovitz, M.; Adam, M.; Boie, Y., et al. *Biochim. Biophys. Acta* **2000**, *1483*, 285.