Computer-Aided Molecular Modeling of a Thromboxane Receptor Antagonist S-145 and Its Related Compounds†

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Conformational analyses on thromboxane A_2 (TxA_2), its receptor agonist, U-46619, and its receptor antagonist, sulotroban, were carried out by molecular mechanics (MMFF) or molecular orbital (MNDO) methods. Two kinds of putative active conformations of TxA_2 and the agonist were proposed on the basis of these results by referring to the hairpin conformation hypothesis. From the superposition of stable conformers of sulotroban on those conformers, the molecular structural requirements for potent TxA_2 receptor antagonism were elucidated. S-145 in which these requirements are satisfied was a very potent TxA_2 antagonist.

Thromboxane A_2 (TxA_2), one of the natural prostanoids, has potent activities for platelet aggregation and constriction of the smooth muscle of vascular and respiratory origin, and plays an important role in the maintenance of vascular homeostasis together with prostacyclin (PGI_2) which has the opposite pharmacological properties. However, oversynthesis of TxA_2 has been considered to be one of the causes of thrombosis, asthma, ischemia, and myocardial infarction. Therefore, TxA_2 receptor antagonists blocking its action at the receptor sites should be clinically useful as therapeutic agents for those diseases.[1]

In this paper, we report on a successful application of computer-aided drug design procedure to develop an effective TxA_2 antagonist.

For a compound to possess antagonist activity, it should have a three-dimensional molecular structure in common with the agonist. Therefore, in order to develop a potent TxA_2 antagonist, the geometrical data of the active form of TxA_2 is needed. However, TxA_2 is a very unstable compound with a life-time of 32 s at 37 °C.[2] Another problem is that the molecular structures of other agonists have not been determined by experimental methods such as X-ray crystallographic analysis. We tried to estimate the putative active conformations of TxA_2 and its agonist, U-46619, by molecular mechanics calculations and by taking into account the hairpin conformation hypothesis proposed by Andersen et al.[3] that receptor binding requires a prostaglandin conformation with a U-shaped or approximately parallel arrangement of the α and the ω side chains.

The majority of the known TxA_2 antagonists are prostanoid analogues such as SQ-29548. However, several non-prostanoid antagonists are known; they seem to depart markedly in structure from the prostanoid one.[4] Of them, sulotroban (BM-13177) is a potent non-prostanoid TxA_2 receptor antagonist.[5] We examined this compound by the conformational analysis method and found it to have an energetically reasonable conformer similar to the putative active one of TxA_2 or U-46619. By stereochemical comparison of the obtained conformers of sulotroban with the active conformers of TxA_2 or U-46619, we were able to identify the molecular structural requirement needed for a potent prostanoid antagonist.

Compound S-145, synthesized by taking this requirement into account, is an extremely potent TxA_2 antagonist.[6] Conformational analysis verified that this compound has energetically stable conformers similar to the putative active form of TxA_2 or U-46619.

Computational Methods

The molecular geometry and conformational energies were evaluated by using the molecular mechanical calculation program MMFF in CHEMLAB-II system (Version 9.1)[7] and the molecular orbital calculation program MNDO.[8] Electron densities on atoms in molecules were obtained by the program CNDO/2.[7a]

As the compounds investigated have many rotable single bonds, many initial structures needed to be optimized. To save computational time, we took the following steps.

For TxA_2 and U-46619, several initial conformers which were designed by referring to the structural data for prostanoids searched from a Cambridge structural database[9] were energetically optimized by the MMFF program. The most stable conformer was selected as a reference structure, from which 19 683 initial conformers were constructed by varying the nine torsion angles shown in Figure 1 at 120° intervals. The summation of the van der Waals, electrostatic, and hydrogen bond energies on all these conformers was calculated. Energy minimization was carried out with the MMFF program only for the initial conformers with an energy difference of less than 10

† Compound names: S-145, (±)-(5*Z*)-7-[3-*endo*-[(phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic acid; U-46619, (15*S*)-15-hydroxy-11,9-(epoxymethano)prosta-5(*Z*),13(*E*)-dienoic acid; SQ-29548, [1*S*-[1α,2β(5Z),3β,4α]]-7-[3-[[2-[(phenylamino)carbonyl]hydrazino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid; sulotroban (BM-13177), [4-[2-[(phenylsulfonyl)amino]ethyl]phenoxy]acetic acid.

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Table I. Conformational Data for Local Minima of TxA_2 and U-46619 by the MMFF Method

conf[a]	ΔEs[b]	Φ_1[c]	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9
T1	54.1	284.1	298.8	184.2	231.9	98.8	189.8	236.2	68.8	176.3
T1H	50.1	269.3	281.6	170.0	249.7	130.3	186.7	246.7	16.5	173.2
T2	54.3	306.1	299.5	178.7	270.2	248.4	67.5	222.8	50.6	170.4
T2H	47.3	312.6	299.4	175.7	272.9	248.6	68.2	223.3	46.7	170.9
T3	54.5	104.1	185.8	188.8	276.0	111.8	189.3	245.3	239.5	176.1
T4	54.8	128.7	183.0	189.8	272.5	110.0	192.7	241.0	66.1	175.5
T5	55.5	104.2	180.1	180.1	89.5	118.7	297.4	232.4	223.3	177.0
T6	56.1	107.7	293.4	291.3	263.1	135.4	298.9	248.8	134.3	62.4
T7	56.3	278.7	290.7	179.1	261.7	130.3	300.1	236.0	31.7	169.1
U1	30.4	103.0	296.5	180.0	247.5	88.8	56.3	271.5	126.7	207.5
U1H	24.4	101.3	295.5	178.2	249.8	89.9	56.7	275.9	124.9	206.6
U2	31.3	100.7	182.4	181.1	246.6	85.5	57.5	289.2	60.6	211.2
U4H	24.5	101.1	293.2	173.1	250.1	85.0	63.8	221.4	174.7	210.1
U5H	25.5	278.8	293.3	178.1	236.3	88.0	54.9	304.2	124.5	205.4
U6H	27.1	46.4	43.8	50.8	170.3	112.0	164.0	270.8	66.0	210.3
U7H	28.5	311.6	300.7	178.9	269.3	260.0	296.4	232.1	136.4	209.4

[a] H indicates that the hydrogen-bonding term is added. [b] Steric energy in kilocalories/mole. [c] See text. Unit is degree.

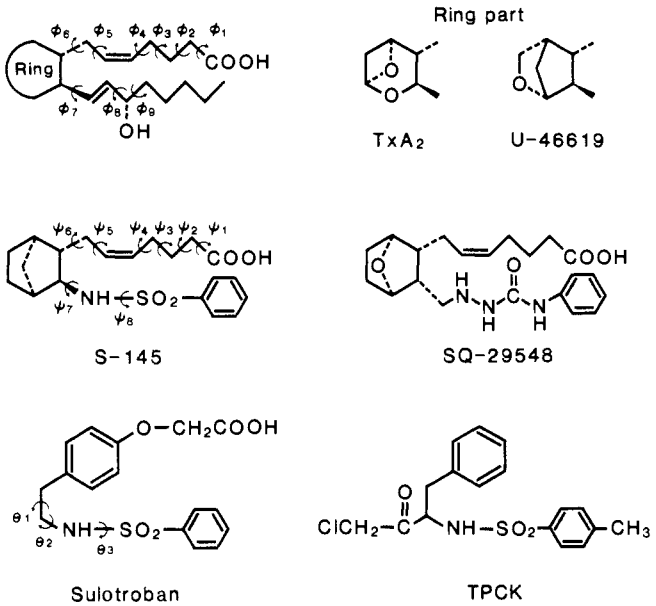

Figure 1. Chemical structures of compounds discussed and nomenclature of torsion angles.

kcal/mol from the lowest total energy.

A reference conformer of the molecule without the oxyacetic acid group from sulotroban was constructed by referring to the molecular structure of L-[1-(tosylamino)-2-phenyl]ethyl chloromethyl ketone (TPCK).[10] The molecular energy of 216 conformers which were constructed from the reference conformer by varying the three torsion angles shown in Figure 1 at 60° intervals was calculated with the MNDO program.[8] Geometry optimization of three torsion angles θ_1, θ_2, and θ_3 and three bond angles ∠ΦCC, ∠CCN, and ∠CNS was carried out for conformers with an energy difference of less than 3 kcal/mol from the lowest total energy. Finally, the oxyacetic acid group was introduced to those conformers, and only the moiety of the group was energetically optimized without any change of the conformation of the other moiety in the molecule by the MNDO method.[8] The molecular geometry of *N*-methylbenzenesulfonamide obtained by the MNDO method agreed with the experimental one. This result suggests that the method is well parameterized for proper prediction of molecular structures of the aromatic sulfonamides.

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Table II. Conformational Data for Local Minima of Sulotroban by the MNDO Method

conf	ΔHs[a]	θ_1[b]	θ_2	θ_3
B1	30.49	175.2	197.4	88.8
B2	30.50	177.0	266.0	261.9
B3	31.26	174.0	121.6	83.3
B4	30.73	60.3	88.6	141.6
B5	31.62	176.4	193.4	262.4
B6	32.25	114.0	147.7	265.3
B7	30.72	166.0	129.7	274.2
B8	30.97	307.1	155.4	260.7

[a] Heat of formation in kilocalories/mole. [b] See text. Unit is degree.

The reference conformer of S-145 was constructed as follows: the bicyclic ring moiety was energetically optimized by the MMFF program and the conformations of the α and the ω side chains were taken from those of the lowest energy conformer of TxA_2 and sulotroban, respectively. Next, $3^6 \times 6^2$ conformers were obtained from the reference conformer by varying six torsion angles of the α side chain at 120° intervals and two angles of the ω side chain at 60° intervals as shown in Figure 1. These conformational energies were calculated by the method used for the energy calculation of TxA_2 and U-46619. Geometric optimization on the torsion angles in Figure 1 was carried out with the MNDO method only for conformers with an energy difference of less than 10 kcal/mol from the lowest total energy.[8]

Results

Steric energies or heat of formation and torsion and bond angles of only interesting conformers of the compounds are listed in Tables I–III, and these molecular structures are shown in Figures 2–5.

Conformation of TxA_2 and U-46619. As shown in Table I, if hydrogen-bonding interaction is not taken into account, the global minimum energy conformation of TxA_2 is displayed by the T1 conformer in Figure 2, and a T2 conformer with steric energy very close to that of T1 conformer also exists. Addition of the hydrogen-bonding term makes conformers T1H and T2H more stable than conformer T1 by 4 kcal/mol and T2 by 7 kcal/mol, respectively; T2H becomes the global minimum energy conformation. These hydrogen-bonding conformers have essentially the same structure as each corresponding non-hydrogen-bonding conformer, except for the distance between the 15-OH group in the ω side chain and the COOH group in the α side chain. In the T1H conformer, the distance between the oxygen atom in the 15-OH and the hydrogen atom in the COOH group is 1.95 Å and that between the hydrogen atom in the former and the carbonyl

Table III. Conformational Data for Local Minima of S-145 by the MNDO Method

conf	ΔHs^a	$\Psi_1{}^b$	Ψ_2	Ψ_3	Ψ_4	Ψ_5	Ψ_6	Ψ_7	Ψ_8
S1	42.8	258.4	83.1	78.5	176.5	113.0	192.3	206.8	236.4
S2	43.2	330.3	183.5	183.9	174.0	255.1	293.5	206.7	270.4
S3	44.5	251.5	76.8	80.8	172.7	124.9	196.6	220.8	199.0
S4	44.8	262.9	81.5	81.3	172.8	125.9	192.6	205.7	84.0
S5	47.3	355.9	87.3	73.5	202.3	219.6	179.4	214.9	88.1

[a] Heat of formation in kilocalories/mole. [b] See text. Unit is degree.

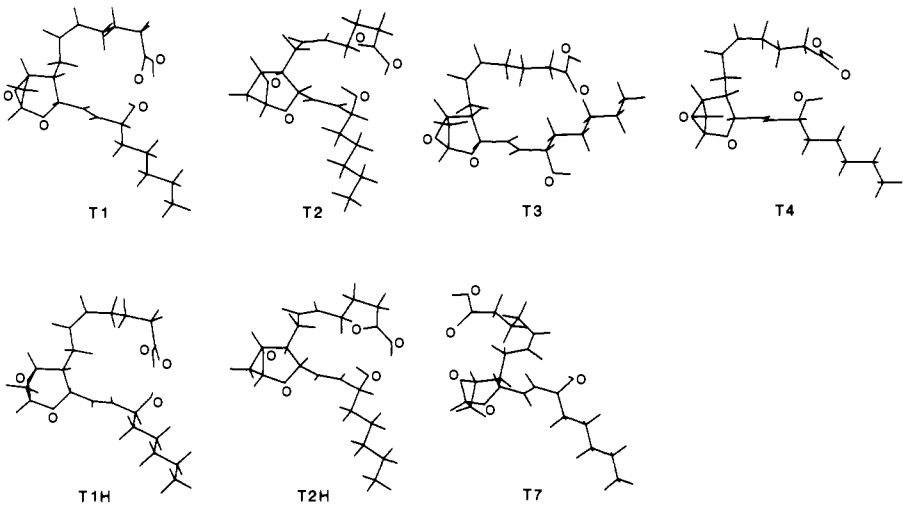

Figure 2. Molecular structures of representative conformers of TxA_2.

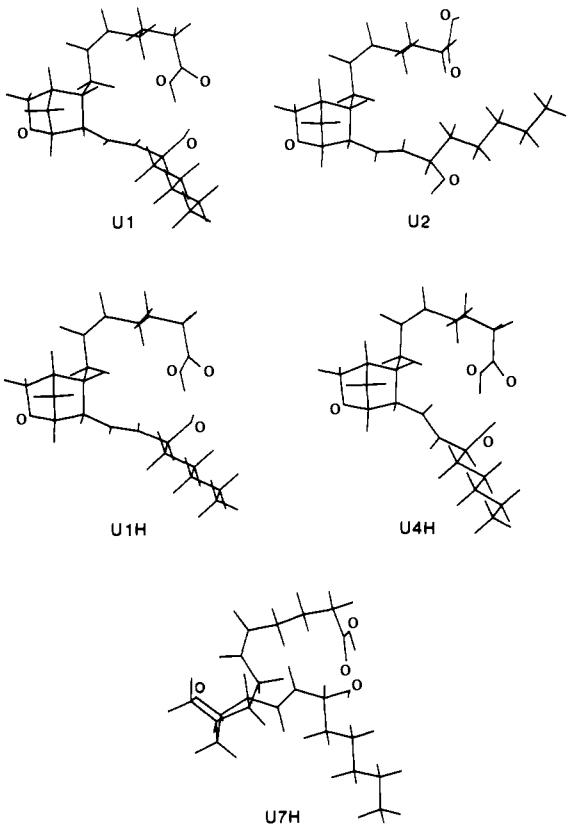

Figure 3. Molecular structures of representative conformers of U-46619.

oxygen atom in the latter is 2.18 Å. These values are reasonable for the distance between atoms associated with hydrogen bonding.[9,11]

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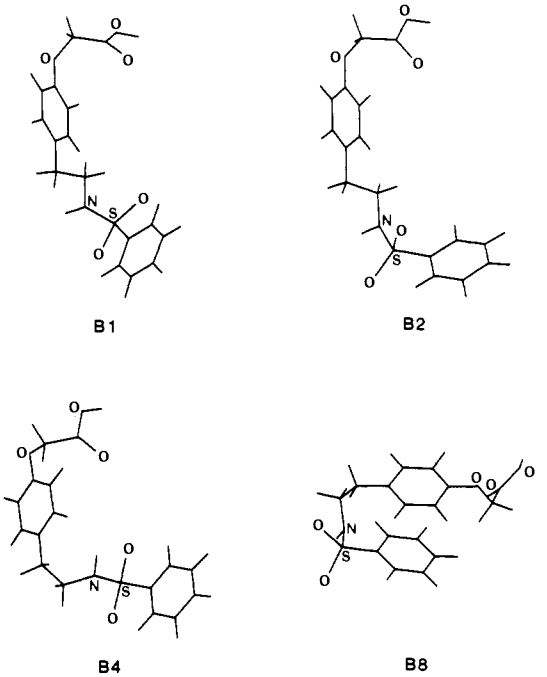

Figure 4. Molecular structures of representative conformers of sulotroban.

Conformers T3 and T4 are hairpin conformers, which have the same steric energy as that of T1 and T2 within computational accuracy. The 15-OH group in T4 is oriented toward the α side chain, but that in T3 is oriented in the opposite direction. The most stable conformation of the stretched structures of TxA_2 is T7, which is less stable than the T1 conformer by about 2 kcal/mol. In general, stretched conformers are less stable than folded conformers.

As shown in Table I and Figure 3, conformers U1 and U1H of U-46619 correspond to conformers T1 and T1H of TxA_2, respectively. The hydrogen-bonding formation

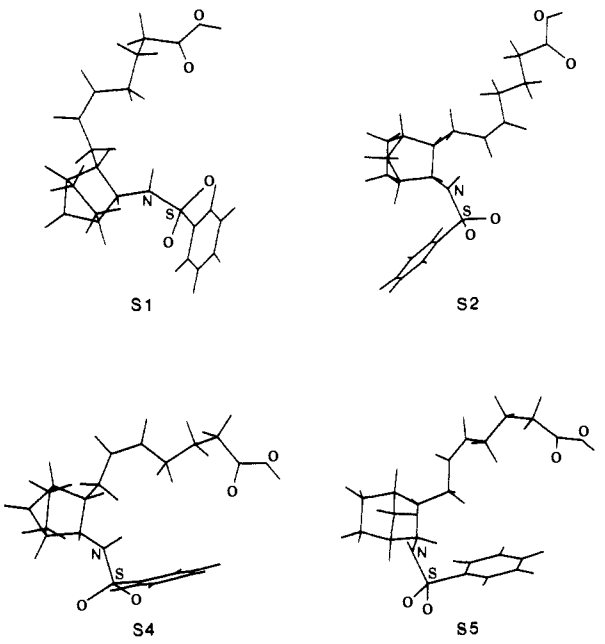

Figure 5. Molecular structures of representative conformers of S-145.

between the COOH group in the α side chain and the 15-OH group in the ω side chain leads to the global minimum energy conformer U1H, which is more stable than conformer U1 by 6 kcal/mol. Conformer U4H is also stable and energetically comparable to conformer U1H. Of the hairpin structures, conformer U2 has the lowest energy and is more unstable than conformer U1 by 1 kcal/mol or conformer U1H by 7 kcal/mol. A conformer corresponding to T2H is conformer U7H, which is less stable than U1H by 4 kcal/mol.

Sulotroban. Table II shows the conformational data for local minima of sulotroban by the MNDO method. Several stable conformers having the same heat of formation were obtained. Of these, conformer B8, which was obtained by geometrically optimizing the conformation of the $PhCH_2CHNHSO_2Ph$ moiety of TPCK in crystals,[10] has the most complete hairpin form. Conformers B2 and B4 are hairpin-like forms. On the other hand, conformers, B1, B5, and B6 are stretched forms.

S-145. As shown in Table III, conformer S1 is the most stable conformer and is similar to conformer T1H of TxA_2. Conformer S2 has a stretched form with a heat of formation comparable to that of S1. Conformers S4 and S5 are hairpin structures and are energetically less stable than S1 by 2 and 4.5 kcal/mol, respectively.

Discussion

As the active conformations of TxA_2, its agonist and its antagonist are not known yet, their putative active conformations were estimated on the basis of two hypotheses: The hairpin conformation hypothesis and the assumption that the active conformation is not very different from a stable conformation in the gaseous state. We elucidated the structural features of the antagonist by comparing three-dimensional structures of the putative active conformation of the agonists with that of the antagonist sulotroban.

Although X-ray crystallographic analyses of many prostanoids have been reported, the geometry of thromboxanes is not known except for that of thromboxane B_2 (TxB_2), which, in crystal form, adopts two conformations, the α-tail and the β-tail scorpion conformations, differing from the hairpin conformation.[12] Those side chains with a carboxyl group are bent, respectively, in α- and β-face directions approximately normal to the mean plane of the pyranose ring of the molecules. We referred to these conformations, but did not adopt them as the primitive active conformation for three reasons. First, in TxB_2 crystals, the 15-OH group in the ω side chain produces intermolecular hydrogen bonds with the OH groups on the pyranose ring and the molecules become associated as carboxylic acid dimers. Such intermolecular hydrogen bonding would lead the molecular structure to an unusual conformation. Second, the conformation of a prostanoid in solution is not always similar to that in the crystal form.[3,13,14] Therefore, the conformation of the molecule in the binding site of the receptor would differ from that in the crystal form since the prostanoid molecule has a very flexible structure.[14] Third, this compound has neither agonist nor antagonist activity.

Kalia and Kothekar[15] showed on the basis of conformational energy maps that the absolute minimum in TxB_2 in solution is in the same region as the crystallographic conformation.[12] However, we were not able to find the corresponding conformation in TxA_2 or U-46619 in the energy region with an energy difference of less than 6 kcal/mol from the lowest total energy. This would be because, in our conformational analysis, rotations were allowed around the nine bonds shown in Figure 1, which play an important role in determining the proper conformation of the molecules, while, in the analysis of Kalia and Kothekar,[15] rotations were allowed around only three bonds in the α side chain and not around any bond in the ω side chain, in spite of the actual existence of many rotatable bonds.

We therefore chose the two conformers T1H and T3 as putative active conformers of TxA_2 and the conformers U1H and U2 for U-46619. The superimpositions of T1H and U1H or T3 and U2 in Figure 6 or 7 show that both compounds have the stereochemically common putative active conformer. The most stable conformer T2H was excluded because the corresponding conformer, U7H, in U-46619 is not the most stable one.

Conformers T1H and U1H do not have complete hairpin structures. In these conformations, an intramolecular hydrogen bond is formed between the carboxyl group in the α side chain and the 15-OH group in the ω side chain. These conformations are consistent with that proposed by Takasuka et al. as a conformation of U-46619 in dilute CCl_4 solution on the basis of infrared spectral analysis.[16]

Conformers T3 and U2 have the hairpin conformation and are less stable than T1H and U1H by only several kilocalories/mole. Such a small energy difference would be sufficiently compensated for via the interaction with the receptor, such as via intermolecular hydrogen bonding of the carbonyl group in the α side chain with the receptor. We could not determine the preferred form of the active conformer, i.e., whether it is the most stable structure or a hairpin one, because we have no information on the receptor structure. If the carboxyl group in the α side chain plays an important role in the interaction with the binding site in the receptor, T3 and U2 may be more fa-

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(15) Kalia, A.; Kothekar, V. *FEBS Lett.* **1985**, *193*, 99.
(16) Takasuka, M.; Yamakawa, M.; Watanabe, F. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1173.

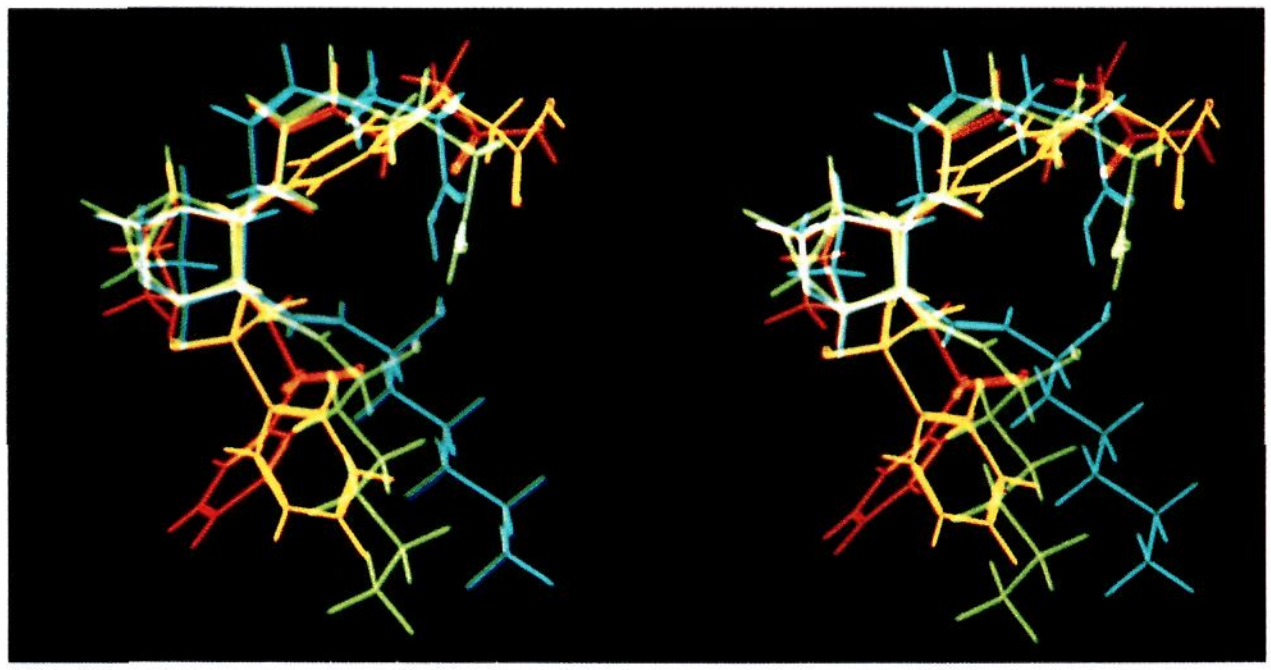

Figure 6. Superimposition of TxA_2 (conformer T1H, green), U-46619 (conformer U1H, blue), sulotroban (conformer B4, orange), and S-145 (conformer S1, red). The superimposition was done by means of a least-squares fit to the four atoms: for TxA_2, U-46619, and S-145, the two atoms in the ring which are bonded to the α and ω side chains, respectively, and the two atoms in the side chains which are bonded to the ring, and for sulotroban, the two aliphatic carbon atoms, the nitrogen atom in the sulfonamido group, and the ipso carbon atom in the benzene ring.

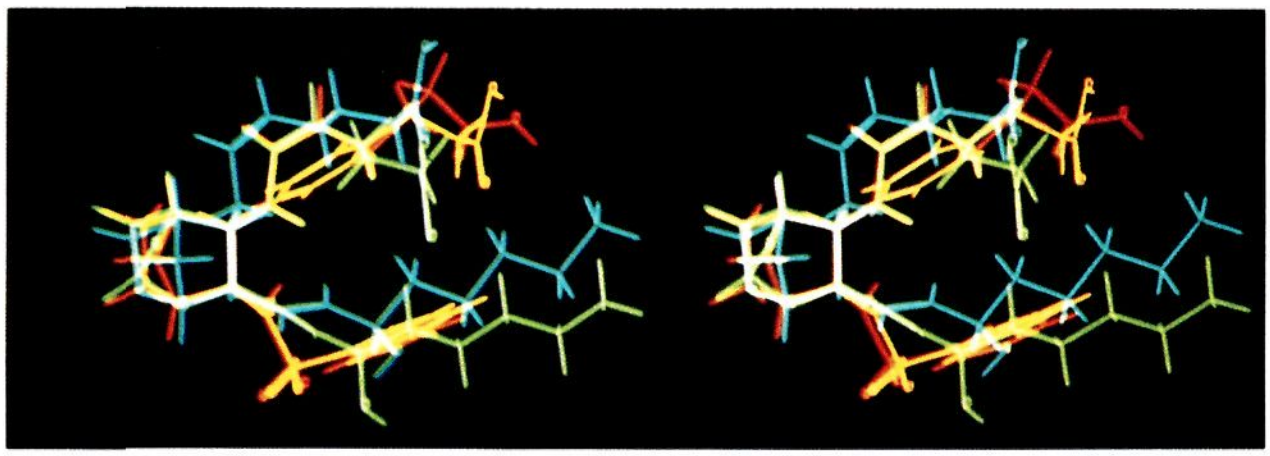

Figure 7. Superimposition of TxA_2 (conformer T3, green), U-46619 (conformer U2, blue), sulotroban (conformer B8, orange), and S-145 (conformer S4, red). The superimposition was done as described in Figure 6.

vorable for the active conformation than T1H and U1H because the carboxyl group in the latter is associated with the 15-OH group in the ω side chain through intramolecular hydrogen bonding but that in the former is not.

For TxA_2 and U-46619, folded conformers, in which the two side chains approach each other, are energetically more favored than stretched conformers in which the chains are situated in opposite directions to each other. This fact suggests that the role of dispersion and intramolecular hydrogen bonding interactions is very important for determining the favorable conformation. The importance of the dispersion force has been evident from conformational analyses of prostanoids by many researchers.[17] Also, the contribution of the intramolecular hydrogen bonding energy to the conformational energy is large: 4 kcal/mol for TxA_2 and 6 kcal/mol for U-46619.

The lowest energy conformer B1 of sulotroban, a TxA_2 receptor antagonist, is not a hairpin structure but a stretched structure as shown in Figure 4. There is little similarity of this conformer to the putative active structures of agonists T1H, U1H, T3, and U2. However, there is a hairpin conformer B8 and hairpin-like conformers B2 and B4 which are less stable than B1 by only $\leq$1 kcal/mol. Furthermore, TPCK in which two phenyl groups are bonded to both terminals of a $SO_2NHCHRCH_2$ moiety, respectively, is a hairpin structure in the crystal form.[10] This is strong evidence for sulotroban having a hairpin-like structure as a stable conformation.

As shown in Figure 6, the hairpin-like conformer B4 can be superimposed on the putative active conformer T1H or U1H. The phenoxyacetic acid group of B4 can be overlaid on the α side chain of T1H or U1H, then the benzenesulfonamido group of B4 would overlap with the ω side chain of T1H or U1H. Superimposition of the hairpin conformer B8 on T3 or U2 also would lead to the same result, as shown in Figure 7.

Thus, these findings indicate that the molecular structural requirements for TxA_2 antagonism are that the ω side chain be a benzenesulfonamido group and that the molecule have a low-energy conformation superimposable with a low-energy or a hairpin-like conformation of TxA_2 or a potent agonist. The bicyclic ring system would be preferable for a molecular structure which can assume the active conformation. A long-chain carboxylic acid group as the α side chain should play an essential role in binding for the TxA_2 receptor because all known TxA_2 agonists and antagonists, except for a few compounds, have this group.

S-145, which satisfies these requirements, was prepared.[6a] A bicyclo[2.2.1]heptane ring was chosen by Ohtani et al.[6a] as a rigid ring analogue of 13-azaprostanoic acid (13-APA),[18] a TxA_2 antagonist, which has a cyclopentane ring. The hept-5-enoic acid and the benzenesulfonamido groups were introduced to the ring as the α and the ω side chains, respectively, according to the proposed molecular structural requirements. A trans configuration between these side chains was adopted by referring to the config-

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uration between the corresponding chains in TxA_2, U-46619, and 13-APA.

The possibility of TxA_2 antagonism of S-145 was examined by using computer-aided molecular modeling. The lowest energy conformer S1, obtained by the MNDO method, was as shown in Figure 5. The superposition of conformer S1 on conformer T1H or U1H indicated that both conformers resembled each other closely, as shown in Figure 6. A benzenesulfonamido group of S-145 overlaid the ω side chain of TxA_2. Conformer S4, which had 2 kcal/mol higher energy than S1, was a hairpin structure. Also, as seen from Figure 7, the superposition of this conformer on T3 or U2 led to the same conclusion. These results strongly suggested that S-145 should be a TxA_2 antagonist.

By analyzing the relationships between the conformation and potency of TxA_2 antagonists, Wilkinson et al.[19] proposed a bioactive conformation of antagonists in which the ω side chain is replaced by a phenyl ring and the bridged bicyclic moiety by cyclohexane, pyranose, and dioxane ring systems. Their results[19] appear to support conformer S4 rather than conformer S1 as the active one though the proposed conformation cannot be compared directly with that of S-145 because the need for the $(CH_2)_3COOH$ moiety in the α side chain was entirely neglected in their conformational analysis.[19]

S-145 synthesized by Narisada et al. possessed high binding affinity to the TxA_2 receptor of human platelets and was a very potent TxA_2 antagonist[6] as anticipated from the above-mentioned results of molecular modeling. The inhibitory activities of S-145 for aggregation of rabbit platelet-rich plasma induced by arachidonic acid, for aggregation of rat washed platelets induced by collagen, and for constriction of rat aorta induced by U-46619 were 9, 1, and 10 times higher than those of SQ-29548,[6] respectively, which has been reported to be promising in preclinical evaluations.[18] These observations justified the proposed molecular structural requirements for TxA_2 antagonism.

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Note Added in Proof: After the manuscript of this paper was submitted to the journal, we learned of a paper by Deleers and Brasseur[20] in which the conformational and charge density analysis of TxA_2 and its analogues were reported. They showed that the most probable conformations of TxA_2 and its potent agonists are similar to each other, appearing to be hairpin-like structures, though no structural parameter was described in the paper, except for van der Waals volume representation (not a stereoview) of the molecules. Recently, many potent TxA_2 antagonists with the benzenesulfonamide group as the ω side chain have been reported in several papers.[21] The reported findings support our proposed molecular structural requirements.

Registry No. TxA_2, 57576-52-0; U-46619, 56985-40-1; BM-13177, 72131-33-0; S-145, 115266-92-7.

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