

# Non-Prostanoid Thromboxane A<sub>2</sub> Receptor Antagonists with a Dibenzoxepin Ring System. 1

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A series of 11-[[2-[(arylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic acids and related derivatives were synthesized. The compounds were tested for their antagonizing effects on guinea pig platelet TXA<sub>2</sub>/PGH<sub>2</sub> receptors. Structure-activity relationships are discussed. (±)-11-[[2-[(Styrylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic acid (4l) and (±)-11-[[2-[(phenylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]thiepin-2-carboxylic acid (4af) were the most promising compounds with K<sub>i</sub> values of 6.5 ± 0.29 and 3.7 ± 0.31 nM, respectively, for the TXA<sub>2</sub>/PGH<sub>2</sub> receptor. These compounds also significantly inhibited U-46619-induced guinea pig platelet aggregation *ex vivo* (10 mg/kg po). Compound 4l was resolved into its optically active form. The (-)-isomer was 60-fold more potent than the (+)-isomer in the TXA<sub>2</sub>/PGH<sub>2</sub> receptor binding assay. Some compounds tested in this study showed both TXA<sub>2</sub>/PGH<sub>2</sub> receptor antagonizing and TXA<sub>2</sub> synthase inhibitory effects.

## Introduction

Thromboxane A<sub>2</sub> (TXA<sub>2</sub>, 1), a short-lived metabolite of arachidonic acid (AA), is a powerful inducer of platelet aggregation and of vascular and pulmonary smooth muscle contractions.<sup>1</sup> Overproduction of TXA<sub>2</sub> has been implicated in several pathological conditions including thrombosis, asthma, ischemia, and myocardial infarction.<sup>2</sup> Efforts to modulate the actions of TXA<sub>2</sub> have focused on agents which would either inhibit the biosynthesis of TXA<sub>2</sub> (TXA<sub>2</sub> synthase inhibitor, TXS-I) or alternatively block the actions of TXA<sub>2</sub> at the receptor level (TXA<sub>2</sub> receptor antagonist, TXRA).<sup>3</sup> TXRAs are classified into TXA<sub>2</sub>/PGH<sub>2</sub> analogues (prostanoids)<sup>4</sup> and compounds structurally unrelated to the prostanoid skeleton (non-prostanoids).<sup>5</sup> Sulotroban (BM13,177, 2) is one of the representative non-prostanoid antagonists.<sup>5a-c</sup>

We recently reported the synthesis and biological properties of a new series of 6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic acid derivatives, of which KW-4994 (3) was identified as a highly potent anti-allergic agent.<sup>6</sup> Further modification of 3 revealed that 11-[[2-[(phenylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic acid (4a) possessed TXA<sub>2</sub> antagonizing activity (Chart I). In order to define the structural requirements for the TXA<sub>2</sub> antagonizing activity of 4a, synthesis and evaluation of a series of derivatives with general structures 4-8 were made. One of the most potent compounds 4l was resolved into its optically active form to examine the optical isomeric effect on TXA<sub>2</sub> antagonizing activity. We also elucidated inhibitory effect of 4-8 on TXA<sub>2</sub> synthase.

This paper describes the synthesis and structure-activity relationships of 11-[[2-[(arylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic acids and re-

- (1) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: a New Group of Biologically Active Compounds Derived from Prostaglandin Endoperoxides. *Proc. Nat. Acad. Sci. U.S.A.* 1975, 72, 2994-2998.
- (2) Moncada, S.; Vane, J. R. Pharmacology and Endogenous Roles of Prostaglandin Endoperoxides, Thromboxane A<sub>2</sub>, and Prostacyclin. *Pharmacol. Rev.* 1979, 30, 293-331. *Enzyme Inhibitors as Drugs*; Sandler, M., Ed.; MacMillan: London, 1980; pp 249.
- (3) For a recent review of TXA<sub>2</sub> synthase inhibitors and TXA<sub>2</sub> receptor antagonists, see: Collington, E. W.; Finch, H. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic: New York, 1990; Vol. 25, pp 99-108.

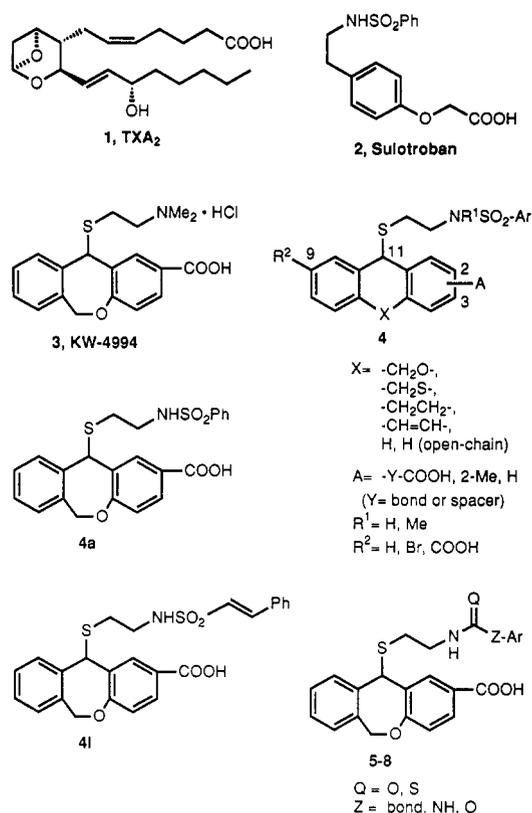
- (4) (a) Jones, R. L.; Peesapati, V.; Wilson, N. H. Antagonism of the Thromboxane-sensitive Contractile Systems of the Rabbit Aorta, Dog Saphenous Vein and Guinea-pig Trachea. *Br. J. Pharmacol.* 1982, 76, 423-438. (b) Mais, D.; Knapp, D.; Halushka, P.; Ballard, K.; Hamanaka, N. Synthesis of Thromboxane Receptor Antagonists with the Potential to Radiolabel with <sup>125</sup>I. *Tetrahedron Lett.* 1984, 25, 4207-4210. (c) Le Breton, G. C.; Lipowski, J. P.; Feinberg, H.; Venton, D. L.; Ho, T.; Wu, K. K. Antagonism of Thromboxane A<sub>2</sub>/Prostaglandin H<sub>2</sub> by 13-Aza-prostanoid Acid Prevents Platelet Deposition to the De-Endothelialized Rabbit Aorta *In Vivo*. *J. Pharmacol. Exp. Ther.* 1984, 229, 80-84. (d) Olanoff, L. S.; Cook, J. A.; Eller, T.; Knapp, D. R.; Halushka, P. V. Protective Effects of *trans*-13-APT, a Thromboxane Receptor Antagonist, in Endotoxemia. *J. Cardiovasc. Pharmacol.* 1985, 7, 114-120. (e) Jessup, C. L.; Jessup, R.; Johnson, M.; Wayne, M. ICI 159995; a Novel Thromboxane A<sub>2</sub> Receptor Antagonist. *Br. J. Pharmacol.* 1985, 86, 808P. (f) Ogletree, M. L.; Harris, D. N.; Greenberg, R.; Haslanger, M. F.; Nakane, M. Pharmacological Actions of SQ29,548, a Novel Selective Thromboxane Antagonist. *J. Pharmacol. Exp. Ther.* 1985, 234, 435-441. (g) Brittain, R. T.; Boutal, L.; Carter, M. C.; Coleman, R. A.; Collington, E. W.; Geisow, H. P.; Hallett, P.; Hornby, E. J.; Humphrey, P. P. A.; Jack, D.; Kennedy, I.; Lumley, P.; McCabe, P. J.; Skidmore, I. F.; Thomas, M.; Wallis, C. J. AH23848: A Thromboxane Receptor-blocking Drug that can Clarify the Pathophysiological Role of Thromboxane A<sub>2</sub>. *Circulation* 1985, 72, 1208-1218. (h) Jessup, C. L.; Jessup, R.; Wayne, M. Pharmacological Actions of ICI 180080, a Novel Thromboxane Receptor Antagonist. *J. Pharm. Pharmacol.* 1986, 38, 754-757. (i) Jessup, C. L.; Jessup, R.; Wayne, M. ICI 185282 a Potent Thromboxane Receptor Antagonist on Platelets. *Br. J. Pharmacol.* 1987, 90, 229P. (j) Brewster, A. G.; Brown, G. R.; Foubister, A. J.; Jessup, R.; Smithers, M. J. The Synthesis of a Novel Thromboxane Receptor Antagonist 4(Z)-6-(2-*o*-Chlorophenyl-4-*o*-hydroxyphenyl-1,3-dioxan-*cis*-5-yl)hexenoic Acid ICI 192605. *Prostaglandins* 1988, 36, 173-178. (k) Narisada, M.; Ohtani, M.; Watanabe, F.; Uchida, K.; Arita, H.; Doteuchi, M.; Hanasaki, K.; Kakushi, H.; Otani, K.; Hara, S. Synthesis and *In Vitro* Activity of Various Derivatives of a Novel Thromboxane Receptor Antagonist, (±)-(5Z)-7-[3-*endo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-oxo-yl]heptenoic Acid. *J. Med. Chem.* 1988, 31, 1847-1854. (l) Nakane, M.; Reid, J. A.; Han, W.; Das, J.; Truc, V. C.; Haslanger, M. F.; Garber, D.; Harris, D. N.; Hedberg, A.; Ogletree, M. L.; Hall, S. E. 7-Oxabicyclo[2.2.1]heptyl Carboxylic Acids as Thromboxane A<sub>2</sub> Antagonists: Aza ω-Chain Analogues. *J. Med. Chem.* 1990, 33, 2465-2476.

lated derivatives (4–8). Sulotroban (2) was used as a reference compound during our series of experiments.

### Chemistry

Compounds listed in Tables I–III were synthesized from the ketones **9** (Scheme I).<sup>6,7</sup> The alcohols **10** prepared by the reduction of **9** were converted to the methyl ethers **11**, which were treated with 2-aminoethanethiol in the presence of BF<sub>3</sub>·Et<sub>2</sub>O to provide **12**.<sup>8a</sup> Treatment of **12a** with a variety of arylsulfonyl chlorides and the subsequent saponification of the resulting esters **13a–p** afforded **4a–p** (Scheme II). Similar treatments converted **12b–j** to the corresponding **4b–aj** in which the tricyclic ring system and connecting group (Y) of **4** were varied. As shown in Scheme III, treatment of **12a** with appropriate acid chlorides, anhydrides, or mixed anhydrides yielded **14a–b** and **14d–i**. The methyl ether of **14b** was cleaved with BBr<sub>3</sub> to provide **14c**. The saponification of **14a–i** afforded amide analogues **5a–i**. Moreover, compounds **6–8** were prepared from **12a** by the treatments with appropriate isocyanate, isothiocyanate, and chloroformate, respectively followed by saponification. Compound **4q** (Table I) was synthesized

Chart I

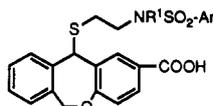


- (5) (a) Patscheke, H.; Stegmeier, K. Investigations on a Selective Non-prostanoid Thromboxane Antagonist, BM 13.177, in Human Platelets. *Thromb. Res.* 1984, 33, 277–288. (b) Stegmeier, K.; Pill, J.; Müller-Beckmann, B.; Schmidt, F. H.; Witte, E.-C.; Wolff, H.-P.; Patscheke, H. The Pharmacological Profile of the Thromboxane A<sub>2</sub> Antagonist BM 13.177. A New Anti-platelet and Anti-thrombotic Drug. *Thromb. Res.* 1984, 35, 379–395. (c) Seeger, W.; Ernst, Ch.; Waimrath, D.; Neuhof, H.; Roka, L. Influence of the Thromboxane Antagonist BM 13,177 on the Arachidonic Acid-induced Increase in Pulmonary Vascular Resistance and Permeability in Rabbit Lungs. *Thromb. Res.* 1985, 40, 793–805. (d) Carrer, R.; Cragoe, E. J.; Ethier, D.; Ford-Hutchinson, A. W.; Girard, Y.; Hall, R. A.; Hamel, P.; Rokach, J.; Share, N. N.; Stone, C. A.; Yusko, P. Studies on L-640,035: a Novel Antagonist of Contractile Prostanoids in the Lung. *Br. J. Pharmacol.* 1984, 82, 389–395. (e) Hall, R. A.; Gillard, J.; Guindon, Y.; Letts, G.; Champion, E.; Ethier, D.; Evans, J.; Ford-Hutchinson, A. W.; Fortin, R.; Jones, T. R.; Lord, A.; Morton, H. E.; Rokach, J.; Yoakim, C. Pharmacology of L-655,240 (3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-indol-2-yl]-2,2-dimethylpropanoic acid); a Potent, Selective, Thromboxane/Prostaglandin Endoperoxide Antagonist. *Eur. J. Pharmacol.* 1987, 135, 193–201. (f) Mais, D. E.; Yoakim, C.; Guidon, Y.; Gillard, J. W.; Rokach, J.; Halushka, P. V.; Photoaffinity Labelling of the Human Platelet Thromboxane A<sub>2</sub>/Prostaglandin H<sub>2</sub> Receptor. *Biochem. Biophys. Acta* 1989, 1012, 184–190. (g) Mais, D. E.; Bowling, N. L.; True, T. A.; Naka, M.; Morinelli, T. A.; Oatis, J. E.; Hamanaka, N.; Halushka, P. V. Novel Synthesis and Biochemical Properties of an [<sup>125</sup>I]-Labeled Photoaffinity Probe for Thromboxane A<sub>2</sub>/Prostaglandin H<sub>2</sub> Receptors. *J. Med. Chem.* 1991, 34, 1511–1514. (h) Rosentreter, U.; Böshagen, H.; Seuter, F.; Perzborn, E.; Fiedler, V. B. Synthesis and Absolute Configuration of the New Thromboxane Antagonist (3R)-3-(4-Fluorophenylsulfonamide)-1,2,3,4-tetrahydro-9-carbazolepropanoic Acid and Comparison with its Enantiomer. *Arzneim.-Forsch./Drug Res.* 1989, 39, 1519–1521. (i) Shiraiishi, M.; Kato, K.; Terao, S.; Ashida, Y.; Terashita, Z.; Kito, G. Quinones. 4. Novel Eicosanoid Antagonists: Synthesis and Pharmacological Evaluation. *J. Med. Chem.* 1989, 32, 2214–2221. (j) Tomiyama, T.; Wakabayashi, S.; Kosakai, K.; Yokota, M. Azulene Derivatives: New Non-Prostanoid Thromboxane A<sub>2</sub> Receptor Antagonists. *J. Med. Chem.* 1990, 33, 2323–2326.
- (6) (a) Ohshima, E.; Kumazawa, T.; Takizawa, H.; Harakawa, H.; Sato, H.; Obase, H.; Oiji, Y.; Ishii, A.; Ishii, H.; Ohmori, K. A New Series of Antiallergic Agents. I. Synthesis and Activity of 11-(2-Aminoethyl)thio-6,11-dihydrodibenz[b,e]oxepin Derivatives. *Chem. Pharm. Bull.* 1991, 39, 2724–2728. (b) Kumazawa, T.; Ohshima, E.; Harakawa, H.; Sato, H.; Obase, H.; Oiji, Y.; Ishii, A.; Ishii, H.; Ohmori, K. A New Series of Antiallergic Agents. II. Synthesis and Activity of New 6,11-dihydrodibenz[b,e]oxepincarboxylic Acid Derivatives. *Chem. Pharm. Bull.* 1991, 39, 2729–2733.

by the method as depicted in Scheme IV. The alcohol **10a** was treated successively with trifluoroacetic anhydride and 2-mercaptoethanol to provide **18**.<sup>8</sup> The reaction of **18** with methanesulfonyl chloride afforded the corresponding unstable mesylate, which was treated with methylamine to furnish **12q**. The amine **12q** was converted to **4q** via the methyl ester **13q** by a similar method as described in Scheme II.

- (7) (a) Stach, K.; Spingler, H. New Heterocyclic Ring Systems. *Angew. Chem.* 1962, 74, 31–32. (b) Ueno, K.; Kubo, S.; Tagawa, H.; Yoshioka, T.; Tukada, W.; Tubokawa, M.; Kojima, H.; Kasahara, A. 6,11-Dihydrodibenz[b,e]oxepinacetic Acids with Potent Antiinflammatory Activity. *J. Med. Chem.* 1976, 19, 941–946. (c) Aultz, D. E.; Helsley, G. C.; Hoffman, D.; McFadden, A. R.; Lassman, H. B.; Wilker, J. C. Dibenz[b,e]oxepinalkanoic Acids as Nonsteroidal Antiinflammatory Agents. 1. 6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-acetic Acids. *J. Med. Chem.* 1977, 20, 66–70. (d) Aultz, D. E.; McFadden, A. R.; Lassman, H. B. Dibenz[b,e]oxepin-alkanoic Acids as Nonsteroidal Antiinflammatory Agents. 3. ω-(6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-yl)alkanoic Acids. *J. Med. Chem.* 1977, 20, 1499–1501. (e) Yoshioka, T.; Kitagawa, M.; Oki, M.; Kubo, S.; Tagawa, H.; Ueno, K.; Tsukada, W.; Tubokawa, M.; Kasahara, A. Nonsteroidal Anti-inflammatory Agents. 2. Derivatives/Analogues of Dibenz[b,e]oxepin-3-acetic Acid. *J. Med. Chem.* 1978, 21, 633–639. (f) Rokach, J.; Cragoe, E. J., Jr.; Rooney, C. S. Dibenz[b,e]oxepin Compounds. US patent 4,282,365; *Chem. Abstr.* 1982, 96, 35124c. (g) Ackrell, J.; Antonio, Y.; Franco, F.; Landeros, R.; Leon, A.; Muchowski, J. M.; Maddox, M. L.; Nelson, P. H.; Rooks, W. H.; Roszkowski, A. P.; Wallach, M. B. Synthesis and Antiinflammatory Activity of 6,11-Dihydro-11-oxodibenz[b,e]thiopyran-alkanoic Acids and Related Compounds. *J. Med. Chem.* 1978, 21, 1035–1044. (h) Dunn, J. P.; Green, D. M.; Harrison, I. T.; Nelson, P. H.; Pfister, J. R.; Roszkowski, A. P.; Untch, K. G. Dibenzotropane- and Dibenzosuberone-carboxylic Acids with Bronchodilator Activity. *J. Med. Chem.* 1979, 22, 1357–1363.
- (8) In this case, trifluoroacetic anhydride initially acted as dehydrating agent to give the dimeric ether of **10a** and resulting trifluoroacetic acid catalyzed the reaction of the ether and 2-mercaptoethanol.

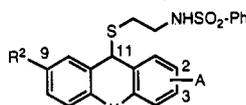
Table I. 11-Substituted-6,11-dihydrodibenz[b,e]oxepin Derivatives (4)



no.	R <sup>1</sup>	Ar	mp, °C	solvent <sup>a</sup>	formula <sup>b</sup>
4a	H	Ph	184–186	IPA	C <sub>25</sub> H <sub>21</sub> NO <sub>5</sub> S <sub>2</sub>
4b	H	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	211–213	IPA	C <sub>23</sub> H <sub>20</sub> N <sub>2</sub> O <sub>7</sub> S <sub>2</sub> ·0.2H <sub>2</sub> O
4c	H	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	190–191 dec	IPA/IPE	C <sub>23</sub> H <sub>20</sub> N <sub>2</sub> O <sub>7</sub> S <sub>2</sub> ·0.5C <sub>3</sub> H <sub>8</sub> O <sup>c</sup> ·0.5H <sub>2</sub> O
4d	H	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	235–237	EA	C <sub>23</sub> H <sub>20</sub> N <sub>2</sub> O <sub>7</sub> S <sub>2</sub>
4e	H	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	207–208	TL	C <sub>24</sub> H <sub>20</sub> F <sub>3</sub> NO <sub>5</sub> S <sub>2</sub>
4f	H	4-FC <sub>6</sub> H <sub>4</sub>	100	IPA	C <sub>23</sub> H <sub>20</sub> FNO <sub>5</sub> S <sub>2</sub>
4g	H	4-ClC <sub>6</sub> H <sub>4</sub>	188–189	IPA	C <sub>23</sub> H <sub>20</sub> ClNO <sub>5</sub> S <sub>2</sub>
4h	H	4-MeC <sub>6</sub> H <sub>4</sub>	181–182	IPA	C <sub>24</sub> H <sub>23</sub> NO <sub>5</sub> S <sub>2</sub>
4i	H	4-MeOC <sub>6</sub> H <sub>4</sub>	189–190	AN	C <sub>24</sub> H <sub>23</sub> NO <sub>6</sub> S <sub>2</sub>
4j	H	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	136–138	AN	C <sub>25</sub> H <sub>25</sub> NO <sub>7</sub> S <sub>2</sub> ·0.2H <sub>2</sub> O
4k	H	2,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	168–172	IPA	C <sub>25</sub> H <sub>25</sub> NO <sub>7</sub> S <sub>2</sub>
4l	H	styryl	176–178	TL	C <sub>25</sub> H <sub>23</sub> NO <sub>5</sub> S <sub>2</sub> ·0.2H <sub>2</sub> O
4m	H	2-naphthyl	150 dec	IPE	C <sub>27</sub> H <sub>23</sub> NO <sub>5</sub> S <sub>2</sub> ·0.3H <sub>2</sub> O
4n	H	2-thienyl	100	IPA	C <sub>21</sub> H <sub>19</sub> NO <sub>5</sub> S <sub>3</sub>
4o	H	3-pyridyl	172–174	IPA/W	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub> S <sub>2</sub> ·H <sub>2</sub> O
4p	H	8-quinolyl	191–193	IPA	C <sub>26</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub> S <sub>2</sub>
4q	Me	Ph	180–181	IPA	C <sub>24</sub> H <sub>23</sub> NO <sub>5</sub> S <sub>2</sub>

<sup>a</sup> Solvent of crystallization: IPA, isopropyl alcohol; IPE, diisopropyl ether; EA, ethyl acetate; TL, toluene; AN, acetonitrile; W, water. <sup>b</sup> All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. <sup>c</sup> C<sub>3</sub>H<sub>8</sub>O, isopropyl alcohol.

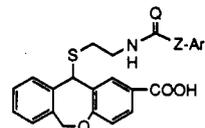
Table II. Substituted 6,11-Dihydrodibenz[b,e]oxepins and Related Compounds



no.	-X-	A, R <sup>2</sup>	mp, °C	solvent <sup>b</sup>	formula <sup>c</sup>
4ab	-CH <sub>2</sub> O-	2-CH <sub>2</sub> COONa	<i>d</i>	<i>e</i>	C <sub>24</sub> H <sub>22</sub> NO <sub>5</sub> S <sub>2</sub> Na
4ac	-CH <sub>2</sub> O-	3-COOH	85	IPE	C <sub>28</sub> H <sub>21</sub> NO <sub>5</sub> S <sub>2</sub> ·0.2C <sub>6</sub> H <sub>14</sub> O <sup>f</sup>
4ad	-CH <sub>2</sub> O-	9-COOH	156–160	TL	C <sub>23</sub> H <sub>21</sub> NO <sub>5</sub> S <sub>2</sub>
4ae	-CH <sub>2</sub> O-	2-COOH, 9-Br	183–185	TL	C <sub>23</sub> H <sub>20</sub> BrNO <sub>5</sub> S <sub>2</sub>
4af	-CH <sub>2</sub> S-	2-COOH	98 dec	IPE	C <sub>23</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>3</sub>
4ag	-CH <sub>2</sub> CH <sub>2</sub> -	2-COOH	141–144	EA/HX	C <sub>24</sub> H <sub>23</sub> NO <sub>4</sub> S <sub>2</sub> ·0.2C <sub>3</sub> H <sub>8</sub> O <sup>g</sup>
4ah	-CH=CH-	2-COOH	167–170	AN	C <sub>24</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub> ·0.1C <sub>3</sub> H <sub>8</sub> O <sup>g</sup>
4ai	H, H <sup>h</sup>	2-COOH	131–132	MT	C <sub>22</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>
4aj	-CH <sub>2</sub> O-	2-Me	99–100	IPE	C <sub>23</sub> H <sub>23</sub> NO <sub>3</sub> S <sub>2</sub>

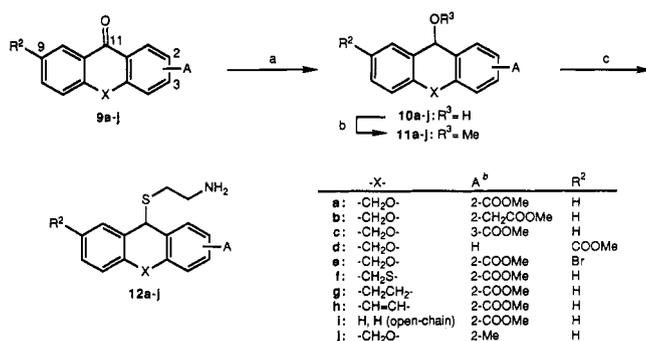
<sup>a</sup> Numbering of substitution positions is conveniently designated according to the general structure illustrated at the top of the table. Consequently, 4ag–ai do not harmonize with the correct nomenclatures of these compounds. <sup>b</sup> Solvent of crystallization: IPE, diisopropyl ether; EA, ethyl acetate; TL, toluene; AN, acetonitrile; MT, methanol; HX, hexane. <sup>c</sup> All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. <sup>d</sup> Extremely hygroscopic. <sup>e</sup> An amorphous powder. <sup>f</sup> C<sub>6</sub>H<sub>14</sub>O, diisopropyl ether. <sup>g</sup> C<sub>3</sub>H<sub>8</sub>O, isopropyl alcohol. <sup>h</sup> An open-chain analogue.

Table III. Substituted 6,11-dihydrodibenz[b,e]oxepins (5–8)

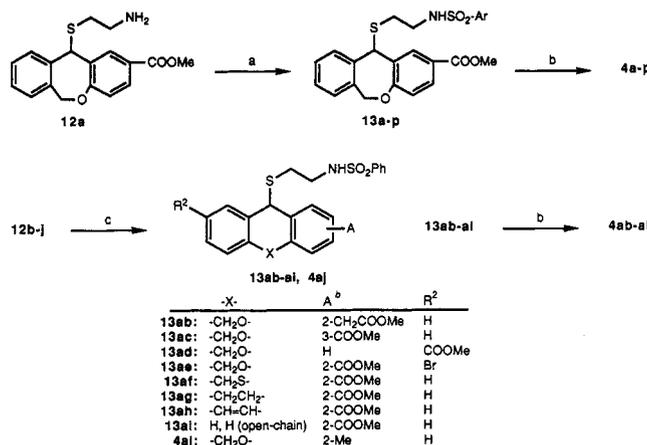


no.	-NHC(=Q)Z-	Ar	mp, °C	solvent <sup>a</sup>	formula <sup>b</sup>
5a	-NHCO-	Ph	193–194	IPA	C <sub>24</sub> H <sub>21</sub> NO <sub>4</sub> S
5b	-NHCO-	2-MeOC <sub>6</sub> H <sub>4</sub>	198–200	IPA	C <sub>25</sub> H <sub>23</sub> NO <sub>5</sub> S
5c	-NHCO-	2-HOC <sub>6</sub> H <sub>4</sub>	125	IPE	C <sub>24</sub> H <sub>21</sub> NO <sub>5</sub> S·0.5H <sub>2</sub> O
5d	-NHCO-	2,6-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	232–234	IPA	C <sub>26</sub> H <sub>26</sub> NO <sub>6</sub> S·0.2H <sub>2</sub> O
5e	-NHCO-	2,3,4-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	214–215.5	IPA	C <sub>27</sub> H <sub>27</sub> NO <sub>7</sub> S
5f	-NHCO-	3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	215–217	TL	C <sub>27</sub> H <sub>27</sub> NO <sub>7</sub> S
5g	-NHCO-	3-Me-2-thienyl	170–172	IPA	C <sub>23</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>
5h	-NHCO-	cyclohexyl	181–182	AN	C <sub>24</sub> H <sub>27</sub> NO <sub>4</sub> S
5i	-NHCO-	<i>n</i> -pentyl	123–125	IPA	C <sub>28</sub> H <sub>27</sub> NO <sub>4</sub> S
6a	-NHCONH-	Ph	160–162	TL	C <sub>24</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> S
6b	-NHCONH-	CH <sub>2</sub> Ph	103–104	IPE	C <sub>25</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> S·0.5H <sub>2</sub> O
7	-NHCSNH-	CH <sub>2</sub> Ph	135–136	TL	C <sub>25</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub> S·0.6C <sub>7</sub> H <sub>8</sub> <sup>c</sup> ·H <sub>2</sub> O
8	-NHCOO-	CH <sub>2</sub> Ph	<i>d</i>	TL <sup>e</sup>	C <sub>25</sub> H <sub>23</sub> NO <sub>5</sub> S·0.1C <sub>7</sub> H <sub>8</sub> <sup>c</sup>

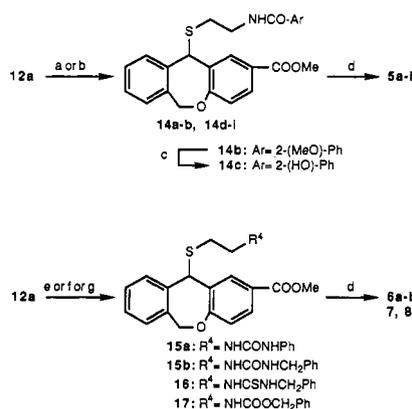
<sup>a</sup> Solvent of crystallization: IPA, isopropyl alcohol; IPE, diisopropyl ether; TL, toluene; AN, acetonitrile. <sup>b</sup> All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. <sup>c</sup> C<sub>7</sub>H<sub>8</sub>, toluene. <sup>d</sup> Hygroscopic. <sup>e</sup> An amorphous powder, triturated with toluene.

Scheme I<sup>a</sup>

<sup>a</sup> (a) NaBH<sub>4</sub>, MeOH; (b) *p*-TsOH, MeOH; (c) 2-aminoethanethiol, BF<sub>3</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Numbering of substitution positions is conveniently designated according to the general structures 9–12. Consequently, g–i series do not harmonize with the correct nomenclatures of these compounds.

Scheme II<sup>a</sup>

<sup>a</sup> (a) ArSO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (b) NaOH, H<sub>2</sub>O, MeOH; (c) PhSO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Numbering of substitution positions is conveniently designated according to the general structure illustrated above. Consequently, 13ag–ai do not harmonize with the correct nomenclatures of these compounds.

Scheme III<sup>a</sup>

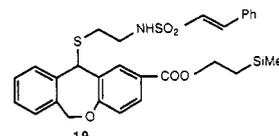
<sup>a</sup> (a) ArCOCl or (ArCO)<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (b) ArCOOH, *i*-BuO-COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (c) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (d) NaOH, H<sub>2</sub>O, MeOH; (e) PhNCO or PhCH<sub>2</sub>NCO, CH<sub>2</sub>Cl<sub>2</sub>; (f) PhCH<sub>2</sub>NCS, CH<sub>2</sub>Cl<sub>2</sub>; (g) PhCH<sub>2</sub>COCl, Et<sub>3</sub>N, *i*-PrOH.

Resolution of racemic **41** was accomplished by HPLC separation of the corresponding 2-(trimethylsilyl)ethyl ester [(±)-**19**] on a CHIRALCEL OD column and subsequent cleavage of the (trimethylsilyl)ethyl group under mild conditions (*n*-Bu<sub>4</sub>NF in THF, at room temperature). Although the corresponding methyl ester [(±)-**131**] was

Scheme IV<sup>a</sup>

<sup>a</sup> (a) (CF<sub>3</sub>CO)<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>; then 2-mercaptoethanol, CH<sub>2</sub>Cl<sub>2</sub>; (b) MeCl, Py; (c) MeNH<sub>2</sub>, MeOH; (d) PhSO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (e) NaOH, H<sub>2</sub>O, MeOH.

separated more easily on the same chromatographic conditions, a slight racemization occurred during subsequent saponification.



## Results and Discussion

The compounds synthesized were tested for their inhibitory effect on the specific binding of [<sup>3</sup>H]U-46619 to guinea pig platelets by the reported method with a slight modification.<sup>9</sup> The results were represented by percent inhibition at 1 and 0.1 μM. K<sub>i</sub> values were determined for the relatively potent compounds (Table IV).

Our research began with the modifications of the aromatic ring moiety (Ar) in **4a**. All of the compounds tested (**4b–p**) showed significant receptor binding affinity and the potency of these derivatives was superior to that of **2** (sulotroban). Compounds possessing 2-nitro (**4b**), 3-nitro (**4c**), 4-(trifluoromethyl) (**4e**), and 4-methoxy (**4i**) groups in the terminal benzene ring demonstrated slightly increased affinities. The insertion of vinylene between the benzene ring and sulfonamide provided **41**, which had significantly enhanced receptor binding affinity. Replacement of the terminal phenyl group with 2-naphthyl (**4m**) and 2-thienyl (**4n**) yielded compounds that retained the activity, while those with 3-pyridyl (**4o**) and 8-quinolyl (**4p**) did not. Compound **4q**, *N*-methyl analogue of **4a**, retained the receptor binding activity of the parent. The result suggests that the hydrogen bonding between the sulfonamide NH group and receptor protein may not play a significant role in the receptor binding of **4a**.

The carboxyl group in the 2-position of the dibenzoxepin ring system proved to be crucial to the enhanced receptor binding affinity of **4a**. 2-Acetic acid and 9-carboxylic acid derivatives (**4ab** and **4ad**) exhibited reduced affinities. Moreover, 3-carboxylic acid and 2-methyl derivatives (**4ac** and **4aj**) were much less active in the binding assay.

Compounds **4af–ai** were synthesized in order to investigate the role of the dibenz[*b,e*]oxepin ring system. Among them, **4af**, possessing a dibenz[*b,e*]thiepin ring system, was 8-fold more potent than **4a**. Compounds **4ag** and **4ah**, dibenz[*a,d*]cycloheptene analogues of **4a**, retained the receptor binding activity of the parent, while an open-chain analogue (**4ai**) showed reduced activity. These data indicated that joining the two benzene rings to form these tricyclic systems was preferable for the receptor binding.

(9) Kattelman, E. J.; Venton, D. L.; Breton, G. C. Characterization of U46619 Binding in Unactivated, Intact Human Platelets and Determination of Binding Site Affinities of Four TXA<sub>2</sub>/PGH<sub>2</sub> Receptor Antagonists (13-APA, BM 13.177, ONO 3708 and SQ 29.548). *Thromb. Res.* 1986, 41, 471–481.

**Table IV.** Biological Activity of 6,11-Dihydrodibenz[*b,e*]oxepin Derivatives 4-8

no.	TXA <sub>2</sub> receptor binding			TXA <sub>2</sub> synthase	
	%			10 μM	IC <sub>50</sub> , <sup>c</sup> nM
	inhibn <sup>a</sup>	1 μM	0.1 μM		
2 (sulotroban)	31 <sup>d</sup>	-5	1,300 ± 140	4	>10000
4a	92 <sup>e</sup>	72 <sup>f</sup>	32 ± 1.4	24	24000
4b	99	72	15 <sup>g</sup>	79	
4c	93	83	14 <sup>g</sup>	54	
4d	90	58		41	
4e	92	70	20 <sup>g</sup>	-9	
4f	93	61		33	
4g	94	64		79	
4h	93	76	27 <sup>g</sup>	77	
4i	93	83	17 <sup>g</sup>	75	
4j	91	49		70	
4k	92	66		62	
(±)-4l	97	92	6.5 ± 0.29	72	
(+)-4l	-	-	250 ± 14	72	4400
(-)-4l	-	-	4.2 ± 0.26	78	3700
4m	95	77	14 <sup>g</sup>	38	
4n	99	86	5.7 ± 1.6	33	
4o	93	67	47 ± 7.9	85	1400
4p	90	44		63	
4q	92	73	33 <sup>g</sup>	80	2200
4ab	84	30		13	
4ac	36	-3		96	370
4ad	64	21		53	
4ae	94	75	6.8 ± 1.6	6	
4af	99	94	3.7 ± 0.31	24	
4ag	95	71	30 ± 1.8	68	
4ah	97	67	25 <sup>g</sup>	74	
4ai	85	41	77 <sup>g</sup>	19	
4aj	27	1		-10	
5a	92	69	44 <sup>g</sup>	63	
5b	97	86	11 <sup>g</sup>	37	
5c	99	90	5.1 ± 0.78	53	
5d	72	20		27	850
5e	97	82	18 <sup>g</sup>	55	
5f	87	50	92 ± 9.8	92	
5g	94	81	10 <sup>g</sup>	79	
5h	66	20		19	
5i	88	51		4	
6a	98	67		58	830
6b	87	47		41	
7	96	80	6.1 ± 1.8	92	
8	96	79	7.7 ± 1.2	56	

<sup>a</sup> *n* = 1. <sup>b</sup> Mean ± SEM, *n* = 3-4. <sup>c</sup> *n* = 1. <sup>d</sup> 31 ± 4% (*n* = 9). <sup>e</sup> 92 ± 4% (*n* = 3). <sup>f</sup> 72 ± 3% (*n* = 3). <sup>g</sup> *n* = 1.

We examined the effects of replacing the sulfonamide linkage with an amide, urea, thiourea, or urethane linkage. The replacement with an amide group (5a-i) exhibited no significant influence on the activity. However, compounds 5h and 5i, possessing terminal cyclohexyl and *n*-pentyl groups on the side chain, respectively, demonstrated somewhat reduced activities. The results suggest that the aromatic ring of the amide group may interact with the receptor. Ortho substituents on the aromatic ring of the side chain enhanced the receptor antagonizing activity (5b, 5c, 5e, and 5g). Compounds 6-8, the urea, thiourea, and urethane analogues, also showed significant receptor binding affinities. Furthermore, 7 and 8 were 4-5-fold more potent than 4a in the receptor binding assay.

Because 4l was one of the most potent receptor antagonists in this series, both optical isomers of 4l were evaluated. The (-)-isomer displaced the TXA<sub>2</sub>/PGH<sub>2</sub> receptor binding of [<sup>3</sup>H]U-46619 concentration-dependently with a *K*<sub>i</sub> value of 4.2 ± 0.26 nM, whereas the (+)-isomer was much less active with a *K*<sub>i</sub> value of 250 ± 14 nM. Similar optical isomeric effects of other non-prostanoid TXRAs

**Table V.** Effects on U-46619-Induced Platelet Aggregation *ex Vivo* in the Guinea Pig<sup>a</sup>

no.	2 h	4 h	7 h
4a	11.8 ± 4.8 (5)	4.5 ± 3.3 (5)	12.3 ± 5.5 (5)
4l	0 ± 0 (3)	2.3 ± 2.3 (3)	10.7 ± 4.1 (3)
4n	14.3 ± 6.3 (5)	2.1 ± 2.1 (5)	12.3 ± 4.2 (5)
4ae	41.0 ± 12.7 (3)	NT	NT
4af	0 ± 0 (3)	0 ± 0 (3)	NT
5a	68.3 ± 5.6 (3)	NT	NT
5c	64.5 ± 5.1 (3)	NT	NT
7	61.7 ± 19.5 (3)	NT	NT
8	8.7 ± 0.9 (3)	57.3 ± 22.2 (3)	NT
2 (sulotroban)			
30 mg/kg	28.0 ± 7.2 (6)	87.0 ± 3.1 (6)	NT
100 mg/kg	12.7 ± 9.9 (6)	57.0 ± 9.3 (6)	NT

<sup>a</sup> Ten milligrams/kilogram of each compound was administered except in the experiments on 2 (sulotroban). The value indicates percent aggregation of platelets after oral administration. Values are mean ± SEM of experiments indicated in parentheses. The control value is 74.6 ± 6.6% (*n* = 12). NT = not tested.

on receptor antagonizing activities were reported recently.<sup>5h,i</sup>

Besides the receptor binding study described above, we elucidated the inhibitory effects of the compounds on U-46619-induced platelet aggregation *in vitro* and *ex vivo*. Platelet aggregation was determined by the reported method.<sup>10</sup> Compounds possessing significant TXA<sub>2</sub>/PGH<sub>2</sub> receptor binding activities also inhibited aggregation of guinea pig platelets *in vitro* (0.03-3 μg/mL).<sup>11</sup> The sulfonamide derivative (±)-4l, one of the most potent compounds in the radioligand receptor assay, inhibited the U-46619 (1 μM) induced guinea pig platelet aggregation *in vitro* with an IC<sub>50</sub> value of 1.36 ± 0.38 × 10<sup>-7</sup> M (*n* = 3). Therefore, inhibitory effects of the selected compounds were elucidated in the guinea pig *ex vivo* experiment. Each inhibition of aggregation was measured at various times following drug administration (10 mg/kg po) and the results are summarized in Table V. More than a 30 mg/kg dose of 2 (sulotroban) was needed to inhibit the U-46619-induced platelet aggregation and the effect was only partial at 4 h after the administration of 100 mg/kg. Compounds 4a, 4l, 4n, and 4af, sulfonamide derivatives, inhibited the platelet aggregation and the effect was observed even 7 h after the administration (4a, 4l, and 4af). Although the introduction of bromine to the 9-position of 4a to afford 4ae enhanced the receptor binding activity

(10) Born, G. V. R. Aggregation of Blood Platelets by Adenosine Diphosphate and its Reversal. *Nature (London)* 1962, 194, 927-929.

(11) Effect of the compounds in this series on U-46619-induced guinea pig platelet aggregation was examined *in vitro*. Blood was withdrawn from the abdominal aorta of pentobarbital-anesthetized guinea pigs 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 induced by U-46619 (0.5-0.1 μM) was measured according to the method of Born,<sup>10</sup> by means of an aggregometer (RAM-31, Rikadenki, or C550, Chrono-Log). A test compound was pretreated for 3 min and the ability to inhibit aggregation was determined (*n* = 2-4). The minimum concentration which inhibits platelet aggregation by 30% or more was defined as the minimum effective concentration (MEC, μg/mL, in parentheses) of the test compound: 4a (0.3), 4b (0.3), 4c (0.3), 4d (0.3), 4e (0.3), 4f (1), 4g (1), 4h (0.3), 4i (0.3), 4j (3), 4k (0.1), (±)-4l (0.03), 4m (0.3), 4n (0.3), 4o (0.1), 4p (3), 4q (1), 4ab (0.3), 4ac (>30), 4ad (3), 4ae (0.03), 4af (3), 4ag (0.3), 4ah (0.3), 4ai (not tested), 4aj (not tested), 5a (0.1), 5b (0.3), 5c (0.3), 5d (1), 5e (1), 5f (0.1), 5g (0.1), 5h (10), 5i (1), 6a (0.3), 6b (not tested), 7 (0.3), 8 (0.3), 2 (sulotroban, 3).

as shown in Table IV, compound 4ae exhibited no significant effect in this test. Moreover, compounds 5a, 5c, and 7, potent receptor antagonists in vitro, were devoid of activity. Interestingly, compound 8, a urethane analogue, exhibited short-acting but potent inhibitory effect in this experiment. Therefore, the sulfonamide linkage was crucial to exert the significant and long-acting antiplatelet effect in vivo.

Canine saphenous vein rings were contracted by U-46619 in the range from 10<sup>-8</sup> to 3 × 10<sup>-5</sup> M.<sup>12</sup> Compound 4a at concentrations of 10<sup>-7</sup>–10<sup>-5</sup> M shifted the concentration–response curve to the right in a concentration-dependent manner with a pA<sub>2</sub> value of 7.74 ± 0.11 (n = 5), and it did not cause any intrinsic agonistic action at concentrations up to 10<sup>-5</sup> M. Moreover, compounds in this series did not alter the antiaggregatory actions of PGI<sub>2</sub>, PGE<sub>1</sub>, and PGD<sub>2</sub> in guinea pig platelet.<sup>13</sup>

Next, the inhibitory effect on TXA<sub>2</sub> synthase was examined by the reported method.<sup>14</sup> The results are represented as the percent inhibition at 10 μM and IC<sub>50</sub> values were determined for the relatively potent compounds (Table IV). Most of the compounds tested showed moderate synthase inhibitory effects, whereas 2 (sulotroban) was devoid of this effect. Interestingly, compound 4ac, which possessed a negligible receptor binding affinity, inhibited TXA<sub>2</sub> synthase significantly (IC<sub>50</sub> = 370 nM). Many TXS-Is possessing 3-pyridyl or 1-imidazolyl moiety and the putative inhibitory mechanism of these compounds have been reported.<sup>15</sup> To our knowledge, however, only a few reports concerning TXA<sub>2</sub> synthase inhibitory effect of TXRAs possessing a sulfonamide moiety have

been presented.<sup>16</sup> Some compounds synthesized in this study eventually possessed both TXA<sub>2</sub>/PGH<sub>2</sub> receptor antagonizing and TXA<sub>2</sub> synthase inhibitory activities. Recently, this type of agent is being considered pharmacologically more beneficial than the antagonist or the synthase inhibitor alone.<sup>17</sup> Therefore, these attractive compounds (4o, 5f, and 7) represent new leads for further investigation of agents possessing two sites of actions. The results of our approach will be reported in the near future.

In conclusion, we found a novel series of non-prostanoid TXA<sub>2</sub>/PGH<sub>2</sub> receptor antagonists with dibenzoxepin skeletons. The structure–activity relationships of 11-[[2-[(arylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid derivatives were defined. The presence of a 2-carboxyl group in the dibenzoxepin ring system was crucial to the enhanced receptor binding activity. Amide, urea, thiourea, and urethane linkages could be substituted for the sulfonamide linkage in the TXA<sub>2</sub>/PGH<sub>2</sub> receptor binding in vitro. However, good oral antiplatelet effect was observed only for the sulfonamide derivatives in the ex vivo experiment. Among them, 4l and 4af were highly potent, orally active, and long-acting TXRAs. The enantiomer (–)-4l was 60-fold more potent than (+)-4l in the TXA<sub>2</sub>/PGH<sub>2</sub> receptor binding.

Although some compounds of this series demonstrated highly potent receptor antagonizing activities in the guinea pig screening models, these antagonists exhibited relatively weak potency for human platelet TXA<sub>2</sub>/PGH<sub>2</sub> receptor (e.g., compound 4af inhibited [<sup>3</sup>H]U-46619 binding to human platelet receptor with a K<sub>i</sub> value of 33 ± 2.7 nM). Therefore, we elaborated another series of compounds, which exhibited remarkable antagonizing effect on human platelet TXA<sub>2</sub>/PGH<sub>2</sub> receptor and the results will be reported in the following paper in this issue.

## Experimental Section

Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrometer. Proton nuclear magnetic resonance spectra (<sup>1</sup>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<sub>3</sub> or DMSO-*d*<sub>6</sub>. 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 doublets; and dt doublet of triplets. 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<sub>4</sub>. 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. CHIRALCEL OD (Daicel Chemical Industries, Ltd.) was used for analytical and preparative HPLC of optical resolution.

**Ketones 9.** Compounds 9a, 9b, 9d, 9e, and 9j were synthesized according to the methods previously reported.<sup>6,7</sup> Ketones 9c and 9f–h were prepared from the corresponding carboxylic acids<sup>7e,h</sup>

- (12) Karasawa, A.; Shirakura, S.; Higo, K.; Kubo, K. Actions of the Novel Thromboxane A<sub>2</sub> Receptor Antagonist Sodium (E)-11-[2-(5,6-Dimethyl-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Monohydrate on Smooth Muscle Preparations. *Arzneim.-Forsch./Drug Res.* 1991, 41, 1237–1241.
- (13) Platelet-rich plasma was preincubated for 2 min with test compound or vehicle before adding one of the antiaggregatory PGs. After a further 1-min incubation, platelets were stimulated by ADP (1 μM).
- (14) Yoshiomoto, T.; Yamamoto, S.; Okuma, M.; Hayashi, O. Solubilization and Resolution of Thromboxane Synthetizing System from Microsomes of Bovine Blood Platelets. *J. Biol. Chem.* 1977, 252, 5871–5874.
- (15) (a) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. Highly Selective Inhibitors of Thromboxane Synthetase. 1. Imidazole Derivatives. *J. Med. Chem.* 1981, 24, 1139–1148. (b) Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Miyamoto, T.; Taniguchi, K.; Hayashi, M.; Iizuka, K.; Nakazawa, M. Highly Selective Inhibitors of Thromboxane Synthetase. 2. Pyridine Derivatives. *J. Med. Chem.* 1981, 24, 1149–1155. (c) Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. Imidazo[1,5-a]pyridines: A New Class of Thromboxane A<sub>2</sub> Synthetase Inhibitors. *J. Med. Chem.* 1985, 28, 164–170. (d) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. Thromboxane Synthetase Inhibitors (TXSI). Design, Synthesis, and Evaluation of a Novel Series of ω-Pyridylalkenoic Acids. *J. Med. Chem.* 1985, 28, 287–294. (e) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. Selective Thromboxane Synthetase Inhibitors. 2. 3-(1H-Imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoic Acid and Analogues. *J. Med. Chem.* 1986, 29, 342–346. (f) Mikashima, H.; Ochi, H.; Muramoto, Y.; Yasuda, H.; Tsuruta, M.; Maruyama, Y. Effects of Y-20811, A Long-Lasting Thromboxane Synthetase Inhibitor, on Thromboxane Production and Platelet Function. *Thromb. Res.* 1986, 43, 455–468. (g) Ushiyama, S.; Ito, T.; Asai, F.; Oshima, T.; Terada, A.; Matsuda, K.; Yamazaki, M. RS-5186, a Novel Thromboxane Synthetase Inhibitor with a Potent and Extended Duration of Action. *Thromb. Res.* 1988, 51, 507–520.

- (16) Perzborn, E.; Seuter, F.; Fiedler, V. B.; Rosentreter, U.; Böshagen, H. Action of the Novel Selective Thromboxane Antagonist (3R)-3-(4-fluorophenylsulfonamido)-1,2,3,4-tetrahydro-9-carbazolepropanoic Acid on Vascular Smooth Muscle Preparations. *Arzneim.-Forsch./Drug Res.* 1989, 39, 1522–1525. It is reported that Bay u3405 inhibits TXB<sub>2</sub> synthesis in human washed platelets at high concentration (2.4 × 10<sup>-5</sup>–2.4 × 10<sup>-4</sup> M) in addition to its TXA<sub>2</sub> receptor antagonizing effect.
- (17) Gressele, P.; Deckmyn, H.; Nenci, G. G.; Vermylen, J. Thromboxane Synthetase Inhibitors, Thromboxane Receptor Antagonists and Dual Blockers in Thrombotic Disorders. *Trends Pharmacol. Sci.* 1991, 12, 158–163.

by an acid-catalyzed esterification (*p*-TsOH, MeOH, reflux). Similarly, **9i** was prepared from commercially available 3-benzoylbenzoic acid (Aldrich).

**Alcohols 10 from 9.** This conversion was performed by the same method as shown in our previous report,<sup>6</sup> in which properties of some of these alcohols were also provided: **10a**<sup>6a</sup> (X = CH<sub>2</sub>O, A = 2-COOMe, R<sup>2</sup> = H), **10b**<sup>6a</sup> (X = CH<sub>2</sub>O, A = 2-CH<sub>2</sub>COOMe, R<sup>2</sup> = H), **10c**<sup>6b</sup> (X = CH<sub>2</sub>O, A = 3-COOMe, R<sup>2</sup> = H), **10d**<sup>6b</sup> (X = CH<sub>2</sub>O, A = H, R<sup>2</sup> = COOMe), **10e**<sup>6b</sup> (X = CH<sub>2</sub>O, A = 2-COOMe, R<sup>2</sup> = Br), **10f** (X = CH<sub>2</sub>S, A = 2-COOMe, R<sup>2</sup> = H; amorphous), **10g** (X = CH<sub>2</sub>CH<sub>2</sub>, A = 2-COOMe, R<sup>2</sup> = H; mp 123–125 °C), **10h** (X = CH=CH, A = 2-COOMe, R<sup>2</sup> = H; amorphous), **10i** (X = open chain, A = 2-COOMe, R<sup>2</sup> = H; oil), **10j**<sup>6a</sup> (X = CH<sub>2</sub>O, A = 2-CH<sub>3</sub>, R<sup>2</sup> = H).

**Methyl Ethers 11 from 10.** The alcohols **10** were converted into the corresponding methyl ethers **11** by a similar method as that described in our previous paper,<sup>6</sup> in which properties of some of these methyl ethers were also provided: **11a**<sup>6a</sup> (X = CH<sub>2</sub>O, A = 2-COOMe, R<sup>2</sup> = H), **11b**<sup>6a</sup> (X = CH<sub>2</sub>O, A = 2-CH<sub>2</sub>COOMe, R<sup>2</sup> = H), **11c** (X = CH<sub>2</sub>O, A = 3-COOMe, R<sup>2</sup> = H; oil), **11d** (X = CH<sub>2</sub>O, A = H, R<sup>2</sup> = COOMe; oil), **11e** (X = CH<sub>2</sub>O, A = 2-COOMe, R<sup>2</sup> = Br; oil), **11f** (X = CH<sub>2</sub>S, A = 2-COOMe, R<sup>2</sup> = H; amorphous), **11g** (X = CH<sub>2</sub>CH<sub>2</sub>, A = 2-COOMe, R<sup>2</sup> = H; mp 82–84 °C), **11h** (X = CH=CH, A = 2-COOMe, R<sup>2</sup> = H; mp 74–77 °C), **11i** (X = open chain, A = 2-COOMe, R<sup>2</sup> = H; oil), and **11j** (X = CH<sub>2</sub>O, A = 2-CH<sub>3</sub>, R<sup>2</sup> = H; mp 52–53 °C).

**Typical Procedure for the Conversion of 11 into 12:** 11-[[2-(2-Aminoethyl)thio]-6,11-dihydrodibenz[*b,e*]joxepin-2-carboxylic Acid Methyl Ester (**12a**, X = CH<sub>2</sub>O, A = 2-COOMe, R<sup>2</sup> = H). To a mixture of **11a** (3.7 g, 13.0 mmol), 2-aminoethanethiol (1.2 g, 15.6 mmol), and dry CH<sub>2</sub>Cl<sub>2</sub> (70 mL) was added BF<sub>3</sub>·Et<sub>2</sub>O (3.9 mL, 31.7 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was washed successively with 1 N NaOH and brine, dried, and concentrated. The residue was chromatographed on silica gel with EtOAc/triethylamine (20/1) as eluent to give 4.1 g (96%) of **12a** (A = 2-COOMe, R<sup>2</sup> = H) as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.30 (s, 2 H), 2.23–2.97 (m, 4 H), 3.79 (s, 3 H), 4.79 and 6.32 (AB syst, *J* = 13 Hz, 2 H), 4.93 (s, 1 H), 6.72 (d, *J* = 8.5 Hz, 1 H), 6.94–7.33 (m, 4 H), 7.65 (dd, *J* = 2.2 and 8.5 Hz, 1 H), 7.83 (d, *J* = 2.2 Hz, 1 H); IR (neat) 3370, 1710, 1240, 1115 cm<sup>-1</sup>.

Compounds **12b–j** were prepared by the same method as described above from the corresponding methyl ethers **11b–j**: **12b** (X = CH<sub>2</sub>O, A = 2-CH<sub>2</sub>COOMe, R<sup>2</sup> = H; oil), **12c** (X = CH<sub>2</sub>O, A = 3-COOMe, R<sup>2</sup> = H; oil), **12d** (X = CH<sub>2</sub>O, A = H, R<sup>2</sup> = COOMe; amorphous), **12e** (X = CH<sub>2</sub>O, A = 2-COOMe, R<sup>2</sup> = Br; oil), **12f** (X = CH<sub>2</sub>S, A = 2-COOMe, R<sup>2</sup> = H; amorphous), **12g** (X = CH<sub>2</sub>CH<sub>2</sub>, A = 2-COOMe, R<sup>2</sup> = H; oil), **12h** (X = CH=CH, A = 2-COOMe, R<sup>2</sup> = H; oil), **12i** (X = open chain, A = 2-COOMe, R<sup>2</sup> = H; oil), **12j** (X = CH<sub>2</sub>O, A = 2-CH<sub>3</sub>, R<sup>2</sup> = H; oil).

**11-[[2-(2-Hydroxyethyl)thio]-6,11-dihydrodibenz[*b,e*]joxepin-2-carboxylic Acid Methyl Ester (**18**).** To a solution of **10a** (40.0 g, 0.15 mol) in CH<sub>2</sub>Cl<sub>2</sub> (400 mL) was added trifluoroacetic anhydride (21.0 mL, 0.15 mol) and the mixture was stirred at room temperature for 1 h. 2-Mercaptoethanol (10.7 mL, 0.15 mol) was added and the solution was stirred for 4 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (500 mL), washed with brine, dried, and evaporated. The crude product was recrystallized from toluene to give 37.6 g (76%) of **18**: mp 128–130 °C dec; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.66 (dt, *J* = 2.1 and 6.0 Hz, 2 H), 3.69 (t, *J* = 6.0 Hz, 2 H), 3.89 (s, 3 H), 4.91 and 6.43 (AB syst, *J* = 12.7 Hz, 2 H), 5.09 (s, 1 H), 6.82–7.98 (m, 7 H). Anal. (C<sub>18</sub>H<sub>18</sub>O<sub>4</sub>S) C, H.

**11-[[2-(2-Methylamino)ethyl]thio]-6,11-dihydrodibenz[*b,e*]joxepin-2-carboxylic Acid Methyl Ester (**12q**).** Compound **18** (3.0 g, 9 mmol) was dissolved in pyridine (50 mL). To the solution was added methanesulfonyl chloride (1 mL, 12.7 mmol) at 0 °C and the resulting mixture was stirred for 2 h under the same conditions. The unstable mesylate obtained in this procedure was not isolated. To the reaction mixture containing the mesylate was added 40% methylamine/MeOH solution (10 mL, 127 mmol) and the mixture was stirred at room temperature overnight. After being concentrated, the crude product was diluted with EtOAc. The organic solution was washed with brine, dried, and evaporated to give crude **12q** as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.15 (bs, 3 H), 2.38–2.78 (m, 4 H), 3.86 (s, 3 H), 4.86 and 6.42 (AB syst, *J* = 12.7 Hz, 2 H), 5.00 (s, 1 H), 6.81 (d, *J* = 8.5 Hz,

1 H), 7.20–7.40 (m, 4 H), 7.75 (dd, *J* = 2.2 and 8.5 Hz, 1 H), 7.93 (d, *J* = 2.2 Hz, 1 H).

**Typical Procedure for Sulfonation of the Amines 12:** 11-[[2-[(Styrylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]joxepin-2-carboxylic Acid Methyl Ester (**13l**). A mixture of **12a** (2.0 g, 6.08 mmol), β-styrenesulfonyl chloride (1.48 g, 7.3 mmol), and triethylamine (10 mL) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (300 mL) containing 2 mL of MeOH. The solution was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with EtOAc as eluent to give 1.86 g (62%) of **13l** as an amorphous powder: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.55 (m, 2 H), 3.10 and 3.14 (AB syst, *J* = 6.4 Hz, 2 H), 3.87 (s, 3 H), 4.88 (bs, 1 H), 4.88 and 6.36 (AB syst, *J* = 12.9 Hz, 2 H), 5.03 (s, 1 H), 6.73 (d, *J* = 15.3 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 7.15–7.49 (m, 10 H), 7.79 (dd, *J* = 2.2 and 8.5 Hz, 1 H), 7.96 (d, *J* = 2.2 Hz, 1 H); IR (CHCl<sub>3</sub>) 3256, 1704, 1610, 1434, 1322, 1244, 1143 cm<sup>-1</sup>; MS *m/z* 495 (M<sup>+</sup>).

The methyl esters **13a–k**, **13m–q**, and **13ab–ai** and the 2-methyl derivative **4ai** were prepared in a similar manner as that described above from appropriate amines **12** and arylsulfonyl chlorides: **13a** (oil), **13b** (amorphous), **13c** (oil), **13d** (mp 144–146 °C), **13e** (oil), **13f** (oil), **13g** (mp 133–134 °C), **13h** (mp 127–128 °C), **13i** (mp 132–133 °C), **13j** (mp 153–154 °C), **13k** (oil), **13m** (amorphous), **13n** (mp 115–116 °C), **13o** (amorphous), **13p** (mp 135–136 °C), **13q** (oil), **13ab** (amorphous), **13ac** (amorphous), **13ad** (oil), **13ae** (oil), **13af** (amorphous), **13ag** (oil), **13ah** (oil), and **13ai** (oil).

**Typical Procedures for Acylation of the Amine 12a.** **Procedure 1:** 11-[[2-[(2-Methoxybenzoyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]joxepin-2-carboxylic Acid Methyl Ester (**14b**). To a solution of **12a** (5.4 g, 16.4 mmol) and triethylamine (10 mL) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added 2-methoxybenzoyl chloride (3.5 mL, 23.5 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL). The solution was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane/EtOAc (1/1) as eluent to give 7.5 g (99%) of **14b** as crystals: mp 123–125 °C (diisopropyl ether); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.50–2.89 (m, 2 H), 3.40–3.79 (m, 2 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.82 and 6.35 (AB syst, *J* = 12.9 Hz, 2 H), 5.05 (s, 1 H), 6.67–8.47 (m, 11 H); IR (KBr) 3372, 1708, 1645, 1602, 1533, 1295, 1253, 768 cm<sup>-1</sup>. Anal. (C<sub>26</sub>H<sub>25</sub>NO<sub>5</sub>) C, H, N.

**Procedure 2:** 11-[[2-[(3,4,5-Trimethoxybenzoyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]joxepin-2-carboxylic Acid Methyl Ester (**14f**). To a solution of 3,4,5-trimethoxybenzoic acid (6.0 g, 28.3 mmol) and triethylamine (20 mL) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added isobutyl chloroformate (3.6 mL, 27.8 mmol) and the mixture was stirred at room temperature for 1 h. A solution of **12a** (3.6 g, 10.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added and the resulting mixture stirred for 10 h. Water (5 mL) was added and the reaction mixture diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated, washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc as eluent to give 4.0 g (70%) of **14f** as an amorphous powder: mp 78–81 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.51–2.83 (m, 2 H), 3.27–3.78 (m, 2 H), 3.84 (s, 12 H), 4.85 and 6.34 (AB syst, *J* = 12.8 Hz, 2 H), 5.04 (s, 1 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 7.01 (s, 2 H), 7.12–7.37 (m, 4 H), 7.73 (dd, *J* = 2.4 and 8.5 Hz, 1 H), 7.93 (d, *J* = 2.4 Hz, 1 H); IR (CHCl<sub>3</sub>) 3400, 2934, 1715, 1633, 1610, 1498, 1332, 1239, 1127, 1005 cm<sup>-1</sup>; MS *m/z* 523 (M<sup>+</sup>).

The methyl esters **14a**, **14d–e**, and **14g–i** were prepared in a similar manner from **12a** and appropriate acid chlorides or acid anhydrides (procedure 1), or carboxylic acids (procedure 2): **14a** (mp 150–151 °C), **14d** (mp 163–164 °C), **14e** (amorphous), **14g** (amorphous), **14h** (amorphous), and **14i** (amorphous).

**11-[[2-[(2-Hydroxybenzoyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]joxepin-2-carboxylic Acid Methyl Ester (**14c**).** Compound **14b** (2.1 g, 4.5 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and the solution was cooled to –75 °C. Boron tribromide (0.6 mL, 6.4 mmol) was added and then the cooling bath was removed. After being warmed to room temperature, the reaction mixture was washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel with hexane/EtOAc (1/1) as eluent and the product was triturated with diisopropyl ether to give 0.7 g (34%) of **14c** as crystals: mp 149–151 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.47–2.86 (m, 2 H), 3.32–3.71 (m,

2 H), 3.83 (s, 3 H), 4.84 and 6.34 (AB syst,  $J = 13.1$  Hz, 2 H), 5.03 (s, 1 H), 6.81 (d,  $J = 8.4$  Hz, 1 H), 6.83–7.55 (m, 8 H), 7.76 (dd,  $J = 2.2$  and 8.4 Hz, 1 H), 7.98 (d,  $J = 2.2$  Hz, 1 H), 12.22 (bs, 1 H); IR (CHCl<sub>3</sub>) 1716, 1646, 1599, 1297, 1252, 1120, 1008 cm<sup>-1</sup>; MS  $m/z$  449 (M<sup>+</sup>). Anal. (C<sub>25</sub>H<sub>23</sub>NO<sub>5</sub>S) C, H, N.

**11-[[2-(3-Phenylureido)ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (15a).** Compound 12a (2.0 g, 6.1 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). Phenyl isocyanate (0.7 mL, 6.4 mmol) was added to the solution and the resulting mixture was stirred at room temperature for 2 h. After being concentrated, the reaction mixture was diluted with EtOAc (200 mL). The solution was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc (2/1) as eluent to give 2.2 g (81%) of 15a as an amorphous powder: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.33–2.70 (m, 2 H), 3.03–3.52 (m, 2 H), 3.81 (s, 3 H), 4.86 and 6.33 (AB syst,  $J = 13.3$  Hz, 2 H), 4.99 (s, 1 H), 5.78–6.15 (m, 1 H), 6.80 (d,  $J = 8.2$  Hz, 1 H), 6.91–7.42 (m, 9 H), 7.65–7.84 (m, 2 H), 7.94 (d,  $J = 2.0$  Hz, 1 H); IR (CHCl<sub>3</sub>) 1715, 1498, 1435, 1237, 1117, 1007 cm<sup>-1</sup>; MS  $m/z$  448 (M<sup>+</sup>).

Compound 15b (amorphous) was prepared in a similar manner as that described above from 12a and benzyl isocyanate.

**11-[[2-(3-Benzylthioureido)ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (16).** A mixture of 12a (2.0 g, 6.1 mmol), benzyl isothiocyanate (1.0 mL, 7.54 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was stirred at room temperature for 1.5 h. The reaction mixture was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc (2/1) as eluent to give 2.25 g (77%) of 16 as an amorphous powder: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.41–2.74 (m, 2 H), 3.43–3.78 (m, 2 H), 3.75 (s, 3 H), 4.56 (d,  $J = 4.0$  Hz, 2 H), 4.80 and 6.25 (AB syst,  $J = 12.8$  Hz, 2 H), 5.02 (s, 1 H), 6.30–6.68 (m, 1 H), 6.76 (d,  $J = 8.6$  Hz, 1 H), 7.01–7.34 (m, 9 H), 7.69 (dd,  $J = 2.2$  and 8.6 Hz, 1 H), 7.90 (d,  $J = 2.2$  Hz, 1 H); IR (CHCl<sub>3</sub>) 3400, 1717, 1610, 1533, 1242, 1118, 1005 cm<sup>-1</sup>; MS  $m/z$  478 (M<sup>+</sup>).

**11-[[2-[(Benzyloxy)carbonyl]amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (17).** A mixture of 12a (2.0 g, 6.08 mmol), benzyl chloroformate (1.2 mL, 8.41 mmol), triethylamine (5 mL), and *i*-PrOH (150 mL) was stirred at room temperature for 0.5 h. After being concentrated, the reaction mixture was diluted with EtOAc (200 mL). The solution was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane/EtOAc (2/1) as eluent to give 2.68 g (95%) of 17 as an amorphous powder: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.34–2.73 (m, 2 H), 3.05–3.48 (m, 2 H), 3.83 (s, 3 H), 4.85 and 6.38 (AB syst,  $J = 11.4$  Hz, 2 H), 5.01 (s, 1 H), 5.09 (s, 2 H), 6.83 (d,  $J = 8.5$  Hz, 1 H), 7.04–7.48 (m, 9 H), 7.77 (dd,  $J = 2.0$  and 8.5 Hz, 1 H), 7.96 (d,  $J = 2.0$  Hz, 1 H); IR (CHCl<sub>3</sub>) 1700, 1609, 1567, 1532, 1431, 1300, 1121, 1013 cm<sup>-1</sup>; MS  $m/z$  463 (M<sup>+</sup>).

**Typical Procedure for Obtaining Carboxylic Acids (4a–g, 4ab–ai, and 5–8) by Hydrolysis:** 11-[[2-[(Styrylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid (4l). A mixture of 13l (1.7 g, 3.1 mmol), 10 N NaOH (2 mL, 20 mmol), H<sub>2</sub>O (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 acidified to pH 3.0 with 4 N HCl and the resultant precipitate was collected. The crude product was recrystallized from toluene to give 1.25 g (84%) of 4l as crystals: mp 176–178 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.5–2.65 (m, 2 H), 2.85–3.20 (m, 2 H), 5.01 and 6.22 (AB syst,  $J = 12.7$  Hz, 2 H), 5.45 (s, 1 H), 6.86 (d,  $J = 8.5$  Hz, 1 H), 7.15–7.55 (m, 11 H), 7.65–7.75 (m, 2 H), 8.01 (d,  $J = 1.8$  Hz, 1 H), 12.75 (br s, 1 H); IR (KBr) 3475, 1696, 1611, 1321, 1254, 1142 cm<sup>-1</sup>. Anal. (C<sub>25</sub>H<sub>23</sub>NO<sub>5</sub>S<sub>2</sub>·0.2H<sub>2</sub>O) C, H, N.

**Resolution of (±)-11-[[2-[(Styrylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (19).** A mixture of (±)-13l (0.31 g, 0.63 mmol), titanium isopropoxide (0.3 mL, 1 mmol), and 2-(trimethylsilyl)ethanol (3 mL, 21 mmol) was stirred at 80 °C for 7 h. Upon cooling, the reaction mixture was chromatographed on silica gel with hexane/EtOAc (2/1) as eluent to give 0.3 g (83%) of (±)-19 as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.05 (s, 9 H), 1.10 (t,  $J = 8.0$  Hz, 2 H), 2.6–2.8 (m, 2 H), 3.0–3.3 (m, 2 H), 4.38 (t,  $J = 8.0$  Hz, 2 H), 4.86 and 6.33 (AB syst,  $J = 12.8$  Hz, 2 H), 5.00 (s, 1 H), 6.70 (d,  $J = 15.1$  Hz, 1 H), 6.81 (d,  $J = 8.6$  Hz, 1 H), 7.43

(d,  $J = 15.1$  Hz, 1 H), 7.2–7.6 (m, 9 H), 7.75 (dd,  $J = 2.2$  and 8.6 Hz, 1 H), 7.92 (d,  $J = 2.2$  Hz, 1 H); MS  $m/z$  581 (M<sup>+</sup>). (±)-19 (200 mg) was resolved by an HPLC column (CHIRALCEL OD, 2 cm i.d. × 50 cm) to give 52 mg of (+)-19 [(peak 1): [α]<sub>D</sub><sup>25</sup> +94.3° (c 1, CHCl<sub>3</sub>); ee ≥ 99.5%, based on HPLC analysis (CHIRALCEL OD, 46 mm i.d. × 25 cm)] and 60 mg of (-)-19 [(peak 2): [α]<sub>D</sub><sup>25</sup> -85.2° (c 1, CHCl<sub>3</sub>); 96% ee] [separation conditions: eluent, hexane/EtOH 3:1; column temperature, 40 °C; flow rate, 9.99 mL/min; pressure, 20 kg/cm<sup>2</sup>; injection, 20 mg in EtOH].

(+)-11-[[2-[(Styrylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid [(+)-4l]. Compound (±)-19 (≥99.5% ee, 52 mg, 0.09 mmol) was dissolved in THF (20 mL) containing 0.37 mmol of *n*-Bu<sub>4</sub>NF. The solution was stirred at room temperature for 2 h and then concentrated. The reaction mixture was diluted with EtOAc (50 mL). The solution was washed with brine, dried, and concentrated. The residue was triturated with toluene to give 12 mg (28%) of (+)-4l: mp 137–138 °C; [α]<sub>D</sub><sup>25</sup> +134° (c 0.2, EtOH); ee ≥ 99.5%, based on HPLC analysis [CHIRALCEL OD, 46 mm i.d. × 25 cm, hexane/EtOH/AcOH (700/300/1) as eluent].

(-)-11-[[2-[(Styrylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid [(-)-4l]. The title compound was prepared from (-)-19 by the same method described above: mp 137 °C; [α]<sub>D</sub><sup>25</sup> -138° (c 0.2, EtOH); ≥99.5% ee.

**Biological Evaluation Procedures. TXA<sub>2</sub>/PGH<sub>2</sub> Receptor Binding Assay.** The receptor binding assay was performed with a slight modification of the method of Kattelman et al.<sup>9</sup> Briefly, arterial blood was withdrawn from male Hartley guinea pigs and mixed with a 1/10 (v/v) anticoagulant consisting of 77 mM 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 precipitate platelets. Thereafter, the platelets were washed and resuspended in 25 mM Tris-HCl buffer (pH 7.5) containing NaCl (138 mM), MgCl<sub>2</sub> (5 mM), EGTA (1 mM), and indomethacin (10 μM). Platelets (1 × 10<sup>8</sup>) were incubated with 10 nM of [<sup>3</sup>H]U-46619 and various concentrations 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. Ice-cold 50 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 three 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 results were expressed by percent inhibitions at 0.1 and 1 μM. *K<sub>i</sub>* values were determined for the relatively potent compounds.

**Effects on U-46619-Induced Platelet Aggregation ex Vivo in the Guinea Pig.** Drug was suspended in 0.3% sodium (carboxymethyl)cellulose so as to make 1 mL of suspension per 100 g of body weight. Blood was withdrawn at fixed times after the oral administration of a drug (10, 30, or 100 mg/kg) from the abdominal aorta of pentobarbital-anesthetized guinea pigs and was collected in a plastic tube containing 3.8% sodium citrate (1 mL for 9 mL blood) as an anticoagulant. Platelet-rich plasma 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 measured according to the method of Born,<sup>10</sup> by means of an aggregometer (RAM-31, Rikadenki, or C550, Chrono-Log). Platelet aggregation was induced by the addition of 1 μM of U-46619 (Sigma) to PRP (0.3 mL) and was determined by measuring the change of optical density of PRP during aggregation. The result was expressed as percent aggregation.

**Thromboxane A<sub>2</sub> Synthase Inhibition.** Bovine platelet microsome was prepared according to the method of Yoshimoto et al.<sup>14</sup> 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<sub>2</sub> 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<sub>2</sub>, the stable hydrolysis product

of thromboxane  $A_2$ , using a specific radioimmunoassay. The result was expressed by percent inhibition at 10  $\mu$ M, and  $IC_{50}$  values were determined for the relatively potent compounds.

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**Registry No.** 4a, 142423-26-5; 4b, 142423-27-6; 4c, 142423-28-7; 4d, 142423-29-8; 4e, 142423-30-1; 4f, 142423-31-2; 4g, 142423-32-3; 4h, 142423-33-4; 4i, 142423-34-5; 4j, 142423-35-6; 4k, 142423-36-7; ( $\pm$ )-4l, 142423-37-8; (+)-4l, 142423-38-9; (-)-4l, 142423-39-0; 4m, 142423-40-3; 4n, 142423-41-4; 4o, 142423-42-5; 4p, 142423-43-6; 4q, 142423-44-7; 4ab, 142423-45-8; 4ac, 142423-46-9; 4ad, 142423-47-0; 4ae, 142423-48-1; 4af, 142423-49-2; 4ag, 142423-50-5; 4ah, 142423-51-6; 4ai, 142423-52-7; 5a, 142423-53-8; 5b, 142423-54-9; 5c, 142423-55-0; 5d, 142423-56-1; 5e, 142423-57-2; 5f, 142423-58-3; 5g, 142423-59-4; 5h, 142423-60-7; 5i, 142423-61-8; 6a, 142423-62-9; 6b, 142423-63-0; 7, 142423-64-1; 8, 142423-65-2; 9a, 79669-87-7; 9b, 55689-64-0; 9c, 105671-04-3; 9d, 79669-80-0; 9e, 138639-76-6; 9f, 142423-66-3; 9g, 37645-29-7; 9h, 4260-62-2; 9i, 21204-86-4; 9j, 23560-66-9; 10a, 142423-67-4; 10b, 142423-68-5; 10c, 142423-69-6; 10d, 142423-70-9; 10e, 142423-71-0; 10f, 142423-72-1; 10g, 142423-73-2; 10h, 142423-74-3; 10i, 142423-75-4; 10j, 142423-76-5; 11a, 140836-72-2; 11b, 142423-77-6; 11c,

142423-78-7; 11d, 142423-79-8; 11e, 142423-80-1; 11f, 142423-81-2; 11g, 142423-82-3; 11h, 142423-83-4; 11i, 142423-84-5; 11j, 142423-85-6; 12a, 142423-86-7; 12b, 142423-87-8; 12c, 142423-88-9; 12d, 142423-89-0; 12e, 142423-90-3; 12f, 142423-91-4; 12g, 142423-92-5; 12h, 142423-93-6; 12i, 142423-94-7; 12j, 142423-95-8; 12q, 142423-96-9; 13a, 142423-97-0; 13b, 142423-98-1; 13c, 142423-99-2; 13d, 142424-00-8; 13e, 142424-01-9; 13f, 142424-02-0; 13g, 142424-03-1; 13h, 142424-04-2; 13i, 142424-05-3; 13j, 142424-06-4; 13k, 142424-07-5; 13l, 142424-08-6; 13m, 142424-09-7; 13n, 142424-10-0; 13o, 142424-11-1; 13p, 142424-12-2; 13q, 142424-13-3; 13ab, 142424-14-4; 13ac, 142424-15-5; 13ad, 142424-16-6; 13ae, 142424-17-7; 13af, 142424-18-8; 13ag, 142424-19-9; 13ah, 142424-20-2; 23ai, 142424-21-3; 14a, 142424-22-4; 14b, 142437-43-2; 14c, 142424-23-5; 14d, 142424-24-6; 14e, 142424-25-7; 14f, 142424-26-8; 14g, 142424-27-9; 14h, 142424-28-0; 14i, 142424-29-1; 15a, 142424-30-4; 15b, 142424-31-5; 16, 142424-32-6; 17, 142424-33-7; 18, 140836-73-3; ( $\pm$ )-19, 142424-34-8; (+)-19, 142437-45-4; (-)-19, 142437-44-3;  $PhSO_2Cl$ , 98-09-9;  $o$ - $NO_2C_6H_4SO_2Cl$ , 1694-92-4;  $m$ - $NO_2C_6H_4SO_2Cl$ , 121-51-7;  $p$ - $NO_2C_6H_4SO_2Cl$ , 98-74-8;  $p$ - $F_3CC_6H_4SO_2Cl$ , 2991-42-6;  $p$ - $FC_6H_4SO_2Cl$ , 349-88-2;  $p$ - $ClC_6H_4SO_2Cl$ , 98-60-2;  $p$ - $MeC_6H_4SO_2Cl$ , 98-59-9;  $p$ - $MeOC_6H_4SO_2Cl$ , 98-68-0; 3,4-( $MeO$ ) $_2C_6H_3SO_2Cl$ , 23095-31-0; 2,5-( $MeO$ ) $_2C_6H_3SO_2Cl$ , 1483-28-9;  $PhCH=CHSO_2Cl$ , 409-26-7;  $PhCH_2NCO$ , 3173-56-6;  $PhNCO$ , 103-71-9;  $PhCH_2NCS$ , 622-78-6;  $PhCH_2COCl$ , 103-80-0; 2-naphthalenesulfonyl chloride, 93-11-8; 2-thiophenesulfonyl chloride, 16629-19-9; 3-pyridinesulfonyl chloride, 16133-25-8; 8-quinolinesulfonyl chloride, 18704-37-5; 2-aminoethanethiol, 60-23-1.

## Non-Prostanoid Thromboxane $A_2$ Receptor Antagonists with a Dibenzoxepin Ring System. 2

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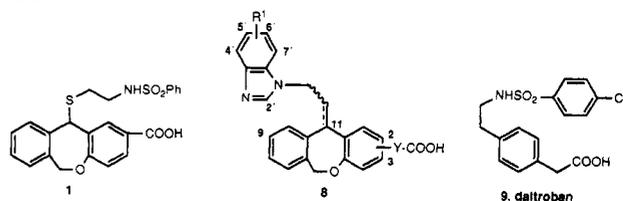
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A series of 11-[2-(1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic acid derivatives and related compounds were synthesized and found to be potent  $TXA_2/PGH_2$  receptor antagonists. Each compound synthesized was tested for its ability to displace [ $^3H$ ]U-46619 binding from guinea pig platelet  $TXA_2/PGH_2$  receptors. Structure-activity relationship studies revealed that the following key elements were required for enhanced activities: (1) an (*E*)-2-(1-benzimidazolyl)ethylidene side chain in the 11-position of the dibenzoxepin ring system and (2) a carboxyl group in the 2-position of the dibenzoxepin ring system. The studies also indicated that the  $TXA_2/PGH_2$  receptor binding affinities of this series of compounds in guinea pig platelet were poorly correlated with those in human platelet. Introduction of substituent(s) to the benzimidazole moiety was effective and sodium (*E*)-11-[2-(5,6-dimethyl-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylate monohydrate (**57**) recorded the highest affinity for human platelet  $TXA_2/PGH_2$  receptor with a  $K_i$  value of  $1.2 \pm 0.14$  nM. It demonstrated potent inhibitory effects on U-46619-induced guinea pig platelet aggregation (in vitro and ex vivo) and human platelet aggregation (in vitro). Compound **57**, now designated as KW-3635, is a novel, orally active, and specific  $TXA_2/PGH_2$  receptor antagonist with neither  $TXA_2/PGH_2$  receptor agonistic nor  $TXA_2$  synthase inhibitory effects. It is now under clinical evaluation.

### Introduction

We reported that the synthesis and  $TXA_2/PGH_2$  receptor antagonizing activity of 11-[[2-[(phenylsulfonyl)amino]ethyl]thio]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic acid (**1**, see Chart I) and its derivatives.<sup>1</sup> Three key elements required both for potent  $TXA_2/PGH_2$  receptor antagonizing activity and for good oral activity were revealed: (1) a terminal arylsulfonylamino group on the side chain, (2) a carboxylic group at the 2-position of the dibenzoxepin ring system, and (3) a dibenzoxepin ring system. On the basis of these findings, further structural modifications of **1** were performed to enhance its receptor

Chart I



antagonizing activity. We began the study by replacing the sulfide linkage ( $-S-$ ) of **1** with a carbon-carbon double bond ( $=C-$ ). The results are summarized in Table I. Compound **2**, possessing *E*-geometry, exhibited moderate binding affinity for guinea pig platelet  $TXA_2/PGH_2$  receptor at 0.1  $\mu$ M, although its *Z*-counterpart (**3**) was devoid of activity at that concentration. Interestingly, shortening of the side chain of **2** to provide **4** resulted in

(1) Ohshima, E.; Takami, H.; Sato, H.; Obase, H.; Miki, I.; Ishii, A.; Karasawa, A.; Kubo, K. *J. Med. Chem.*, preceding paper in this issue.