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Synthesis and Biological Activity of 4-Methyl-3,5-dioxane Derivatives as Thromboxane A_2 Receptor Antagonists

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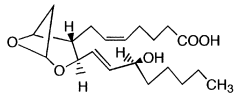
Abstract—The synthesis and biological activity of novel 4-methyl-3,5-dioxane analogues are described. All compounds were produced through modification of the substituent formally corresponding to the ω-octenol side chain of thromboxane A_2 (TXA_2), in reference to the structure of SQ29548. Several compounds were found to be potent TXA_2 receptor antagonists. Compound **8b** was the most effective inhibitor of 9,11-epoxymethano PGH_2 (U-46619)-induced human platelet aggregation ($IC_{50} = 7.4$ nM). © 1999 Elsevier Science Ltd. All rights reserved.

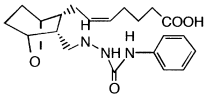
Introduction

Thromboxane A_2 (TXA_2) **1**[1,2] is a potent stimulator of platelet aggregation[3,4] and also induces contraction of smooth muscle.[5] Blocking the action of TXA_2 is becoming an established method for treating asthma and various cardiovascular diseases in the clinic.[6–10] Several drugs and development candidates with prostanoid structures having a semicarbazide or a semicarbazone moiety, such as SQ29548 **2**,[11,12] SQ27825 **3**[13] and EP045 **4**[14] or dioxane derivatives, such as ICI180080 **5a**,[15] ICI185282 **5b**,[16] ICI192605 **5c**[17,18] and with non-prostanoid structures, such as Sulotroban 6[19–21] have been discovered and confirmed as selective TXA_2 receptor antagonists.

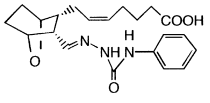
After investigation of conformational similarities between SQ29548 and TXA_2, we identified a 4-methyl-3,5-dioxane skeleton, which includes two oxygen atoms in its ring system like TXA_2, as a new structurally stable lead for TXA_2 receptor antagonists. In addition, based on earlier studies[22] on the side chain stereochemistry of the ring system, we chose the *cis*-substituted compound **7a**, which has similar activity to SQ29548, as a useful prototype for a novel series of TXA_2 receptor antagonists. In order to improve TXA_2 receptor antagonistic activity, we maintained certain structural features of TXA_2, particularly the 1,3-dioxane ring system and the α-heptenoic acid chain, and chose to alter the nature of the substituent formally corresponding to the ω-octenol side chain. In the course of these studies, we discovered (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-aza-2(((phenyamino)thioxomethyl)amino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoic acid **8a**, which possesses specific and potent TXA_2 receptor antagonistic activity. The synthesis and biological properties of **8a** and **8b** and certain structural analogues are described below.



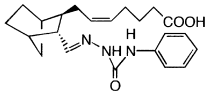
TXA_2 (**1**)



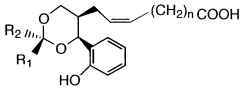
SQ29548 (**2**)



SQ27825 (**3**)



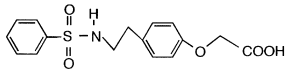
EP045 (**4**)



ICI 180080 (**5a**) : R_1 = -CH_3, R_2 = -CH_3, n = 3

ICI 185282 (**5b**) : R_1 = -CF_3, R_2 = -H, n = 3

ICI 192605 (**5c**) : R_1 =  , R_2 = -H, n = 2



Sulotroban (**6**)

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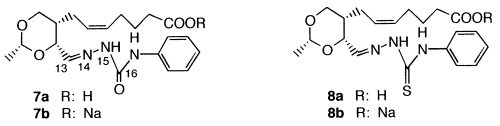


Chemistry

The synthesis of the key intermediate **19** for the 4-methyl-3,5-dioxane analogues proceeded from commercially available glucose derivative **9** and is outlined in Scheme 1. 1,3-Dioxane diol **11** was obtained by $NaIO_4$ oxidation[23,24] of **9**, followed by reaction of the intermediate aldehyde **10** with $NaBH_4$ in EtOH, as described in the literature.[25] Protection of the primary hydroxy group in **11** with *t*-butyldimethylsilyl (TBDMS) chloride, followed by Moffatt oxidation provided the ketone **13**. Wittig reaction of **13** with ethyl (triphenylphosphoranylidene)acetate afforded the ester **14** (E/Z mixture), which was then subjected to catalytic reduction on 10% Pd-C in EtOH, followed by silica gel chromatography (*n*-hexane–AcOEt) to afford the desired ester **15** (55.7% from **14**, major product). Diisobutylaluminium hydride (DIBAL) reduction of **15** gave aldehyde **16**, which was then treated with the Wittig reagent prepared from (4-carboxybutyl) triphenylphosphonium bromide and dimsyl sodium in DMSO, to yield acid **17**. The acid was methylated with CH_3I and the TBDMS group in the resulting ester **18** easily removed by treatment with *n*-Bu_4NF, to afford the desired intermediate alcohol **19**.

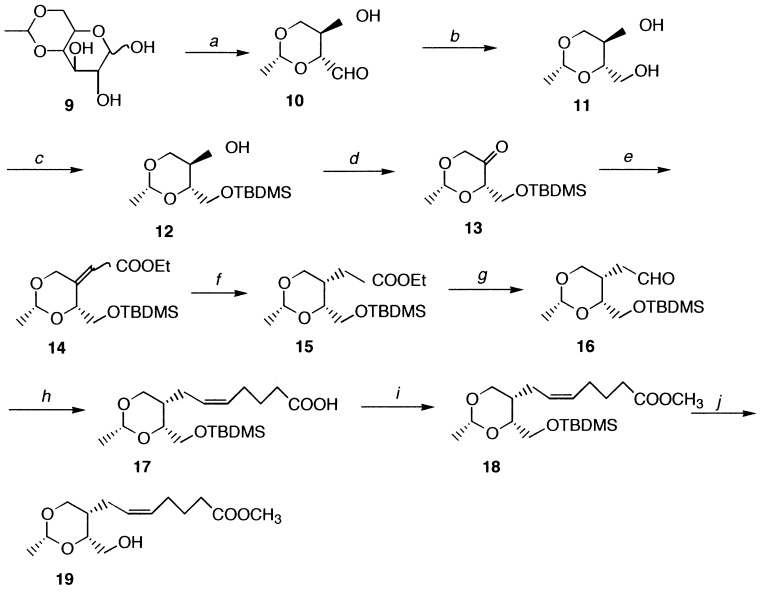
Analogues in which a nitrogen atom was located at the 14-position were synthesized as outlined in Schemes 2 and 3. Oxidation of the alcohol **19** with Collins' reagent gave the aldehyde **20**. Conversion of **20** to imines (for example, **39**–**42**), where R represents the substituents (R_1 and R_2) shown in Scheme 2, was accomplished by coupling **20** with the appropriate amine, followed by hydrolysis with 1 N NaOH/MeOH, and provided the target compounds **7a**, **8a**, **21**–**25**. For compounds **7a** and **8a**, sodium salts **7b** and **8b** were also synthesized. Sodium cyanoborohydride ($NaBH_3CN$) reduction of the imines gave the corresponding amines, which were then treated with 1 N NaOH/MeOH to afford the desired compounds **27**–**29**. Compound **26** was obtained from **7a** by treatment with $NaBH_3CN$.

Conversion of **19** to the phthalimide **30** was accomplished by displacement of the corresponding tosylate with potassium phthalimide. Treatment of **30** with hydrazine hydrate afforded the amine **31**, which was then condensed with the appropriate isocyanate or acid, followed by alkaline hydrolysis or was treated with 1 N NaOH/MeOH followed by condensation with the appropriate isocyanate, to provide the desired compounds **32**–**34**.

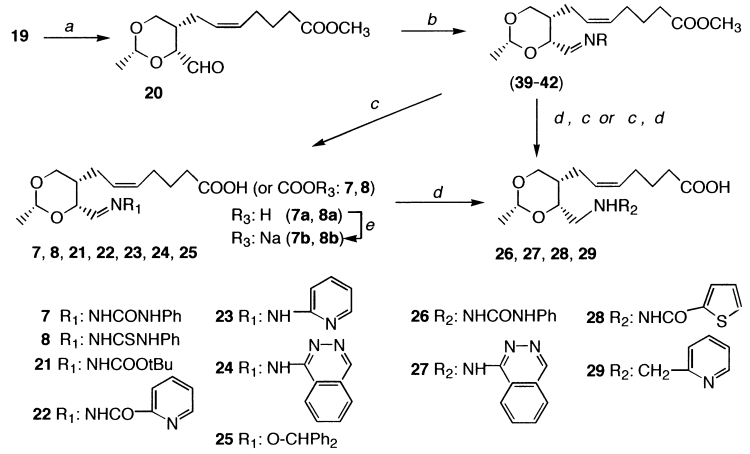
Analogues in which an oxygen atom was located at the 14-position were synthesized as outlined in Scheme 4. Treatment of **19** with phenylisocyanate or 2-picolyl chloride afforded urethane **35** and ether **37**, respectively, which were then treated with 1 N NaOH in aqueous methanol, to yield target compounds **36** and **38**.

Results and Discussion

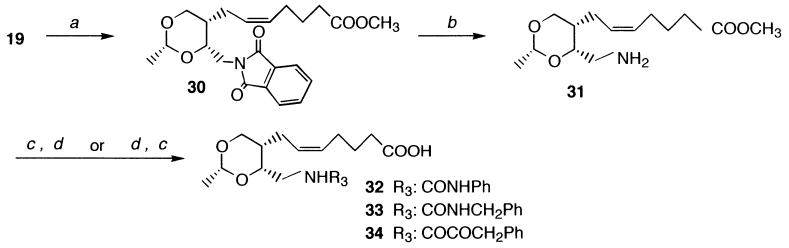
We assumed that the semicarbazide and semicarbazone structures corresponding to the ω-octenol side chain were very important for TXA_2 receptor antagonistic activity, as shown by the activity of SQ29548, SQ27825 and EP045. In addition, we thought that pyridine derivatives and the like were their equivalents, so we synthesized one group of analogues which possess a stable



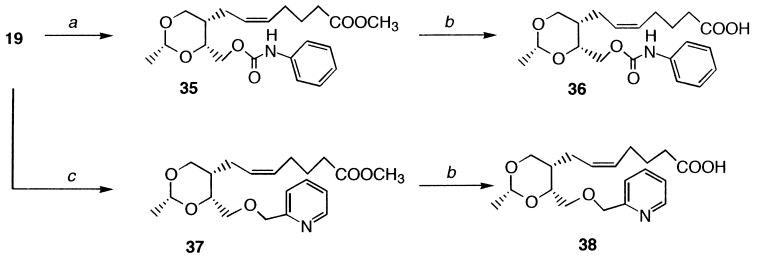
Scheme 1. (a) $NaIO_4/H_2O$, 5°C; (b) $NaBH_4$/EtOH, 5°C; (c) TBDMSCl/imidazole/DMF, rt; (d) DMSO/DCC/TFA/pyridine/benzene, rt; (e) $Ph_3P=CHCOOEt$/THF, rt; (f) 10%Pd-C/H_2(3atm)/EtOH, rt then silica gel column; (g) DIBAL-H/toluene, −78°C; (h) NaH/DMSO, 75°C then ($Ph_3PC_4H_9COOH$) + Br−/DMSO, rt; (i) CH_3I/K_2CO_3/DMF, rt; (j) *n*-Bu_4NF/THF, rt.



Scheme 2. (a) CrO_3·2pyridine/CH_2Cl_2, rt; (b) R_1NH_2 or R_2NH_2/AcOH/MeOH, rt; (c) 1 N NaOH/MeOH, rt; (d) $NaBH_3CN$/AcOH/MeOH, rt; (e) 1 N NaOH/MeOH, rt then treated at pH > 10.



Scheme 3. (a) TsCl/pyridine, rt then potassium pthalimide/DMSO, 100°C; (b) H_2NNH_2·H_2O/EtOH, rt; (c) PhNCO/pyridine, rt or $PhCH_2NCO$/pyridine, rt or $PhCH_2COCOOH$/DCC/EtOAc, rt; (d) 1 N NaOH/MeOH, rt.



Scheme 4. (a) PhNCO/pyridine, rt; (b) 1 N NaOH/MeOH, rt; (c) 2-picolylchloride·HCl/NaH/DMF, rt.

imine functionality (**7a**, **8a**, **21**–**25**) at the 14 position and another group of analogues which possess a stable amine functionality (**26**, **27**–**29**, **32**–**34**) at the 14 position, in order to find a novel potent TXA_2 receptor antagonist and to extract the important attributes in the case of 4-methyl-3,5-dioxane analogues.

The target compounds described in Schemes 2 and 3 were evaluated for their ability to inhibit platelet aggregation of rabbit platelet-rich plasma (PRP) induced by 9, 11-azo PGH_2[26,27] (5 μL, final concentration 1 μM) or adenosine diphosphate (ADP, 5 μL, final concentration 2.5 μM). The concentrations (IC_{50}) that caused 50% inhibition of platelet aggregation are shown in Table 1. Consistent with their mechanism of action, none of the compounds was effective in inhibiting ADP induced platelet aggregation.

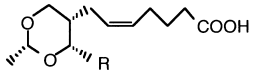
As shown from the results for both groups in Table 1, replacement of the NH group at the 15 position led to a significant loss in TXA_2 receptor antagonistic activity. Therefore, we confirmed the importance of the NH group at the 15 position on the ω side chain. Replacement of the anilino group next to the carbonyl group at the 16 position of **7a** with a pyridy 1 group, as in **22** significantly decreased the potency ($IC_{50} > 100$ μM). This tendency was apparent for the reduced compound **26** and the thienyl compound **28** as well. In addition, comparison of compounds **22** and **23** showed that deletion of the carbonyl group leads to an increase in activity. This suggests that the NH group at the 15 position does not behave as an acidic proton in its biological activity.

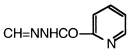
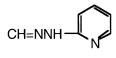
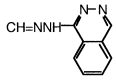
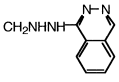
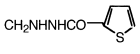
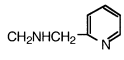
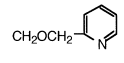
Comparison between compounds **7a** and **26** demonstrates that reduction of the imine functionality leads to a decrease in potency, in contrast with the result[28,29] for SQ29548, but consistent with the result for a series of norbornane semicarbazones.[30] Up to the present date, the cloning of a human TXA_2 receptor has been done[31]

and a detailed analysis of the TXA_2 receptor–TXA_2 receptor antagonist interaction has been reported.[32] Furthermore, estimation of intramolecular hydrogen bonding[33] in TXA_2 receptor antagonists and proposal of a common spatial pharmacophore[34] for TXA_2 receptor antagonists has also been reported. However, we believe that it is very dificult to explain such a difference in activity clearly using the above information. In this series of 4-methyl-3,5-dioxane analogues, it is assumed that the imine functionality is more suitable than the amine one from the results shown in Table 1.

In an attempt to explore further possibilities for the ω side chain of the 4-methyl-3,5-dioxane skeleton, we synthesized ether derivatives (**36**, **38**) at the 14 position, as described in Scheme 4, but TXA_2 receptor antagonistic activity was not observed (Table 1). These results also demonstrated the requirement for the NH group at the 15 position to maintain antagonistic activity.

Table 1. In vitro activity of 4-methyl-3,5-dioxane analogues



Compound	R	Inhibition of rabbit platelet aggregation (IC_{50}, μM[a])	
		9,11-azo PGH_2	ADP
7a	CH = NNHCONHPh	0.26	> 100
8a	CH = NNHCSNHPh	0.055	> 100
21	CH = NNHCOOtBu	53	> 100
22		> 100	> 100
23		36	> 100
24		35	> 100
25	CH = N−OCHPh$_2$	> 100	> 100
26	$CH_2NHNHCONHPh$	16	> 100
27		52	> 100
28		> 100	> 100
29		> 100	> 100
32	$CH_2NHCONHPh$	> 100	> 100
33	$CH_2NHCONHCH_2Ph$	> 100	> 100
34	$CH_2NHCOCOCH_2Ph$	> 100	> 100
36	$CH_2OCONHPh$	> 100	> 100
38		> 100	> 100
	SQ 29, 548	0.23	> 100

[a] IC_{50} values were calculated by regression analyses from three dose groups, using three different preparations.

From these results, we concluded that the optimal new ω side chain was a 2-aza-2{[(phenylamino)thioxomethyl]amino}vinyl group from this study. In order to clarify this and to further evaluate activity with a view to selecting a potential drug candidate, we then synthesized **8b**, the sodium salt of **8a**, together with **7b**, the sodium salt of **7a**, and examined additional biological activities, as shown in Tables 2–5. In a radioligand binding assay with guinea-pig platelets, we confirmed that **7b** and **8b** inhibited the binding of U-46619[35,36] with IC_{50} values of 1.6×10^{-7} M and 7.7×10^{-8} M, respectively and possessed high affinity for the TXA_2 receptor (Table 2).

We selected compound **8b** through these experiments, and next evaluated in vitro inhibitory activities against U-46619- and collagen-induced platelet aggregation in various species. As shown in Table 3, **8b** displayed highly specific inhibitory activity, especially against human and monkey platelets. In addition, we evaluated inhibitory activity against ex vivo platelet aggregation induced by U-46619, following oral administration of **8b** to guinea-pigs, and confirmed the activity, as shown in Table 4. Furthermore, compound **8b** was effective in the arachidonic acid-induced pulmonary infraction mouse model, which is well known for evaluating TXA_2 receptor antagonists (Table 5). The stability of these 4-methyl-3,5-dioxane skeleton was also demonstrated through the effectiveness of these oral administration experiments as we expected.

Conclusion

We have investigated various modifications of the substituent formally corresponding to the ω-octenol side chain of TXA_2, and concluded that the NH group at the 15 position is of importance for the activity of 4-methyl-3,5-dioxane analogues. Through evaluation of these derivatives, compound **8b** was found to be the most potent

Table 2. Potencies of **7b** and **8b** for inhibition of [^{3}H]-U46619 binding to washed guinea-pig platelets

Compound	**7b**	**8b**
IC_{50}[a]	1.6×10^{-7} M	7.7×10^{-8} M

[a] IC_{50} values were calculated by regression analyses from five dose groups, using three different reparations.

Table 3. In vitro activities of compound **8b** in various species

Species	Agonist	IC_{50}, M[a]
Human	U-46619	7.4×10^{-9}
	Collagen	5.0×10^{-9}
Monkey	U-46619	5.6×10^{-9}
Dog	Collagen	2.0×10^{-7}
Guinea-pig	U-46619	5.2×10^{-8}
	Collagen	7.5×10^{-8}
Rat	Collagen	2.2×10^{-7}

[a] IC_{50} values were calculated by regression analyses from three dose groups, using four different preparations.

Table 4. Inhibition of ex vivo platelet aggregation by oral administration of compound **8b** in guinea-pig

	8b (mg/kg)	Inhibition (%)[a]
U-46619	1.0	45.1
	3.2	98.3**
Collagen	1.0	60.5*
	3.2	87.5**

[a] $*P<0.05$ and $**P<0.01$, compared with control group. Data represents the average percent of inhibition in a group of 5 animals.

Table 5. Effects of **8b** in the arachidonic acid-induced pulmonary infraction mice model

Compound		**8b**	
Dose (mg/kg, po)	3.2	10	32
Inhibition (%)[a]	30	50	100

[a] Data represents the survival percent in a group of 10 mice.

and specific in inhibiting U-46619 or collagen induced human platelet aggregation (7.4×10^{-9} M, 5.0×10^{-9} M, respectively). Our further studies on optimizing this activity will be the subject of subsequent papers.

Experimental

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AM-200 spectrometer using tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid -d_4 sodium salt (TSP-d_4) as an internal reference. The ESI mass spectra (MS) were recorded on a Plateform LC-MS spectrometer (Micromass). Column chromatography was carried out on silica gel 60 (E. Merck, 70–200 mesh). Thin-layer chromatography (TLC) was performed on 0.5 or 2 mm precoated silica gel plates from E. Merk (Kieselgel 60F_{254}).

(2*R*,4*S*,5*R*)-2-Methyl-4-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-1,3-dioxan-5-ol (12). A mixture of (2*R*,4*S*,5*R*)-4-hydroxymethyl-2-methyl-1,3-dioxan-5-ol **11** (13.0 g, 87.7 mmol), *tert*-butylchlorodimethylsilane (14.5 g, 133 mmol) and imidazole (13.1 g, 192 mmol) in *N,N*-dimethylformamide (130 mL) was stirred at room temperature for 2 h and the mixture was diluted with ethyl acetate (500 mL). The solution was washed successively with water, diluted hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo to give 24.2 g (100%) of **12** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.10 (3H, s), 0.12 (3H, s), 0.91 (9H, s), 1.32 (3H, d, $J=5$ Hz), 3.3–3.6 (3H, m), 3.7–3.8 (2H, m), 3.94 (1H, dd, $J=4$, 9 Hz), 4.13 (1H, dd, $J=5$, 9 Hz), 4.70 (1H, q, $J=5$ Hz). ESI-MS m/z: 263 $(M+H)^+$.

(2*R*,4*S*)-2-Methyl-4-[(1,1,2,2-tetramethyl-1-silapropoxy)-methyl]-1,3-dioxan-5-one (13). A solution of **12** (4.2 g, 16.0 mmol) in a mixture of benzene (30 mL) and dimethylsulfoxide (5.7 mL, 73.6 mmol) was added to pyridine (1.3 mL, 16.1 mmol), trifluoroacetic acid (0.62 mL, 8.05 mmol) and *N,N*′-dicyclohexylcarbodiimide (9.90 g, 48.0 mmol) under cooling in an ice bath and the mixture was stirred at room temperature for 3 h. The resulting solution was added to a mixture of ethyl acetate (50 mL) and water (30 mL), and stirred for 30 min. After removal of insoluble urea by filtration, the organic layer was separated and washed successively with water and brine. The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo to give a crude oil. The oil was purified by a silica gel column (50 g; *n*-hexane:ethyl acetate = 10:1) to give 3.22 g (77.3%) of **13** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.47 (3H, d, $J=5.5$ Hz), 3.98 (2H, d, $J=3.5$ Hz), 4.3–4.5 (3 H, in), 5.11 (1H, q, $J=5.5$ Hz). ESI-MS m/z: 261 $(M+H)^+$.

Ethyl (2*R*,4*R*)-{4-methyl-2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-3,5-dioxanylidene}acetate (14). A mixture of **13** (2.50 g, 9.60 mmol) and ethyl (triphenylphosphoranylidene)acetate (4.00 g, 12.0 mmol) in tetrahydrofuran (25 mL) was stirred at room temperature for 24 h and the solvent was evaporated in vacuo. The residue was chromatographed on a silica gel column (50 g) with a mixture of *n*-hexane and ethyl acetate (10:1) as eluent to give 2.09 g (65.9%) of **14** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.38 (3H, t, $J=7.5$ Hz), 1.47 (1H, d, $J=5.0$ Hz), 3.83 (1H, dd, $J=9$, 11 Hz), 3.87 (1H, dd, $J=9$, 11 Hz), 4.17 (1H, q, $J=7.5$ Hz), 4.30 (1H, m), 4.56 (1H, dd, $J=17$, 2 Hz), 4.93 (1H, q, $J=5$ Hz), 5.44 (1H, d, $J=17$ Hz), 5.89 (1H, m). ESI-MS m/z: 331 $(M+H)^+$.

Ethyl (1*S*,2*R*,4*R*)-{4-methyl-2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-3,5-dioxanyl}acetate (15). A solution of **12** (17.0 g, 51.4 mmol) in ethanol (170 mL) was shaken under hydrogen (3 atm) with 10% palladium on carbon at room temperature for 1.5 h. After removal of the catalyst by filtration, the solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (500 g) with a mixture of *n*-hexane and ethyl acetate (20:1) as eluent to give 9.52 g (55.7%) of **15** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 1.26 (3H, t, $J=7$ Hz), 1.31 (3H, d, $J=5.0$ Hz), 2.06 (1H, m), 2.43 (1H, m), 2.71 (1H, dd, $J=10$, 16 Hz), 3.52 (1H, dd, $J=7$, 11 Hz), 3.68 (1H, dd, $J=7$, 11 Hz), 3.83 (1H, dt, $J=2$, 11 Hz), 3.89 (1H, dt, $J=3$, 7 Hz), 4.06 (1H, d, $J=12$ Hz), 4.14 (2H, q, $J=7$ Hz), 4.72 (1H, q, $J=5$ Hz). ESI-MS m/z: 333 $(M+H)^+$.

(1*S*,2*R*,4*R*)-{4-Methyl-2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-3,5-dioxanyl}ethanal (16). A solution of **15** (9.3 g, 28.0 mmol) in toluene (93 mL) was cooled in a dry ice acetone bath and to the solution was added dropwise diisobutyl aluminum hydride (1.5 M solution in toluene, 26.4 mL, 39.6 mmol). The mixture was stirred at the same temperature for 1 h. After quenching the mixture with saturated aqueous anunonium chloride, to the solution was added a mixture of ethyl acetate (300 mL) and water (300 mL). Insoluble materials were filtered off. The filtrate was extracted with ethyl acetate and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (250 g) with a mixture of *n*-hexane and ethyl

acetate (10:1) as eluent to live 6.61 g (81.9%) of **16** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.31 (3H, d, J = 5.5 Hz), 2.19 (1H, m), 2.63 (1H, dd, J = 5, 17 Hz), 2.88 (1H, dd, J = 9, 17 Hz), 3.50 (1H, dd, J = 10, 11 Hz), 3.68 (1H, dd, J = 7, 11 Hz), 3.8–4.1 (2H, m), 4.74 (1H, q, J = 5.5 Hz). ESI-MS m/z: 289 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-3,5-dioxanyl}hept-5-enoic acid (17). A suspension of sodium hydride (3.49 g, 60% in oil, 87.3 mmol) in dimethylsulfoxide (75 mL) was heated at 75°C for 1 h and the resulting solution was cooled to room temperature. To the solution was added dropwise (4-carboxybutyl)triphenylphosphonium bromide (32.2 g, 72.6 mmol) in dimethylsulfoxide (100 mL). After stirring at room temperature for 15 min, to the mixture was added **16** (6.3 g, 21.8 mmol) in dimethylsulfoxide (10 mL) and the solution was stirred at room temperature for 1.5 h. To the reaction mixture was added aqueous ammonium chloride (100 mL) and the mixture adjusted to pH 4 with oxalic acid. The mixture was extracted with ethyl acetate and the organic layer washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (150 g) with a mixture of *n*-hexane and ethyl acetate (10:1–1:1) as eluent to give 5.50 g (67.7%) of **17** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 1.31 (3H, d, J = 5 Hz), 1.50 (1H, m), 1.6–1.8 (2H, m), 2.0–2.2 (3H, m), 2.3–2.6 (3H, m), 3.5–3.8 (3H, m), 3.89 (1H, m), 4.02 (1H, d, J = 11 Hz), 4.73 (1H, q, J = 5 Hz), 5.3–5.6 (2H, m). ESI-MS m/z: 371 $(M-H)^-$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-4-methyl-2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-3,5-dioxanyl}hept-5-enoate (18). To a solution of **17** (4.75 g, 12.7 mmol) in *N,N*-dimethylformamide (50 mL) was added potassium carbonate (1.76 g, 12.7 mmol) and methyl iodide (1.62 mL, 26.0 mmol), and the mixture stirred at room temperature for 5 h. The solution was poured into water and extracted with ether. The organic layer was washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (75 g) with a mixture of *n*-hexane and ethyl acetate (20:1) as eluent to give 4.17 g (67.6%) of **18** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.96 (9H, s), 1.31 (3H, d, J = 5 Hz), 1.48 (1H, m), 1.6–1.8 (2H, m), 2.0–2.2 (3H, m), 2.3–2.6 (3H, m), 3.5–3.7 (3H, m), 3.68 (3H, s), 3.89 (1H, m), 4.00 (1H, d, J = 11 Hz), 4.72 (1H, q, J = 5 Hz), 5.3–5.6 (2H, m). ESI-MS m/z: 387 $(M+H)^+$.

Methyl (*Z*)-7-((1*S*,2*R*,4*R*)-2-hydroxymethyl-4-methyl-3,5-dioxanyl)hept-5-enoate (19). A mixture of **18** (4.00 g, 10.3 mmol) and tetra-*n*-butyl ammonium fluoride (15 mL of 1 M solution, 15 mmol) in tetrahydrofuran (40 mL) was stirred at room temperature for 3 h and the solvent was evaporated in vacuo. The residue was chromatographed on a silica gel column (80 g) with a mixture of *n*-hexane and ethyl acetate (20:15) as eluent to give 2.88 g (100%) of **19** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (3H, d, J = 5.0 Hz), 1.43 (1H, m), 1.6–1.8 (2H, m), 1.9–2.2 (3H, m), 2.3–2.6 (3H, m), 3.68 (3H, s), 3.7–3.9 (3H, m), 3.93 (1H, m), 4.00 (1H, dd, J = 2, 12.5 Hz), 4.76 (1H, q, J = 5.0 Hz), 5.3–5.6 (2H, m). ESI-MS m/z: 273 $(M+H)^+$.

Methyl (*Z*)-7-((1*S*,2*R*,4*R*)-2-formyl-4-methyl-3,5-dioxanyl)hept-5-enoate(20). To a solution of pyridine (1.64 mL, 20.3 mmol) in dichloromethane (45 mL) was added chromium trioxide (1.07 g, 10.7 mmol) at 10°C and the solution was stirred at room temperature for 1 h. The solution was cooled in an ice bath and a solution of **19** (500 mg, 1.84 mmol) in dichloromethane (3 mL) added. After 2 h, the solution was diluted with ether (100 mL) and passed through a silica gel column. The eluate was evaporated in vacuo and the residue was chromatographed on a silica gel column (20 g) with a mixture of *n*-hexane and ethyl acetate (1:1) as eluent to give 336 mg (67.7%) of 20 as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (3H, d, J = 5.5 Hz), 1.5–1.8 (3H, m), 1.91 (1H, m), 2.0–2.2 (2H, m), 2.3–2.4 (2H, m), 2.55 (1H, m), 3.69 (3H, s), 3.78 (1H, m), 4.03 (1H, dd, J = 2, 11 Hz), 4.27 (1H, d, J = 2 Hz), 4.80 (1H, q, J = 5.5 Hz), 5.3–5.6 (2H, m), 9.62 (1H, s). ESI-MS m/z: 271 $(M+H)^+$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-aza-2-(((phenyamino)-thioxomethyl)amino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (40). To a mixture of **20** (62 mg, 0.229 mmol) and hydrazino(phenylamino)methan-l-thione (46 mg, 0.275 mmol) in ethanol (2 mL) was added acetic acid (1 drop) and the solution was stirred at room temperature for 4 h. The mixture was diluted with chloroform (15 mL) and washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give 110 mg (100%) of **40** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (3H, d, J = 5 Hz), 1.5–1.8 (3H, m), 2.0–2.2 (3H, m), 2.2–2.4 (2H, m), 2.53 (1H, m), 3.69 (3H, s), 3.85 (1H, m), 4.05 (1H, m), 4.53 (1H, dd, J = 3, 4.5 Hz), 4.82 (1H, m), 5.3–5.6 (2H, m), 7.2–7.5 (4H, m), 7.62 (3H, m), 9.04 (1H, s), 9.73 (1H, s). ESI-MS m/z: 420 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-Aza-2-(((phenyamino)thioxomethyl)amino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoic acid (8a). A solution of **40** (110 mg, 0.262 mmol) in a mixture of methanol (2 mL) and 1 N sodium hydroxide (1.00 mL, 1.00 mmol) was stirred at room temperature for 2 h and the reaction mixture adjusted to pH 7 with 1 N hydrochloric acid. Solvent was evaporated in vacuo and the residue was dissolved in a mixture of chloroform and methanol (3:1, 10 mL). The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo to give a crude oil. The crude product was purified by preparative TLC to give 65 mg (61.1%) of **8a** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (3H, d, J = 5 Hz), 1.5–1.8 (3H, m), 2.0–2.2 (2H, m), 2.3–2.6 (4H, m), 3.88 (1H, dd, J = 11.7, 2 Hz), 4.10 (1H, d, J = 11.5 Hz), 4.56 (1H, dd, J = 2.3, 5.2 Hz), 4.83 (1H, q, J = 5 Hz), 5.55 (2H, m), 7.2–7.7 (6H, m), 9.07 (1H, s), 10.8 (1H, br s). ESI-MS m/z: 404 $(M-H)^-$.

Sodium (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-aza-2-(((phenyamino)-thioxomethyl)amino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (8b). A solution of **8a** (1.39 g, 3.43 mmol) in a mixture of methanol (10 mL) and 1 N sodium hydroxide (3.43 mL, 3.43 mmol) was stirred at room temperature

for 2 h and the solvent then evaporated in vacuo. The residue was dissolved in water (50 mL) and the solution applied to a column of Diaion HP-20 (trademark, sold by Mitsubishi Chemical Industries Ltd.) (200 mL). The column was washed with water (500 mL) and the object compound was eluted with a mixture of water and methanol (1:1, 1 L). The organic solvent was removed in vacuo and the aqueous residue was lypholyzed to give 1.77 g (100%) of **8b** as a pale yellow powder: ^{1}H NMR (200 MHz, D_2O) δ 1.39 (3H, d, J = 5.5 Hz), 1.5–1.7 (3H, m), 1.9–2.1 (3H, m), 2.1–2.3 (4H, m), 2.37 (1H, m), 4.05 (1H, s), 4.98 (1H, q, J = 5.5 Hz), 4.8–5.1 (2H, m), 7.3–7.5 (6H, m). ESI-MS m/z: 404 $(M-H)^-$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-(2-aza-2-((*N*-phenylcarbamoyl)amino)vinyl]-4-methyl-3,5-dioxanyl)hept-5-enoate (39). By the procedure used for **40**, **20** (300 mg, 1.11 mmol) and hydrazino(phenylamino)methan-l-one (227 mg, 1.50 mmol) gave 403 mg (90.0%) of **39** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (3H, d, J = 5.5 Hz), 1.6–1.8 (3H, m), 2.0–2.2 (3H, m), 2.2–2.4 (2H, m), 2.55 (1H, m), 3.69 (3H, s), 3.85 (1H, m), 4.04 (1H, m), 4.57 (1H, dd, J = 3, 4.5 Hz), 4.85 (1H, m), 5.3–5.6 (2H, m), 7–09 (1H, t, J = 7 Hz), 7.18 (1H, d, J = 5 Hz), 7.35 (2H, m), 7.50 (3H, m), 7.95 (1H, s), 8.53 (1H, s). ESI-MS m/z: 404 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-Aza-2-((*N*-phenylcarbamoyl)amino)vinyl]-4-methyl-3,5-dioxanyl)hept-5-enoic acid (7a). By the procedure used for **8a**, **39** (403 mg, 0.999 mmol) and 1 N sodium hydroxide (5.00 mL, 5.00 mmol) gave 203 mg (52.2%) of **7a** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (3H, d, J = 5.5 Hz), 1.5–1.8 (3H, m), 2.0–2.2 (2H, m), 2.3–2.6 (3H, m), 3.87 (1H, dd, J = 2, 13 Hz), 4.09 (1H, d, J = 13 Hz), 4.55 (1H, dd, J = 2, 5 Hz), 4.83 (1H, q, J = 5.5 Hz), 5.4–5.6 (2H, m), 7.10 (1H, t, J = 7.5 Hz), 7.2–7.4 (4H, m), 7.50 (2H, m), 8.05 (1H, s), 9.40 (1H, s). ESI-MS m/z: 388 $(M-H)^-$.

Sodium (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-aza-2-((*N*-phenylearbamoyl)amino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (7b). By the procedure used for **8b**, **7a** (117 mg, 0.300 mmol) and 1 N sodium hydroxide (0.300 mL, 0.300 mmol) gave 123 mg (100%) of **7b** as a powder: ^{1}H NMR (200 MHz, D_2O) δ 1.41 (3H, d, J = 5.5 Hz), 1.5–1.7 (3H, m), 1.8–2.4 (8H, m), 4.02 (1H, s), 4.95 (1H, q, J = 5.5 Hz), 5.3–5.6 (2H, m), 7.21 (1H, m), 7.4–7.5 (5H, m). ESI-MS m/z: 388 $(M-H)^-$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-aza-2-(1-phthalazinylamino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (41). By the procedure used for **40**, **20** (500 mg, 1.84 mmol) and 1-hydrazinophthalazine hydrochloride (393 mg, 2.00 mmol) gave 481 mg (63.5%) of **41** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 5.5 Hz), 1.6–1.8 (3H, m), 2.0–2.2 (2H, m), 2.43 (2H, t, J = 8 Hz), 2.67 (1H, m), 3.67 (1H, m), 3.85 (1H, d, J = 12 Hz), 4.05 (1H, d, J = 12 Hz), 4.88 (1H, dd, J = 3, 4 Hz), 4.87 (1H, q, J = 5.5 Hz), 5.3–5.6 (2H, m), 7.51 (1H, m), 7.6–7.7 (2H, m), 7.88 (1H, m), 7.36 (1H, m), 10.48 (1H, broad). ESI-MS m/z: 413 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-Aza-2-(1-phthalazinylamino)vinyl]-4-methyl-3,5- dioxanyl}hept-5-enoic acid (24). By the procedure used for **8a**, **41** (125 mg, 0.303 mmol) and 1 N sodium hydroxide (1.00 mL, 1.00 mmol) gave 79.8 mg (65.9%) of **24** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (3H, d, J = 5.5 Hz), 1.6–1.9 (3H, m), 2.0–2.2 (3H, m), 2.3–2.6 (3H, m), 3.90 (1H, dd, J = 2, 11 Hz), 4.18 (1H, d, J = 11 Hz), 4.70 (1H, dd, J = 3, 4 Hz), 4.88 (1H, q, J = 5.5 Hz), 5.4–5.7 (2H, m), 7.56 (1H, m), 7.6–7.8 (2H, m), 7.90 (1H, m), 7.98 (1H, m), 8.41 (1H, m). ESI-MS m/z: 397 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-Aza-2-((*tert*-butoxy)carbonylamino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoic acid (21). By the procedure used for **40** and **8a**, **20** (270 mg, 1.00 mmol), *tert*-butoxy(hydrazino)methan-1-one (160 mg, 1.20 mmol) and 1 N sodium hydroxide (2.00 mL, 2.00 mmol) gave 94.6 mg (28.1% from **20**) of **21** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–1.5 (1H, m), 1.35 (3H, d, J = 5 Hz), 1.50 (9H, s), 1.6–1.8 (3H, m), 2.0–2.2 (2H, m), 2.35 (2H, d, J = 6.5 Hz), 2.46 (1H, m), 3.77 (1H, m), 4.04 (1H, d, J = 11 Hz), 4.57 (1H, m), 4.80 (1H, m), 5.3–5.5 (2H, m), 7.21 (1H, m), 7.26 (1H, s). ESI-MS m/z: 369 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-Aza-2-((2-pyridyl)carbonylamino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoic acid (22). By the procedure used for **40** and **8a**, **20** (270 mg, 1.00 mmol), hydrazino(2-pyridyl)methan-1-one (165 mg, 1.20 mmol) and 1 N sodium hydroxide (2.00 mL, 2.00 mmol) gave 175 mg (46.6% from **20**) of **22** as an oil: ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.26 (3H, d, J = 5 Hz), 1.45–1.65 (3H, m), 2.0–2.2 (4H, m), 2.3–2.5 (2H, m) 3.86 (2H, m), 4.6 (1H, m), 4.82 (1H, q, J = 5 Hz), 5.42 (1H, m), 7.54 (1H, dd, J = 5, 2 Hz), 7.78 (1H, d, J = 5 Hz), 8.32 (1H, dd, J = 5, 2 Hz), 8.74 (1H, d, J = 5 Hz), 9.08 (1H, s). ESI-MS m/z: 374 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-Aza-2-(2-pyridylamino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoic acid (23). By the procedure used for **40** and **8a**, **20** (40 mg, 0.148 mmol), 2-hydrazinopyridine (20 mg, 0.183 mmol) and 1 N sodium hydroxide (1.00 mL, 1.00 mmol) gave 51.4 mg (100% from **20**) of **23** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (3H, d, J = 5 Hz), 1.53 (1H, m), 1.6–1.9 (2H, m), 2.0–2.2 (2H, m), 2.35–2.55 (4H, m), 3.90 (1H, dd, J = 11.3, 2.5 Hz), 4.08 (1H, d, J = 11.3 Hz), 4.55 (1H, dd, J = 5, 3 Hz), 4.83 (1H, q, J = 5 Hz), 5.4–5.6 (2H, m), 6.76 (1H, br t, J = 6 Hz), 7.25 (1H, d, J = 9 Hz), 7.40 (1H, d, J = 5.5 Hz), 7.62 (1H, m), 7.93 (1H, br d, J = 5.5 Hz). ESI-MS m/z: 346 $(M-H)^-$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[(*E*)-2-aza-2-(diphenylmethoxy)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (42). A mixture of **20** (326 mg, 1.21 mmol), hydroxylamine hydrochloride (374 mg, 5.38 mmol) and sodium hydrogen carbonate (374 mg, 4.45 mmol) in a mixture of methanol (6 mL) and water (3 mL) was stirred at room temperature for 3 h. To the solution was added chloroform and brine and the organic layer separated, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on a silica gel column (15 g) with a mixture of *n*-hexane and ethyl acetate (5:1) as eluent. Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[(*Z*)-2-aza-2hydroxyvinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (100 mg, 29.1%) was obtained from the first fractions as an oil: ^{1}H NMR

(200 MHz, $CDCl_3$) δ 1.35 (3H, d, $J=5$ Hz), 1.6–1.8 (3H, m), 1.9–2.2 (4H, m), 2.34 (2H, d, $J=7.5$ Hz), 2.57 (1H, m), 3.69 (3H, s), 3.81 (1H, d, $J=11.5$ Hz), 3.98 (1H, d, $J=11.5$ Hz), 4.79 (1H, q, $J=5$ Hz), 4.98 (1H, dd, $J=3.5$, 4.5 Hz), 5.4–5.6 (2H, m), 6.78 (1H, d, $J=3.5$ Hz), 8.00 (1H, s). ESI-MS m/z: 286 $(M+H)^+$. Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[(*E*)-2-aza-2-hydroxyvinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (142 mg, 41.3%) was obtained from the second fractions as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (3H, d, $J=5$ Hz), 1.58 (1H, m), 1.6–1.8 (2H, m), 2.0–2.2 (2H, m), 2.27 (1H, m), 2.55 (1H, m), 2.85 (2H, t, $J=7.5$ Hz), 3.69 (3H, s), 3.80 (1H, d, $J=11.5$ Hz), 4.03 (1H, d, $J=11.5$ Hz), 4.55 (1H, dd, $J=2$, 4.5Hz), 4.80 (1H, q, $J=5$ Hz), 5.3–5.6 (2H, m), 7.43 (1H, d, $J=4.5$ Hz), 7.83 (1H, s). ESI-MS m/z: 286 $(M+H)^+$.

To a solution of methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[(*E*)-2-aza-2-hydroxyvinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (100 mg, 0.350 mmol) in *N,N*-dimethylformamide (5 mL) was added sodium hydride (14 mg, 60% in oil, 0.350 mmol) at 5°C. After being stirred at the same temperature for 30 min, bromodiphenylmethane (86.6 mg, 0.350 mmol) was added and the mixture stirred in an ice bath for an additional 2 h. The solution was diluted with ethyl acetate and washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the crude residue was purified by preparative TLC with a mixture of *n*-hexane and ethyl acetate (4:1) as eluent to give 130 mg (82.1%) of **42** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (3 H, d, $J=5$ Hz), 1.49 (1H, m), 1.6–1.8 (3H, m), 2.0–2.2 (3H, m), 2.32 (2H, t, $J=7.5$ Hz), 2.55 (1H, m), 3.68 (3H, s), 3.70 (1H, d, $J=11.5$ Hz), 3.96 (1H, d, $J=11.5$ Hz), 4.49 (1H, dd, $J=2$, 5.5 Hz), 4.74 (1H, q, $J=5$ Hz), 5.2–5.5 (2H, m), 6.23 (1H, s), 7.2–7.4 (11H, m), 7.59 (1H, d, $J=5.5$ Hz). ESI-MS m/z: 452 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-2-[(*E*)-2-Aza-2-(diphenylmethoxy)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoic acid (25). By the procedure used for **8a**, **42** (95 mg, 0.210 mmol) and 1 N sodium hydroxide (1.00 mL, 1.00 mmol) gave 62.0 mg (67.5%) of **25** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (3H, d, $J=5$ Hz), 1.50 (1H, m), 1.6–1.8 (3H, m), 2.0–2.2 (3H, m), 2.85 (2H, t, $J=7.5$ Hz), 2.59 (1H, m), 3.77 (1H, m), 3.96 (1H, d, $J=11.5$ Hz), 4.50 (1H, dd, $J=2.5$, 5.5 Hz), 4.74 (1H, m), 5.00 (1H, dd, $J=2.5$, 4.5 Hz), 5.2–5.6 (2H, m), 6.22 (1H, s), 6.78 (1H, d, $J=4.5$ Hz), 7.2–7.4 (11H, m), 7.56 (1H, d, $J=5.5$ Hz). ESI-MS m/z: 436 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[(((*N*-phenycarbamoyl)amino)amino)methyl]-3,5-dioxanyl}hept-5-enoic acid (26). To a solution of **7a** (48 mg, 0.123 mmol) in ethanol (2 mL) was added sodium cyanoborohydride (15 mg, 0.239 mmol) and acetic acid (1 drop), and the mixture stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the residue was extracted with chloroform at pH 3. The organic layer were combined and dried over magnesium sulfate. Solvent was evaporated in vacuo and the crude product purified by preparative TLC with ethyl acetate to give 22 mg (45.6%) of **26** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (3H, d, $J=5$ Hz), 1.6–1.9 (2H, m), 2.0–2.2 (4H, m), 2.36 (2H, t, $J=7$ Hz), 2.4–2.6 (1H, m), 2.85 (1H, dd, $J=2.6$, 12.8 Hz), 3.05 (1H, dd, $J=9.7$, 12.8 Hz), 3.72 (1H, m), 4.01 (1H, m), 4.70 (1H, q, $J=5$ Hz), 5.4–5.6 (2H, m), 7.04 (1H, t, $J=7.3$ Hz), 7.30 (2H, m), 7.45 (2H, d, $J=7.5$ Hz), 8.28 (1H, s). ESI-MS m/z: 390 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[2-((1-phthalazinylamino)amino)methyl]-3,5-dioxanyl}hept-5-enoic acid (27). To a solution of **41** (450 mg, 1.09 mmol) in a mixture of methanol (4 mL) and acetic acid (2 mL) was added sodium cyanoborohydride (125 mg, 1.99 mmol), and the mixture stirred at room temperature for 2 h. The solution was adjusted to pH 7 with saturated aqueous sodium hydrogen carbonate and the resulting mixture diluted with chloroform. The solution was washed successively with water and brine, dried over magnesium sulfate, and solvent evaporated in vacuo to give methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-4-methyl-2-[2-((1-phthalazinylamino)amino)methyl]-3,5-dioxanyl}hept-5-enoate that was dissolved in a mixture of methanol (5 mL) and 1 N aqueous sodium hydroxide (2.00 mL, 2.00 mmol). After stirring at room temperature overnight, the mixture was neutralized with 1 N hydrochloric acid and the resulting solution evaporated to dryness in vacuo. The residue was purified by preparative thin layer chromatography with a mixture of chloroform and methanol (10:1) as eluent to give 96.3 mg (22.0% from **41**) of **27** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (1H, d, $J=5$ Hz), 1.5–1.9 (3H, m), 1.9–2.2 (3H, m), 2.3–2.6 (3H, m), 3.88 (1H, d. $J=12.5$ Hz), 4.15 (1H, d, $J=12.5$ Hz), 4.70 (1H, m), 4.87 (1H, q, $J=5$ Hz), 5.4–5.7 (2H, m), 7.57 (1H, m), 7.6–7.8 (2H, m), 7.9–8.1 (2H, m), 8.41 (1H, m), 9.60 (1H, s). ESI-MS m/z: 399 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[((2-thienylearbonyl)amino)methyl]-3,5-dioxanyl}hept-5-enoic acid (28). By the procedure used for **40** and **27**, **20** (47.0 mg, 0.174 mmol), hydrazino(2-thienyl)methan-1-one (27.0 mg, 0.171 mmol) and sodium cyanoborohydride (20.0 mg, 0.318 mmol), 1 N sodium hydroxide (0.40 mL, 0.40 mmol) gave 55.0 mg (85.9% from **20**) of **28** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (3H, d, $J=5$ Hz), 1.5–1.9 (2H, m), 2.0–2.5 (4H, m), 2.36 (2H, t, $J=7$ Hz), 3.03 (1H, dd, $J=3.8$, 12.5 Hz), 3.18 (1H, dd, $J=8.1$, 12.5 Hz), 3.74 (2H, m), 4.04 (3H, m), 4.75 (1H, q, $J=5$ Hz), 5.3–5.6 (2H, m), 7.10 (1H, m), 7.55 (2H, m). ESI-MS m/z: 367 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[(2-pyridylmethylamino)-methyl]-3,5-dioxanyl}hept-5-enoic acid (29). By the procedure used for **40** and **27**, **20** (200 mg, 0.740 mmol), 2-(aminomethyl)pyridine (0.150 mL, 1.46 mmol) and sodium cyanoborohydride (100 mg, 1.59 mmol), and 1 N sodium hydroxide (3.00 mL, 3.00 mmol) gave 135 mg (57.6% from **20**) of **29** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (1H, m), 1.30 (1H, d, $J=5$ Hz), 1.45 (1H, m), 1.5–1.8 (2H, m), 2.05 (1H, m), 2.2–2.4 (4H, m), 2.8–3.0 (2H, m), 3.72 (1H, dd, $J=1.5$, 11.5 Hz), 3.9–4.2 (4H, m), 4.73 (1H, q, $J=5$ Hz), 5.3–5.6 (2H, m), 5.94 (1H, broad), 7.2–7.4 (2H, m), 7.72 (1H, dt, $J=1.5$, 10 Hz), 8.65 (1H, d, $J=5$ Hz). ESI-MS m/z: 347 $(M-H)^-$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[(1,3-dioxoisoindolin-2-yl)-methyl]-4-methyl-3,5-dioxanyl}hept-5-enoate (30). To a solution of **19** (456 mg, 1.64 mmol) in pyridine (2 mL) was added *p*-toluenesulfonyl chloride (640 mg, 3.36 mmol) and the mixture was stirred at room temperature for 2 h. The

reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate. The organic layers were combined and washed with aqueous sodium bicarbonate (5 mL) and brine (5 mL), and dried over sodium sulfate. The solvent was evaporated in vacuo and the crude product was dissolved in dimethylsulfoxide (2 mL). To the solution was added potassium phthalimide (550 mg 2.97 mmol) and the mixture was stirred at 100°C for 6 h. The reaction mixture was cooled, added to water, and extracted with ether. The organic layers were combined and dried over anhydrous sodium sulfate. Solvent was evaporated in vacuo and the crude product was purified by preparative TLC to give 400 mg (59.5%) of **30** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (3H, d, J = 5 Hz), 1.3–1.9 (4H, m), 2.0–2.5 (5H, m), 2.63 (1H, m), 3.69 (3H, s), 3.6–3.8 (2H, m), 4.00 (2H, m), 4.18 (1H, m), 4.63 (1H, q, J = 5 Hz), 5.3–5.6 (2H, m), 7.7–7.9 (4H, m). ESI-MS m/z: 402 $(M+H)^+$.

Methyl (*Z*)-7-((1*S*,2*R*,4*R*)-2-aminomethy-4-methyl-3,5-dioxanyl)hept-5-enoate (31). To a solution of **30** (54 mg, 0.135 mmol) in ethanol (2 mL) was added hydrazine monohydrate (0.007 mL, 0.144 mmol) and the mixture stirred at room temperature overnight. Solvent was evaporated in vacuo and the crude product purified by preparative TLC (chloroform:methanol:concd aqueous ammonia = 85:15:0.1) to give 13 mg (35.6%) of **31** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 5 Hz), 1.69 (2H, m), 1.9–2.2 (3H, m), 2.32 (2H, t, J = 7.6 Hz), 2.3–2.6 (2H, m), 2.71 (1H, m), 2.94 (1H, dd, J = 9, 13 Hz), 3.68 (3H, s), 3.65–3.85 (2H, m), 3.98 (1H, d, J = 11.2 Hz), 4.73 (1H, q, J = 5 Hz), 5.3–5.6 (2H, m). ESI-MS m/z: 272 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[((*N*-phenylcarbamoyl)amino)methyl]-3,5-dioxanyl}hept-5-enoic acid (32). To a solution of (*Z*)-7-((1*S*,2*R*,4*R*)-2-aminomethy-4-methyl-3,5-dioxanyl)hept-5-enoic acid (50 mg, 0.194 mmol), which was prepared from **31** as described for the preparation of **8a**, in pyridine (0.5 mL) was added phenyl isocyanate (0.10 mL, 0.920 mmol) and stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate and the organic layer washed with 1 N hydrochloric acid. The organic layer was evaporated in vacuo and the crude product purified by preparative TLC to give 27 mg (36.9% from **31**) of **32** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (3H, d, J = 5 Hz), 1.45 (1H, m), 1.5–1.8 (2H, m), 2.0–2.4 (4H, m), 2.37 (2H, t, J = 6.5 Hz), 3.2–3.5 (2H, m), 3.68 (1H, dd, J = 11.3, 2 Hz), 3.94 (1H, m), 4.03 (1H, d, J = 11.3 Hz), 4.71 (1H, q, J = 5 Hz), 5.4–5.6 (2H, m), 5.74 (1H, br t, J = 6 Hz), 7.02 (1H, m), 7.1–7.4 (4H, m), 7.55 (1H, br s). ESI-MS m/z: 375 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[((benzylamino)carbonylamino)methyl]-3,5-dioxanyl)hept-5-enoic acid (33). To a solution of **31** (13 mg and 0.0479 mmol) in pyridine (0.3 mL) was added benzyl isocyanate (0.020 mL, 0.162 mmol) and the mixture stirred at room temperature for 60 min. Water (0.1 mL) was added to the reaction mixture, and the solvent was evaporated in vacuo to give methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-4-methyl-2[((benzylamino)-carbonylarnino)methyl]-3,5-dioxanyl}hept-5-enoate as a crude residue. By the procedure used for **8a**, this residue and 1 N sodium hydroxide (0.300 mL, 0.300 mmol) gave 20 mg (100% from **31**) of **33** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (3H, d, J = 5 Hz), 1.68 (2H, m), 1.9–2.3 (3H, m), 2.32 (2H, t, J = 6.5 Hz), 3.18 (1H, m), 3.38 (1H, m), 3.6–4.1 (3H, m), 4.2–4.4 (2H, m), 4.63 (1H, q, J = 5 Hz), 5.3–5.7 (3H, m), 7.1–7.4 (5H, m). ESI-MS m/z: 389 $(M-H)^-$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[(2-oxo-3-phenylpropanoylamino)methyl]-3,5-dioxanyl}hept-5-enoic acid (34). To a solution of **31** (35 mg, 0.129 mmol) in ethyl acetate (2.4 mL) was added *N,N′*-dicyclohexylcarbodiimide (36 mg, 0.163 mmol) and 2-oxo-3-phenylpropanoic acid (27 mg, 0.164 mmol), and the mixture stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was evaporated in vacuo to give crude methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-4-methyl-2-[((phenylcarbonyl)carbonylamino)methyl]-3,5-dioxanyl}hept-5-enoate. By the procedure used for **8a**, this residue and 1 N sodium hydroxide (0.500 mL, 0.500 mmol) gave 12 mg (23.1% from **31**) of **34** as an oil: ^{1}H NMR (200 MHz, $CDC1_3$) δ 1.30 (3H, d, J = 5 Hz), 1.5–1.8 (2H, m), 2.0–2.2 (2H, m), 2.36 (2H, t, J = 7 Hz), 2.47 (1H, m), 3.21 (1H, m), 3.5–4.0 (4H, m), 4.22 (2H, s), 4.67 (1H, q, J = 5 Hz), 5.3–5.6 (2H, m), 7.1–7.4 (5H, m). ESI-MS m/z: 402 $(M-H)^-$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-4-methyl-2-[(*N*-phenylcarbamoyloxy)methyl]-3,5-dioxanyl}hept-5-enoate (35). To a solution of **19** (108 mg, 0.397 mmol) in pyridine (0.5 mL) was added phenyl isocyanate (0.100 mL, 0.920 mmol) and the mixture was stirred at room temperature for 30 min. Water (1 mL) was added, and the solution extracted with ether. The organic layers were combined and dried over anhydrous sodium sulfate. Solvent was evaporated in vacuo and the crude product was purified by preparative TLC (*n*-hexane:ether = 1:1) give 140 mg (90.2%) of **35** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (3H, d, J = 5 Hz), 1.4–1.8 (3H, m), 2.0–2.3 (3H, m), 2.33 (2 H, t, J = 7 Hz), 2.4–2.6 (1H, m), 3.67 (3H, s), 3.72 (1H, m), 3.95–4.25 (4H, m), 4.75 (1H, q, J = 5 Hz), 5.3–5.6 (2H, m), 6.94 (1H, br s), 7.07 (1H, m), 7.3–7.5 (4H, m). ESI-MS m/z: 392 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[(*N*-phenylcarbamoyloxy)methyl]-3,5-dioxanyl)hept-5-enoic acid (36). By the procedure used for **8a**, **35** (140 mg, 0.358 mmol) and 1 N sodium hydroxide (1.00 mL, 1.00 mmol) gave 115 mg (85.2%) of **36** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (3H, d, J = 5 Hz), 1.4–1.8 (3H, m), 2.0–2.3 (3H, m), 2.38 (2H, t, J = 7 Hz), 2.4–2.6 (1H, m), 3.73 (1H, m), 4.0–4.4 (4H, m), 4.75 (1H, q, J = 5 Hz), 5.3–5.6 (2H, m), 6.88 (1H, br s), 7.0–7.15 (1H, m), 7.3–7.5 (4H, m). ESI-MS m/z: 376 $(M-H)^-$.

Methyl (*Z*)-7-{(1*S*,2*R*,4*R*)-4-methyl-2-[(2-pyridylmethoxy)methyl]-3,5- dioxanyl}hept-5-enoate (37). To a solution of **19** (183 mg, 0.671 mmol) in *N,N*-dimethylformamide (10 mL) was added sodium hydride (53.6 mg, 60% in oil, 1.34 mmol) and 2-(chloromethyl)pyridine hydrochloride (110 mg, 0.671 mmol) and the mixture stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride and the resulting solution extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. Solvent was evaporated in vacuo and

the residue was purified by preparative thin layer chromatography with ethyl acetate as eluent to give 201 mg (82.5%) of **37** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (3H, d, J = 5.5 Hz), 1.47 (1H, m), 1.6–1.8 (3H, m), 1.9–2.2 (3H, m), 2.2–2.4 (2H, m), 2.50 (1H, m), 3.57 (1H, dd, J = 5, 10 Hz), 3.67 (3H, s), 3.74 (1H, m), 4.00 (1H, d, J = 12 Hz), 4.13 (1H, m), 4.70 (2H, ABq, J = 13 Hz), 4.78 (1H, q, J = 5.5 Hz), 5.3–5.6 (2H, m), 7.19 (1H, dd, J = 5, 7 Hz), 7.45 (1H, d, J = 8 Hz), 7.71 (1H, dt, J = 1.5, 8 Hz), 8.55 (1H, d, J = 5 Hz). ESI-MS m/z: 364 $(M+H)^+$.

(*Z*)-7-{(1*S*,2*R*,4*R*)-4-Methyl-2-[(2-pyridylmethoxy)methyl]-3,5-dioxanyl}hept-5-enoic acid (38). By the procedure used for **7a**, **37** (190 mg, 0.520 mmol) and 1 N sodium hydroxide (2.00 mL, 2.00 mmol) gave 145 mg (78.1%) of **38** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 5 Hz), 1.49 (1H, m), 1.6–1.9 (3H, m), 2.0–2.3 (4H, m), 2.38 (2H, t, J = 7 Hz), 3.6–3.8 (2H, m), 4.0–4.1 (2H, m), 4.70 (2H, ABq, J = 13 Hz), 4.77 (1H, q, J = 5 Hz), 5.4–5.6 (2H, m), 7.33 (1H, dd, J = 5, 7 Hz), 7.48 (1H, d, J = 8 Hz), 7.80 (1H, dt, J = 1.5, 8 Hz), 8.69 (1H, d, J = 5 Hz). ESI-MS m/z: 348 $(M-H)^-$.

Biological methods

Inhibitory effects on 9,11-azo PGH_2-induced platelet aggregation in rabbit. Blood was collected from the carotid artery of male rabbits into plastic vessels containing 0.1 volume of 3.8% aqueous sodium citrate. Platelet-rich plasma (PRP) was then prepared by centrifugation at 150×g for 15 min. Platelet-poor plasma (PPP) was prepared from the remaining blood after removing PRP, by centrifugation at 1500×g for 10 min. PRP was then adjusted to a concentration of 6.0×10^5 cells/μL by using PPP. Platelet aggregation was investigated using the turbidometric method with an aggregometer (NKK HEMATRACER 1 Model 4A). To 225 μL of PRP, 25 μL of the test compound solution or vehicle solution was added, and the whole stirred at 1000 rpm for 2 min at 37°C. Next, 5 μL of 9,11-azo PGH_2 (final concentration 1.0 μM) or ADP (final concentration 2.5 μM, Sigma) was added as an aggregating inducer. The concentration which caused 50% inhibition (IC_{50}) of 9,11-azo PGH_2-induced maximum aggregation was obtained by regression analysis of the concentration versus inhibition of aggregation curve.

Inhibitory effects of 7b and 8b on ^{3}H-U46619 binding to washed guinea-pig platelets. This was carried out according to the modified method of Kattelman et al.[37] PRP was prepared as described above from male Hartley strain guinea-pigs and treated with aspirin (final concentration 1 mM), then centrifuged at 150×g for 15 min to remove residual contaminating red blood cells. PGI_2 (final concentration 40 nM, Funakoshi) was added to aid in resuspension of the platelets. The PRP was then spun at 1100×g for 15 min to pellet the cells. The platelet free plasma was discarded, and the platelet pellets were gently resuspended in buffer (sodium chloride (138 mM), potassium chloride (5 mM), magnesium chloride (5 mM), glucose (5.5 mM) and Tris–HCl (25 mM), pH 7.4) to a final cell count of approximately 1.0×10^9 cells. Aliquots of platelet suspension (1.0 mL) were incubated with approximately 5 nM (final concentration) [^{3}H]-U46619 ([15−^{3}H(N)]-9,11-epoxymethano PGH_2, 22.4 Ci/mmole, NEN) plus various concentrations of the compound **7b** or **8b** for 5 min at 37°C with stirring, In order to block U-46619-induced platelet activation, the cells were treated with PGI_2 (final concentration 250 nM) for 45 s prior to mixing them with drugs. After mixing, a 0.4 mL aliquot of the binding assay mixture was transferred to a 1.5 mL Eppendorf tube, and the incubation was terminated at the appropriate time by centrifugation at 15 000 rpm for 1 min in a Eppendorf 5414 centrifuge. The supernatant was quickly removed by aspiration, and the inside of the Eppendorf tubes, as well as the surface of the pellet was rinsed twice with 0.4 mL of ice cold resuspension buffer, which was immediately removed by aspiration. The tip of the tube was cut off, and placed in a polyethylene vial (Wheaton) including 0.4 mL of tissue solubilizer (NCS, Amersham). The mixture was incubated for 3–4 h at 50°C, then 5 mL of toluene scintilator (OMNIFLUOR 4 g/L toluene) was added to the mixture. The radioactivity was measured in a liquid scintillation counter.

Inhibitory effect of 8b on U-46619- or collagen-induced platelet aggregation in human, monkey, dog, guinea-pig or rat. These tests were performed by a similar procedure to the test for platelet aggregation in rabbits. In this case, the final concentration of U-46619 (Cyman Chemical) was 1 μM (Human), 2 μM (Monkey) or 0.5 μM (Guinea-pig), and that of collagen (Horm) was 0.5 μg/mL (human, guinea-pig or rat) or 20 μg/mL (dog). The concentration of PRP was adjusted to 3.0×10^5 cells/mL in the case of human, monkey and dog.

Inhibitory effect of 8b on ex vivo platelet aggregation in guinea-pig. Male Hartley strain guinea-pigs weighing about 300 g were used after overnight fasting. Blood was collected from the abdominal artery at 1 h after oral administration of **8b** or vehicle. PRP was prepared as described before, and platelet aggregation was induced by adding 5 μL of U-46619 (final concentration, 0.5 μM) or collagen (fmal concentration, 0.5 μg/mL) to 250 μL of PRP.

Protective effects of 8b against arachidonic acid-induced pulmonary infraction in mice. Male ddY mice weighing about 30 g were used after overnight fasting. Compound **8b** was orally administered in saline at doses from 3.2 to 32 mg/kg. Control animals were given only saline. At 1 h after administration of **8b** or saline, arachidonic acid (90 mg/kg, Sigma) was injected intravenously for 20 s. The effect of **8b** was evaluated by measuring the incidence of death within 5 min of injection. Results are expressed as percent survival. Each group comprised of 10 mice.

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