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Synthesis and thromboxane A_2 antagonistic activity of indane derivatives

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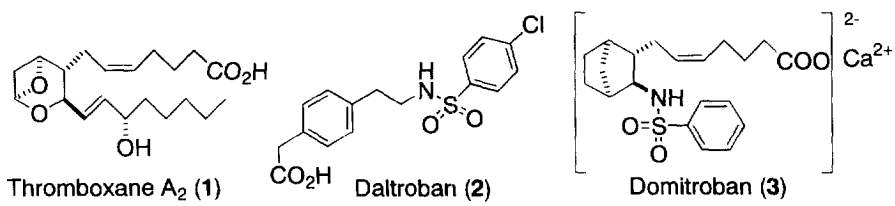
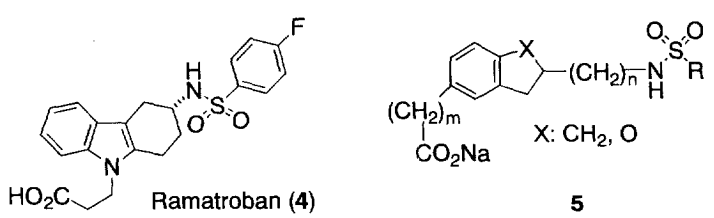
Abstract: A new series of indane derivatives were prepared and evaluated for their thromboxane A_2 (TXA_2, **1**) antagonistic activity. Among these compounds, **24a (Z-335)** was found to be a potent TXA_2 antagonist in oral administration.

Keywords: Antagonists, Receptors

Introduction It has been elucidated that TXA_2 (**1**)[1], one of the unstable metabolites of arachidonic acid via the cyclooxygenase is a potent inducer of platelet aggregation, vasoconstriction and bronchoconstriction. The potent biological activities of TXA_2 may play an important role in many diseases such as asthma[2], thrombosis[3], myocardial infarction[4] and chronic obstructive arterial disease[5]. During the development of TXA_2 antagonists[6], several TXA_2 antagonists such as daltroban (**2**)[7], domitroban (**3**)[8] and ramatroban (**4**)[9], which have a carboxylic acid, sulfonamide group and a spacer of these functional groups as a common structure have been reported. The structure of daltroban (**2**) which has a phenylethyl group as a spacer is the simplest of these compounds.



Thromboxane A_2 (**1**) Daltroban (**2**) Domitroban (**3**)



Ramatroban (**4**) **5**

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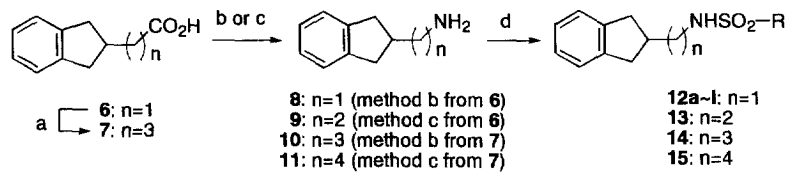
Domitroban (**3**) and ramatroban (**4**) have a rigid cyclic group and alkylene group as a spacer, respectively. On the whole, examination of the alkylene group as a spacer is scarcely reported[10]. In this context, we were led to propose the introduction of indane and dihydrobenzofuran ring as a part of the structural rigid spacer in place of the phenylethyl group of daltroban, and then the length of the spacer was optimized by the conversion of the alkylene length with the hope of increasing the TXA_2 antagonistic activity. Indansulfonamide derivatives such as compound **39** were hitherto known as platelet antiaggregatory compounds[11], however TXA_2 antagonistic activities of these compounds were not investigated by that time. In this paper, we describe the syntheses and the structure-activity relationships of indane and dihydrobenzofuran derivatives (**5**).

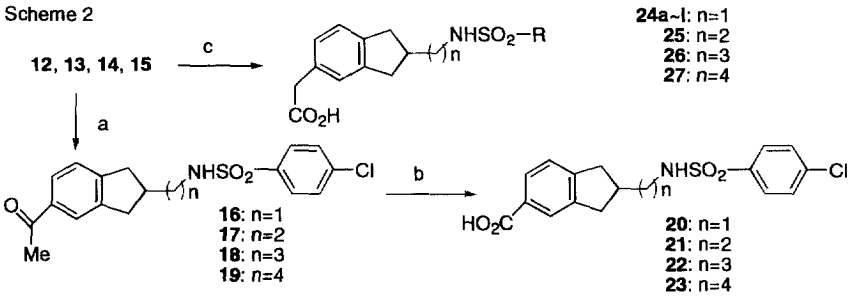
Chemistry The syntheses of 2-(4-chlorophenylsulfonylaminoalkyl)indane derivatives as convergent intermediates have been carried out as shown in Scheme 1. The reaction of indan-2-ylacetic acid (**6**) with diphenylphosphoryl azide (DPPA) in the presence of triethylamine, followed by the addition of benzyl alcohol afforded 2-(benzyloxycarbonylaminomethy)indane in a 64% yield. Reductive deprotection of the benzyloxycarbonyl group, followed by sulfonylation by aryl or alkylsulfonyl chloride gave sulfonamide **12a~i** in a good yield. On the other hand, lithium aluminum hydride reduction of the corresponding carboxylamide, prepared from carboxylic acid **6**, provided 2-(2-aminoethyl)indane (**9**), which was easily converted to sulfonamide **13**. Wittig reaction of indan-2-ylacetaldehyde which had been synthesized from **6** afforded benzyl 4-(indan-2-yl)-2-butenoate, which was hydrogenated to give **7**. Compound **7** was converted to **14** and **15** in the same manner as described in the syntheses of **12** and **13**, respectively. A series of 2-substituted indan-5-ylacetic acid and indan-5-ylcarboxylic acid derivatives (**20~27**) were synthesized as shown in scheme 2. Friedel Crafts reaction of **12**, **13**, **14** and **15** with ethyl α-chloro-α-methylthioacetate[12], followed by a reductive elimination of the methylthio group with zinc dust in acetic acid, alkaline hydrolysis gave indan-5-ylacetic acid derivatives (**24a~i**, **25**, **26**, **27**). A series of 5-acetylindane derivatives (**16**, **17**, **18**, **19**), easily prepared from **12**, **13**, **14**, **15** by acetylation under Friedel Crafts condition were treated with NaOBr to give indancarboxylic acid derivatives (**20**, **21**, **22**, **23**). A series of 2-substituted indan-5-ylalkanoic acid derivatives (**31**, **32**, **33**) were synthesized as shown in scheme 3. Friedel Crafts reaction of **12** with $ClCO(CH_2)_nCO_2Et$ (n = 1, 3) or succinic anhydride gave the corresponding 5-acylindane derivatives (**28**, **29**, **30**) in a good yield. Reduction of carbonyl group of **28**, **29** and **30** were achieved by Wolff-Kishner reduction or Clemmensen reduction, followed by alkaline hydrolysis to afford the corresponding alkanoic acid derivatives (**31**, **32**, **33**). Dihydrobenzofuran derivative **38** was synthesized as shown in scheme 4. Epoxidation of 4-allylphenol (**34**), followed by the treatment with MeOH-K_2CO_3 gave 2-hydroxymethyl-1*H*-2,3-dihydrobenzofuran (**35**). Alcohol **35** was transformed to amine **36** in 3 steps. Amine **36**

Scheme 1



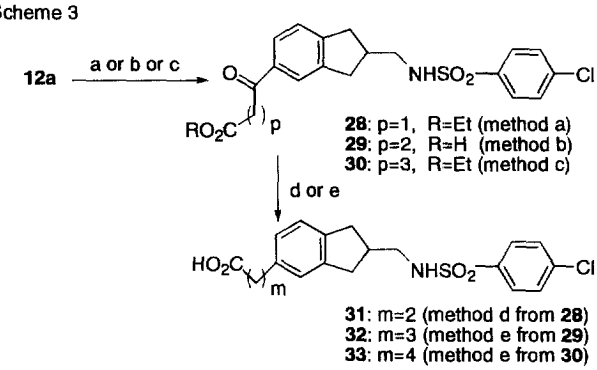
a) i) $LiAlH_4$, ii) PCC, iii) $[Ph_3PCH_2COOBn]^+Br^-$, iv) H_2,Pd; b) i) DPPA, BnOH, ii) H_2, Pd; c) i) $SOCl_2$, ii) NH_4OH, iii) $LiAlH_4$; d) RSO_2Cl, K_2CO_3

Scheme 2



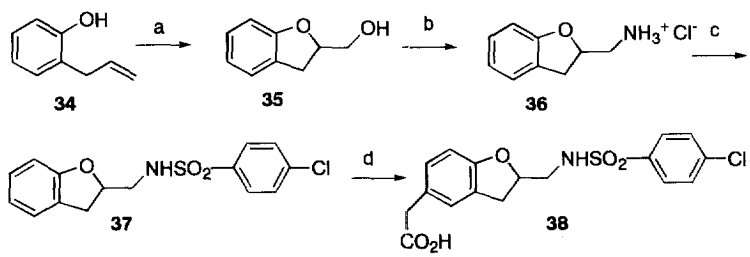
a) CH_3COCl, $AlCl_3$; b) NaOH, Br_2 ; c) i) Cl(MeS)$CHCO_2Et$, $SnCl_4$, ii) Zn, AcOH, iii) NaOH, H_2O

Scheme 3



a) i) $ClCOCH_2CO_2Et$, $AlCl_3$; b) Succinic Anhydride, $AlCl_3$; c) $ClCO(CH_2)_3CO_2Et$, $AlCl_3$; d) NaOH, NH_2NH_2; e) i) Zn, $HgCl_2$, HCl, ii) NaOH, H_2O

Scheme 4

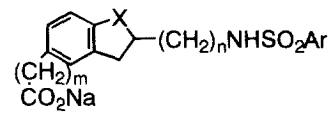


a) i) m-CPBA, ii) K_2CO_3, MeOH; b) i) TsCl, NEt_3, ii) $NaN(CHO)_2$, iii) HCl, EtOH; c) 4-chlorophenylsulfonyl chloride, K_2CO_3; d) i) Cl(MeS)$CHCO_2Et$, $SnCl_4$, ii) Zn, AcOH, iii) NaOH, H_2O

was converted to **38** in the same manner as described in the syntheses of **24**. Enantiomers of **32** were obtained by the HPLC separation using Chiralcel-OD (Daicel). All of the synthesized compounds were converted to sodium salts, and subjected to pharmacological evaluation.

Results and discussion The synthesized compounds were initially evaluated for their inhibitory activities on the aggregation of rabbit platelets induced by U-46619 (4 μM) and their inhibitory activity on U-46619 (0.1 μM)-induced contraction of rat aorta according to the standard methods[13]. As shown in Table 1, in a series of indan-5-ylcarboxylic acid (**20~23**) and indan-5-ylacetic acid derivatives (**24a**, **25~27**), compounds **20** (m = 0, n = 1), **34** (m = 1, n = 0), **24a** (m = 1, n = 1) and **25** (m = 1, n = 2) were found to be potent TXA_2 antagonists. The potency remarkably decreased with the increase of the alkylene length substituted at the 2-position. From these results, it became clear that n = 0 ~ 1 would be a suitable length. Furthermore, in the series of 2-(4-chlorophenylsulfonylaminomethyl)indan-5-ylalkanoic acids (**24a**, **31~33**), compounds **24a** and **31** were found to be potent TXA_2 antagonists *in vitro*. Subsequently, the replacement of the 4-chlorophenyl group of **24a** by phenyl, 3-pyridyl, benzyl, 1-naphtyl, 2-naphtyl, 2-thienyl, cyclohexyl or *n*-pentyl was examined. Although the phenyl and 2-naphtyl derivatives (**24b**, **24f**) exhibited potent TXA_2 antagonistic activities, the potency of other compounds were relatively weak. TXA_2 antagonistic activity for dihydrobenzofuran derivative **38**, which replaced the indane part of **24a** by dihydrobenzofuran was almost equal in potency to **24a** with regard to aggregation of platelets, however it was weak in contracting rat aorta. In *in vitro* tests, compounds **20**, **24a**, **24b**, **24f**, **25**, **31** and **32** were found to have potent TXA_2 antagonistic activities, especially in contracting rat aorta. Secondary evaluations of these compounds except for **24b** were performed to investigate the inhibitory activities on the aggregation of guinea pig platelets induced by arachidonic acid (100 μM) and U-46619 (1 μM) *ex vivo*. Compound **24a**, **24f** and **32** exhibited complete inhibition for the aggregation of platelets at 0.3 mg/kg oral administration. However, the compound **31** was the most potent TXA_2 antagonist *in vitro* but was nevertheless a weaker inhibitor of aggregation of platelets *ex vivo*. These three compounds (**24a**, **24f**, **32**) were further evaluated for inhibitory activity on U-46619 (1 μM)-induced aggregation of guinea pig platelets and human platelets *in vitro* and the ED_{50} value for inhibitory activity on U-46619 (4 μM)-induced aggregation of guinea pig platelets *ex vivo*. Although the anti-aggregation activities of **24a**, **24f** and **32** were only slightly more potent than daltroban against guinea pig platelets *in vitro*, these compounds were 4~8 times more potent and long-acting [14] than daltroban *ex vivo*. In addition, the activity of enantiomers of **32** in inhibiting aggregation of guinea pig platelets was studied. The (+)-enantiomer of **32** (IC_{50} = 0.19 μM) was 2 times more potent than the (-)-enantiomer, indicating that the activity did not largely differ between enantiomers.

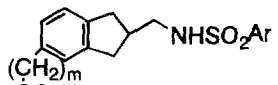
Table 1. Thromboxane A_2 Antagonistic Activities of Indane Derivatives and a Related Compound



					in vitro		*ex vivo*	
					Platelets[a]	Aorta[b]	Inhibition (%)	
No	m	n	X	Ar	IC_{50}(μM)	IC_{50}(nM)	AA[c]	U-46619[d]
20	0	1	CH_2	4-ClPh	1.32	26.3	29	58
21	0	2	CH_2	4-ClPh	7.76	66.1		
22	0	3	CH_2	4-ClPh	6.60	85.1		
23	0	4	CH_2	4-ClPh	>100	479		
39	1	0	CH_2	4-ClPh	0.36	2.19		
24a	1	1	CH_2	4-ClPh	0.36	3.02	100	100
24b	1	1	CH_2	Ph	1.02	12.9		
24c	1	1	CH_2	3-pyridyl	>100	1900		
24d	1	1	CH_2	benzyl	>100	5900		
24e	1	1	CH_2	1-naphtyl	47.9	295		
24f	1	1	CH_2	2-naphtyl	0.95	22.4	100	100
24g	1	1	CH_2	2-thienyl	2.81	85.1		
24h	1	1	CH_2	cyclohexyl	17.8	1200		
24i	1	1	CH_2	*n*-pentyl	77.6	1400		
38	1	1	O	4-ClPh	0.32	141		
25	1	2	CH_2	4-ClPh	1.48	31.6	83	96
26	1	3	CH_2	4-ClPh	72.4	513		
27	1	4	CH_2	4-ClPh	>100	977		
31	2	1	CH_2	4-ClPh	0.16	14.8	57	98
32	3	1	CH_2	4-ClPh	1.34	38.9	100	100
33	4	1	CH_2	4-ClPh	2.88	35.5		
			daltroban		0.46	37.1	25	55

a) Inhibitory effect on the aggregation of rabbit platelets induced by U-46619 (4 μM).; b) Inhibitory effect on U-46619 (0.1 μM)-induced contraction of rat aorta.; c) Inhibitory effect on the aggregation of guinea pig platelets induced by arachidonic acid (100 μM) *in ex vivo* (0.3 mg/kg, p.o).; d) Inhibitory effect on the aggregation of guinea pig platelets induced by U-46619 (1 μM) *in extra vivo* (0.3 mg/kg, p.o).

Table 2. Inhibitory Effects on the Aggregation of Platelets of Indane Derivatives



			in vitro IC_{50} (μM)		*ex vivo* ED_{50} (mg)
No	m	Ar	guinea pig[a]	human[b]	guinea pig[c]
24a	1	4-ClPh	0.27	0.28	0.063
24f	1	2-naphtyl	0.31	0.29	0.130
32	3	4-ClPh	0.23	2.69	0.083
daltroban			0.50	0.37	0.530

a) Inhibitory effect on the aggregation of guinea pig platelets induced by U-46619 (4 μM) *in vitro*.; b) Inhibitory effect on the aggregation of human platelets induced by U-46619 (1 μM) *in vitro*.; c) Inhibitory effect on the aggregation of guinea pig platelets induced by U-46619 (4 μM) *in extra vivo*.

In conclusion, the adoption of the indane ring and optimization of the alkylene length as the spacer caused enhancement of TXA_2 antagonistic activities for *in vitro* tests, especially for contraction of rat aorta. In *ex vivo* test, indane derivatives **24a**, **24f** and **32** exhibited a more potent TXA_2 antagonistic activity than daltroban. Compound **24a** (**Z-335**) is currently under clinical trial as an orally active TXA_2 antagonist.

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