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

Acknowledgment. We are grateful to Mr. T. Yasuzawa, Mr. H. Ueno, Mrs. Y. Otaki, and Ms. I. Hattori for analytical and spectral data, and especially to Drs. T. Kumazawa and K. Suzuki for their continuous support and pertinent discussion.

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; (±)-**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; (±)-**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; $PhCH_2COOCl$, 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

Etsuo Ohshima, Hitoshi Takami, Hideyuki Sato, Shinichiro Mohri, Hiroyuki Obase,* Ichiro Miki, Akio Ishii, Shiro Shirakura, Akira Karasawa, and Kazuhiro Kubo

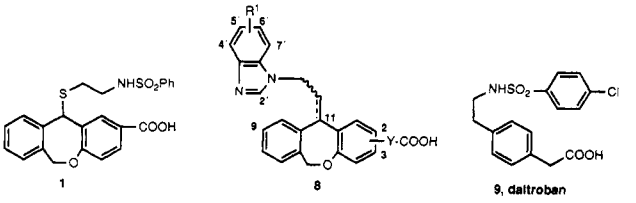
Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Company, Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka-ken, 411 Japan. *Received January 22, 1992*

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 [^{3}H]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 ± 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.[1] 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 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 μM, 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

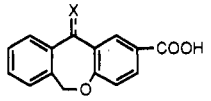
Chart I

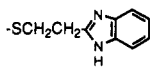
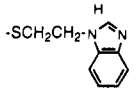
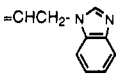


(1) Ohshima, E.; Takami, H.; Sato, H.; Obase, H.; Miki, I.; Ishii, A.; Karasawa, A.; Kubo, K. *J. Med. Chem.*, preceding paper in this issue.

0022-2623/92/1835-3402$03.00/0

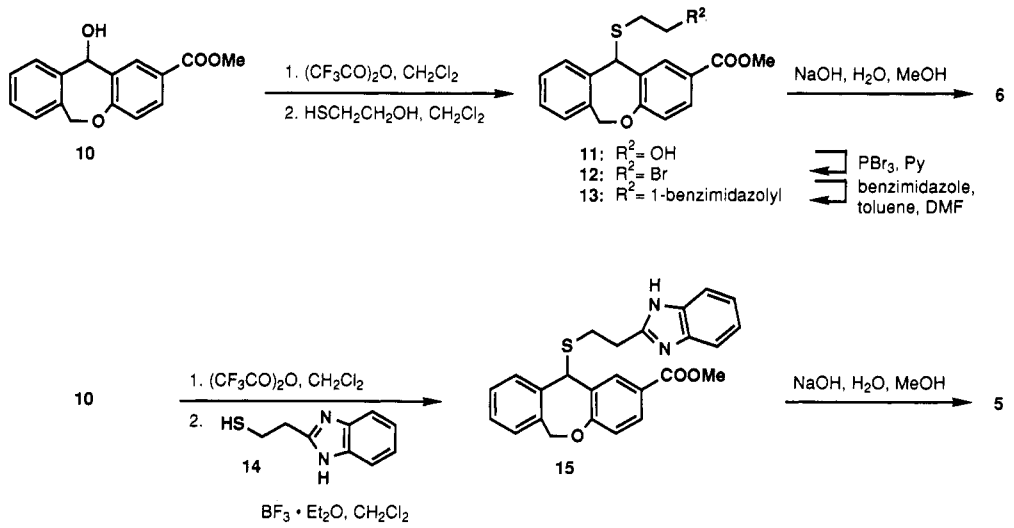
Table I. 11-Substituted-6,11-dihydrodibenz[*b,e*]oxepin Derivatives



no.	X	mp, °C (solvent)[a]	formula[b]	TXA_2/PGH_2 receptor binding: guinea pig WP K_i,[c] nM (*n*), or % inhibn[d] at 0.1 μM	U46619-induced platelet aggregation ex vivo in the guinea pigs: % aggregation (*n*)[e]
1	$-SCH_2CH_2NHSO_2Ph$	184–186 (IPA)	$C_{23}H_{21}NO_5S_2$	32 ± 1.4 (3)	11.8 ± 4.8 (5)
2	$=CHCH_2CH_2NHSO_2Ph$ (*E*)	211–212 (IPA/IPE)	$C_{24}H_{21}NO_5S$	50%	59.3 ± 15.9 (3)
3	$=CHCH_2CH_2NHSO_2Ph$ (*Z*)	130 (IPE[f])	$C_{24}H_{21}NO_5S \cdot 0.5C_3H_8O$[g]	−6%	NT[h]
4	$=CHCH_2NHSO_2Ph$ (*E*)	254–257 dec (AN)	$C_{23}H_{19}NO_5S \cdot 0.25H_2O$	11 (1)	25.0 ± 1.4 (3)
5		164–166 (IPA)	$C_{24}H_{20}N_2O_3S \cdot 1.5H_2O$	7.6 ± 0.088 (3)	66.3 ± 9.1 (3)
6[i]		230–232 dec (AN)	$C_{24}H_{20}N_2O_3S \cdot HCl$	9%	NT[h]
7[j]		>250 (AC/W)	$C_{24}H_{17}N_2O_3Na \cdot 0.6H_2O$	15 ± 2.3 (4)	0 ± 0 (5)
9, daltroban				63 ± 5.3 (3)	0 ± 0 (6)

[a] Solvent of crystallization: IPA, isopropyl alcohol; IPE, diisopropyl ether; AC, acetone; AN, acetonitrile; W, water. [b] All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. [c] Values are mean ± SEM of experiments indicated in parentheses. [d] *n* = 1–2. [e] Mean ± SEM of experiments indicated in parentheses. The value indicates percent aggregation of platelets at 2 h after administration of each compound (10 mg/kg po). The control value is 72.7 ± 13.8% (*n* = 5). [f] Trituration solvent. [g] C_3H_8O, isopropyl alcohol. [h] Not tested. [i] HCl salt. [j] Na salt.

Scheme I

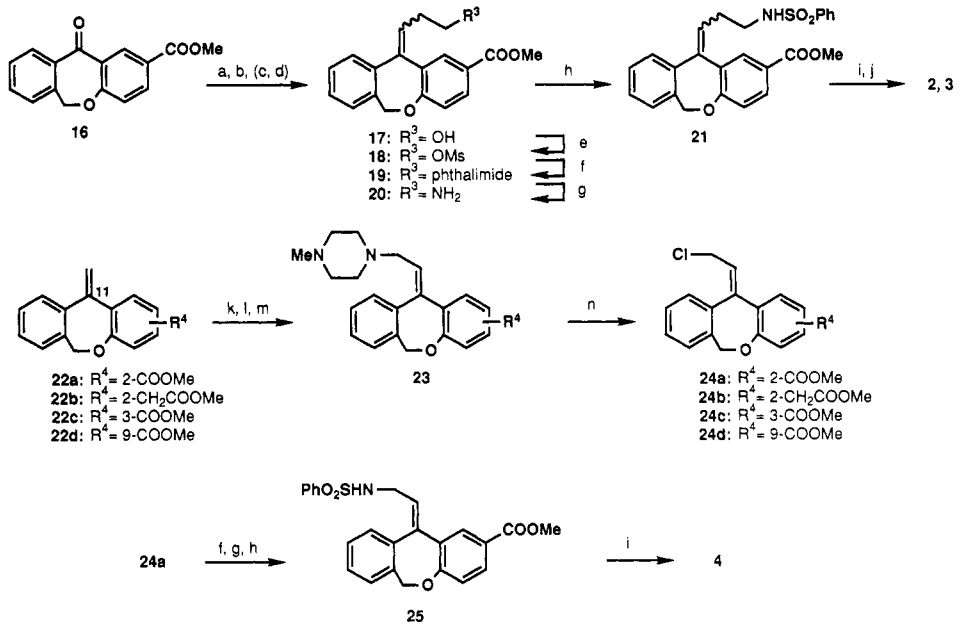


a significant enhancement in the affinity (K_i = 11 nM). However, compounds 2 and 4 failed to exhibit superior effect to the lead compound (1) on U-46619-induced guinea pig platelet aggregation ex vivo after oral administration of 10 mg/kg of each compound. We also examined the effects of replacing the benzenesulfonamide moiety of 1 with a benzimidazole, a structural equivalent of *N*-arylurea or *N*-arylamide moiety, since our previous studies[1] revealed that the amide, urea, thiourea, and urethane analogues of 1 retained the TXA_2/PGH_2 receptor binding affinity. The results are also shown in Table I. Compound 5 exhibited approximately 4-fold higher TXA_2/PGH_2 receptor binding affinity than 1. However, no significant oral antiplatelet effect of 5 was observed in the ex vivo experiment. Compound 6, a connecting positional isomer of 5, was devoid of affinity. Surprisingly, compound 7, in which the ethylthio connecting group of 6 is replaced by an (*E*)-ethylidene group, showed significant receptor binding activity (K_i = 15 ± 2.3 nM) and its potency was 4-fold higher than that of daltroban (9). Furthermore, compound 7 demonstrated potent inhibitory effect on the platelet aggregation in the ex vivo experiment. Therefore, we selected 7 as a new lead and performed its structural optimization.

This paper describes the synthesis and structure–activity relationships of 11-[2-(1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b,e*]oxepin derivatives (8, see Chart I) and related compounds. Daltroban (9),[2] one of the repre-

(2) Stegmeier, K.; Pill, J.; Müller-Beckmann, B.; Sponer, G.; Patscheke, H. Sulfonamidephenylcarboxylic Acids as a New Class of Selective and Competitive Non-prostanoic Thromboxane Receptor Antagonists. *Thromb. Haemostasis* **1985**, *54*, 292.

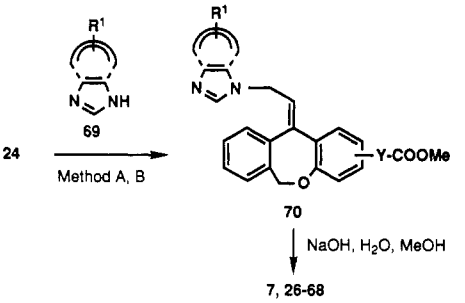
Scheme II[a]



[a] (a) Ph_3P^+–$CH_2CH_2CH_2OTHPBr^-$, *n*-BuLi, THF; (b) *p*-TsOH, H_2O, dioxane; (c) *p*-TsOH, AcOH; (d) *p*-TsOH, MeOH; (e) MsCl, Py; (f) potassium phthalimide, DMF; (g) H_2NNH_2, MeOH; (h) $PhSO_2Cl$, Py; (i) NaOH, MeOH, H_2O; (j) fractional crystallization; (k) 1-methylpiperazine, $(CH_2O)_n$, CF_3COOH, AcOH, dichloroethane; (l) fractional crystallization; (m) saturated $NaHCO_3$; (n) ClCOOEt, AcONa, dichloroethane.

sentative non-prostanoid TXA_2/PGH_2 receptor antagonists,[3] was used as a reference compound during our series of experiments.

Scheme III



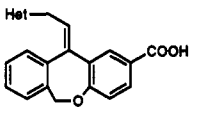
Chemistry

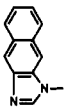
Compounds possessing a sulfide linkage, **5** and **6**, listed in Table I, were prepared by the procedure as depicted in Scheme I. The alcohol **10** was converted to **11** by the method reported in our preceding paper.[1] Treatment of **11** with PBr_3 provided **12**, which was allowed to react with benzimidazole and subsequent alkaline saponification furnished **6**. Similarly, successive treatments of **10** with trifluoroacetic anhydride and 2-(2-mercaptoethyl)benzimidazole (**14**) in the presence of BF_3·Et_2O provided **15**, which was saponified to **5**. Scheme II illustrates the synthesis of **2**–**4** (Table I). Wittig olefination[4] of **16** and the subsequent cleavage of tetrahydropyranyl ether afforded **17** (E/Z = 3/7), which was treated with methanesulfonyl chloride to furnish **18**. The unstable mesylate **18** was immediately submitted to the reaction with potassium phthalimide to provide **19**, which was converted to **20** with hydrazine in methanol. Sulfonylation of the crude **20** with benzenesulfonyl chloride afforded **21** (E/Z = 3/7), which was saponificated and subsequently purified by fractional crystallization to provide **3** possessing *Z*-geometry. No

(3) (a) Patscheke, H.; Stegmeier, K. Investigations on a Selective Non-prostanoic 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_2 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_2/Prostaglandin H_2 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 [^{125}I]-Labeled Photoaffinity Probe for Thromboxane A_2/Prostaglandin H_2 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 (3*R*)-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) Shiraishi, 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_2 Receptor Antagonists. *J. Med. Chem.* **1990**, *33*, 2323–2326.

(4) Schow, S. R.; McMorris, T. C. Utility of the Wittig Reaction for the Construction of Side Chains of Steroids Starting from Pregnenolone. *J. Org. Chem.* **1979**, *44*, 3760–3765.

Table II. 11-Ethylidene-6,11-dihydrodibenz[*b,e*]oxepin Derivatives

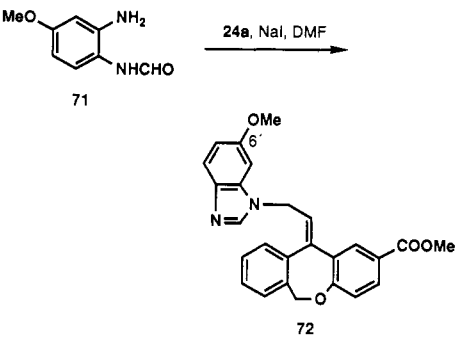


no.	Het	method[a]	mp, °C	solvent[b]	formula[c]	TXA_2/PGH_2 receptor binding: guinea pig WP K_i,[d] nM (*n*), or % inhibn[e] at 0.1 μM
26		A	215–216	IPA/W	$C_{23}H_{17}N_3O_3$	35%
27		B	287–290 dec	DMF	$C_{28}H_{20}N_2O_3 \cdot 0.25H_2O$	280 ± 21 (3)
28		A	260–263 dec	IPA	$C_{23}H_{17}N_2O_3$	29 ± 3.2 (3)
29		A	236–237	DMF	$C_{23}H_{17}N_3O_3 \cdot H_2O$	−6%
30		A	264–265 dec	MA	$C_{20}H_{16}N_2O_3 \cdot 0.2H_2O$	600 ± 34 (3)
31		A	275–276	IPA	$C_{26}H_{20}N_2O_3$	37 ± 2.6 (3)
32		A	145 dec	IPA	$C_{32}H_{24}N_2O_3$	164 ± 24 (3)

[a] See the text. [b] Solvent of crystallization: IPA, isopropyl alcohol; W, water; DMF, dimethylformamide; MA, methanol. [c] All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. [d] Values are mean ± SEM of experiments indicated in parentheses. [e] n = 1–2.

detectable isomerization was observed during the conversion from **17** to **21** and under the subsequent saponification conditions. Chemical isomerization of the double bond of the *Z*-rich intermediate **17** was performed in order to obtain the *E*-isomer (**2**). The *Z*-rich **17** was heated with *p*-TsOH in AcOH and subsequently esterified to *E*-rich **17** (E/Z = 7/3), which was converted to **2** by the same procedure as described above. Compound **4** was prepared from olefin **22a** (R^4 = 2-COOMe) via chloride **24a** (R^4 = 2-COOMe).[5] The starting compounds **22** were obtained by Wittig olefination of the corresponding ketones.[6] The

Scheme IV



olefins **22** were treated with 1-methylpiperazine under Mannich reaction conditions to provide **23** (E/Z = 9/1). Compounds **23** (E > 99%) separated by the fractional crystallization of the corresponding acid addition salts of the crude **23** were treated with ethyl chloroformate to provide **24** with negligible isomerization.[7] The chloride **24a** was converted to **25** in a similar manner as described in the synthesis of **21** from **18**, and subsequent saponification provided **4**.

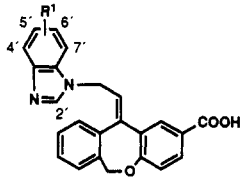
Compounds **7** and **26–68**, listed in Tables I–IV, were also prepared from the chlorides **24** (Scheme III). Compounds **24** were treated with appropriate benzimidazole derivatives and related heterocyclic compounds (**69**) to provide **70** under the following reaction conditions: method A, **69** (5 equiv), toluene/DMF, reflux; method B, **69** (1 equiv), NaH (1 equiv), THF, reflux. Unsymmetrically substituted benzimidazoles led to yields of **70** as a mixture of two isomers in these reaction conditions.[8] Each isomer was

(5) (a) Ohshima, E.; Kumazawa, T.; Otaki, S.; Obase, H.; Ohmori, K.; Ishii, H.; Manabe, H.; Tamura, T.; Shuto, K. EP patent 235796; *Chem. Abstr.* **1988**, *108*, 167330*t*. (b) Ohshima, E.; Otaki, S.; Sato, H.; Kumazawa, T.; Obase, H.; Ishii, A.; Ishii, H.; Ohmori, K.; Hirayama, N. Synthesis and Antiallergic Activity of 11-(Aminoalkylidene)-6,11-dihydrodibenz[*b,e*]oxepin Derivatives. *J. Med. Chem.* **1992**, *35*, 2074–2084.

(6) (a) 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. (b) 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. (c) 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. (d) 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. (e) Rokach, J.; Cragoe, E. J., Jr.; Rooney, C. S. Dibenz[*b,e*]oxepin Compounds. US patent 4,282,365; *Chem. Abstr.* **1982**, *96*, 35124*c*.

(7) Tanabe, K.; Katagiri, T.; Tanaka, J. Highly Stereoselective Syntheses of Nerol and Geraniol. *Chem. Lett.* **1977**, 1025–1026.

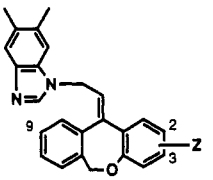
Table III. 6,11-Dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Derivatives

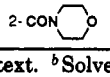


no.	R^1	method[a]	mp, °C	solvent[b]	formula[c]	TXA_2/PGH_2 receptor binding, K_i,[d] nM (*n*) guinea pig WP	human WP
7	H[e]	A	>250	AC/W	$C_{24}H_{17}N_2O_3Na\cdot0.6H_2O$	15 ± 2.3 (4)	13 ± 1.5 (3)
33	5'-NO_2	A	290–293	IPA/W	$C_{24}H_{17}N_3O_5\cdot0.2H_2O$	1.8 ± 0.17 (3)	9.2 ± 3.3 (3)
34	6'-NO_2	A	287–290	IPA	$C_{24}H_{17}N_3O_5$	9.5 ● 0.32 (3)	9.1 ± 0.09 (3)
35	5'-COOH	A	318–319 dec	IPA	$C_{25}H_{18}N_2O_5\cdot0.25H_2O$	30 ± 3.4 (3)	NT[f]
36	6'-COOH	A	321–323 dec	EA	$C_{25}H_{18}N_2O_5$	190 ● 11 (3)	NT[f]
37	5'-$CONHCH_2Ph$	A	>300 dec	IPE	$C_{23}H_{25}N_3O_4$	0.91 ± 0.20 (3)	7.4 ± 1.7 (3)
38	6'-$CONHCH_2Ph$	A	242–245	IPE	$C_{23}H_{25}N_3O_4\cdot H_2O$	10 ± 0.64 (3)	14 (1)
39	5'-CF_3	A	290–291 dec	IPA	$C_{25}H_{17}F_3N_2O_3\cdot0.5C_3H_8O$[g]	2.2 ± 0.28 (3)	85 ± 11 (4)
40	6'-CF_3	B	286–288 dec	IPA	$C_{25}H_{17}F_3N_2O_3$	60 ± 3.5 (3)	NT[f]
41	5'-F	B	174–177	IPA	$C_{24}H_{17}FN_2O_3$	8.3 ● 0.73 (3)	15 ± 3.1 (3)
42	6'-F	B	287–288	IPA	$C_{24}H_{17}FN_2O_3$	9.6 ● 1.4 (3)	NT[f]
43	5'-Cl	A	277–278	IPA	$C_{24}H_{17}ClN_2O_3\cdot0.5H_2O$	6.0 ± 1.9 (6)	11 ± 0.91 (3)
44	6'-Cl	A	310–312	IPA	$C_{24}H_{17}ClN_2O_3\cdot0.25H_2O$	15 ± 5.8 (5)	19 ● 1.2 (3)
45	4'-Me	B	276	IPA	$C_{25}H_{20}N_2O_3$	17 ± 3.7 (3)	38 ± 20 (3)
46	5'-Me	B	163–165	IPA	$C_{25}H_{20}N_2O_3$	15 ± 1.2 (3)	110 ± 22 (3)
47	6'-Me	B	165–167	IPA	$C_{25}H_{20}N_2O_3$	23 ± 1.7 (3)	12 ± 1.2 (3)
48	7'-Me	B	280 dec	IPA	$C_{25}H_{20}N_2O_3$	46 ● 7.8 (3)	8.0 ± 1.2 (3)
49	5'-OMe	B	257–258	MA	$C_{25}H_{20}N_2O_4\cdot0.2H_2O$	3.2 ± 0.14 (3)	17 ± 4.1 (3)
50	6'-OMe	C	272–273	MA	$C_{25}H_{20}N_2O_4\cdot0.3H_2O$	12 ± 2.0 (3)	7.4 ± 1.3 (4)
51	4'-OH	A	232–233	DO	$C_{24}H_{18}N_2O_4\cdot0.5C_4H_8O_2$[h]	46 ± 9.0 (3)	NT[f]
52	5'-(CHOH)Ph	B	182–184	AN	$C_{31}H_{24}N_2O_4\cdot H_2O$	6.1 ± 1.8 (3)	NT[f]
53	6'-(CHOH)Ph	B	270–271 dec	AN	$C_{31}H_{24}N_2O_4\cdot1.5H_2O$	17 ± 0.58 (3)	NT[f]
54	5',6'-Cl_2	A	287–289	AN/IPA	$C_{24}H_{16}Cl_2N_2O_3$	53 ± 9.2 (3)	NT[f]
55	4',5'-Me_2	A	302–306	TL	$C_{26}H_{22}N_2O_3$	3.6 ● 0.47 (3)	46 ± 6.9 (3)
56	4',6'-Me_2[i]	B	324 dec	DO	$C_{26}H_{22}N_2O_3$	3.9 ● 1.9 (3)	7.6 ± 2.3 (3)
57	5',6'-Me_2[e]	A	>300 dec	MA/W	$C_{26}H_{21}N_2O_3Na\cdot H_2O$	2.7 ± 0.22 (6)	1.2 ± 0.14 (3)
58	4',6'-$(MeO)_2$	B	259–261 dec	AN	$C_{26}H_{22}N_2O_5\cdot0.25H_2O$	88 ● 12 (3)	9.1 ± 1.1 (3)
59	5',6'-$(MeO)_2$	B	290–292 dec	IPA	$C_{26}H_{22}N_2O_5$	3.4 ● 0.12 (3)	2.2 ± 0.03 (3)
60	5',7'-$(MeO)_2$	B	278–279 dec	AN	$C_{26}H_{22}N_2O_5$	6.1 ± 1.0 (3)	6.7 ± 2.0 (3)
61	5',6'-(methylenedioxy)	A	273 dec	IPA	$C_{25}H_{18}N_2O_5\cdot0.5H_2O$	2.7 ± 0.12 (3)	3.8 ± 0.32 (3)
62	2'-SMe	A	234–236 dec	IPA	$C_{26}H_{22}N_2O_3S\cdot0.25H_2O$	11%[j]	NT[f]
63	2'-Me	A	318 dec	IPA	$C_{25}H_{20}N_2O_3$	4%[j]	NT[f]
64	2'-OH	A	293–295	MA	$C_{24}H_{18}N_2O_4$	4%[j]	NT[f]
9, daltroban						63 ± 5.3 (3)	19 ± 0.3 (3)

[a] See the text. [b] Solvent of crystallization: AC, acetone; W, water; IPA, isopropyl alcohol; EA, ethyl acetate; IPE, diisopropyl ether; MA, methanol; DO, dioxane; AN, acetonitrile; TL, toluene. [c] All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. [d] Values are mean ± SEM of experiments indicated in parentheses. [e] Na salt. [f] Not tested. [g] C_3H_8O, isopropyl alcohol. [h] $C_4H_8O_2$, dioxane. [i] E/Z = 93/7. [j] Percent inhibition at 0.1 μM (*n* = 1–2).

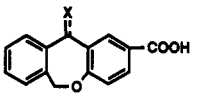
Table IV. 11-[2-(5,6-Dimethyl-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin Derivatives

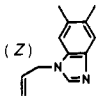
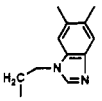


no.	Z	method[a]	mp, °C	solvent[b]	formula[c]	TXA_2/PGH_2 receptor binding: guinea pig WP K_i,[d] nM (*n*), or % inhibn[e] at 0.1 μM
65	3-COOH	A	267–268 dec	EA/IPA	$C_{26}H_{22}N_2O_3\cdot0.5C_3H_8O$[f]	18000 ± 1300 (3)
66	9-COOH	A	291–292 dec	DO	$C_{26}H_{22}N_2O_3\cdot0.25H_2O$	1300 ± 92 (3)
67	2-CH_2COOH	A	277–278	IPA	$C_{27}H_{24}N_2O_3$	63 ± 17 (4)
68	2-COOMe	A	*g*	HX[h]	$C_{27}H_{24}N_2O_3$	31%
73			265–266	DO	$C_{33}H_{27}N_3O_4\cdot0.25C_4H_8O_2$[i]	6%
74			90	HX[h]	$C_{30}H_{29}N_3O_3\cdot H_2O$	−4%

[a] See the text. [b] Solvent of crystallization: EA, ethyl acetate; IPA, isopropyl alcohol; DO, dioxane; HX, hexane. [c] All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. [d] Values are mean ± SEM of experiments indicated in parentheses. [e] *n* = 1. [f] C_3H_8O, isopropyl alcohol. [g] An amorphous powder. [h] Trituration solvent. [i] $C_4H_8O_2$, dioxane.

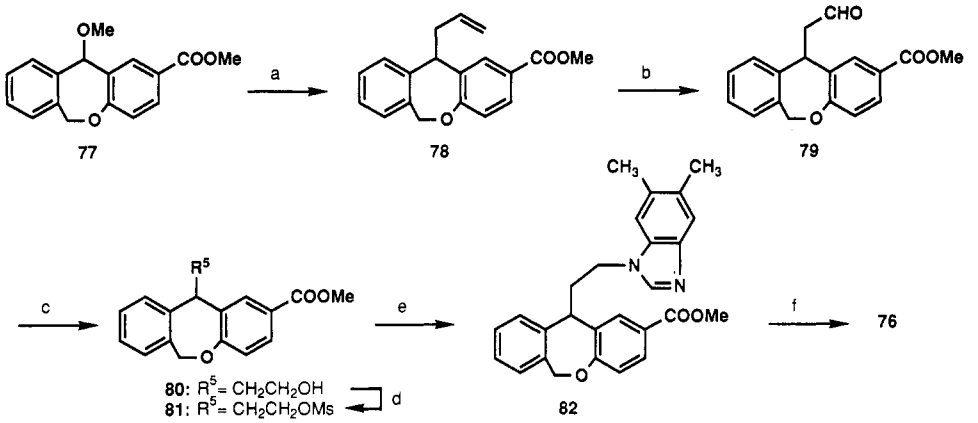
Table V. 11-Ethylidene- and 11-Ethyl-6,11-dihydrodibenz[*b*,*e*]oxepin Derivatives



no.	X	method[a]	mp, °C	solvent[b]	formula[c]	TXA_2/PGH_2 receptor binding: guinea pig WP K_i,[d] nM (*n*)
75		A	282–283 dec	IPA	$C_{26}H_{22}N_2O_3 \cdot 0.5H_2O$	64 ± 22 (3)
76		*e*	150–151	IPA	$C_{26}H_{24}N_2O_3 \cdot 0.8H_2O$	18 ± 0.88 (3)

[a] See the text. [b] Solvent of crystallization: IPA, isopropyl alcohol. [c] All new compounds had C, H, and N microanalyses within 0.4% of the theoretical values. [d] Values are mean ± SEM of experiments indicated in parentheses. [e] Scheme V.

Scheme V[a]



[a] (a) $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2; (b) $NaIO_4$, OsO_4, Et_2O, H_2O; (c) $NaBH_4$, MeOH, THF; (d) MsCl, Py; (e) 5,6-dimethylbenzimidazole, toluene, DMF; (f) NaOH, H_2O, MeOH.

isolated in pure form by chromatography and crystallization. The purity of the final products was greater than 99% on the basis of HPLC analyses and the structure of each isomer was determined by NOE NMR experiments.[9]

A regioselective synthesis of **70** was also accomplished employing the previously reported method[10] (method C) and an example is demonstrated in Scheme IV. 1,2-Phenylenediamine derivative **71** was treated with **24a** in the presence of NaI in DMF to provide **72** in a yield of 56% and the regioselectivity was over 99%. The amides **73** and **74** (Table IV) were obtained by the coupling reaction between **57** and the appropriate amines.

Compound **75** (Table V) possessing *Z*-geometry was prepared from *Z*-rich **23a** (R^4 = 2-COOMe, *E*/*Z* = 4/6) which was obtained from the mother liquor of the crystallization of the crude **23a** (Scheme II). Reduction of the double bond of **57** to afford **76** (Table V) was unsuccessful under several reaction conditions (catalytic hydrogenation, reduction with diimide, and reduction by hydride-transfer reagents), because the opening of the dibenzoxepin ring occurred preferentially. Therefore, an alternative procedure based on a Lewis acid catalyzed carbon–carbon bond formation in the 11-position was developed (Scheme V). Since the methoxy group in the 11-position of the dibenzoxepin ring system was regarded as the vinylogue of a ketal, the allylation of **77** with allyltrimethylsilane in the presence of $TiCl_4$ was examined.[11] Compound **77** was successfully converted to **78** almost quantitatively. The olefin **78** was subjected successively to oxidative cleavage of double bond, $NaBH_4$ reduction, and mesylation to provide **81**, which was converted to **76** in a similar manner as described in the preparation of **6** from **12**.

Results and Discussion

The compounds synthesized were tested for inhibitory effects on the specific binding of [^{3}H]U-46619 to guinea pig platelets according to the reported method[12] with a slight modification. The results were represented by K_i

(8) Exceptionally, the reaction of **24a** and 4,6-dimethylbenzimidazole furnished **121** as sole isomer, which was the precursor of **56**. The positional isomers of **85**, **86**, and **88** (the corresponding methyl esters of **28**, **29**, and **31**, respectively) were not isolated.

(9) For example, on the ^{1}H-NMR study of **50**, significant NOE (31.0%) was observed between H-7′ and the allylic methylene protons. This result confirmed the substitution position of the methoxy group (6′-OMe). The *E*-geometry of the double bond at the 11-position was determined by the observed NOE (28.6%) between the vinylic proton and H-1.

(10) Tanaka, K.; Ino, M.; Murakami, Y. Cyclization of [(4- or 5-Substituted-2-benzimidazolyl)thio]acetic Acids. Isolation and Identification of Two Possible Isomers of Substituted Thiazolo[3,2-*a*]benzimidazol-3(2H)-one. *Chem. Pharm. Bull.* **1981**, *29*, 1876–1886.

(11) Sakurai, H. Reactions of allylsilanes and application to organic synthesis. *Pure Appl. Chem.* **1982**, *54*, 1–22.

(12) 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_2/PGH_2 Receptor Antagonists (13-APA, BM 13.177, ONO 3708 and SQ 29.548). *Thromb. Res.* **1986**, *41*, 471–481.

values or percent inhibitions at 0.1 μM (Tables I–V).

The effects of replacing the benzimidazole moiety of 7 with a related heterocyclic group were examined (Table II). Benzotriazole and naphth[2,3-*d*]imidazole derivatives (26 and 27) showed markedly reduced affinities in the receptor binding assay. The compound possessing a 5-azabenzimidazole (29) was devoid of activity, although 28, the 4-azabenzimidazole derivative of 7, demonstrated somewhat reduced TXA_2/PGH_2 receptor binding activity. Compound 31, possessing a 4′-phenylimidazole moiety, exhibited nearly half the potency of 7, while the corresponding imidazole and 4′,5′-diphenylimidazole derivatives (30 and 32) showed extremely reduced affinities. These results indicated that the benzimidazole moiety was critical for the enhanced TXA_2/PGH_2 receptor binding affinity of 7, and encouraged us to focus our research on the synthesis and evaluation of a series of compounds represented by the general structure 8 (Chart I).

The influence of the substituent(s) of the benzimidazole moiety on the receptor binding affinity was examined. The inhibitory effect on the specific binding of [^{3}H]U-46619 to human platelets was also evaluated in order to elucidate species differences in the structure–affinity relationships of this series of compounds. The results are summarized in Table III. Most compounds tested (7 and 33–64), except 36, 58, and 62–64, showed significant binding affinities for the guinea pig platelet TXA_2/PGH_2 receptor, and the potency of these derivatives was superior to that of 9 (daltroban). Substitution in the 2′-position remarkably reduced activity (62–64). A variety of substituents in the 5′-position enhanced the binding affinity for the guinea pig platelet receptor (33, 37, 39, 41, 43, 49, and 52), irrespective of the nature of the substituents, whereas some 6′-substituents reduced the activity (36, 40, and 47). Although every positional isomer of methyl-substituted benzimidazole derivatives (45–48) showed negligible enhancement in the affinities, dimethylbenzimidazole derivatives (55–57) were 2–4-fold more potent than 7 in the guinea pig platelet receptor binding assay. Similarly, 5′,6′-dimethoxy, 5′,7′-dimethoxy, and 5′,6′-(methylenedioxy) derivatives (59–61) demonstrated enhanced affinities, whereas 5′,6′-dichloro and 4′,6′-dimethoxy derivatives (54 and 58) exhibited reduced affinities. Of all compounds tested, 37, which possesses a (benzylamino)carbonyl group in the 5′-position, was the most potent antagonist for the guinea pig platelet TXA_2/PGH_2 receptor with a K_i value of 0.91 ± 0.20 nM.

On the other hand, compound 57, containing a 5,6′-dimethylbenzimidazole moiety, was the most potent human platelet TXA_2/PGH_2 receptor antagonist with a K_i value of 1.2 ± 0.14 nM. Similarly, introduction of 5′,6′-dimethoxy (59) and 5′,6′-(methylenedioxy) (61) to the benzimidazole moiety enhanced affinity for the human platelet receptor. In the compounds with other substitution patterns of the benzimidazole moiety, however, no dramatic enhancement of affinity for the human platelet receptor was achieved; markedly reduced activities of 5′-methyl and 5′-CF_3 derivatives (39 and 46) were observed, although these compounds showed fairly good affinities for the guinea pig platelet receptor. Consequently, the TXA_2/PGH_2 receptor binding affinities of 22 compounds of this series (7, 33, 34, 37–39, 41, 43–50, 55–61) in human platelet were poorly correlated with those in guinea pig platelet (r = 0.190).

The remarkably reduced activities of compounds listed in Table IV indicated the significance of a 2-carboxyl group. The acetic acid derivative (67) exhibited somewhat decreased activity. Moreover, 3- and 9-carboxylic acid analogues (65 and 66) showed much reduced receptor binding affinities. These results were parallel with those observed in our arylsulfonamide type antagonists described previously.[1] Furthermore, ester and amide derivatives (68, 73, and 74) were devoid of activity.

The results shown in Table V indicated that the 11-ethylidene connecting group with *E*-geometry was critical for the enhanced receptor binding affinity of 57. Compounds with corresponding *Z*-olefin (75) and carbon–carbon single bond (76) exhibited approximately 20- and 6-fold lower potency than 57 in the binding assay (guinea pig platelet). It is noteworthy that 75, the positional isomer of 66 (Table IV) in view of the oxygen atom in the dibenzoxepin ring system, showed 20-fold higher receptor binding affinity than 66. This observation indicated that the oxygen in the dibenzoxepin ring system played a crucial role in the TXA_2/PGH_2 receptor binding of this series of compounds.

From the structural point of view, compound 57 has one of the most rigid structures among the known TXA_2/PGH_2 receptor agonists and antagonists. This series of compounds, therefore, would be a beneficial tool for further investigation on the putative structure of TXA_2/PGH_2 receptor protein(s).[13]

Besides the receptor binding studies described above, we elucidated the inhibitory effects of the compounds on U-46619-induced platelet aggregation[14] in vitro. Compounds possessing significant guinea pig platelet TXA_2/PGH_2 receptor binding activities also inhibited the aggregation of guinea pig platelets in vitro.[15] Compound 57, one of the most potent human platelet TXA_2/PGH_2 receptor antagonists among the compounds synthesized, inhibited U-46619 (1 μM) induced human platelet aggregation with an IC_{50} value of 20.3 nM (n = 6), while 9 (daltroban) inhibited that with an IC_{50} value of 255 nM (n = 3). Therefore, compound 57 exhibits an approximately 12-fold higher inhibitory effect than 9 on the U-46619-induced human platelet aggregation. Additionally,

(13) A human platelet TXA_2 receptor has been cloned and sequenced; see: Hirata, M.; Hayashi, Y.; Ushikubi, F.; Yokota, Y.; Kageyama, R.; Nakanishi, S.; Narumiya, S. Cloning and expression of cDNA for a human thromboxane A_2 receptor. *Nature* **1991**, *349*, 617–620.

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

(15) The 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 200*g* for 15 min at room temperature. Platelet-poor plasma (PPP) was obtained by further centrifuging the precipitate at 2000*g* for 10 min. Platelet aggregation induced by U-46619 (0.5–0.1 μM) was measured according to the method of Born,[14] 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: **2** (1), **3** (30), **4** (0.1), **5** (0.3), **6** (3), **7** (0.1), **26** (3), **27** (0.1), **28** (0.3), **29** (1), **30** (3), **31** (30), **32** (10), **33** (0.1), **34** (0.1), **35** (0.3), **36** (10), **37** (0.01), **38** (0.03), **39** (0.1), **40** (0.03), **41** (0.1), **42** (0.1), **43** (0.03), **44** (0.3), **45** (not tested), **46** (not tested), **47** (not tested), **48** (not tested), **49** (0.1), **50** (1), **51** (0.03), **52** (0.1), **53** (1), **54** (1), **55** (0.1), **56** (0.1), **57** (0.1), **58** (3), **59** (0.3), **60** (0.1), **61** (0.1), **62** (10), **63** (30), **64** (>30), **65** (30), **66** (>30), **67** (0.3), **68** (not tested), **73** (30), **74** (10), **75** (1), **76** (1), **9** (daltroban, 0.1).

compound 57 (10^{-8}–10^{-6} M) inhibited the human platelet aggregation induced by collagen (1.5 μg/mL). However, it did not affect the primary phase of platelet aggregation induced by adenosine diphosphate or epinephrine at concentrations up to 10^{-5} M. Furthermore, compound 57 at 10^{-5} M did not affect the antiaggregatory effects of PGI_2, PGE_1, and PGD_2. In the guinea pig ex vivo experiment, compound 57 (3 and 10 mg/kg po) inhibited the aggregations induced by U-46619, collagen, and arachidonate. The effects lasted for longer than 7 h following oral administration of 57 (10 mg/kg po).[16]

Compound 57 exhibited inhibitory effects on U-46619-induced contractions of isolated guinea pig aorta and canine saphenous vein with pA_2 values of 7.74 ± 0.16 and 8.11 ± 0.12, respectively. In that canine smooth muscle preparation, 57 did not exhibited intrinsic agonist activity.[17] Moreover, radioligand receptor binding studies revealed that it did not affect the receptors of PGI_2, PGE_2, PAF, and other neurotransmitters at concentrations up to 10 μM. Furthermore, it possessed negligible inhibitory effects on TXA_2 synthase, cyclooxygenase, 5-lipoxygenase, and 12-lipoxygense at 1 μM.[18] Compound 57 was regarded as one of the specific TXA_2/PGH_2 receptor antagonists and the detail of its pharmacological profile will be reported separately.[19] In conclusion, we discovered a novel series of non-prostanoid TXA_2/PGH_2 receptor antagonists in which a benzimidazole group was one of the crucial structural requirements for potent receptor binding activity. To our knowledge, no report has been presented concerning non-prostanoid and prostanoid TXA_2/PGH_2 receptor antagonists[3,20] possessing a benzimidazole moiety. Structure–activity studies revealed that the presence of the 2-carboxyl group was another key element and that the introduction of substituent(s) to the benzimidazole moiety significantly influenced the receptor binding activity. Furthermore, species differences were observed in the structure–affinity relationship of this series of compounds. Of all compounds synthesized in this study, 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 and it demonstrated potent inhibitory effects on U-46619-induced human platelet aggregation. Compound 57, now designated as KW-3635, is a novel, orally active, and specific TXA_2/PGH_2 receptor antagonist and may prove itself as a beneficial drug for the treatment of TXA_2-mediated diseases such as circulatory disorders and asthma.

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 (^1H NMR) were recorded on 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

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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 $MgSO_4$. 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 with a YMC A-312 column (ODS type, Yamamura Chemical Lab. Co., Ltd.) and 0.01 M octanesulfonic acid in MeOH/H_2O (2/1) as eluent.

Starting Materials 10, 16, and 77. These compounds were synthesized according to the methods previously reported.[6]

Olefins 22. Compounds **22a** and **22b** were prepared by the method previously reported,[5] and **22c** (mp 129–131 °C) and **22d** (mp 115–117 °C) were similarly obtained from the corresponding ketones.[1,6]

11-[[2-(1-Benzimidazolyl)ethyl]thio]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (13). To a solution of **10** (40.0 g, 0.15 mol) in CH_2Cl_2 (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 stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with brine, dried, and evaporated. The crude product was recrystallized from toluene to give 37.6 g (76%) of **11**: mp 128–130 °C dec; ^{1}H NMR ($CDCl_3$) 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. ($C_{18}H_{18}O_4S$) C, H.

To a solution of **11** (3.5 g, 10.6 mmol) in pyridine (50 mL) was added PBr_3 (2.3 mL, 12.7 mmol) at 0 °C and the solution was stirred at room temperature for 1 h. The reaction mixture was concentrated (<40 °C) and then diluted with EtOAc. The organic solution was washed with brine, dried, and evaporated to give crude **12** (1.6 g, 38%). This crude bromide was used in the next reaction without further purification. A mixture of the crude **12** (1.6 g), benzimidazole (1.4 g, 12.1 mmol), toluene (100 mL), and DMF (10 mL) was refluxed for 5 h. After being concentrated, the mixture was diluted with EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc/triethylamine (10/10/1) as eluent to give 0.9 g (50%) of **13** as an amorphous powder: ^{1}H NMR ($CDCl_3$) δ 2.79 (t, J = 6.9 Hz, 2 H), 3.82 (s, 3 H), 4.01 (t, J = 6.9 Hz, 2 H), 4.76 (s, 1 H), 4.76 and 6.25 (AB syst, J = 12.8 Hz, 2 H), 6.64–7.91 (m, 12 H).

11-[[2-(2-Benzimidazolyl)ethyl]thio]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (15). To a solution of **10** (2.0 g, 7.4 mmol) in CH_2Cl_2 (180 mL) was added trifluoroacetic anhydride (1.3 mL, 9.2 mmol) and the mixture was stirred at room temperature for 1 h. 2-(2-Mercaptoethyl)benzimidazole (2.0 g, 11.1 mmol) and BF_3·Et_2O (1 mL, 8.1 mmol) were added to the solution. After being stirred for 2 h, the reaction mixture was concentrated and then diluted with EtOAc. The organic solution was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane/EtOAc/triethylamine (10/20/1) as eluent to give 2.2 g (69%) of **15** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.53–3.25 (m, 4 H), 3.74 (s, 3 H), 4.79 (s, 1 H), 4.68 and 6.17 (AB syst, J = 13.1 Hz, 2 H), 6.64–7.90 (m, 11 H).

(*E*,*Z*)-11-(3-Hydroxypropylidene)-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (17). To a suspension of [3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl]triphenylphosphonium bromide[4] (40 g, 82 mmol) in THF (250 mL) was added *n*-BuLi (1.6 M solution in hexane, 50 mL, 80 mmol) dropwise at 0 °C and the mixture was stirred at room temperature for 1 h. A solution of **16** (15 g, 56 mmol) in THF (200 mL) was added and the mixture stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc. The solution was washed with brine, dried, and concentrated. The residue was dissolved with a mixture of dioxane (500 mL) and water (200 mL) containing *p*-TsOH·H_2O (1.0 g, 0.5 mmol) and the mixture refluxed for 1 h. After being concentrated, the reaction mixture was diluted with EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc (1/1) to give 9.8 g (56%) of a mixture of geometrical isomers **17** (E/Z = 3/7) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.17–2.72 (m, 2 H), 3.37–3.76 (m, 2 H), 3.77 (s, 3 H), 4.68–5.43 (br, 2 H), 5.70 (t, J = 7.4 Hz, 0.7 H, for *Z*-isomer), 6.40 (t, J = 6.9 Hz, 0.3 H, for *E*-isomer), 6.52–8.12 (m, 7 H).

Acid-Catalyzed Isomerization of 17. Compound **17** (E/Z = 3/7, 4.8 g, 16 mmol) was dissolved in AcOH (250 mL) containing 10.0 g (52 mmol) of *p*-TsOH·H_2O and the solution stirred at 100 °C for 42 h. After being concentrated, the reaction mixture was diluted with MeOH (100 mL). The solution was refluxed for 3 h and then concentrated. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic solution was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc (1/1) to give 4.5 g (90%) of **17** (E/Z = 7/3).

(*E*,*Z*)-11-[3-[(Phenylsulfonyl)amino]propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (21). To a solution of **17** (E/Z = 7/3, 3.5 g, 11.3 mmol) in pyridine (50 mL) was added methanesulfonyl chloride (1.7 mL, 22 mmol) at 0 °C and the solution was stirred under the same conditions for 1 h. A few pieces of crushed ice were added, and the mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc. The organic solution was washed successively with 1 N HCl and brine, dried, and evaporated (<30 °C) to give crude **18** (E/Z = 7/3) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 2.1 H, for *E*-isomer), 3.00 (s, 0.9 H, for *Z*-isomer). The unstable mesylate **18** was used without purification in the next reaction.

A mixture of the mesylate **18** obtained above (E/Z = 7/3, 4.3 g, 11.0 mmol) and potassium phthalimide (2.5 g, 13.5 mmol) was stirred at room temperature for 2 days. After being concentrated, the reaction mixture was diluted with CH_2Cl_2. The solution was washed with brine, dried, and concentrated. Crude product was recrystallized from toluene to give 1.6 g (33%) of **19** as a mixture of geometrical isomers (E/Z = 7/3). Anal. ($C_{27}H_{21}NO_5$) C, H, N.

A mixture of the above obtained **19** (1.5 g, 3.42 mmol), hydrazine (anhydrous, 0.2 mL), and MeOH (100 mL) was refluxed for 7 h. Evaporation of the solvent gave (1.0 g) crude **20** as an oil (E/Z = 7/3): MS m/z 309 (M^+). The crude **20** was use in the next reaction without purification.

The crude **20** was dissolved in pyridine (50 mL). Benzenesulfonyl chloride (0.7 mL, 5.12 mmol) was added and the mixture stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc and the organic solution washed successively with 1 N HCl and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane/EtOAc (1/1) as eluent to give 0.97 g (63%) of **21** as a syrup (E/Z = 7/3): ^{1}H NMR ($CDCl_3$) δ 2.22–2.62 (m, 2 H), 2.82–3.26 (m, 2 H), 3.81 (s, 3 H), 4.95–5.57 (m, 2 H), 5.52 (t, J = 6.9 Hz, 0.3 H, for *Z*-isomer), 5.91 (t, J = 6.9 Hz, 0.7 H, for *E*-isomer), 6.71–8.05 (m, 13 H); MS m/z 449 (M^+).

Compound **25** was prepared by the same method as described above from **24a** as an oil: ^{1}H NMR ($CDCl_3$) δ 3.40–3.57 (m, 2 H), 3.78 (s, 3 H), 5.11 (bs, 2 H), 5.91 (t, J = 7.4 Hz, 1 H), 6.65 (d, J = 9.6 Hz, 1 H), 6.90–7.98 (m, 12 H); MS m/z 435 (M^+).

(*E*)-11-[2-(4-Methylpiperazino)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (23a: R^4 = 2-COOMe, *E* > 99%). A mixture of **22a** (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 the trifluoroacetic acid salt of **23a** (*E* > 99%). The salt was suspended in a mixture of EtOAc (1 L) and H_2O (1.2 L). The medium was cooled to 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 **23a** (*E* > 99%) as an amorphous powder: ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 2.21–2.71 (m, 8 H), 3.14 (d, J = 7.0 Hz, 2 H), 3.82 (s, 3 H), 4.7–5.4 (br, 2 H), 6.20 (t, J = 7.0 Hz, 1 H), 6.72 (d, J = 8.6 Hz, 1 H), 7.02–7.42 (m, 4 H), 7.72 (dd, J = 2.2 and 8.6 Hz, 1 H), 7.98 (d, J = 2.2 Hz, 1 H); IR ($CHCl_3$) 2945, 2810, 1710, 1250, 1111, 1010 cm^{-1}; MS m/z 378 (M^+).

Compounds **23b** (R^4 = 2-CH_2COOMe, E > 99%, oil), **23c** (R^4 = 3-COOMe, E > 99%, oil), and **23d** (R^4 = 9-COOMe, E > 99%, oil) were prepared by a similar method as that described above from the corresponding olefins.

Compound **23a** (E/Z = 4/6, oil) was obtained by concentration of the crystallization mother liquor of the crude **23a** and subsequent extraction with EtOAc as described above.

(*E*)-11-(2-Chloroethylidene)-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (24a). To a mixture of **23a** (E > 99%, 31 g, 81 mmol), NaOAc (33 g, 406 mmol), and dichloroethane (460 mL) was added ClCOOEt (39 mL, 406 mmol) dropwise. After being stirred for 2 h at room temperature, insoluble salts were filtered off. The filtrate was concentrated and then diluted with CH_2Cl_2. The solution was washed with brine, dried, and concentrated. The residue was recrystallized from 2-propanol to give 9.2 g (58%) of **24a** as colorless needles: mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 4.16 (d, J = 8.1 Hz, 2 H), 4.88 (br, 1 H), 5.57 (br, 1 H), 6.31 (t, J = 8.1 Hz, 1 H), 6.79–8.04 (m, 7 H); MS m/z 314 (M^+). Anal. ($C_{18}H_{15}ClO_3$) C, H.

Chlorides **24b** (R^4 = 2-CH_2COOMe, mp 127–128 °C), **24c** (R^4 = 3-COOMe, mp 102–104 °C), **24d** (R^4 = 9-COOMe, mp 83–85 °C), and **24a** (E/Z = 4/6, amorphous) were prepared by a similar method as that described above from **23b–d** (E > 99%) and **23a** (E/Z = 4/6).

Method A: (*E*)-11-[2-(5,6-Dimethyl-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (68). A mixture of **24a** (E > 99%, 22.0 g, 69.9 mmol), 5,6-dimethylbenzimidazole (51.1, g, 350 mmol), toluene (1.1 L), and DMF (0.11 L) was refluxed for 3 h. After being concentrated, the reaction mixture was diluted with EtOAc. The solution was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with EtOAc/triethylamine (10/1) as eluent to give 30.8 g (100%) of **68** as an amorphous powder: ^{1}H NMR ($CDCl_3$) δ 2.32 (br s, 6 H), 3.89 (s, 3 H), 4.82 (d, J = 7.0 Hz, 2 H), 4.67–5.71 (br, 2 H), 6.25 (t, J = 7.0 Hz, 1 H), 6.71–8.11 (m, 10 H); IR ($CHCl_3$) 2924, 1720, 1607, 1489, 1293, 1232, 1003 cm^{-1}; MS m/z 424 (M^+). Anal. ($C_{27}H_{24}N_2O_3$) C, H, N.

The methyl esters of **7**, **26**, **28–38**, **43**, **44**, **51**, **54**, **55**, **61–68**, and **75** were prepared in a similar manner as that described above: **83** (benzimidazolyl, amorphous), **84** (benzotriazolyl, oil), **85** (4′-azabenzimidazolyl, oil),[8] **86** (5′-azabenzimidazolyl, oil),[8] **87** (imidazolyl, amorphous), **88** (4′-phenylimidazolyl, amorphous),[8] **89** (4′,5′-diphenylimidazolyl, mp 145 °C dec), **90** and **91** (5′-NO_2/6′-NO_2, 1/1, oil), **92** (5′-COOMe, oil), **93** (6′-COOMe, mp 231–232 °C), **94** and **95** (5′-$CONHCH_2Ph$/6′-$CONHCH_2Ph$, 1/1, oil), **96** (5′-Cl, oil), **97** (6′-Cl, oil), **98** (4′-OH, oil), **99** (5′,6′-Cl_2, oil), **100** (4′,5′-Me_2, oil), **101** (5′,6′-(methylenedioxy), oil), **102** (2′-SMe, oil), **103** (2′-Me, amorphous), **104** (2′-OH, oil), **105** (3-COOMe, oil), **106** (9-COOMe, mp 202–203 °C), **107** (2-CH_2COOMe, oil), and **108** (5′,6′-Me_2, $Z \geq$ 99%, oil).

Method B: (*E*)-11-[2-[5-(Trifluoromethyl)-1-benzimidazolyl]ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (109) and (*E*)-11-[2-[6-(Trifluoromethyl)-1-benzimidazolyl]ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (110). To a suspension of NaH (60% in oil, 0.77 g, 19.1 mmol) in THF (100 mL) was added 5-(trifluoromethyl)benzimidazole (3.56 g, 19.1 mmol) and the mixture was stirred at room temperature for 1 h. Compound **24a** (E > 99%, 5.0 g, 15.9 mmol) was added and then refluxed for 3 h. Upon cooling, the reaction mixture was diluted with EtOAc. The organic solution was washed with brine, dried, and concentrated. The two positional isomers were separated by chromatography on silica gel with hexane/EtOAc/triethylamine (10/7/1) as eluent to give 3.2 g (43%) of **109** and 2.85 g (39%) of **110**, in order of elution. **109** (oil): ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.90 (d, J = 7.0 Hz, 2 H), 4.8–5.6 (br, 2 H), 6.24 (t, J = 7.0 Hz, 1 H), 6.80 (d, J = 8.5 Hz, 1 H), 7.0–8.3 (m, 10 H); IR ($CHCl_3$) 1712, 1608, 1328, 1251, 1166, 1112, 995 cm^{-1}; MS m/z 464 (M^+). **110** (oil): ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.88 (d, J = 7.0 Hz, 2 H), 4.8–5.6 (br, 2 H), 6.25 (t, J = 7.0 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 7.1–8.1 (m, 10 H); IR ($CHCl_3$) 1712, 1607, 1344, 1243, 1162, 1005 cm^{-1}; MS m/z 464 (M^+).

The methyl esters of **27**, **41**, **42**, **45–49**, **52**, **53**, **56**, and **58–60** were prepared in a similar manner as that described above: **111** (naphtho[2,3-*d*]imidazolyl, oil), **112** (5′-F, amorphous), **113** (6′-F, amorphous), **114** and **115** (4′-Me/7′-Me, 3/7, oil), **116** and **117** (5′-Me/6′-Me, 1/1, oil), **118** (5′-OMe, mp 99–101 °C), **119** (5′-CH(OH)Ph, oil), **120** (6′-CH(OH)Ph, oil), **121** (4′,6′-Me_2, oil),[8] **122** (4′,6′-$(OMe)_2$, oil), **123** (5′,6′-$(OMe)_2$, oil), and **124** (5′,7′-$(OMe)_2$, oil).

Method C: (*E*)-11-[2-(6-Methoxy-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (72). A mixture of **24a** (R^4 = 2-COOMe, 5.68 g, 18.1 mmol), NaI (2.68 g, 18.1 mmol), 2-amino-4-methoxyformanilide (**71**)[10] (3.60 g, 21.7 mmol), and DMF (40 mL) was stirred at 60-70 °C (internal temperature) for 2 h and then concentrated. The reaction mixture was diluted with EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The crude product was recrystallized from acetonitrile to give 4.33 g (56%) of **72**: mp 179–180 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.88 (s, 3 H), 4.87 (d, J = 7.1 Hz, 2 H), 4.7–5.7 (br, 2 H), 6.29 (t, J = 7.1 Hz, 1 H), 6.54 (d, J = 2.2 Hz, 1 H), 6.72–8.01 (m, 10 H); IR ($CHCl_3$) 3450, 1717, 1505, 1485, 1249, 1004, 818, 767 cm^{-1}. Anal. ($C_{26}H_{22}N_2O_4$) C, H, N.

11-Allyl-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (78). To a solution of **77** (12.0 g, 42 mmol) and allyltrimethylsilane (7 mL, 44 mmol) in CH_2Cl_2 (200 mL) was added $TiCl_4$ (1 M solution in CH_2Cl_2, 47 mL, 47 mmol) dropwise at −60 °C and the resulting mixture was stirred under the same conditions for 1 h. Methanol (10 mL) was added at 0 °C and the mixture was diluted with CH_2Cl_2 and water. The organic phase was separated, washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane/EtOAc (5/1) as eluent to give 11.7 g (95%) of **78** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.87 (t, J = 7.5 Hz, 2 H), 3.88 (s, 3 H), 3.98 (t, J = 7.5 Hz, 1 H), 4.75–5.00 (m, 2 H), 5.01 and 5.59 (AB syst, J = 13.9 Hz, 2 H), 5.4–5.9 (m, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 7.0–7.3 (m, 4 H), 7.74–7.87 (m, 2 H); MS m/z 294 (M^+).

11-(Formylmethyl)-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (79). A mixture of **78** (2.46 g, 8.37 mmol), OsO_4 (65 mg, 0.26 mmol), $NaIO_4$ (7.3 g, 34.1 mmol), ether (100 mL), and water (100 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with ether. The organic phase was separated, washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc (3/1) as eluent to give 2.43 g (98%) of **79** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.30 (dt, J = 1.5 and 7.2 Hz, 2 H), 3.88 (s, 3 H), 4.68 (t, J = 7.2 Hz, 1 H), 5.07 and 5.53 (AB syst, J = 14.3 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 1 H), 7.0–7.35 (m, 4 H), 7.85 (dd, J = 2.1 and 8.4 Hz, 1 H), 7.95 (d, J = 2.1 Hz, 1 H), 9.72 (t, J = 1.5 Hz, 1 H); IR (neat) 1710 cm^{-1}; MS m/z 296 (M^+).

11-(2-Hydroxyethyl)-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (80). To a solution of **79** (2.43 g, 8.2 mmol) in a mixture of THF (50 mL) and MeOH (100 mL) was added $NaBH_4$ (0.49 g, 13 mmol) and the mixture was stirred at room temperature for 30 min. Acetic acid (0.8 mL, 14 mmol) was added and the resultant mixture stirred for 5 min. After being concentrated, the reaction mixture was diluted with EtOAc. The organic solution was washed with brine, dried, and evaporated to give 2.41 g (98.5%) of **80** a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.2–2.45 (m, 2 H), 3.59 (t, J = 6.1 Hz, 2 H), 3.88 (s, 3 H), 4.15 (t, J = 7.3 Hz, 1 H), 4.98 and 5.60 (AB syst, J = 13.8 Hz, 2 H), 6.94 (d, J = 8.4 Hz, 1 H), 7.0–7.25 (m, 4 H), 7.80 (dd, J = 2.1 and 8.4 Hz, 1 H), 7.93 (d, J = 2.1 Hz, 1 H); MS m/z 298 (M^+).

11-[2-(5,6-Dimethyl-1-benzimidazolyl)ethyl]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid Methyl Ester (82). To a solution of **80** (2.2 g, 7.4 mmol) in pyridine (5 mL) was added methanesulfonyl chloride (0.8 mL, 10.3 mmol) at 0 °C and the mixture was stirred under the same conditions for 2 h. The reaction mixture was diluted with cold EtOAc (<10 °C). The organic solution was washed successively with cold 1 N HCl and brine, dried, and concentrated (<10 °C) to give (2.7 g) of crude 11-[2-(methylsulfonyl)ethyl]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid methyl ester (**81**) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.4–2.7 (m, 2 H), 2.99 (s, 3 H), 3.89 (s, 3 H), 3.9–4.25 (m, 3 H), 5.01 and 5.55 (AB syst, J = 14.4 Hz, 2 H), 7.01 (d, J = 7.9 Hz, 1 H), 7.0–7.3 (m, 4 H), 7.8–7.9 (m, 2 H). The crude **81** was used in the next step without further purification.

5,6-Dimethylbenzimidazole (1.9 g, 13.0 mmol) was dissolved in a mixture of THF (40 mL) and DMF (5 mL). To the solution was added NaH (60% in oil, 0.5 g, 12.5 mmol) at 0 °C and the mixture was stirred under the same conditions for 1 h. A solution of the crude 81 in THF (20 mL) was added and the mixture refluxed for 1 h. Upon cooling, the mixture was diluted with EtOAc. The organic solution was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc/triethylamine (50/10/6) as eluent to give 2.47 g (79%) of **82** as an amorphous powder: ^1H NMR ($CDCl_3$) δ 2.35 and 2.37 (each s, total 6 H), 2.60–2.87 (m, 2 H), 3.88 (s, 3 H), 3.91 (t, J = 7.9 Hz, 1 H), 4.05 (dt, J = 3.1 and 7.3 Hz, 2 H), 5.04 and 5.54 (AB syst, J = 14.5 Hz, 2 H), 6.94 (s, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 7.1–7.2 (m, 2 H), 7.25–7.31 (m, 2 H), 7.55 (s, 1 H), 7.82 (d, J = 2.2 Hz, 1 H), 7.88 (dd, J = 2.2 and 8.4 Hz, 1 H); MS m/z 426 (M^+).

Typical Procedure for Obtaining the Target Carboxylic Acids (2–7, 26–67, 75, and 76) by Saponification: (*E*)-11-[2-(5,6-Dimethyl-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid (125). A mixture of **68** (31.0 g, 0.073 mol), NaOH (11.7 g, 0.292 mol), MeOH (1.5 L), and H_2O (0.5 L) was refluxed for 1.5 h. The reaction mixture was diluted with water and the medium adjusted to pH 5.5 with 4 N HCl. The resultant precipitate was collected and dried. The crude product was suspended with a mixture of 2-propanol (0.5 L) and H_2O (0.5 L). The suspension was refluxed for 0.5 h. Upon cooling to room temperature, the insoluble material was collected to give 22.1 g (74%) of **125** as its 0.25-hydrate: mp 275–277 °C; ^1H NMR (DMSO-d_6) δ 2.25 (s, 3 H), 2.28 (s, 3 H), 2.48–2.51 (m, 2 H), 4.8–5.4 (m, 4 H), 6.24 (t, J = 7.0 Hz, 1 H), 6.80 (s, 1 H), 6.82 (d, J = 8.5 Hz, 1 H), 7.38 (s, 1 H), 7.45–7.65 (m, 4 H), 7.71 (dd, J = 2.2 and 8.5 Hz, 1 H), 7.93 (d, J = 2.2 Hz, 1 H), 8.02 (s, 1 H); IR (KBr) 1683, 1606, 1488, 1244, 1002 cm^{-1}. Anal. ($C_{26}H_{22}N_2O_3 \cdot 0.25H_2O$) C, H, N.

Sodium (*E*)-11-[2-(5,6-Dimethyl-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate Monohydrate (57). Compound **125** (5.0 g, 12.2 mmol) was suspended with MeOH (300 mL) containing 28% NaOMe/MeOH solution (2.4 g, 12.4 mmol). The suspension was stirred at room temperature until the suspension turned into a solution. After concentration, the reaction mixture was recrystallized from MeOH/H_2O (4/1) to give 2.6 g (47%) of **57**: mp >300 dec. Anal. ($C_{26}H_{21}N_2O_3Na \cdot H_2O$) C, H, N.

(*E*)-11-[2-(5,6-Dimethyl-1-benzimidazolyl)ethylidene]-2-(morpholinocarbonyl)-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate Monohydrate (74). To a suspension of **57** (2.0 g, 4.9 mmol) in CH_2Cl_2 (100 mL) containing triethylamine (0.8 mL, 5.9 mmol) was added oxalyl chloride (0.5 mL, 5.9 mmol) at 0 °C and the mixture was stirred at room temperature for 5 h. After being concentrated, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and the solution was added to a solution of morpholine (0.9 mL, 10 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred at room temperature for 5 h. The solution was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane/EtOAc/triethylamine (10/40/1) as eluent to give 1.3 g (54%) of **74** as an amorphous powder: mp 90 dec; ^1H NMR ($CDCl_3$) δ 2.25 and 2.27 (each s, total 6 H), 3.2–3.6 (m, 8 H), 4.6–5.6 (m, 4 H), 6.23 (t, J = 6.9 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 6.80 (s, 1 H), 7.24 (dd, J = 2.1 and 8.4 Hz, 1 H), 7.40–7.67 (m, 6 H), 8.07 (s, 1 H); MS m/z 479 (M^+).

Compound **73** was obtained in a similar manner as that described above.

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.[12] Briefly, arterial blood was withdrawn from male Hartley guinea pigs or human volunteers 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), $MgCl_2$ (5 mM), EGTA (1 mM), and indomethacin (10 μM). Platelets (1×10^8) were incubated with 10 nM of [^{3}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 to 8 mL of Scintisol EX-H. The radioactivity on the filter was counted by a liquid scintillation counter. The results were expressed by K_i values.

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 2 h after the oral administration of a drug (10 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,[14] 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.

Acknowledgment. We are grateful to Mr. T. Yasuzawa, Mr. H. Ueno, Mrs. Y. Otaki, and Ms. I. Hattori for analytical and spectral data, and especially to Drs. T. Kumazawa and K. Suzuki for their continuous support and pertinent discussion.

Registry No. **1**, 123226-46-0; **2**, 123227-00-9; **3**, 123227-01-0; **4**, 123226-59-5; **5**, 127190-31-2; **6**, 142535-56-6; **7**, 127166-22-7; **9**, 79094-20-5; **10**, 79669-90-2; **11**, 124907-75-1; **12**, 142610-74-0; **13**, 127167-04-8; **14**, 2242-96-8; **16**, 79669-87-7; (*Z*)-**17**, 123227-44-1; (*E*)-**17**, 123227-43-0; (*Z*)-**18**, 123227-46-3; (*E*)-**18**, 123227-45-2; (*Z*)-**19**, 142535-57-7; (*E*)-**19**, 123227-47-4; (*Z*)-**20**, 123227-42-9; (*E*)-**20**, 123227-42-9; (*Z*)-**21**, 123226-96-0; (*E*)-**21**, 123226-95-9; **22a**, 79670-12-5; **22b**, 113836-34-3; **22s**, 142535-89-5; **22d**, 142535-90-8; **23a**, 113805-87-1; **23b**, 113835-69-1; **23c**, 142535-91-9; **23d**, 142535-92-0; (*E*)-**24a**, 127167-47-9; (*Z*)-**24a**, 142535-88-4; **24b**, 127167-51-5; **24c**, 127167-48-0; **24d**, 127167-49-1; **25**, 142563-83-5; **26**, 127166-57-8; **27**, 127166-53-4; **28**, 127166-54-5; **29**, 142535-58-8; **30**, 127166-19-2; **31**, 142535-59-9; **32**, 142535-60-2; **33**, 127166-30-7; **34**, 127166-31-8; **35**, 127166-37-4; **36**, 127166-38-5; **37**, 127166-63-6; **38**, 127166-64-7; **39**, 127166-27-2; **40**, 127166-33-0; **41**, 127166-25-0; **42**, 127166-26-1; **43**, 127166-28-3; **44**, 127166-29-4; **45**, 142535-61-3; **46**, 127166-59-0; **47**, 127166-60-3; **48**, 142535-62-4; **49**, 127166-32-9; **50**, 127166-34-1; **51**, 142535-63-5; **52**, 127166-35-2; **53**, 127166-36-3; **54**, 127166-52-3; **55**, 127166-46-5; (*E*)-**56**, 127166-21-6; (*Z*)-**56**, 142535-93-1; **57**, 127166-41-0; **58**, 127166-50-1; **59**, 127166-49-8; **60**, 127166-51-2; **61**, 127166-48-7; **62**, 127166-55-6; **63**, 127166-56-7; **64**, 127167-43-5; **65**, 127166-44-3; **66**, 127166-45-4; **67**, 127166-43-2; **68**, 127165-95-1; **71**, 6721-26-2; **72**, 127165-74-6; **73**, 142535-64-6; **74**, 142535-65-7; **75**, 142535-66-8; **76**, 142535-67-9; **77**, 79670-00-1; **78**, 142535-68-0; **79**, 142535-69-1; **80**, 142535-70-4; **81**, 142535-71-5; **83**, 127165-70-2; **84**, 127166-02-3; **85**, 142535-73-7; **86**, 142535-74-8; **87**, 142535-75-9; **88**, 142535-76-0; **89**, 142535-77-1; **90**, 127165-71-3; **91**, 142535-78-2; **92**, 127190-30-1; **93**, 142535-79-3; **94**, 127165-89-3; **95**, 127165-90-6; **96**, 127165-80-4; **97**, 127165-81-5; **98**, 142535-80-6; **99**, 127165-97-3; **100**, 127165-91-7; **101**, 142535-81-7; **102**, 127166-00-1; **103**, 127166-01-2; **104**, 127167-37-7; **105**, 127166-07-8; **106**, 127166-08-9; **107**, 127166-06-7; **108**, 142535-82-8; **109**, 127165-78-0; **110**, 127165-79-1; **111**, 127165-98-4; **112**, 127165-76-8; **113**, 127165-81-5; **114**, 142535-83-9; **115**, 142535-84-0; **116**, 127165-85-9; **117**, 127165-86-0; **118**, 127165-73-5; **119**, 127165-82-6; **120**, 127165-83-7; **121**, 127165-95-1; **122**, 142535-85-1; **123**, 127165-96-2; **124**, 127165-94-0; **125**, 127166-39-6; $ClCO_2Et$, 541-41-3; 2-mercaptoethanol, 60-24-2; 1-methylpiperazine, 109-01-3; potassium phthalimide, 1074-82-4; benzenesulfonamide, 98-10-2; 5,6-dimethylbenzimidazole, 582-60-5; benzimidazole, 51-17-2; benzotriazole, 95-14-7; 4-azabenzimidazole, 273-21-2; 5-azabenzimidazole, 272-97-9; imidazole, 288-32-4; 4-phenylimidazole, 670-95-1; 4,5-diphenylimidazole, 668-94-0; 5-nitroimidazole, 94-52-0; 6-nitroimidazole, 94-52-0; methylbenzimidazol-5-yl-

carboxylate, 26663-77-4; 5-(benzylaminocarboxy)benzimidazole, 142535-86-2; 5-chlorobenzimidazole, 4887-82-5; 4-hydroxybenzimidazole, 67021-83-4; 5,6-dichlorobenzimidazole, 6478-73-5; 4,5-dimethylbenzimidazole, 69557-55-7; 5,6-methylenedioxybenzimidazole, 267-87-8; 2-methylthiobenzimidazole, 7152-24-1; 2-methylbenzimidazole, 615-15-6; 2-hydroxybenzimidazole, 615-16-7; 5-(trifluoromethyl)benzimidazole, 326-55-6; naphtho[2,3-*d*]imidazole, 269-07-8; 5-fluorobenzimidazole, 1977-72-6; 7-methylbenzimidazole, 4887-83-6; 5-methylbenzimidazole, 614-97-1; 5-methoxybenzimidazole, 4887-80-3; 5-(α-hydroxybenzyl)benzimidazole, 142535-87-3; 4,6-dimethylbenzimidazole, 69557-54-6; 4,6-dimethoxybenzimidazole, 90557-59-8; 5,6-dimethoxybenzimidazole, 72721-02-9; [3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-propyl]triphenylphosphonium bromide, 70665-02-0.

Reversible Inhibitors of the Gastric (H^+/K^+)-ATPase. 3. 3-Substituted-4-(phenylamino)quinolines

Robert J. Ife,* Thomas H. Brown, David J. Keeling,† Colin A. Leach, Malcolm L. Meeson, Michael E. Parsons, David R. Reavill, Colin J. Theobald, and Kenneth J. Wiggall

SmithKline Beecham Pharmaceuticals R&D, The Frythe, Welwyn, Herts, AL6 9AR, England. *Received February 28, 1992*

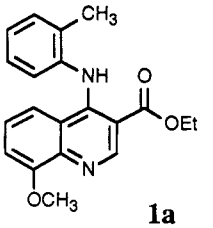
Previously, gastric (H^+/K^+)-ATPase inhibitors such as **2** have been prepared as analogues of **1a** on the presumption that the 3-carbethoxy substituent plays a key role in establishing the orientation of the 4-arylamino group. In this paper we explore further the contribution made to activity by the quinoline 3-substituent. We show that, for compounds bearing such a substituent, only a particular combination of properties provides high activity, both in vitro and as inhibitors of gastric acid secretion in vivo. The ability of the substituent to affect activity by restricting rotation about the C_{quin}–N bond through a combination of both a π-electron withdrawal and hydrogen bonding is supported by the current study. However, high activity is only achieved if the effect of this group on the quinoline pK_a is kept to a minimum. 3-Acyl substituents provide an optimum combination of electronic properties. From this series, compound **17c** (SK&F 96067) was shown to be a potent inhibitor of histamine-stimulated gastric acid secretion after oral dosing in the Heidenhain pouch dog and was selected for further development and evaluation in man.

Introduction

Sustained suppression of gastric acid secretion, by either long-acting histamine H_2-receptor antagonists, e.g. loxtidine, or irreversible proton pump inhibitors, namely omeprazole, has been associated with the formation of gastric carcinoids in long-term carcinogenicity studies[1,2] and has led to the so-called gastrin hypothesis.[3] With this background, reversible (H^+/K^+)-ATPase inhibitors, as shorter acting inhibitors of gastric acid secretion, have begun to attract attention as potential therapies for acid-related gastrointestinal disorders.[4] Acting on the final stage of secretion, such compounds have the potential to combine profound inhibition of acid secretion, elicited by all stimuli, with the dosing flexibility available with the short-acting H_2-receptor antagonists. Furthermore, with less sustained elevations of plasma gastrin levels, such compounds should have a greatly reduced potential for the formation of gastric carcinoids in long-term toxicology studies.

In the first papers of this series[5,6] we described how we used the 3-carbethoxyquinoline derivative **1a**, which we showed to be a reversible K^+-competitive gastric (H^+/K^+)-ATPase inhibitor, as the starting point for a series of antisecretory compounds based on conformationally restricted pyrroloquinolines such as **2**. The basis for preparing these compounds was the supposition that in compounds such as **1**, the ester group might be responsible for fixing the conformation about the 4-phenylamino moiety through a combination of intramolecular hydrogen-bonding and π-electron delocalization.

In this paper we describe our efforts to elucidate further the role of the 3-substituents in these compounds. This



1a

2

work has led to the identification of the potent, orally active, reversible (H^+/K^+)-ATPase inhibitor 3-butyryl-4-[(2-methylphenyl)amino]-8-methoxyquinoline (**17c**, SK&F 96067), which is currently undergoing clinical trials.

* To whom correspondence should be addressed.
† Present address: Department of Cell Biology, Astra Hässle AB, S-431 83, Mölndal, Sweden.

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0022-2623/92/1835-3413$03.00/0