Dibenzoxepin Derivatives: Thromboxane A_2 Synthase Inhibition and Thromboxane A_2 Receptor Antagonism Combined in One Molecule

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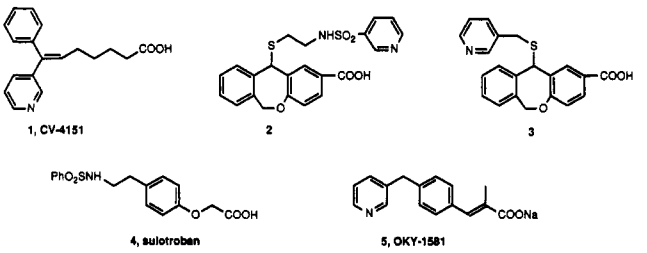
A new series of 6,11-dihydrodibenz[*b*,*e*]oxepin derivatives exerting both thromboxane synthase inhibitory (TXS-I) and thromboxane receptor antagonist (TXRA) activities is described. (−)-11-[(3-Pyridylmethyl)thio]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid [(−)-**3**] and (*E*)-11-[2-(3-pyridyl)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid methanesulfonate (**11*E***) exhibited potent inhibitory effects on bovine platelet thromboxane synthase with IC_{50} values of 4.0 and 14 nM, respectively, and these derivatives also antagonized guinea pig platelet TXA_2/PGH_2 receptors with K_i values of 85 and 180 nM, respectively. Compound **11*E*** exhibited the dual inhibitory activity in ex vivo experiments and demonstrated a significant protective effect in a rat acute renal failure model.

Thromboxane A_2 (TXA_2), a short-lived metabolite of arachidonic acid (AA), is a powerful inducer of platelet aggregation and of vascular and pulmonary smooth muscle contractions.[1] Overproduction of TXA_2 has been implicated in several pathophysiological conditions including thrombosis, asthma, ischemia, renal failure, and myocardial infarction.[2] Efforts to control the actions of TXA_2 have focused on agents which would either inhibit the biosynthesis of TXA_2 (TXA_2 synthase inhibitor, TXS-I) or alternatively block the actions of TXA_2 at the receptor level (TXA_2 receptor antagonist, TXRA).[3] Not only does TXS-I prevent the formation of TXA_2, but it reorients the arachidonic acid cascade into an overproduction of other prostanoids such as PGD_2, $PGF_{2\alpha}$, PGE_2, and PGI_2, some of which can inhibit platelet reaction.[4,5] Despite these interesting premises, the first clinical trials with TXS-Is have been disappointing.[6] One of the reasons for the lack of efficacy might be the accumulation of PGH_2 that accompanies TXA_2 synthase inhibition; PGH_2 can interact with the platelet and vessel wall TXA_2/PGH_2 receptors, thus inducing vasoconstriction and platelet activation.[7,8]

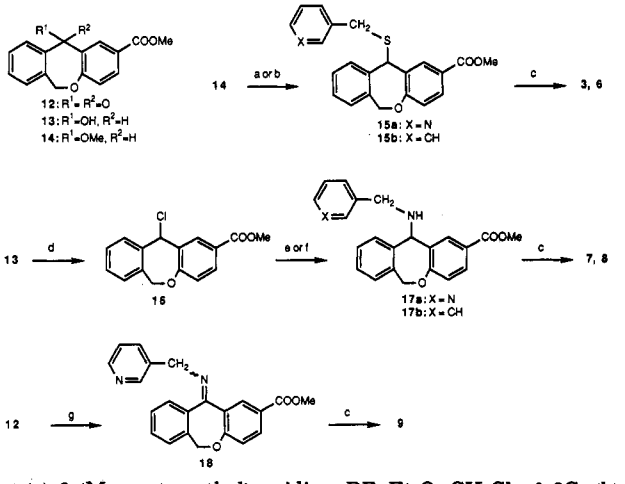
It has been proposed that the use of a combination of TXS-I and TXRA for the treatment of the clinical conditions cited above would be more beneficial than the use of either agent alone.[9] Moreover, several compounds have been presented recently which possess both TXS-I and TXRA properties in one molecule.[10–14] CV-4151 (**1**)[11,12] has been reported as this type of agent.

We have recently described the synthesis and biological properties of a new series of 6,11-dihydrodibenz[*b*,*e*]-oxepin-2-carboxylic acid derivatives,[15–17] of which compound **2** was identified as a highly potent TXRA with weak TXS-I activity.[17] In order to obtain a compound with well-balanced dual modes of action, modification of **2** was begun by shortening of the side chain at the 11-position. The initial study revealed that 11-[(3-pyridylmethyl)thio]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid (**3**) possessed enhanced TXS-I activity as well as moderate TXRA activity (see Table I). This result encouraged us to synthesize some derivatives of **3** and resolve the racemate (±)-**3** into its optically active form to examine the optical isomeric effect on the activities.

Chart I



Scheme I[a]



[a] (a) 3-(Mercaptomethyl)pyridine, BF_3·Et_2O, CH_2Cl_2, 0 °C; (b) benzyl mercaptan, BF_3·Et_2O, CH_2Cl_2, 0 °C; (c) NaOH, MeOH, H_2O, reflux; (d) $SOCl_2$, CH_2Cl_2, O °C; (e) 3-(aminomethyl)pyridine, *N*,*N*-dicyclohexylmethylamine, CH_2Cl_2, 0 °C; (f) benzylamine, *N*,*N*-dicyclohexylmethylamine, CH_2Cl_2, 0 °C; (g) 3-(aminomethyl)pyridine, $TiCl_4$, *N*,*N*-dicyclohexylmethylamine, benzene, reflux.

In this paper, we describe the synthesis and structure–activity relationships of a new series of dibenz[*b*,*e*]oxepin derivatives. In addition to CV-4151 (**1**), sulotroban (**4**),[18–20] a representative nonprostanoid TXRA,[21–27] and OKY-1581 (**5**),[28,29] a TXS-I possessing a 3-pyridyl moiety, were used as reference compounds during our series of experiments.

Chemistry

Compounds **3** and **6**–**11** listed in Table I were prepared from **12** and its related derivatives (**13** and **14**, see Scheme

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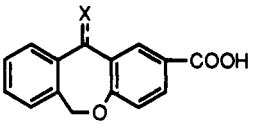
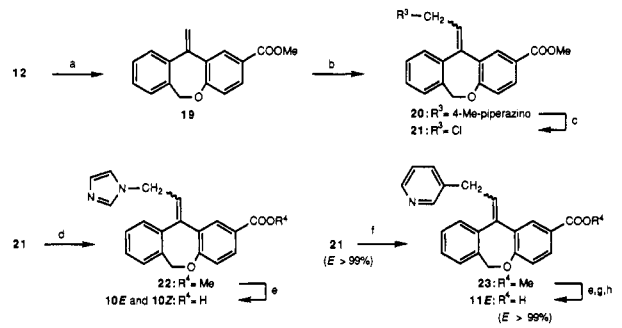
Table I. New Dibenz[*b*,*e*]oxepin Derivatives



no.	X	mp, °C solvent[a]	formula[b]	TXA_2/PGH_2 receptor binding: guinea pig washed platelet K_i,[c] nM	TXA_2 synthase: bovine platelet microsome IC_{50},[c] nM
(±)-**3**	SCH_2(3-pyridyl)	233–235 EE[d]	$C_{21}H_{17}NO_3S$	250 ± 24 (3)	10 ± 1.2 (4)
(+)-**3**[e]	SCH_2(3-pyridyl)	246–247 IPA[d]	$C_{21}H_{17}NO_3S$	8200 ± 1400 (3)	400 ± 12 (3)
(−)-**3**[f]	SCH_2(3-pyridyl)	246–247 IPA[d]	$C_{21}H_{17}NO_3S$	85 ± 10 (3)	4.0 ± 0.7 (4)
(±)-**6**	SCH_2Ph	211–212 TL	$C_{22}H_{18}O_3S$	40 (1)	19% at 10 μM[g]
(±)-**7**	$NHCH_2$(3-pyridyl)	190–191 W	$C_{21}H_{18}N_2O_3$	12% at 1 μM[g]	54 (1)
(±)-**8**	$NHCH_2Ph$	145–147 W	$C_{22}H_{19}NO_3$	6% at 1 μM[g]	−4% at 10 μM[g]
9[h]	$=NCH_2$(3-pyridyl)	244–246 IPA	$C_{21}H_{16}N_2O_3$	120 ± 6.6 (3)	1900 (1)
10*E*[i]	$=CHCH_2$(1-imidazolyl)	264–265 MA	$C_{20}H_{16}N_2O_3 \cdot 0.2H_2O$	600 ± 34 (3)	450 (1)
10*Z*[i]	$=CHCH_2$(1-imidazolyl)	284 dec MA	$C_{20}H_{16}N_2O_3$	4500 (1)	17000 (1)
11*E*[i]	$=CHCH_2$(3-pyridyl)	231–232 EA–AN	$C_{22}H_{17}NO_3 \cdot CH_3SO_3H$[j]	180 ± 28 (3)	14 ± 3.7 (5)
1, CV-4151				2700 (2)	2.9 ± 0.29 (3)
(±)-**2**				47 ± 7.9 (3)	1400 (1)
4, sulotroban				1300 ± 140 (3)	94100 ± 3500 (3)
5, OKY-1581				14 ± 3% at 100 μM[k]	4.3 ± 0.59 (3)

[a] EE, diethyl ether; IPA, 2-propanol; TL, toluene; W, water; MA, methanol; EA, ethyl acetate; AN, acetonitrile. [b] All new compounds had C, H, and N microanalyses within 0.4% of theoretical values. [c] Values are mean ± SEM of numbers indicated in parentheses. [d] Trituration solvent. [e] 99.2% ee; $[\alpha]_D$ + 186.0° (*c* = 0.1, EtOH). [f] 98.6% ee; $[\alpha]_D$ −179° (*c* = 0.1, EtOH). [g] Percent inhibition, *n* = 1. [h] A mixture of geometrical isomers (9/1). The stereochemistry of the carbon–nitrogen double bond was not determined. [i] The geometry about the olefin was determined by NOE experiments. [j] Methanesulfonic acid. [k] Percent inhibition, *n* = 3.

Scheme II[a]



[a] (a) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, 0 °C, and then **12**, THF, room temperature; (b) 1-methylpiperazine, paraformaldehyde, CF_3COOH, AcOH, dichloroethane, reflux; (c) ClCOOEt, dichloroethane; (d) imidazole, toluene, DMF, 100 °C; (e) NaOH, H_2O, MeOH, reflux; (f) pyridine, $LiAlH_4$, room temperature, and then **21**, pyridine, −10 °C; (g) $MeSO_3H$, MeOH; (h) fractional crystallization.

I).[15] The saponification of the esters **15a–b**, **17a–b**, and **18** provided compounds **3** and **6–9**, respectively. The esters **15a–b** were prepared by the treatments of **14** with 3-(mercaptomethyl)pyridine[30] and benzyl mercaptan, respectively, in the presence of $BF_3 \cdot Et_2O$.[15] Resolution of racemic **15a** was accomplished by HPLC separation on a Chiralcel OD column. Subsequent saponification provided the corresponding enantiomers of **3**. Treatment of **13** with $SOCl_2$ afforded **16**, which was converted into **17a–b** with 3-(aminomethyl)pyridine and benzylamine, respectively. Titanium(IV) chloride mediated condensation[31] of **12** and 3-(aminomethyl)pyridine in the presence of *N*,*N*-dicyclohexylmethylamine,[32] a proton scavenger, provided **18** as a mixture of geometrical isomers. The ratio (9/1)[33] was retained during the subsequent alkaline saponification; the resulting two isomers of **9** were not isolated.

As shown in Scheme II, chloride **21** was a key intermediate for the preparation of **10** and **11**. The olefin **19** synthesized from **12** was treated with 1-methylpiperazine under Mannich reaction conditions to provide **20** (*E*/*Z* = 9/1), which was converted into **21** with ethyl chloroformate.[34,35] Treatment of **21** (*E*/*Z* = 9/1) with imidazole afforded **22**, which was hydrolyzed to **10**. Each geometrical isomer of **10** was isolated by fractional crystallization. Moreover, the *E*-isomer of **20**, isolated by fractional crystallization, was converted to **21** with negligible isomerization, from which **10*E*** was prepared selectively. Lithium tetrakis(*N*-dihydropyridyl)aluminate,[36,37] generated by the treatment of pyridine with $LiAlH_4$, was allowed to react with **21** (*E* > 99%) to provide **23**. However, considerable isomerization (10–20%) of the double bond occurred during this conversion. After saponification of the geometrical mixture, the crude product was converted to the methanesulfonic acid addition salt, which was recrystallized to afford **11*E***.

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[38,39] and on bovine platelet TXA_2 synthase.[40,41] Results are represented by K_i and IC_{50} values, respectively (Table I).

The connecting group between the dibenzoxepin ring system and pyridine (or imidazole or phenyl) moiety proved to be crucial for the modulation of the biological activities. Replacing the sulfide linkage of **3** with an amino bond to provide **7** resulted in a loss of the TXRA activity. Thus compound **7** was regarded as a pure TXS-I (IC_{50} = 54 nM). A similar reduction in TXRA activity was observed in benzyl derivatives (**6** vs **8**). On the other hand, compound **9** possessing an imino linkage (=N—) lost the TXS-I activity. Compounds **6** and **8**, lacking heme-binding heterocycles,[12] exhibited negligible activities in the TXS-I assay, while **6** exhibited much higher TXRA activity than **3**. These data suggested that the presence of nitrogen atom in the pyridine moiety was not crucial for the TXA_2 receptor binding of this series of compounds. Compound **6** and **9** eventually proved to be novel nonprostanoid TXRAs and their affinities (K_i = 40 and 120 nM,

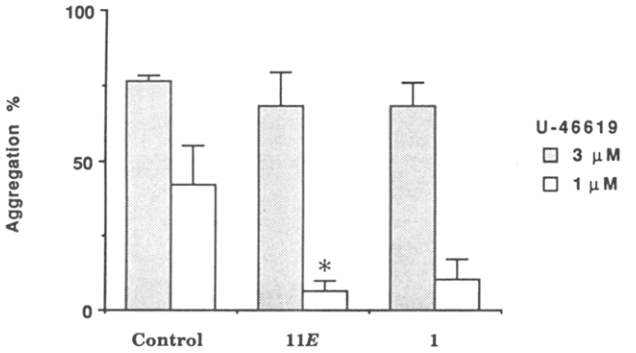


Figure 1. Effects on U-46619-induced platelet aggregation ex vivo in the guinea pig. Compounds **11*E*** (30 mg/kg) and **1** (CV-4151) (30 mg/kg) were orally administered. The value indicates percent aggregation of platelets and is the mean ● SEM (n = 4). *, $p < 0.05$ (student's t-test).

respectively) were approximately 30–10-fold more potent than that of sulotroban (**4**).

Comparison between **3** and **11*E*** revealed that the (*E*)-ethylidene connecting group was an equivalent of the thiomethylene (SCH_2) group of **3** in terms of both TXS-I and TXRA activities. The geometry of the double bond in the 11-position affected the TXS-I activity more significantly than the TXRA activity. Compound **10*E*** was approximately 40-fold more potent than **10*Z*** as a TXS-I, whereas it was approximately 7-fold more active than **10*Z*** as a TXRA. Additionally, 3-pyridyl group was found to be more favorable than 1-imidazolyl as a terminal basic aromatic moiety on the side chain for both TXS-I and TXRA activities (**10*E*** vs **11*E***).

Since racemic **3** was one of the most interesting compounds with the dual (TXS-I and TXRA) activities, both optical isomers of **3** were evaluated. The enantiomer (−)-**3** inhibited the specific receptor binding of [^{3}H]U-46619 concentration-dependently with a K_i value of 85 nM, whereas (+)-**3** was much less active (K_i = 8200 nM). Similarly (−)-**3** was 100-fold more potent than (+)-**3** as a TXS-I; (−)-**3** was the most potent TXS-I among the compounds synthesized in this study, and its potency (IC_{50} = 4.0 nM) was comparable to that of OKY-1581 (**5**), a pure TXS-I. Therefore, both biological effects of racemic **3** were mainly attributable to those of (−)-**3**.

In clinical conditions, the proposed efficacy will be elicited only from a compound which exhibits both TXS-I and TXRA activities at a low concentration established in the living system. Compound **11*E*** had significant affinity for the guinea pig platelet TXA_2/PGH_2 receptors (K_i = 180 nM), and the activity was 15-fold more potent than that of CV-4151 (**1**), while it retained sufficient effect as TXS-I (IC_{50} = 14 nM). Additionally, compound **11*E*** inhibited U-46619 (3 μM)-induced human platelet aggregation in vitro ($IC_{50} = 9.6 \times 10^{-6}$ M, n = 2), whereas CV-4151 shows a weak inhibitory effect on the aggregation ($IC_{50} = 2.8 \times 10^{-4}$ M, n = 2).

Compound **11*E*** proved to exhibit its dual activities in in vivo and ex vivo experiments. The TXB_2 level in rat serum was significantly decreased at even 24 h after a single administration of **11*E*** (10 mg/kg, po). Compound (−)-**3**, which demonstrated significant activities in in vitro assays, was relatively weak and short acting TXS-I in vivo (<10 h, 10 mg/kg, po, rat). Moreover, **11*E*** (30 mg/kg, po) inhibited guinea pig platelet aggregation induced by a low concentration (1 μM) of U-46619 significantly at 2 h after administration (Figure 1).[42] The achiral compound **11*E*** was selected for further evaluation.

Table II. [a] Effects on sCR and BUN in Rats with Acute Renal Failure after Reperfusion

	time after the reperfusion			
	24 h		48 h	
	sCR	BUN	sCR	BUN
sham	0.60 ± 0.01	12.98 ± 0.47	0.59 ± 0.01	13.91 ± 0.87
control	2.30 ± 0.30	54.06 ± 4.28	1.98 ± 0.49	50.42 ± 8.26
11*E* (30 mg/kg, po)	1.48 ± 0.24*	34.18 ± 4.25**	1.16 ± 0.18	30.37 ± 5.30*
control	2.13 ± 0.47	53.82 ± 5.46	1.76 ± 0.61	47.33 ± 10.86
1 (30 mg/kg, po)	2.07 ± 0.55	58.07 ± 16.98	2.02 ± 1.07	48.38 ± 18.05

[a] Values are expressed as mean ± SEM (n = 6–9). * and **: $p <$ 0.05 and $p < 0.01$ vs control, respectively. sCR, serum creatinine; BUN, blood urea nitrogen.

We examined protective effects of **1** (CV-4151) and **11*E*** on acute renal failure in rats (Table II).[43] Acute renal failure was caused by the occlusion of renal arteries followed by reperfusion. Twenty-four and forty-eight hours after the reperfusion insult, the values of the serum creatinine (sCR) and blood urea nitrogen (BUN) were 4–5 times higher than those in the sham-operated rats. Compound **11*E*** (30 mg/kg, po) significantly prevented the elevations of sCR and BUN, while **1** was ineffective.[44]

In conclusion, we found a novel series of 6,11-dihydrodibenz[*b*,*e*]oxepin derivatives possessing TXS-I and/or TXRA activities. Modifications in the connecting group between the dibenzoxepin ring system and terminal pyridine (or imidazole) moiety affected both TXS-I and TXRA properties. Furthermore, the stereochemistry around the 11-position of the dibenzoxepin ring system proved to be crucial for both biological activities. Compound **11*E***, (*E*)-11-[2-(3-pyridyl)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid methanesulfonate, is the most promising as an orally active nonprostanoid TXS-I/TXRA.

Experimental Procedures

Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a JASCO IR-400 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a JEOL PMX-60 (60 MHz), a Hitachi R-90H (90 MHz), or a JEOL GX-270 (270 MHz) spectrometer. All spectra were determined in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in δ units downfield from the internal standard tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak; dd, doublet of doublet; and dt, doublet of triplet. Mass spectra (MS) were recorded on a JEOL D300 mass spectrometer. Elemental analyses were performed by the analytical department of our laboratories. Solutions in organic solvents were dried over anhydrous $MgSO_4$. For column chromatography, silica gel:Kieselgel 60 (Merck, 70–230 or 230–400 mesh) was used. HPLC was carried out on a Hitachi L-6000 liquid chromatograph. *E*/*Z* ratios were measured by HPLC: column, YMC A-312 (Yamamura Chemical Lab. Co., Ltd.); eluent, 0.01 M octanesulfonic acid in MeOH/H_2O (2/1). Chiralcel OD (Daicel Chemical Industries, Ltd.) was used for analytical and preparative HPLC of optical resolution.

(±)-11-[(3-Pyridylmethyl)thio]-6,11-dihydrodibenz[*b*,*e*]-oxepin-2-carboxylic Acid Methyl Ester (15a). To a mixture of **14**[15] (4.0 g, 14 mmol), 3-(mercaptomethyl)pyridine[30] (2.0 g, 16 mmol), and dry CH_2Cl_2 (100 mL) was added BF_3·Et_2O (2.0 mL, 16 mmol) at 0 °C under an Ar atmosphere. The resultant mixture was stirred under the same conditions for 3 h. The reaction mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc/triethylamine (10/20/1) as eluent to give 1.75 g (33%) of **15a** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 2H), 3.82 (s, 3H), 4.86 (s, 1H), 4.84 and 6.36 (AB syst, *J*

= 13.4 Hz, 2H), 6.70–7.90 (m, 9H), 8.35–8.58 (m, 2H); IR ($CHCl_3$) 2954, 1715, 1612, 1575, 1437, 1296, 1008 cm^{-1}.

Compound **15b** (oil, 84%) was prepared in a method similar to that described above.

Resolution of (±)-15a. (±)-**15a** (150 mg) was resolved by an HPLC column (Chiralcel OD, 2-cm i.d. × 50 cm) to give 60 mg of (+)-**15a** (1st peak): $[\alpha]_D$ +152.4° (*c* 1, $CHCl_3$); ee ≥ 99.5%, based on HPLC analysis (Chiralcel OD, 1-cm i.d. × 25 cm) and 58 mg of (−)-**15a** (2nd peak): $[\alpha]_D$ −143.1° (*c* 1, $CHCl_3$); 96% ee [separation conditions: eluent, hexane/EtOH/diethylamine 50/450/1; column temperature, 40 °C; flow rate, 9.99 mL/min for preparative and 1.5 mL/min for analytical HPLC].

(±)-11-[(3-Pyridylmethyl)amino]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (17a). Compound **13**[15] (6.0 g, 22.2 mmol) was dissolved in dry CH_2Cl_2 (100 mL), and $SOCl_2$ (3.0 mL, 41.1 mmol) was added to the solution at 0 °C. The mixture was stirred at room temperature for 1 h and concentrated (<30 °C) to give the unstable chloride **16**, which was used in the next reaction without purification. Chloride **16** dissolved in CH_2Cl_2 (20 mL) was added to a solution containing 3-(aminomethyl)pyridine (8 mL, 78.6 mmol) and *N,N*-dicyclohexylmethylamine (6 mL, 28.3 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred at room temperature for 12 h. The reaction mixture was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc/triethylamine (10/10/2) as eluent to give 2.3 g (29%) of **17a** as an amorphous powder: ^1H NMR ($CDCl_3$) δ 2.20 (br, 1H), 3.70 (s, 2H), 3.83 (s, 3H), 4.67 (s, 1H), 4.81 and 6.65 (AB syst, *J* = 11.9 Hz, 2H), 6.83–7.97 (m, 9H), 8.28–8.58 (m, 2H); IR ($CHCl_3$) 2950, 1705, 1610, 1285, 1240 cm^{-1}.

Compound **17b** (oil, 52%) was prepared in a method similar to that described above.

(*E,Z*)-11-[(3-Pyridylmethyl)imino]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (18). To a solution of **12**[15] (5.0 g, 18.7 mmol), 3-(aminomethyl)pyridine (12.0 mL, 118 mmol), and *N,N*-dicyclohexylmethylamine (15.8 mL, 74.4 mmol) in dry benzene (150 mL) was added $TiCl_4$ (4.1 mL, 37.4 mmol) dropwise, and the mixture was refluxed for 3.5 h. Saturated $NaHCO_3$ was added, and the insoluble material was filtered off. The filtrate was diluted with EtOAc, and the organic phase was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc/triethylamine (10/5/1) as eluent and the product was recrystallized from diisopropyl ether to give 1.3 g (19%) of **18** as crystals: mp 111–112 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 4.79 (br s, 2H), 5.14 (br s, 2H), 6.73–8.05 (m, 9H), 8.33–8.66 (m, 2H); IR (KBr) 1715, 1610, 1490, 1435, 1250, 1120, 1005, 765 cm^{-1}.

11-Methylene-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (19). To a suspension of methyltriphenylphosphonium bromide (25 g, 70 mmol) in THF (100 mL) was added a 1.6 N solution of *n*-BuLi in hexane (40 mL, 64 mmol) under N_2 atmosphere at 0 °C, and the mixture was stirred under the same conditions for 0.5 h. A solution of **12** (15 g, 56 mmol) in THF (250 mL) was added, and the resultant mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc. The organic solution was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc (3/1) to give 12.6 g (84%) of **19**: mp 73–76 °C (MeOH); ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.15 (s, 2H), 5.29 (s, 1H), 5.74 (s, 1H), 6.69–8.22 (m, 7H); MS *m/z* 266 (M^+).

11-[2-(4-Methylpiperazino)ethylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (20). A mixture of **19** (80.3 g, 0.3 mol), 1-methylpiperazine (67 mL, 0.6 mol), paraformaldehyde (4.5 g), trifluoroacetic acid (230 mL), acetic acid (160 mL), and dichloroethane (1.6 L) was refluxed for 1 h. More paraformaldehyde (4.5 g) was added, and reflux was continued for 1 h. Paraformaldehyde (4.5 g) was added again, and reflux was maintained for another 1 h. After being concentrated, the reaction mixture was diluted with water and EtOAc. The organic phase was separated, washed with brine, dried, and concentrated. The residue (*E/Z* = 9/1) was purified by fractional crystallization with 2-propanol to give 110 g of trifluoroacetic acid salt of **20** (*E* > 99%). The salt was suspended in a mixture of EtOAc (1 L) and H_2O (1.2 L). The medium was cooled under 5 °C and adjusted to pH 10 with 2 N NaOH. The organic phase was separated, washed with brine, dried, and concentrated to give 79 g (71%) of **20** (*E* > 99%) as an amorphous powder: ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 2.21–2.71 (m, 8H), 3.14 (d, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 4.7–5.4 (br, 2H), 6.20 (t, *J* = 7.0 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 7.02–7.42 (m, 4H), 7.72 (dd, *J* = 2.2 and 8.6 Hz, 1H), 7.98 (d, *J* = 2.2 Hz, 1H); IR ($CHCl_3$) 2945, 2810, 1710, 1250, 1111, 1010 cm^{-1}; MS *m/z* 378 (M^+).

11-(2-Chloroethylidene)-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (21). To a mixture of **20** (*E* > 99%, 31 g, 81 mmol), NaOAc (33 g, 406 mmol), and dichloroethane (460 mL) was added ClCOOEt (39 mL, 406 mmol) dropwise. After the reaction mixture was stirred for 2 h at room temperature, the insoluble salts were filtered off. The filtrate was concentrated, diluted with CH_2Cl_2, washed with brine, dried, and concentrated. The residue was recrystallized from 2-propanol to give 9.2 g (58%) of **21** (*E* > 99%) as colorless needles: mp 134–135 °C; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 4.16 (d, *J* = 8.1 Hz, 2H), 4.88 (br, 1H), 5.57 (br, 1H), 6.31 (t, *J* = 8.1 Hz, 1H), 6.79–8.04 (m, 7H); MS *m/z* 314 (M^+).

(*E,Z*)-11-[2-(1-Imidazolyl)ethylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (22). A mixture of **21** (*E/Z* = 9/1, 5.0 g, 15.9 mmol), imidazole (4.8 g, 70.5 mmol), dimethylformamide (30 mL), and toluene (230 mL) was stirred at 100 °C for 6 h. After being concentrated, the reaction mixture was diluted with CH_2Cl_2, washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc/MeOH/triethylamine (10/1/1) as eluent to give 4.8 g (87%) of **22** (*E/Z* = 9/1) as an amorphous powder: ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 4.60 (d, *J* = 7.6 Hz, 2H), 4.55–5.56 (m, 2H), 6.17 (t, *J* = 7.2 Hz, 1H), 6.66–8.04 (m, 10H); IR ($CHCl_3$) 2950, 1713, 1609, 1296, 1121, 1005 cm^{-1}.

(*E,Z*)-11-[2-(3-Pyridyl)ethylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (23). Lithium aluminum hydride (7.5 g, 0.198 mol) was added to pyridine (150 mL) at 0 °C by potions under Ar atmosphere, and the mixture was stirred at room temperature 24 h. Pyridine (50 mL) and LiI (7.0 g, 0.052 mol) were added, and the mixture was stirred under the same reaction conditions for 1 h. A solution of **21** (*E* > 99%, 10.0 g, 0.0318 mol) in pyridine (120 mL) was added dropwise at −10 to −5 °C, and the mixture was stirred under the same conditions for 2 h. An ice-cooled solution of AcOH (15 mL, 0.26 mol) in water (100 mL) was added, and the mixture was stirred for 1 h. After being concentrated, the reaction mixture was slurried with THF at 50 °C, and the insoluble salts were filtered off. The filtrate was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with EtOAc/triethylamine (10/1) as eluent to give 6.7 g (59%) of **23** (*E/Z* = 4/1) as an oil: ^1H NMR ($CDCl_3$) δ 3.53 (d, *J* = 6.5 Hz, 2H), 3.87 (s, 3H), 5.60–6.00 (br, 2H), 6.25 (t, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 7.10–7.55 (m, 6H), 7.79 (dd, *J* = 2.2 and 8.6 Hz, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 8.38–8.49 (m, 2H); IR (neat) 1711, 1606, 1244, 1117, 1003 cm^{-1}; MS *m/z* 357 (M^+).

Typical Procedure for Obtaining Carboxylic Acids 3–11 by Hydrolysis: (*E*)-11-[2-(1-Imidazolyl)ethylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid (10*E*) and Its Geometrical Isomer (10*Z*). A mixture of **22** (*E/Z* = 9/1, 4.8 g, 13.9 mmol), 10 N NaOH (5 mL, 50 mmol), H_2O (50 mL), and MeOH (150 mL) was refluxed for 2.5 h. The reaction mixture was concentrated and then diluted with water. The solution was neutralized with 4 N HCl and the hydrolyzed product separated by chromatography using HP-10 with MeOH as eluent. The crude product was washed with hot MeOH (3 times) to give 1.7 g (37%) of **10*E*** as crystals: ^1H NMR (DMSO-d_6) δ 4.50–5.70 (br, 4H), 6.23 (t, *J* = 7.0 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.92 (br s, 1H), 7.17 (br s, 1H), 7.35–7.59 (m, 4H), 7.63 (br s, 1H), 7.73 (dd, *J* = 2.2 and 8.6 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H); IR (KBr) 3120, 2336, 1695, 1603, 1455, 827 cm^{-1}. Anal. ($C_{20}H_{16}N_2O_3 \cdot 0.2H_2O$) C, H, N.

The washings containing the *Z*-isomer were allowed to stand at room temperature for 2 days. The resultant precipitate was collected to give 0.1 g (2.2%) of **10*Z*** as crystals: ^1H NMR (DMSO-d_6) δ 4.99 (d, *J* = 6.8 Hz, 2H), 5.33 (br s, 2H), 5.85 (t, *J* = 6.8 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.96 (br s, 1H), 7.31–7.47 (m, 5H), 7.73–7.82 (m, 2H), 7.83 (br s, 1H); IR (KBr) 3118, 1690, 1605, 1288, 1245, 1099, 1001 cm^{-1}. Anal. ($C_{20}H_{16}N_2O_3$) C, H, N.

Compounds listed in Table I were prepared in a manner similar to that described above. (±)-**3**: ^1H NMR (DMSO-d_6) δ 3.67 and 3.78 (AB syst, *J* = 13.6 Hz, 2H), 4.95 and 6.13 (AB syst, *J* = 12.7 Hz, 2H), 5.23 (s, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 7.28–7.41 (m, 6H),

7.65 (dd, J = 1.9 and 8.4 Hz, 1H), 7.80 (d, J = 1.9 Hz, 1H), 8.41 (br s, 2H). Anal. ($C_{21}H_{17}NO_3S$) C, H, N. (±)-6: ^{1}H NMR (DMSO-d_6) δ 3.65 and 3.84 (AB syst, J = 12.9 Hz, 2H), 5.06 and 6.23 (AB syst, J = 12.8 Hz, 2H), 5.32 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.24–7.49 (m, 9H), 7.71 (dd, J = 2.2 and 8.5 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H). Anal. ($C_{22}H_{18}O_3S$) C, H, N. (±)-7: ^{1}H NMR (DMSO-d_6) δ 3.62 and 3.70 (AB syst, J = 14.0 Hz, 2H), 4.80 (s, 1H), 5.01 and 6.61 (AB syst, J = 12.0 Hz, 2H), 6.83 (d, J = 8.5 Hz, 1H), 7.28–7.88 (m, 8H), 8.40–8.45 (m, 2H). Anal. ($C_{21}H_{18}N_2O_3$) C, H, N. (±)-8: ^{1}H NMR (DMSO-d_6) δ 3.60 and 3.64 (AB syst, J = 13.8 Hz, 2H), 4.77 (s, 1H), 5.01 and 6.64 (AB syst, J = 11.8 Hz, 2H), 6.83 (d, J = 8.5 Hz, 1H), 7.20–7.44 (m, 9H), 7.71 (dd, J = 2.2 and 8.5 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H). Anal. ($C_{22}H_{19}NO_3$) C, H, N. 9: ^{1}H NMR (DMSO-d_6) δ 4.50–5.50 (m, 4H), 6.96 (d, J = 8.6 Hz, 1H), 7.37–7.80 (m, 6H), 7.87 (dd, J = 2.2 and 8.6 Hz, 1H), 8.34 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 3.9 Hz, 1H), 8.57 (br s, 1H); IR (KBr) 2374, 1701, 1630, 1606, 1486, 1428, 1312, 1236, 1047, 1005 cm^{-1}. Anal. ($C_{21}H_{16}N_2O_3$) C, H, N. 11*E* (free base): mp 252–255 °C (2-propanol); ^{1}H NMR (DMSO-d_6) δ 3.51 (br s, 2H), 5.05 (br s, 1H), 5.53 (br s, 1H), 6.26 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 7.31–7.65 (m, 6H), 7.81 (dd, J = 2.2 and 8.6 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H), 8.41 (br s, 2H); IR (KBr) 1702, 1606, 1487, 1428, 1242, 1126, 1000 cm^{-1}. Anal. (methanesulfonate) ($C_{23}H_{21}NO_6S$) C, H, N.

Biological Evaluation Procedures. TXA_2/PGH_2 Receptor Binding Assay. The receptor binding assay was performed with a slight modification of the method of Kattelman et al.[38,39] Briefly, arterial blood was withdrawn from male Hartley guinea pigs and mixed with an anticoagulant consisting of 1/10 (v/v) of 77 mL of EDTA 2Na containing 100 μM indomethacin. The blood was centrifuged at 120g for 12 min to obtain platelet-rich plasma (PRP). The PRP was further centrifuged at 900g for 10 min to sediment platelets. Thereafter, the platelets were washed and resuspended in 25 mM Tris-HCl buffer (pH 7.5) containing NaCl (138 mM), $MgCl_2$ (5 mM), EGTA (1 mM), and indomethacin (10 μM); 1 × 10^8 platelets were incubated with 10 nM of [^{3}H]U-46619 and various concentration of assay sample in a total volume of 200 μL at 37 °C for 30 min. Nonspecific binding was determined in the presence of 100 μM U-46619 and was 10–40% in each experiment. Ice-cold 100 mM Tris-HCl buffer (pH 7.4) containing 100 mM NaCl was added to the tube. This reaction mixture was filtered through a Whatman GF/C glass filter and washed 3 times with 3 mL of ice-cold buffer. The filter was dried and added 8 mL of Scintisol EX-H. The radioactivity on the filter was counted by a liquid scintillation counter. The result was expressed by K_i values which were determined by means of Cheng and Prusoff equation.[45]

Thromboxane A_2 Synthase Inhibition. Bovine platelet microsome was prepared according to the method of Yoshimoto et al.[40] An assay sample and 50 μg of the microsome were incubated in 80 μL of 100 mM Tris-HCl buffer (pH 7.4) for 5 min at 4 °C. The mixture was incubated with 1 μM of PGH_2 for 5 min at 4 °C. The reaction was terminated by the addition of 2.9 mL of ice-cold 100 mM potassium phosphate buffer (pH 7.4) containing 0.9% (w/v) NaCl, 0.1% (w/v) gelatin and 0.1 μM of OKY-1581, a selective thromboxane synthase inhibitor. The effect on thromboxane synthase was examined by determining the concentration of thromboxane B_2, the stable hydrolysis product of thromboxane A_2, using a specific radioimmunoassay.[41] The result was expressed by IC_{50} values.

Effects on U-46619-Induced Platelet Aggregation ex Vivo in the Guinea Pig.[42] Drug was dissolved in a small amount of 0.05 N NaOH solution and then diluted with saline for oral administration, so as to make 0.5 mL of solution per 100 g of body weight. Blood was drawn from the abdominal aorta 2 h after compound administration and was collected in a plastic tube containing 3.8% sodium citrate (1 mL for 9 mL blood) as an anticoagulant. Platelet-rich plasma (PRP) was obtained from the blood by centrifugation at 200g for 15 min at room temperature. Platelet-poor plasma (PPP) was obtained by further centrifuging the precipitate at 2000g for 10 min. Platelet aggregation was induced by the addition of 1 or 3 μM of U-46619 (Sigma) to PRP (0.3 mL). The aggregation was measured by a turbidimetric method[46] by means of an aggregometer (Erma Optical Works, Japan). The extent of aggregation was assessed by the maximum change of light transmittance within 5 min after adding U-46619. The result was expressed as percent aggregation.

Effect on Ischemic Renal Failure in Rats.[43] Male Sprague–Dawley rats (Charles River, Japan), weighing 300 ± 20 g were used for the experiments. All animals had free access to standard rat chow and water. A right unilateral nephrectomy through a flank incision was performed on each rat under sodium pentobarbital (50 mg/kg, ip) anesthesia. Three days was allowed for recovery. Then the left kidney was exposed by a flank incision under sodium pentobarbital (50 mg/kg, ip) anesthesia, and the renal arteries were occluded for 70 min followed by reperfusion. Immediately after reperfusion, the incisions were closed, and animal was allowed to recover from anesthesia. Drugs or vehicle were administered orally 1 h prior to the renal ischemia. At fixed times after reperfusin, blood samples were obtained from the abdominal aorta under sodium pentobarbital (50 mg/kg, ip) anesthesia for the measurements of serum creatinine (sCR) and blood urea nitrogen (BUN). Determinations of sCR and BUN were carried out by means of an autoanalyzer (AV-510, Olympus, Japan).

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