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ROLE OF SULFONAMIDE MOIETY IN NON-PROSTANOID TXA_2 RECEPTOR ANTAGONIST KT2-962 : MODIFICATIONS OF THIS MOIETY AND THE RESULTING ACTIVITIES

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Abstract: Modification of sulfonamide moiety in non-prostanoid thromboxane A_2 (TXA_2) receptor antagonist, KT2-962 with double amide, sulfonamide-amide, (thio)semicarbazone, inverse sulfonamide and N-sulfonylcarboxamide is described. Unlike prostanoid TXA_2 antagonists, the importance of sulfonamide moiety for the activity of non-prostanoid TXA_2 receptor antagonist, KT2-962 was confirmed.

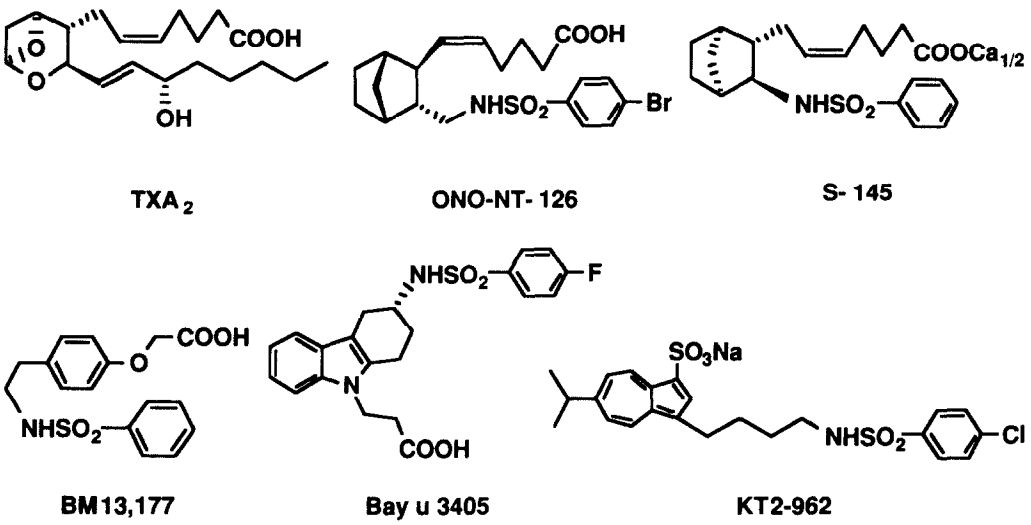
TXA_2 is known to contract different types of smooth muscles and to activate circulating blood cells. TXA_2 usually constricts blood vessels, contracts respiratory smooth muscles and induces aggregation or adhesion of platelets, erythrocytes and perhaps endothelial cells. [1] Agents which modulate the actions of TXA_2 are classified as TXA_2 synthetase inhibitors and TXA_2 receptor antagonists.

In general, TXA_2 synthetase inhibitors have been disappointing in terms of their efficacy in circulatory disorders in humans. However, TXA_2 receptor antagonists may be more useful than TXA_2 synthetase inhibitors, because these compounds also antagonize the effect of endoperoxides and they do not lead to accumulation of endoperoxide intermediate. Therefore, TXA_2 receptor antagonists appear to have greater potential as therapeutics. [2]

TXA_2 receptor antagonists are classified as prostanoid TXA_2 receptor antagonists (P-TRAs) and non-prostanoid TXA_2 receptor antagonists (NP-TRAs). P-TRAs are reported to have partial agonistic activities [3] and NP-TRAs are considered not to have partial agonistic activities. [4]

In the search for P-TRAs and NP-TRAs, a number of compounds (ONO-NT-126, [5] S-145, [6] BM13,177, [7] Bay u 3405 [8]), having sulfonamide moiety, have been reported and sulfonamide seems to be one of the active functionalities in P-TRAs and NP-TRAs. Several attempts to modify allylic alcohol functionality in P-TRAs were made and replacements of the allylic alcohol moiety with double amide [9] and semicarbazone [10] on omega chain have been described.

We have previously reported the synthesis of a series of azulene derivatives, one of which is 6-isopropyl-3-[4-(p-chlorobenzenesulfonylamino)]butylazulene-1-sulfonic acid sodium salt (KT2-962), a potent and



long-acting NP-TRA.[4] As a continuation of our study in the structural requirement of KT2-962, an attempt was made to replace sulfonamide moiety to gain further information on the activity of NP-TRAs. We designed and synthesized various derivatives of KT2-962, replacing sulfonamide moiety with double amide and sulfonamide-amide, semicarbazone and thiosemicarbazone, inverse sulfonamide and N-sulfonylcarboxamide.

The target compounds were synthesized by methods A-D in Scheme 1. The azulene derivatives **1**, **4**, **7** and **11** were prepared from methyl 6-isopropyl-2-oxo-2H-cyclohept[b]furan-3-carboxylate according to the method reported by Takase.[11]

Double amides **2** and sulfonamide-amides **3** were synthesized by method A. Treatment of phthalimide **1** with hydrazine hydrate afforded the amine, which was then transformed into the double amides or sulfonamide-amides by condensation with the appropriate glycine derivatives in the presence of 1.3-dicyclohexylcarbodiimide. Hydrolysis of esters with 10% aqueous NaOH gave the carboxylic acids **2** and **3**.

Semicarbazones **5** and thiosemicarbazones **6** were synthesized by method B. Hydrolysis of the acetal **4** with 10% aqueous HCl followed by condensation with arylsemicarbazides or arylthiosemicarbazides in AcOH-H_2O-THF, resulted in the formation of semicarbazones or thiosemicarbazones. Hydrolysis of esters gave the carboxylic acid sodium salts **5** and **6**.

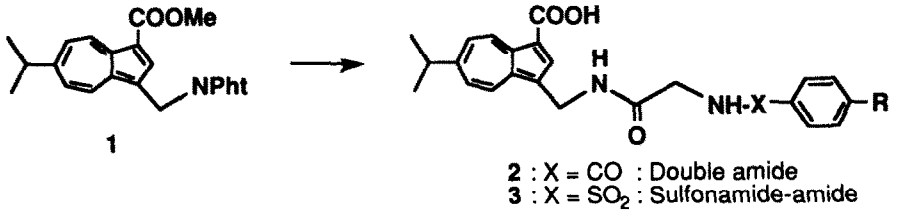
Inverse sulfonamides **9** and **10** were synthesized by method C. Deprotection of the tetrahydropyranyl ether of **7** with p-toluenesulfonic acid in MeOH followed by bromination of alcohols with PPh_3 and CBr_4 afforded the bromides **8**. Sulfonation of **8** with $NaHSO_3$ in aqueous dioxane provided the sodium sulfonates. Chlorination of sodium sulfonates with thionyl chloride followed by condensation with anilines gave the inverse sulfonamides. Hydrolysis of esters gave the carboxylic acids **9**. Sodium sulfonates **10** were obtained according to the reported method.[12]

N-sulfonylcarboxamides **13** and **16** were synthesized by method C. Hydrolysis of diester **11** with 10% aqueous NaOH at room temperature gave selectively the mono acid **12**. Condensation of **12** with arylsulfonamides in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 4-di-

methylaminopyridine followed by hydrolysis of esters yielded the carboxylic acids **13**. Additionally, diester **11** was converted to the sodium sulfonates **16**. Demethoxycarbonylation of diester **11** by treatment with anhydrous phosphoric acid yielded **14**, which was then transformed into the N-sulfonylcarboxamides **15** by hydrolysis and condensation with arylsulfonamides. Sulfonation of **15** with pyridine-sulfur trioxide complex followed by treatment with sodium methoxide gave the sodium sulfonates **16**.

Scheme 1. Modification of Sulfonamide Moiety in KT2-962

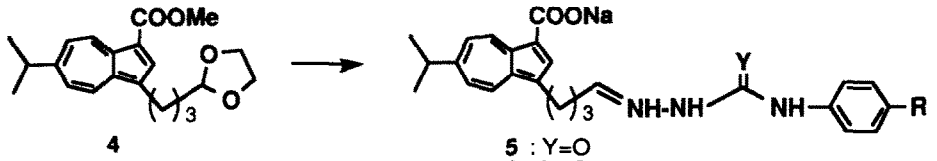
Method A : Double Amide and Sulfonamide - Amide Derivatives



1

2 : X = CO : Double amide
3 : X = SO_2 : Sulfonamide-amide

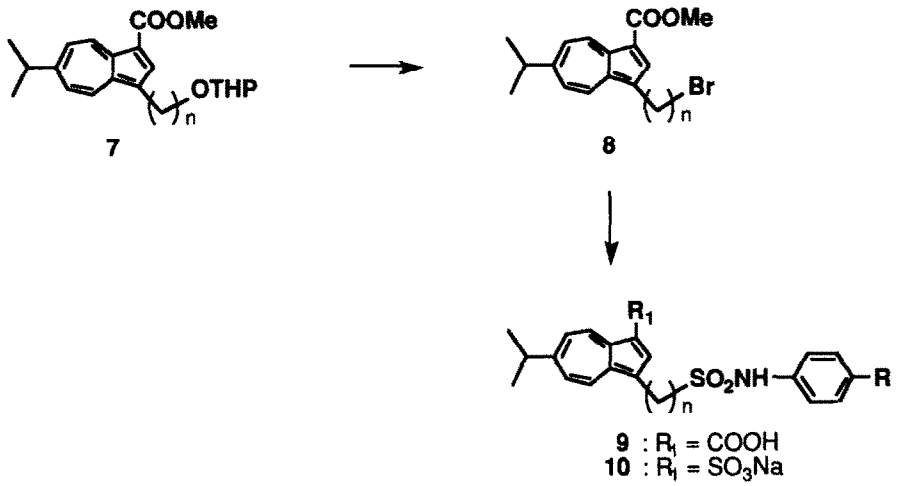
Method B : Semicarbazone and Thiosemicarbazone Derivatives



4

5 : Y=O
6 : Y=S

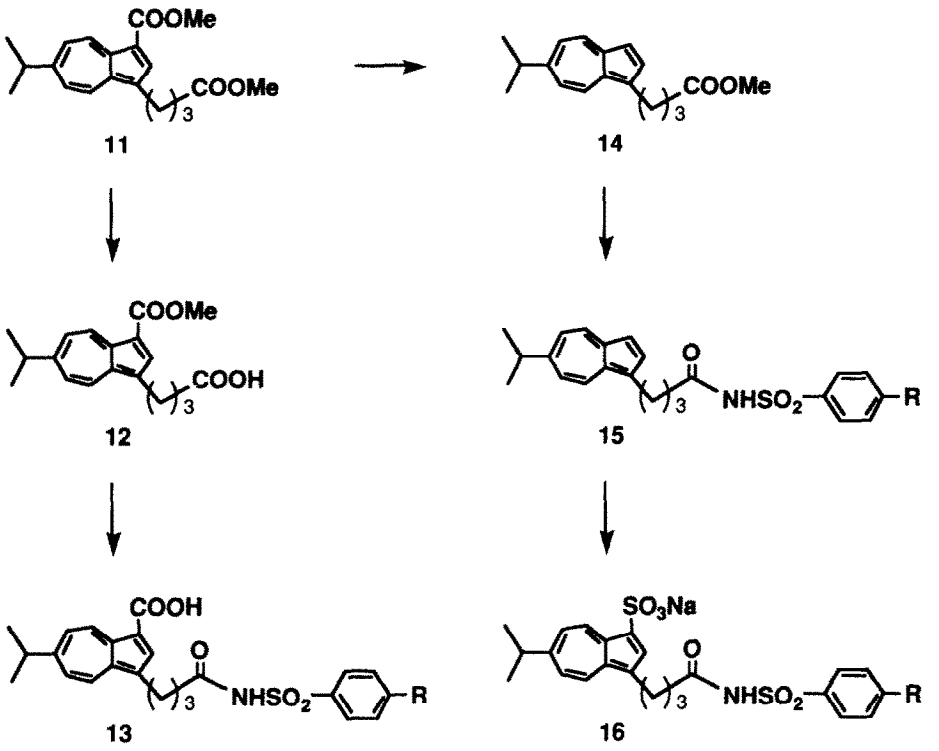
Method C : Inverse Sulfonamide Derivatives



7 **8**

9 : R_1 = COOH
10 : R_1 = SO_3Na

Method D : N-Sulfonylcarboxamide Derivatives



The synthetic compounds listed in Table 1 were compared in TXA_2 antagonistic activities with KT2-962 and BM13,177 as reference compounds. They were tested for the effects on isolated rat thoracic aorta (τ -receptor) precontracted by U-46619 (3.0×10^{-8} M). [13] The concentrations that caused 50% relaxation are shown in Table 1. All tested compounds were found to be less potent than BM13,177, except for inverse sulfonamides **9f** and **10b-f**, with **10e** being the most potent, about 10 times more potent than BM13,177. Among inverse sulfonamide derivatives (compounds **9a-f** and **10a-f**), introduction of a chlorine atom into the para position of the phenyl ring (compounds **9d-f** and **10d-f**) increased the activity more than non-halogenated compound (compounds **9a-c** and **10a-c**). Replacement of the carboxyl group in the 1-position of the azulene ring with the sulfonic acid sodium salt (compounds **10a-f**) resulted in increased activity. The most active compound **10e** (the IC_{50} value of 2.2×10^{-7} M), however, had 3 orders of magnitude less activity as compared to KT2-962 (the IC_{50} value of 9.0×10^{-10} M). We also investigated the inhibitory effects of compounds **2a**, **3a**, **5a**, **6a**, **9e**, **10e**, **13b** and **16b** on platelet-rich plasma (α -receptor) of rabbit. [14] The concentrations which cause 50% inhibition of the maximal aggregation are expressed as IC_{50} values and they are shown in Table 1. All compounds were less antagonistic for α -receptors than BM13,177 and KT2-962 but **10e** was more selective antagonistic for τ -receptors than BM13,177.

Squibb groups reported that the introduction of double amide [9] and semicarbazone [10] to P-TRAs, showed improvement in the inhibitory activity as compared to the allylic compound. However, these modifications

may not be applicable to NP-TRA such as KT2-962. The present study, therefore, indicates the importance of sulfonamide moiety for the activity of NP-TRA, KT2-962. Furthermore, non-peptide oxytocin [15] and fibrinogen [16] receptor antagonists, having sulfonamide moiety, were recently reported to increase non-covalent interactions at receptor sites. The study also suggests that there is a specific structural or non-covalent requirement for NP-TRAs which is different from that for P-TRAs.

Table 1. Structures and TXA_2 Receptor Antagonistic Activities In Vitro of Azulene Derivatives

				IC_{50} (M)[a]	
comp.	R	n	mp °C	contraction[b]	aggregation[c]
2a	H	-	222 - 224	$> 10^{-5}$	$> 10^{-4}$
2b	Cl	-	223 - 225	$> 10^{-5}$	
3a	H	-	205 - 206	$> 10^{-5}$	$> 10^{-4}$
3b	Cl	-	195 - 197	$> 10^{-5}$	
5a	H	-	188 - 191	$> 10^{-5}$	$> 10^{-4}$
5b	Cl	-	169 - 171	$> 10^{-5}$	
6a	H	-	182 - 184	$5.9 \pm 0.1 \times 10^{-6}$	$> 10^{-4}$
6b	Cl	-	228 - 231	$> 10^{-5}$	
9a	H	3	145 - 146	$1.2 \pm 0.7 \times 10^{-5}$	
9b	H	4	177 - 178	$8.7 \pm 2.7 \times 10^{-6}$	
9c	H	5	189 - 190	$1.5 \pm 0.5 \times 10^{-6}$	
9d	Cl	3	143 - 144	$9.1 \pm 3.4 \times 10^{-6}$	
9e	Cl	4	175 - 176	$2.6 \pm 1.1 \times 10^{-6}$	$> 10^{-4}$
9f	Cl	5	171 - 172	$1.7 \pm 0.2 \times 10^{-6}$	
10a	H	3	171 - 172	$8.7 \pm 3.2 \times 10^{-6}$	
10b	H	4	216 - 218	$1.5 \pm 0.2 \times 10^{-6}$	
10c	H	5	212 - 213	$1.4 \pm 0.3 \times 10^{-6}$	
10d	Cl	3	222 - 223	$8.6 \pm 0.2 \times 10^{-7}$	
10e	Cl	4	206 - 207	$2.2 \pm 1.1 \times 10^{-7}$	$> 10^{-4}$
10f	Cl	5	207 - 208	$8.6 \pm 4.0 \times 10^{-7}$	
13a	H	-	173 - 175	$> 10^{-5}$	
13b	Cl	-	189 - 191	$1.9 \pm 0.2 \times 10^{-5}$	$>10^{-4}$
16a	H	-	131 - 132	$6.5 \pm 1.3 \times 10^{-5}$	
16b	Cl	-	195 - 197	$5.4 \pm 0.1 \times 10^{-5}$	5.6×10^{-5}
KT2-962				$9.0 \pm 0.7 \times 10^{-10}$	8.7×10^{-6}
BM13,177				$1.5 \pm 0.1 \times 10^{-6}$	7.1×10^{-6}

[a] IC_{50} values represent the mean ± SEM and calculated by regression analysis from the three dose groups of four different preparations. [b] Contraction of rat aorta was induced by 3.0×10^{-8} M of U-46619. [c] Aggregation of rabbit platelet-rich plasma was induced by 4.0×10^{-6} M of U-46619.

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14. Blood was obtained from male NZW rabbits and platelet-rich plasma (PRP, ab. 3×10^8 cell/ml) was prepared by centrifugation. Platelet aggregation was measured by the method of Born. The inhibitory effect of each compound on the platelet aggregation induced by U-46619 (4.0×10^{-6} M) was examined and 50% inhibitory concentration (IC_{50}) for each compound was calculate. see Born, G. V. R. *Nature (London)* **1962**, *194*, 927.
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