Bicyclo[2.2.1]heptane and 6,6-Dimethylbicyclo[3.1.1]heptane Derivatives: Orally Active, Potent, and Selective Prostaglandin D_2 Receptor Antagonists

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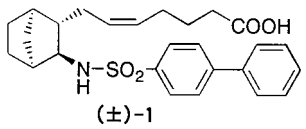
Prostaglandin D_2 (PGD_2), the major cyclooxygenase metabolite produced by mast cells in response to IgE-dependent stimuli,[1] has a variety of inflammatory effects.[2] PGD_2 is considered to be an important mediator in various allergic diseases such as allergic rhinitis, atopic asthma, allergic conjunctivitis, and atopic dermatitis. However, only one compound is available as a tool for pharmacological examination of the PGD_2 receptor,[3] and there has been no report on the efficacy of PGD_2 receptor antagonists in animal allergic models or against human allergic diseases. We thought that a selective PGD_2 receptor antagonist may be of therapeutic value for various allergic disorders.

Our attempt to develop PGD_2 receptor antagonists was undertaken upon discovery of a lead compound by screening of our compound library for their inhibitory effects on specific [^{3}H]PGD_2 binding to human platelet membranes. We found that (±)-(5*Z*)-7-[3-[(biphenyl-4-ylsulfonyl)amino]bicyclo[2.2.1]hept-2-yl]hept-5-enoic acid (**1**), previously reported to be a thromboxane A_2 (TXA_2) receptor antagonist,[4] exhibited fairly strong binding to PGD_2 receptor (Figure 1). We synthesized the two enantiomers of this compound to determine their biological activities. A comparison of (+)-**1** and **3** with their (−)-enantiomers revealed that the (+)-enantiomers were suitable for our purpose, since the (−)-enantiomers exhibited strong TXA_2 receptor binding activity and no effect on nasal blockage in the *in vivo* model (Tables 1 and 2). Next, a structure−activity relationship study was performed with bicyclic ring systems and *ω*-side chains. Since these studies revealed that the 6,6-dimethylbicyclo[3.1.1]heptane ring system was also effective for inhibiting PGD_2 binding, two different types of structures were synthesized to obtain the desired compounds.

Chemistry

(1*S*,2*R*,3*R*,4*R*)-(5*Z*)-7-(3-Aminobicyclo[2.2.1]hept-2-yl)-hept-5-enoic acid methyl ester and (1*R*,2*R*,3*S*,5*S*)-(5*Z*)-7-(2-amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic acid methyl ester were prepared by methods described in the literature.[4,5] Coupling these amino derivatives with sulfonyl chloride or carbonyl chloride prepared by conventional methods readily produced the desired esters in good yield.[6] Hydrolysis of these esters using aqueous potassium hydroxide in methanol produced the target molecules in almost quantitative yields (Schemes 1 and 3). Compound **13** was obtained from



(±)-1

Figure 1.

Table 1. Inhibition of DP, TP, and IP Receptor Binding and Biological Activity in Human Platelets

	IC_{50} (μM)[a−c]			
	DP		TP:	IP:
compd	binding	cAMP	binding	cAMP
(+)-**1**	0.60	0.45	1.1	5.0
(−)-**1**	0.46	0.52	0.044	>10
(+)-**3**	1.2	0.42	0.67	8.9
(−)-**3**	4.9	>1	0.00013	3.3
4	0.72	0.78	1.3	>10
5	0.027	0.32	1.3	>10
6	0.0086	0.25	0.28	>10
7	0.13	0.070	1.7	1.5
8	1.1	0.25		4.5
9	0.027	0.068	>10	5.9
10	3.0	>1		1.4
13	0.047	0.12	1.2	>10
15	5.2	0.36	0.81	>10
16	1.6	0.038	2.1	>10
17	0.032	0.064	3.1	>10
18	0.032	0.022	0.38	>10
19	0.00040	0.0010	0.096	>10
20	0.00027	0.0018	0.43	>10
21	0.0013	0.0028	0.41	>10
22	0.026	0.0056	0.21	>10
23	0.54	0.38	0.15	>10
24	0.032	0.22	0.27	7.5
25	1.3	>1	0.74	3.4
26	0.78	>1	0.24	>10

[a] PGD_2 receptor (DP) assay. Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[9] and cAMP formation evoked by PGD_2 in human platelets.[10] The human platelet membranes were incubated with various concentrations of the test compounds and 5 nM [^{3}H]PGD_2 for 60 min at 4 °C. Human platelets were stimulated with 0.1 μM PGD_2 for 2 min following 10-min preincubation with various concentrations of the test compounds at 37 °C in the presence of 3-isobutyl-1-methylxanthine (IBMX). [b] TXA_2 receptor (TP) assay. Inhibition of [^{3}H](+)-S-145 specific binding to human platelet membranes.[11] The human platelet membranes were incubated with various concentrations of the test compounds and 2 nM [^{3}H](+)-S-145 for 60 min at room temperature. [c] PGI_2 receptor (IP) assay. Inhibition of cAMP formation by carbacyclin.[10] Human platelets were incubated with 0.1 μM carbacyclin for 2 min following 10-min preincubation with various concentrations of the test compounds at 37 °C in the presence of IBMX. IC_{50} represents the mean value of two or three measurements.

11 by the Sonogashira reaction,[7] followed by Pd-catalyzed cyclization reaction (Scheme 2).[8]

Biological Results and Discussion

The structure−activity relationship study revealed that, for exhibition of the potent antagonism of the PGD_2 receptor, sulfonylamino and carbonylamino groups are required for the compounds with bicyclo[2.2.1]heptane ring and 6,6-dimethylbicyclo[3.1.1]heptane ring systems, respectively. In the case of compounds with a bicyclo[2.2.1]heptane ring system, phenyl- or biphenylylsulfonylamino derivatives having various substituents did not show improved activity. Since the conformation of the biphenyl ring seemed to be important, we prepared some compounds having a spacer between the two phenyl rings of **1** to change their conformation. Good activity was obtained as illustrated by compounds **4**−**6**

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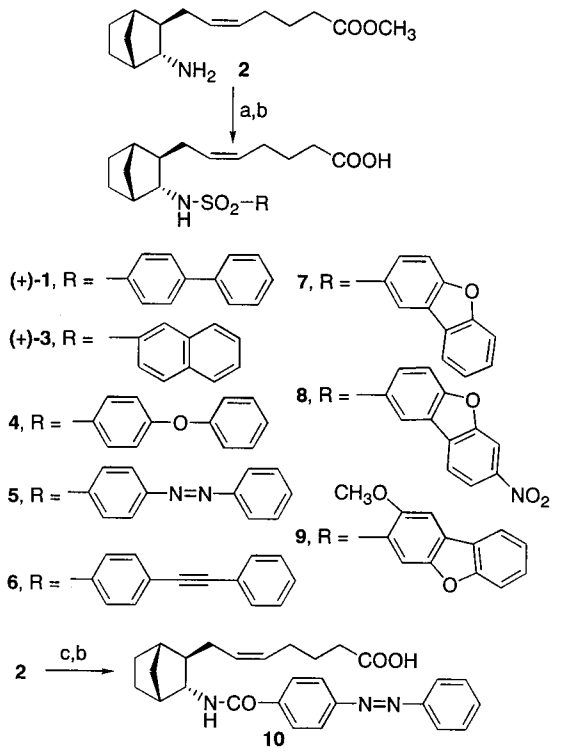
Table 2. Inhibition of Antigen-Induced Nasal Blockage in Guinea Pigs

	rhinitis model	
compd	% inhibn at 1 mg/kg (iv)[a]	ED_{50} (mg/kg, po)[b]
(+)-**1**	39 ± 17[c]	
(−)-**1**	−20 ± 24[c]	
(+)-**3**	54 ± 9[d]	
(−)-**3**	6 ± 24	
4	25 ± 9	
6	25 ± 12	
7	82 ± 4[d]	3.5[e]
9	80 ± 3[d]	2.2
13	60 ± 7[d]	7.2
16	77 ± 5[d]	5.1
19	78 ± 8[d]	2.1
20		1.0

[a] Inhibition of antigen-induced increase in intranasal pressure in actively sensitized guinea pigs, according to ref 12. Compounds were administered iv 10 min before the antigen challenge. Values are the mean ± SEM; $n = 5-10$/group. [b] Dose required to inhibit 50% of antigen-induced increase in intranasal pressure. Compounds were administered po 1 h before the challenge. Dose−response data was determined for $n = 5-10$ animals/data point. [c] Tested at 3 mg/kg. [d] Significantly different from each control, $p < 0.01$ (Student's *t*-test). [e] Na salt was used.[13]

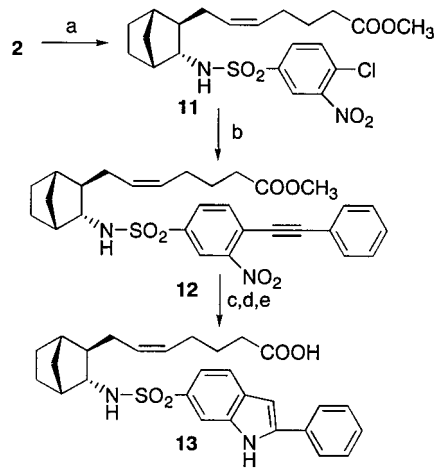
Scheme 1[a]



[a] Reagents: (a) RSO_2Cl, Et_3N; (b) KOH; (c) $RCOCl$, Et_3N.

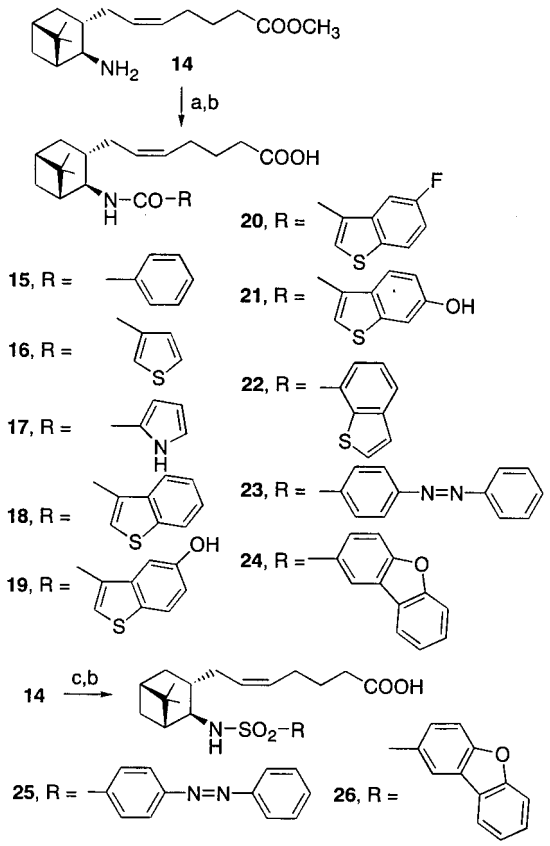
(Table 1). The same was attempted with compounds having carbonylamino groups, but no improved activity was observed as shown by compound **10**. Next, we linked each phenyl group of **4** by a C−C bond to make a rigid conformation of diphenyl ether group. This attempt enhanced *in vivo* activity, as illustrated by compound **7** (Table 2). A similar modification was performed for compound **6**. The corresponding compound **13** also exhibited *in vivo* activity higher than did **6**. Various kinds of substituents were tested for compound **7**, and introduction of an electron-donating group to the aromatic ring systems resulted in higher *in vitro* activities, as demonstrated by comparison of compounds **7**, **8**, and **9**.

Scheme 2[a]



[a] Reagents: (a) RSO_2Cl, Et_3N; (b) $Pd(PPh_3)_2Cl_2$, phenylacetylene; (c) Fe, NH_4Cl; (d) $PdCl_2$; (e) KOH.

Scheme 3[a]



[a] Reagents: (a) RCOCl, Et_3N; (b) KOH; (c) RSO_2Cl, Et_3N.

On the other hand, in the case of compounds with a 6,6-dimethylbicyclo[3.1.1]heptane ring system, carbonylamino groups gave better activity than sulfonylamino groups in the *in vitro* assay, as demonstrated by comparison of compounds **23**, **24**, **25**, and **26**. Among the compounds having carbonylamino groups, the simple compound **15** exhibited fairly good activity, and replacing the phenyl group with a thiophene group enhanced the activities in both assays as shown by compound **16**. Further modification of this moiety, mainly by replacement with heterocyclic aromatic rings, was performed to obtain the highly active compounds **17**−**22**.

Further evaluation was performed for the selected compounds **9**, **16**, **19**, and **20**, which markedly inhibited

Table 3. Effect of Orally Administered DP Antagonists on PGD_2- and Antigen-Induced Increase in Vascular Permeability in Conjunctiva and Antigen-Induced Increase in Specific Airway Resistance in Guinea Pigs

	conjunctivitis model ED_{50} (mg/kg)[a]		asthma model % inhibn at 10 mg/kg:[b]
compd	PGD_2	antigen	antigen
9	1.6	6.6	42 ± 12
16	3.5	9.5	15 ± 21
19	0.12	2.0	70 ± 5[c]
20	3.5	8.9	69 ± 9[c]

[a] Dose required to inhibit 50% of the increase in conjunctival microvascular permeability caused by topical application of 0.1% PGD_2 in normal guinea pigs[2d] or antigen in guinea pigs which actively sensitized with ovalbumin.[12] Dose−response data was determined for $n = 3-10$ animals/data points. [b] Inhibition of increase in specific airway resistance by antigen inhalation in conscious guinea pigs. All antagonists were administered po 1 h before the challenge. Values represent the mean ± SEM, $n = 4-11$ animals/group. [c] Significantly different from each control, $p < 0.01$ (Student's *t*-test).

PGD_2- and antigen-induced increase in conjunctival microvascular permeability. In the asthma model, these compounds, particularly **19** and **20**, also inhibited an antigen-induced increase in specific airway resistance at 10 mg/kg (po) (Table 3). Since PGD_2 is thought to exert a contractile response of airway smooth muscle by directly acting on the TXA_2 receptor not via the PGD_2 receptor,[3a,14,15] there is a possibility that the antiasthmatic activity of these compounds arose from their TXA_2 receptor antagonistic activity. However, this possibility was ruled out by our finding that all four of these compounds did not meaningfully affect the bronchoconstriction induced by intravenous injection of U-46619, a TXA_2 mimetic, at 10 mg/kg (po) in the guinea pig model[14] (data not shown). Thus the PGD_2 receptor mediated component may have a role in the antigen-induced increase in specific airway resistance.[2c] We also evaluated the effect of compound **19** on antigen-induced eosinophil infiltration in allergic rhinitis and asthma models. Compound **19** effectively reduced the increase in eosinophil number in nasal lavage fluid at 5 h after intranasal antigen challenge in actively sensitized guinea pigs[16] and in bronchoalveolar lavage fluid at 72 h after inhalation of aerosol antigen,[17] the percent inhibition at 10 mg/kg (po) being 80% ($p < 0.01$) and 43% ($p < 0.05$), respectively.

We have described here novel PGD_2 receptor antagonists, containing bicyclo[2.2.1]heptane and 6,6-dimethylbicyclo[3.1.1]heptane ring systems with characteristic sulfonylamino or carbonylamino groups, which were originally synthesized in our laboratories. Although there are numerous reports on the contribution of PGD_2 to the pathogenesis of allergic diseases on the basis of local production of PGD_2 after antigen challenge,[18] this study provides experimental evidence suggesting that the PGD_2 receptor antagonist is effective for alleviating various allergic diseases. This is the first report of promising drug candidates for diseases caused by excess production of PGD_2.

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Supporting Information Available: Experimental details with spectral data (20 pages). Ordering information is given on any current masthead page.

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