Communications to the Editor

Dibenz[b,e]oxepin Derivatives: Novel Antiallergic Agents Possessing Thromboxane A_2 and Histamine H_1 Dual Antagonizing Activity. 1

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Thromboxane A_2 (TXA_2), a short-lived metabolite of arachidonic acid (AA), is a powerful inducer of platelet aggregation and of vascular smooth muscle contraction.[1] In addition, TXA_2 has been implicated in the pathophysiological conditions of asthma, since it has been shown to produce bronchoconstriction[2] and contribute to airway hyperresponsiveness,[3-7] a key feature of asthma.[8] Therefore, intensive efforts have been made to discover TXA_2 synthase inhibitors (TXS-I) and TXA_2 receptor antagonists (TXRA), and presently several of TXS-Is and TXRAs are undergoing clinical evaluations as new antiasthmatic agents.[9] Since multiple mediators are involved in asthma,[7] an agent which inhibits other mediator(s) in addition to TXA_2 should be clinically more effective than selective TXS-I or TXRA. We have recently reported antiallergic and histamine H_1 receptor antagonizing activities of KW-4994 (**1**)[10] and **2**[11] (Chart I). Moreover, dibenz[b,e]oxepin derivatives **3**[12] and **4**[13] were found to be potent TXRAs. Thus we attempted to synthesize an antiallergic agent possessing TXA_2 and histamine H_1 dual antagonizing activity. Taking the compatibility between the structure–activity relationships of **1–4**, we designed the general structure **5**. The tertiary amino group in the side chain of **5** was expected to be an equivalent of the benzimidazole moiety that was crucial for the enhanced TXRA activity of **4**.

In this paper, we will describe the synthesis and structure–activity relationships of a new series of 6,11-dihydrodibenz[b,e]oxepin derivatives (**5**). Sulotroban (**6**),[14-16] one of the representative non-prostanoid TXRAs,[17-23] was used as a reference compound during our series of experiments.

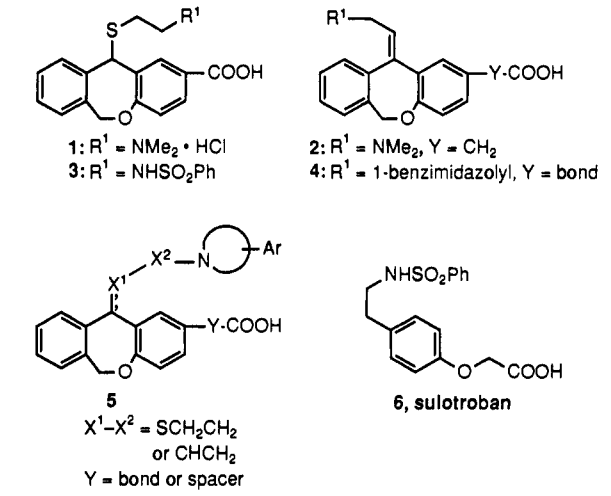
Chemistry

Compounds **7–17**, listed in Table I, were obtained by the alkaline saponification of the corresponding esters **22–32**, which were prepared from **18** as depicted in Scheme I.

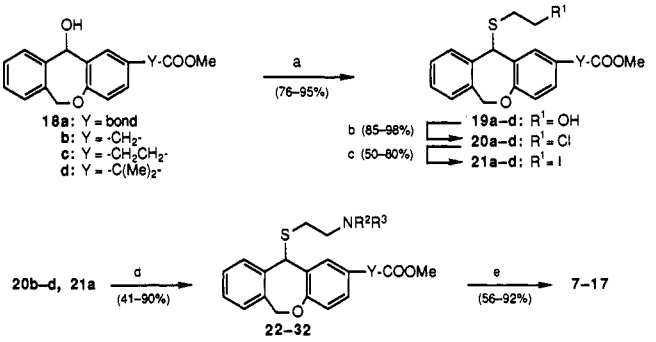
Compounds **18** were treated with trifluoroacetic anhydride and subsequently with 2-mercaptoethanol to provide **19**,[10,12] which were converted into iodides **21** by consecutive treatments with MsCl/LiCl/DMF and NaI/CH_3CN. However, since the iodides **21b–d** were unstable, the chlorides **20b–d** were used in the next reaction. Compounds **20b–d** and **21a** were allowed to react with a secondary amine (HNR^2R^3) in refluxing EtOH to afford **22–32**. Resolution of racemic **12**, one of the most promising examples in this study, was accomplished by HPLC separation of the precursor (±)-**27** on a Chiralcel OD column and subsequent saponification.

Compounds **33** and **34** (Table II) were prepared by the methods depicted in Schemes II and III, respectively. A dibenzoxepin derivative possessing an (*E*)-2-chloroethylidene substituent (**35**)[11] was treated with 1-(4-fluo-

Chart I

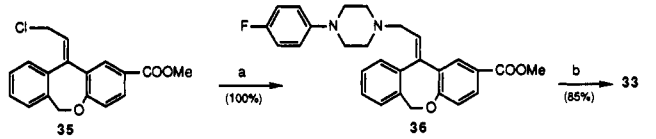


Scheme I [a]



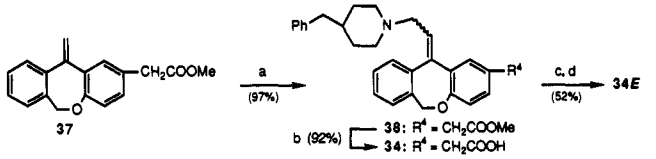
[a] (a) (i) $(CF_3CO)_2O$, CH_2Cl_2; (ii) 2-mercaptoethanol, CH_2Cl_2; (b) MsCl, LiCl, 2,4,6-collidine, DMF; (c) NaI, acetonitrile; (d) HNR^2R^3, EtOH; (e) NaOH, H_2O, MeOH.

Scheme II [a]



[a] (a) 1-(4-fluorophenyl)piperazine, EtOH; (b) NaOH, H_2O, MeOH.

Scheme III [a]



[a] (a) $(HCHO)_n$, 4-benzylpiperidine, CF_3COOH, AcOH, dichloroethane; (b) NaOH, H_2O, MeOH; (c) fumaric acid; (d) fractional crystallization.

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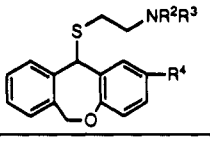
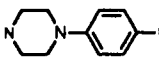
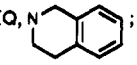
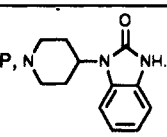
Table I. New Dibenz[*b*,*e*]oxepin Derivatives



no.	NR^2R^3 [a]	R^4	precursor	mp, °C (solvent)[b]	TXA_2/PGH_2 receptor binding (guinea pig washed platelet) K_i,[c] nM	H_1 receptor binding (guinea pig cerebellum) K_i,[c] nM
1, KW-4994	NMe_2	COOH			18% at 1 μM[d]	9.0 ± 1.6 (3)
3	$NHSO_2Ph$	COOH			32 ± 1.4 (3)	0% at 1 μM[d]
6, sulotroban					1300 ± 140 (3)	0% at 1 μM[d]
7[e]	morpholino	COOH	22	220–224 (IPA-MA)	1900 ± 62 (3)	42 ± 6.7 (3)
8[f]	4-Ph-piperazino	COOH	23	244–246 dec (AC)[g]	210 ± 20 (3)	47 ± 5.6 (3)
9	FPP	COOH	24	165–166 dec (IPA)[g]	400 ± 52 (3)	41 ± 5.4 (3)
10[f]	4-Bn-piperazino	COOH	25	112–115 dec (IPE)[g]	490 ± 48 (3)	14 ± 2.2 (3)
11[h]	4-Ph-piperidino	COOH	26	182–184 dec (IPA)	990 ± 60 (3)	20 ± 1.0 (3)
(±)-12[h,i]	4-Bn-piperidino	COONa	(±)-27	78–80 dec (IPA-W)	140 ± 3 (3)	18 ± 3.8 (3)
(+)-12[f,j]	4-Bn-piperidino	COONa	(+)-27	79–81 dec (IPA-W)	14000 ± 1100 (3)	9,9 ± 0.29 (3)
(−)-12[f,k]	4-Bn-piperidino	COONa	(−)-27	79–81 dec (IPA-W)	42 ± 3.8 (3)	740 ± 69 (3)
13	4-Bn-piperidino	CH_2COOH	28	157–158 (TL)[g]	430 ± 52 (3)	10 ± 1.1 (1)
14	4-Bn-piperidino	$C(Me)_2COOH$	29	163–165 (EA)	1600 ± 78 (3)	17 ± 3.2 (3)
15	4-Bn-piperidino	CH_2CH_2COOH	30	141–142 (IPA)	340 ± 67 (3)	12 ± 1.4 (3)
16[l]	THIQ	COOH	31	139–141 (IPE)	240 ± 51 (3)	6.9 ± 0.25 (3)
17[m]	OBIP	COOH	32	185–188 (AN-IPA)	130 ± 14 (3)	500 ± 31 (3)

[a] Ph, phenyl; Bn, benzyl; FPP,  ; THIQ,  ; OBIP,  . [b] IPA, 2-propanol; MA, methanol; AC, acetone; IPE, isopropyl ether; W, water; TL, toluene; EA, ethyl acetate; AN, acetonitrile. [c] Values are mean ± SEM of numbers indicated in parentheses. [d] Percent inhibition, $n = 2$. [e] HCl salt. [f] Monohydrate. [g] Trituration solvent. [h] Hemihydrate. [i] KW-4099. [j] ≥99.5% ee; $[\alpha]_D$ +84.1° (c = 1, MeOH). [k] ≥99.5% ee; $[\alpha]_D$ −95.8° (c = 1, MeOH). [l] Dihydrate. [m] 0.25-Hydrate.

rophenyl)piperazine to furnish **36**, which was saponified to provide **33**. No detectable isomerization of the double bond occurred during the conversion. Olefin **37** was treated with 4-benzylpiperidine under Mannich reaction conditions to provide **38** (E/Z = 3.2/1).[11] Compound **38** was saponified and subsequently purified by fractional crystallization to afford the *E*-isomer (**34***E*). Concentration of the mother liquor of the crystallization of the crude **34***E* yielded *Z*-rich **34**, which was esterified, converted to the corresponding oxalate, and purified by crystallization to afford **38***Z* that was the precursor of **34***Z*.

Results and Discussion

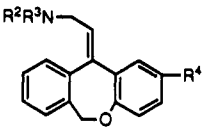
The compounds synthesized were tested for their inhibitory effects both on the specific binding of [^{3}H]U-46619 to guinea pig platelets TXA_2/PGH_2 receptors[12,24] and on the specific binding of [^{3}H]pyrilamine to guinea pig cerebellum histamine H_1 receptors.[11,25] Results are represented by K_i values (Tables I and II).

Most of the compounds, listed in Table I, exhibited both TXA_2 and H_1 antagonizing activities.[26] The terminal structure on the side chain (i.e., NR^2R^3) proved to be important to modulate the biological activities. Compound with 4-phenylpiperazine and its derivatives (**8**–**10**) possessed significant TXRA activities in addition to potent H_1 antagonizing activities, whereas **1** and its morpholine analogue **7** failed to exhibit potent TXRA activity. These data confirmed that the presence of an aromatic ring moiety (i.e., Ar in **5**) was crucial for good TXRA activity. Similarly, a compound with 4-phenylpiperidine (**11**) was potent in both receptor assays, although its TXRA activity (K_i = 990 nM) was approximately 4-fold weaker than that of the corresponding piperazine derivative **8**. Replacement of the phenyl group of **11** with benzyl group to afford (±)-**12** increased the affinity for TXA_2/PGH_2 receptor (K_i = 140 nM). Moreover, the results of **16** indicated that the substitution with tetrahydroisoquinoline, a benzene-fused piperidine, was tolerable and enhanced the affinity for H_1 receptor. On the other hand, compound **17**, possessing a benzimidazolone-substituted piperidine, was much less active than (±)-**12** in the H_1 binding assay, while it retained the TXRA activity (K_i = 130 nM).

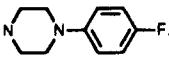
Insertion of a spacer in the acidic moiety (i.e., Y in **5**) caused a decrease in TXRA activity, while its influence was negligible on affinity for H_1 receptor. Compounds with a straight alkylene spacer (**13** and **15**) exhibited 2–3-fold weaker affinities for TXA_2/PGH_2 receptor than (±)-**12**. Insertion of dimethylmethylene group, which provided **14**, resulted in a considerable reduction in TXRA activity. This observation suggested that a steric hindrance around the carboxyl group might affect the interaction between the acidic group and a putative proton-accepting moiety of TXA_2/PGH_2 receptor protein.[27]

Although compound (±)-**12** (KW-4099) was seemingly one of the most promising TXA_2/H_1 dual antagonists in this series, the two modes of actions of (±)-**12** were divided into the optical isomers. Compound (−)-**12** inhibited the specific receptor binding of [^{3}H]U-46619 concentration-dependently with a K_i value of 42 nM and its potency was 30-fold more potent than that of sulotroban (**6**), a pure TXRA. In addition, (−)-**12** possessed a moderate H_1 receptor binding affinity (K_i = 740 nM). On the other hand, (+)-**12** proved to be a potent and selective H_1 antagonist (K_i = 9.9 nM). Therefore, the configuration at the 11-position of the molecule was crucial on the ligand

Table II. New Dibenz[*b*,*e*]oxepin Derivatives



no.	NR^2R^3 [a]	R^4	mp, °C (solvent)[b]	TXA_2/PGH_2 receptor binding (guinea pig washed platelet) K_i,[c] nM	H_1 receptor binding (guinea pig cerebellum) K_i,[c] nM
2	NMe_2	CH_2COOH		>1000 (1)	11 ± 0.9 (3)
4	1-benzimidazolyl	COONa		15 ± 2.3 (4)	NT[d]
33[e,f]	FPP	COOH	236–238 (IPA)	2300 ± 130	3% at 1 μM[g]
34*E*[h,i]	4-Bn-piperidino	CH_2COOH	187–188 (ET)[j]	740 ± 44 (3)	20 ± 0.8 (3)
34*Z*[h,k]	4-Bn-piperidino	CH_2COOH	120 dec (IPA)	2600 (1)	15 ± 1.6 (3)

[a] Bn, benzyl; FPP,  [b] IPA, 2-propanol; ET, ethanol. [c] Values are mean ± SEM of numbers indicated in parentheses. [d] Not tested. [e] Monohydrate. [f] Scheme II. [g] Percent inhibition, $n = 2$. [h] Fumarate half salt. [i] Scheme III. [j] Trituration solvent. [k] Possessing *Z*- geometry.

recognition of each receptor which was recently cloned and shown to possess a similar transmembrane topology to that of rhodopsin.[27,28] X-ray crystallographic data relative to absolute configuration determination will be reported separately.[29]

The enhanced TXRA activity of 4 encouraged us to synthesize some derivatives which possess an ethylidene connecting group. The preliminary results are shown in Table II. Replacement of the benzimidazole moiety of 4 with 4-(4-fluorophenyl)piperazine to provide **33** resulted in a remarkable reduction of TXRA activity. Moreover, **33** was devoid of H_1-receptor binding activity. Interestingly, compound **34***E* exhibited both of TXA_2 antagonizing (K_i = 740 nM) and H_1 antagonizing (K_i = 20 nM) activities. The geometry of the double bond at the 11-position affected the TXRA activity more significantly than the H_1 antagonizing activity. Compound **34***E* was approximately 3-fold more potent than **34***Z* as a TXRA, whereas it was slightly less active than **34***Z* as an H_1 antagonist. Selectivity of **34***E* was also assessed. It showed negligible activities at concentration of 10 μM in the following receptor binding assays: α_1 and α_2 adrenergic, muscarinic 1, H_2 histamine, serotonin, dopamine, platelet-activating factor, PGE_2, and PGI_2.

Compound **34***E* showed potent inhibitory effect on 48 h homologous passive cutaneous anaphylaxis (PCA) in rats (ED_{50} = 0.73 mg/kg, po).[11] In this model, antihistamines **1**, **2**, and ketotifen[30] exhibited inhibitory effects with ED_{50} values of 0.92, 0.077, and 4.8 mg/kg, po, respectively, while sulotroban (**6**) and **4** did not show any efficacy in this model. Histamine- and U-46619-induced bronchoconstrictions in guinea pigs were prevented by the oral pretreatment of **34***E* (0.3 mg/kg and 10 mg/kg, respectively).[31] In addition to the good oral activities described above, **34***E* has a great safety margin to effect both of receptor antagonizing activities (e.g., LD_{50} > 1000 mg/kg, po, rats).[32]

In conclusion, we have demonstrated the successful modifications of the structures of TXRAs and H_1 antagonists possessing a dibenzoxepin ring system to obtain a TXA_2/H_1 dual receptor antagonist. (*E*)-11-[2-(4-Benzylpiperidino)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid fumarate half salt (**34***E*) represents the first of the antiallergic agents to combine TXA_2/H_1 dual antagonism in one molecule. Compound **34***E* (KF15766) is selected for the new lead of further modifications to obtain a better-balanced TXA_2/H_1 dual antagonist. The results of this endeavor will be addressed in future publications.

Acknowledgment. We are grateful to A. Nakamura, T. Yasuzawa, and K. Yamaguchi for spectral data, and especially to Drs. N. Hirayama, T. Kumazawa, and K. Suzuki for their continuous support and pertinent discussion. Appreciation is expressed for excellent technical assistance by T. Watanabe.

Supplementary Material Available: Experimental procedures for the synthesis of **22–38**, procedures for the histamine-1 receptor and TXA_2/PGH_2 receptor binding assays, and elemental analyses (8 pages). Ordering information is given on any current masthead page.

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(26) Compound (+)-**12**, an example possessing a potent H_1 receptor binding affinity demonstrated significant inhibitory effect on histamine-induced contraction of guinea pig tracheal preparation (pA_2 = 8.57). In addition, (−)-**12**, possessing an affinity for TXA_2/PGH_2 receptor-inhibited U-46619-induced contraction of the same tracheal preparation (pA_2 = 7.22). Any agonistic effect of the compounds was not observed in the experiments.

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(30) Ketotifen, an antiallergic agent possessing a similar tricyclic skeleton, was used as a reference compound.

(31) Male Hartley guinea pigs (400–600 g) were pretreated with **34***E* (po) and propranolol (3 mg/kg, ip) 1 h and 30 min before spasmogen injection, respectively. Bronchoconstriction induced by histamine (50 μg/kg, iv) or U-46619 (1.05 μg/kg, iv) was measured by the method of Konzett and Rōssler: Konzett, H.; Rōssler, R. *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.* **1940**, *195*, 71–74. Compound **34***E* showed 83.5% (n = 7) and 98.0% (n = 6) inhibitions at 0.3 and 1 mg/kg po, respectively, on the histamine-induced bronchoconstriction, while **34***E* exhibited 71.3% (n = 7) and 87.4% (n = 7) at 10 and 30 mg/kg po, respectively, on the U-46619-induced bronchoconstriction.

(32) Effects of **34***E* on other experimental models as well as advantages of the dual antagonist over a pure TXRA or an H_1 antagonist will be reported in a separate paper.