results in the thioamide sulfur atom pointing away from the 18-membered ring while the phenyl ring of the adjacent Phe[2] residue is positioned over the central space of the macrocycle in close proximity to the methyl group of *N*-methyl Phe[6]. Interestingly, no upfield chemical shift for the *N*-methyl group of **9** was observed by ^{1}H NMR, relative to **3**, indicating that the positioning of the phenyl ring is likely a function of crystal packing.

The successful introduction into **3** of a single thioamide moiety afforded the opportunity of selectively obtaining the PheΨ[CH_2NH]Ile reduced peptide analogues. This modification has been useful for obtaining enzyme inhibitors[28] and hormone antagonists.[29,30] Further, it was anticipated that this change would augment the aqueous solubility of the products. Desulfurization of **9** with Raney nickel gave the expected **10**. In contrast to **9**, the OT and AVP receptor affinities of **10** were drastically reduced.

In sum, the selective chemical transformations carried out on the *Streptomyces silvensis* derived OT antagonist **3** have led to several analogues with improved OT receptor-binding potency, OT/AVP selectivity, and/or aqueous solubility. Compound **8**, the optimal example of these efforts, has been characterized as a functional OT antagonist similar to **3** in the blockade of OT-stimulated rat uterine contractions in vitro and in vivo.[18] Moreover, it shows no agonist activity in stimulating phosphatidyl inositol turnover in vitro or rat uterine contractions in vitro or in vivo. Details of these studies will be reported separately. Our results illustrate how subtle structural modifications can have dramatic effects on the ability of these compounds to bind to the oxytocin receptor, presumably through effects on conformation and/or hydrogen-bonding potential. These initial findings together with results obtained from totally synthetic analogues[31] have provided compounds of greater utility as research tools and have set the stage for the development of therapeutic agents.

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Azulene Derivatives: New Non-Prostanoid Thromboxane A_2 Receptor Antagonists

Numerous studies have demonstrated the potent vasoconstrictive and platelet-aggregative activities of thromboxane A_2 (TXA_2) in vivo[1,2] and in vitro.[3,4] TXA_2 has also been implicated in the etiology and pathology of many disorders such as coronary vasospasm,[5] myocardial ischemia,[6] asthma,[7] and peptic ulcer.[8,9] TXA_2/PGH_2 receptor antagonists may be more useful than TXA_2 synthetase inhibitors, because these compounds also antagonize the effects of endoperoxides and do not lead to accumulation of endoperoxide intermediates.[10] On the other hand, TXA_2 synthetase inhibitors are less effective in a disease in which TXA_2 may be continuously produced.[10] Recently, we found that an azulene derivative, 3-Ethyl-7-isopropyl-1-azulenesulfonic acid sodium salt-0.33 hydrate (KT1-32), showed a mild TXA_2 antagonistic activity.[11] Therefore, we synthesized various azulene derivatives in order to evaluate their TXA_2 antagonistic activity in two major TXA_2/PGH_2 receptor subtypes, α-receptor for platelet aggregation and τ-receptor for vascular contraction.[12] In this study, selectivity of compounds for one or the other receptor subtype is examined.

The target compounds were synthesized according to the routes shown in Scheme I. Condensation of 6-Isopropyl-3-(methoxycarbonyl)-2*H*-cyclohepta[*b*]furan-2-one (**1**) with morpholino enamines of aldehydes (n = 3–5),[13,14] followed by cleavage of the benzyl ether, resulted in alcohols **3**. Tosylation of **3** and subsequent displacement of tosylates with sodium salts of benzenesulfonamides afforded N-substituted sulfonamides **4**. Hydrolysis of **4** furnished carboxylic acids **5** (Scheme I). Sulfonic acid sodium salt derivatives **7** were prepared from **4** according to the method reported previously.[13] The synthesis of **10** started with **6** by using Anderson's stepwise construction of the acetic acid homologue.[15] α,β-Unsaturated carboxylic acid derivatives **13** were prepared by the Vilsmeier–Haack formylation of **6** followed by Horner–Emmons reaction[16]

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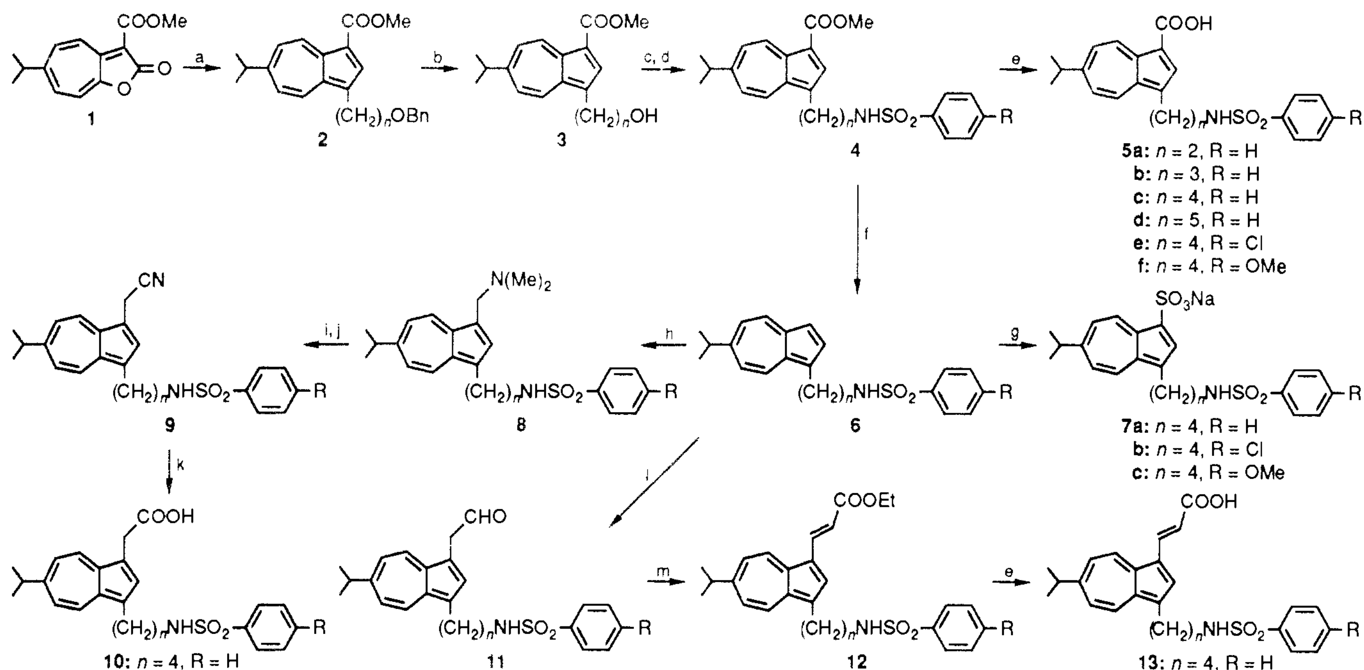
Scheme I[a]



[a]Reagents: (a) $BnO(CH_2)_nCH_2CHO$, morpholine; (b) $AlCl_3$, anisole; (c) p-TsCl, Py; (d) $NH_2SO_2C_6H_4R$, NaH; (e) 10% NaOH; (f) 100% phosphoric acid; (g) (1) SO_3Py, (2) MeONa/MeOH; (h) $(Me)_2NCH_2N(Me)_2$, $(HCOH)_n$, AcOH; (i) MeI; (j) KCN; (k) 0.6 M KOH; (l) $POCl_3$, DMF; (m) $(EtO)_2P(O)CH_2COOEt$, NaH.

of the aldehydes with triethyl phosphonoacetate. Hydrolysis of esters **12** gave acids **13**. The structures of these compounds were confirmed by spectral data and elemental analysis.

The synthetic compounds listed in Table I were compared in TXA_2 antagonism assays with the non-prostanoid antagonist sulotroban[17] as a reference compound. They were tested for effects on isolated rabbit thoracic aorta precontracted by TXA_2 mimetic (15*S*)-hydroxy-11α,9α-(epoxymethano)prosta-5(*Z*), 13(*E*)-dienoic acid (U-46619)[18,19] (3×10^{-8} M). The concentrations that caused 50% relaxation are shown in Table I. All tested compounds were found to be more potent than sulotroban, except for **5a–d**, **10**, and **13**, with **7b** being the most potent, about 30 times more potent than sulotroban. The activity of **7b** was significantly greater than other non-prostanoid antagonists.[20,21] The greatest activity of compound **5c** vs shorter homologues **5a** and **5b** and longer chain compound **5d** suggests that there is an optimal chain length of four carbon atoms. Introduction of a chlorine or a methoxy group into the para position of the phenyl ring (compound **5e** and **5f**) also increased the activity. However, the extension of carbon chain into the 1-position of the azulene ring (compound **10** and **13**) decreased the activity. Replacement of the carboxyl group with the sulfonic acid sodium salt (compound **7a–c**) also resulted in increased activity. Compound **7b** was a potent inhibitor of U-

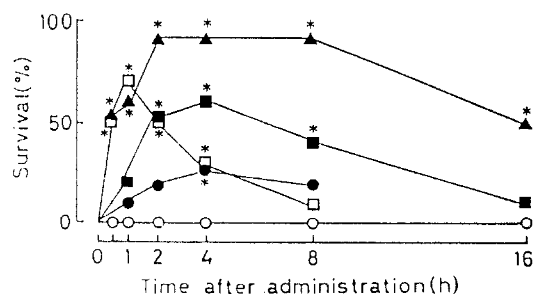


Figure 1. Protective effects of **7b** and sulotroban against U-46619-induced sudden death in mice. **7b** (●, 0.3 mg/kg; ■, 3 mg/kg; ▲, 30 mg/kg), sulotroban (□, 30 mg/kg), or vehicle (○, no drug) were pretreated by oral administration prior to injection of U-46619 (800 μg/kg). At the indicated time after administration of each compound or vehicle, U-46619 was injected intravenously. The effect of each compound was determined by measuring the incidence of death within 5 min of injection. Results are expressed as percent survival and were compared with the χ^2 statistic (*, $p < 0.05$). Each group was comprised of 15 mice.

(17) Sulotroban: 4-[2-(benzenesulfonamido)ethyl]phenoxyacetic acid (BM13,177) is a TXA_2 antagonist. It was synthesized in our laboratories. (Bush, L. R.; Smith, S. G. *Thromb. Res.* **1988**, *44*, 377).

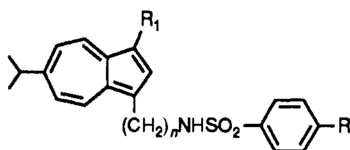
(18) U-46619: (15*S*)-hydroxy-11α,9α-(epoxymethano)prosta-5-(*Z*),13(*E*)-dienoic acid, a stable PGH_2 analogue and TXA_2/PGH_2 receptor agonist (Malmsten, C. *Life Sci.* **1976**, *18*, 169), was purchased from Cayman Chemical Co., Ann Arbor, MI.

(19) Male rabbits (New Zealand) weighing 2.0–2.5 kg were decapitated, and the thoracic aortas were excised, cleaned, and cut into spiral strips (3 mm width and 15 mm length). The tissues were placed in 20-mL organ baths containing Krebs bicarbonate solution (NaCl, 120.3; KCl, 4.8; $CaCl_2$, 1.2; KH_2PO_4, 1.2; $MgSO_4$, 1.3; $NaHCO_3$, 24.2; dextrose, 10.0 mM), kept at 37 °C while bubbling 95% O_2 and 5% CO_2 through the solution. A resting tension of 1.5 g was applied, and after equilibration for 1 h, the isomeric tension was recorded on a polygraph (Nihon Kohden) through a force displacement transducer (Nihon Kohden). After the increase in isometric tension due to 3×10^{-8} M U-46619 became stable, cumulative concentrations of each compound were added to the bath. The concentration which caused a 50% relaxation of a U-46619-induced maximal change in tension was obtained by regression analysis of the concetration–relaxation curve.

(20) The IC_{50} value of (*E*)-7-phenyl-7-(3-pyridyl)-6-heptanoic acid (CV-4151) is 1.5×10^{-6} M in rabbit aorta. See: Imura, Y.; Terashita, Z.; Shibouta, Y.; Nishikawa, K. *Eur. J. Pharmacol.* **1988**, *147*, 359.

(21) The IC_{50} value of BM13,505 is 6.0×10^{-7} M in rabbit aorta. See: Swayne, G. T. G.; Maguire, J.; Dolan, J.; Raval, P.; Dane, G.; Greener, M.; Owen, D. A. A. *Eur. J. Pharmacol.* **1988**, *152*, 311.

Table I. Structures and Inhibition of U-46619-Induced Rabbit Aorta Contraction and Rabbit Platelet Aggregation by Azulene Derivatives



compd	R_1	R	*n*	formula[a]	% yield[b]	mp, °C	IC_{50},[c] M contrn[d]	IC_{50},[c] M aggrn[e]	select. index[f]
5a	COOH	H	2	$C_{22}H_{23}NO_4S$	30.4	165–166	$1.4 \pm 0.1 \times 10^{-5}$	$>10^{-4}$	>7
5b	COOH	H	3	$C_{23}H_{25}NO_4S$	31.8	120–122	$1.4 \pm 0.1 \times 10^{-5}$	$>10^{-4}$	>7
5c	COOH	H	4	$C_{24}H_{27}NO_4S$	37.6	167–168	$1.6 \pm 0.1 \times 10^{-6}$	$>10^{-4}$	>63
5d	COOH	H	5	$C_{25}H_{29}NO_4S$	36.2	75–76	$3.4 \pm 0.5 \times 10^{-6}$	$>10^{-4}$	>29
5e	COOH	Cl	4	$C_{24}H_{26}ClNO_4S$	19.4	185–186	$1.5 \pm 0.1 \times 10^{-7}$	$>10^{-4}$	>667
5f	COOH	OMe	4	$C_{25}H_{29}NO_5S$	29.2	166–167	$4.3 \pm 0.5 \times 10^{-7}$	$>10^{-4}$	>233
7a	SO_3Na	H	4	$C_{23}H_{26}NO_5S_2Na$	30.4	207–208	$1.1 \pm 0.1 \times 10^{-6}$	$>10^{-4}$	>91
7b (KT2-962)	SO_3Na	Cl	4	$C_{23}H_{25}ClNO_5S_2Na$	19.4	201	$2.3 \pm 0.5 \times 10^{-8}$	$8.7 \pm 0.5 \times 10^{-6}$	378
7c	SO_3Na	OMe	4	$C_{24}H_{28}NO_6S_2Na \cdot {}^2/_3H_2O$	15.7	205–206	$9.7 \pm 1.3 \times 10^{-8}$	$6.4 \pm 0.7 \times 10^{-5}$	660
10	CH_2COOH	H	4	$C_{25}H_{29}NO_4S$	18.2	51–52	$3.0 \pm 0.7 \times 10^{-6}$	$>10^{-4}$	>33
13	CH=CHCOOH (trans)	H	4	$C_{26}H_{29}NO_4S$	36.0	58–60	$1.6 \pm 0.3 \times 10^{-5}$	$>10^{-4}$	>6
sulotroban							$1.3 \pm 0.2 \times 10^{-6}$	$7.1 \pm 0.4 \times 10^{-6}$	5

[a] All compounds had elemental analysis (C, H, N, S) that were within 0.4% of theoretical value. [b] Overall yield from I. [c] IC_{50} values represent the mean ± SEM and were calculated by regression analysis from the three dose groups of four different preparations. [d] Contraction of rabbit aorta was induced by 3×10^{-8} M of U-46619. [e] Aggregation of rabbit platelet-rich plasma (PRP) was induced by 2.5×10^{-6} M of U-46619. [f] The selectivity index for τ-receptor was the difference between the IC_{50} values in the aggregation and contraction assays.

46619-induced contraction of rat aorta, the pA_2[22] value of **7b** being 9.78 (Schild analysis[23]), (slope = 1.04, n = 4). Compound **7b** had no inhibitory effect up to 10^{-5} M on contractile responses induced by norepinephrine, Ca^{2+}, histamine, or serotonin, indicating that compound **7b** was a specific TXA_2/PGH_2 receptor antagonist. Needleman et al. first reported that platelet and vascular TXA_2/PGH_2 receptors might be different.[24] Therefore, we investigated the inhibitory effects of compounds **5a–f**, **7a–c**, **10**, and **13** on platelet aggregation with rabbit platelet-rich plasma (PRP).[25,26] The concentrations which cause 50% inhibition of the maximum aggregation are expressed as IC_{50} values and are also shown in Table I. Compound **7b** is equipotent with sulotroban, but the other compounds were less effective in inhibiting platelet aggregation. The selectivity for τ-receptor (rabbit aorta) as compared to α-receptor (rabbit PRP) of each compound was calculated and is shown in Table I. In this comparison, **5e**, **5f**, **7b**, and **7c** are >600, >200, >350, and 660 times more potent in assays against τ-receptors than α-receptors, respectively, and are more selective for τ-receptors (higher indices) than sulotroban.

In an in vivo experiment of U-46619-induced sudden death in mice, a minimum orally effective dose of **7b** was 0.3 mg/kg and its duration was over 8 h at a dose of 3 mg/kg, whereas the duration of subtroban was 4 h at a dose of 30 mg/kg (Figure 1). Myers et al. have reported that the mortality induced by U-46619 in mice may be due to a combination of vasoconstriction and thrombosis.[27] These results suggest that **7b** prevents vasoconstriction and thrombosis. Compound **7b** had no effect on TXA_2 formation in human platelets when evaluated at concentration up to 10^{-4} M.[28] Compound **7b** had no partial agonistic activity at concentrations to 10^{-5} M in rabbit aorta and up to 10^{-4} M in rabbit PRP, although other prostanoid TXA_2/PGH_2 receptor antagonists tend to be partial agonists.[29–31]

(22) pA_2 is the negative logarithm of the dose of antagonist that requires a doubling of the agonist dose to compensate for its action.

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(25) Male rabbits (New Zealand) weighing 2.0–2.5 kg were anesthetized with ether; blood was withdrawn from the carotid artery through a cannulation tube with a syringe containing trisodium citrate (3.18%, 1/10 volume). Platelet-rich plasma (PRP) was then prepared by centrifugation at 300 g for 15 min. The supernatant was decanted, and the remaining pellet was centrifuged at 1000*g* for 20 min to produce platelet-poor plasma (PPP), which was used as a zero calibration. Platelet aggregation was measured with an aggregometer (Chrono-Log) by the method of Born.[26] PRP (500 μL) placed in a cuvette was warmed at 37 °C for 2 min, and then a solution of the compound or vehicle was added. Exactly 2 min later, 2.5×10^{-6} M of U-46619 was added to PRP. The change in light transmission was recorded, with the light transmissions for PRP and PPP taken as 0% and 100%, respectively, and the maximum light transmissions after addition of U-46619 as the maximum aggregation. The concentration which caused 50% inhibition of a U-46619-induced maximum aggregation was obtained by regression analysis of the concentration–inhibition curve.

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(28) Human blood was obtained from antecubital vein from healthy volunteers. Platelet-rich plasma (PRP) was prepared by centrifugation at 200*g* for 20 min. The PRP was further centrifuged at 2000*g* for 10 min, and the resulting pellet was washed twice with 25 mM phosphate buffer. The washed platelets were resuspended in 50 mM phosphate buffer (pH 7.4) containing 1 mM EDTA, sonicated, and stored at −80 °C until use. Sonicated platelets were preincubated with test compounds in the presence of 1 mM GSH at 37 °C for 5 min, and then the mixture was incubated with [1-^{14}C]arachidonic acid (0.1 μCi) at 37 °C for 5 min. Each reaction was terminated by the addition of 2.5 mL of cold ether/methanol (30:4, v/v) and the mixture was acidified with 200 mM citric acid. ^{14}C-labeled eicosanoids were extracted and separated by thin-layer chromatography. The areas corresponding to each eicosanoid were removed and the radioactivity was counted. Thromboxane formation was calculated from the amount of thromboxane B_2 generated from [^{14}C]arachidonic acid. The IC_{50} values were obtained by regression analysis of the concentration–inhibition curve.

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In summary, the azulene derivatives have potent TXA_2/PGH_2 receptor antagonist activities. In this series, compounds having carboxylic acid or the sulfonic acid sodium salt group at the 1-position have greatest activity, with **7b** being the most potent, orally effective, and τ-receptor-selective antagonist without partial agonistic activity. On the basis of these data, we suggest that TXA_2/PGH_2 receptor antagonists derived from azulene derivatives possess good in vitro and in vivo activities.

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Articles

1,2,4-Triazolo[4,3-*a*]pyrazine Derivatives with Human Renin Inhibitory Activity. 1. Synthesis and Biological Properties of Alkyl Alcohol and Statine Derivatives

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A series of 1,2,4-triazolo[4,3-*a*]pyrazine derivatives with human renin inhibitory activity, which incorporate (1*S*,2*S*)-2-amino-1,3-dicyclohexyl-1-hydroxypropane, statine (Sta), and (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACHPA) transition-state mimetics, have been prepared. Structure–activity relationships for renin inhibitory activity in the series are consistent with the 2-[8-isobutyl-6-phenyl-1,2,4-triazolo[4,3-*a*]pyrazin-3-yl]-3-(3-pyridyl)propionic acid moiety **10b** acting as a non-peptidic replacement for the P_4–P_2 (Pro-Phe-His) residues of the natural substrate angiotensinogen. Compounds **12m**, **12o**, and **12q** were potent inhibitors of partially purified human renin (IC_{50} values 1.7, 6.8, and 3.7 nM, respectively), and also effectively lowered blood pressure in anesthetized, sodium depleted marmosets following intravenous administration. On oral administration however, no blood pressure lowering activity could be detected, and absorption studies in bile duct cannulated rats indicate that this may be due primarily to poor oral absorption, rather than rapid biliary excretion. The reason for the observed poor oral activity is not clear, but it seems unlikely that poor aqueous solubility or metabolic instability to gut enzymes are rate-determining, and other factors such as high molecular weight may also be very important.

The renin–angiotensin system is a multiregulated proteolytic cascade of enzyme-mediated events that converts angiotensinogen to angiotensin I (AI), angiotensin II (AII), and angiotensin III (AIII), and so provides a major regulatory mechanism for the control of blood pressure in mammals[1] (Scheme I). Inhibition of angiotensin converting enzyme (ACE), which cleaves AI to AII, has demonstrated that blockade of this system is an effective means of reducing blood pressure in a large majority of hypertensive patients.[2] The conversion of angiotensinogen to AI by the enzyme renin is the first and rate-limiting step in the cascade. Animal studies comparing an ACE inhibitor with a renin inhibitor have shown the two agents to be equieffective.[3] Moreover, renin inhibitors may have the potential for fewer side effects, since, unlike ACE,

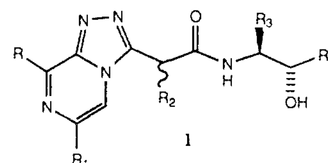

Figure 1. General inhibitor structure.

which hydrolyzes a variety of biologically important peptides,[4] renin is uniquely specific, having angiotensinogen as its only known substrate.[5]

Most of the currently available renin inhibitors, although highly potent in vitro, are peptidic in nature. As a consequence, these compounds tend to suffer from all the

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