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ANTAGONISM OF THE TXA2 RECEPTOR BY SERATRODAST : A STRUCTURAL APPROACH

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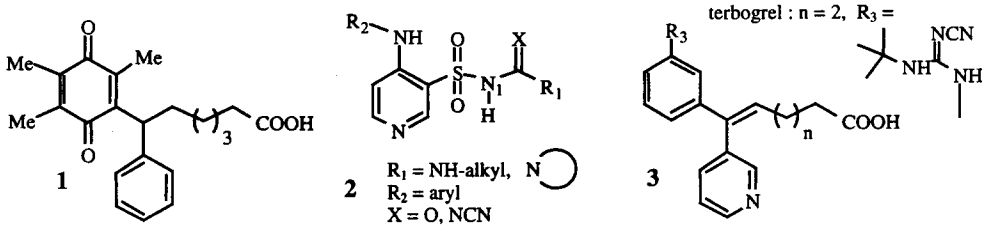
Abstract: The crystal structure of seratrodast (AA-2414), a potent thromboxane A2 (TXA2) receptor antagonist, served as starting point to docking studies with the modeled human TXA2 receptor. This structural approach provides rational basis for the design of new antagonists within the aryl sulfonamide family.

Seratrodast ((±)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid, **1**, AA-2414) is the only thromboxane A2 (TXA2) receptor antagonist launched and proposed as antiasthmatic.[1] It inhibits U-46619-induced contraction of the guinea pig lung (pA_2 = 8.29) and U-44069-induced aggregation of the guinea pig platelet (IC_{50} = 3.5 x 10^{-7} M). It also shows very potent inhibitory effects on induced bronchoconstriction in guinea pigs and on prostaglandin induced contraction of tracheal strips.



As part of our effort in the design of TXA2 receptor antagonists, a series of original aryl sulfonamides (**2**) were synthesized and tested.[2]
Starting from the crystal structure of **1**, docking studies with the modeled human TXA2 receptor. provide us rational basis for the design of new antagonists within the aryl sulfonamide family.

Crystal structure of 1. Seratrodast was isolated from the commercial available tablets (Bronica^{TM}). The spectral data (I.R., NMR), the elemental analyses, and the melting point (129°C) correspond to the reported value.[1]
The crystal used for the structure determination[3] was obtained by slow evaporation of a concentrated solution in EtOH. Molecule **1** adopts an extended conformation in the crystal structure. The molecular cohesion results from an hydrogen bond (Table I) implying the terminal carboxylic acid groups and van der Waals interactions between the aromatic rings of the molecule.

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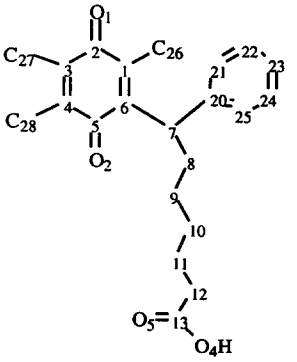
Table I. Selected geometric features resulting from the crystallographic structure of **1**.



Distances

C_{13}-O_4 = 1.204(6) Å, C_{13}-O_5 = 1.282(6) Å

O_4-$O_5{}^{i}$ = 2.647(6) Å (*i* = 3-x,1-y,-z)

X_1-C13 = 8.31 Å, X_2-C13 = 10.23 (X_1 and X_2 centroids of [C_1-C_6] and [C_{20}-C_{25}] rings respectively)

Torsion angles

C_5-C_6-C_7-C_8 = -67.5(5)°, C_6-C_7-C_8-C_9 = -59.2(5)°

C_7-C_8-C_9-C_{10} = 177.0(4)°, C_9-C_{10}-C_{11}-C_{12} = 171.5(4)°

C_{10}-C_{11}-C_{12}-C_{13} = 175.5(4)°, C_{11}-C_{12}-C_{13}-O_4= -176.6(4)°

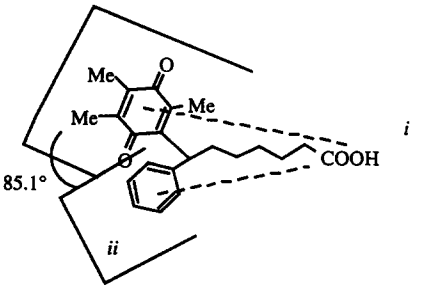
Dihedral angle

between the [C_1-C_6] and [C_{20}-C_{25}] planes = 85.1(2)°

The selected geometric features summarized in Table I can be used to characterize the extended conformation of **1** and derive structurally relevant information such as :

i the position of the terminal COOH group and

ii orientations of the phenyl and benzoquinone rings.



Docking of 1 into the human TXA2 receptor. In order to elucidate the mode of TXA2 receptor - ligand interaction at the molecular level, a model for the human receptor was constructed on the basis of its amino acid sequence.[4] A strategy similar to that presented by Yamamoto *et al.*[5] was adopted to model the seven transmembrane helices of the G protein-coupled receptor, using the program Swiss-Model (http://expasy.hcuge.ch/swissmod/SWISS-MODEL.htm). The crystal structure of seratrodast served as starting point to docking studies with the modeled human TXA2 receptor.[6]

According to the work of Yamamoto *et al.*[5] the terminal COOH group was placed in electrostatic binding distance (2.6 Å) from Arg_295 and the aromatic rings occupy hydrophobic pockets within the binding site. Both the *R* and the *S* isomers were studied. The final geometry of the TXA2 receptor - antagonist complex is illustrated for the *R* isomer in Figure 1. The residues forming the two hydrophobic pockets stabilizing the benzoquinone and phenyl rings are presented in yellow (Ile_C113, Gly_C116, Leu_D168, Ser_E201) and blue (Trp_D157, Leu_D163, Val_E208, Phe_E212) respectively. These two hydrophobic pockets appear large enough to accomodate different lipophilic substituents of antagonists/ligands. The present approach is still qualitative. To our knowledge, no mutational data were reported for the receptor that could identify (*a priori*) or check (*a posteriori*) the influence of amino acids in the binding of ligands. The binding of the *R* isomer (total energy = -73.10 kcal/mol) to the TXA2 receptor is predicted to be favored with respect to the binding of the *S* isomer (total energy = -70.21 kcal/mol).[6] This is at least consistent with biological data[1] and give some support to the present model.

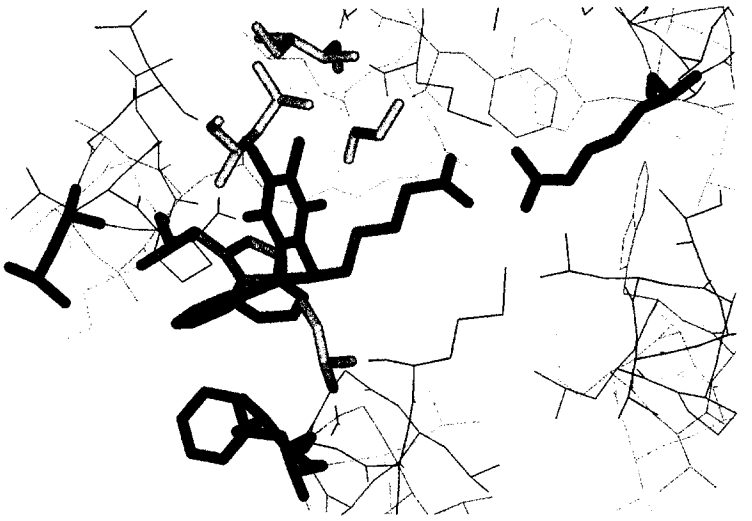


Figure 1. Geometry of **1** (*R* isomer) docked into the binding site of human TXA2 receptor.

Generalization to other families of antagonists. The pharmacophore derived from the crystal structure of **1** and its docking into the binding site of the modeled TXA2 receptor was used to examine other antagonists. Indeed, isbogrel and terbogrel (**3**), reported as combined TXA2 receptor antagonists and synthase inhibitors[7], can fit the pharmacophore elements deduced from seratrodast. These molecules illustrate the fact that the benzoquinone and phenyl rings of **1** can be replaced by other groups provided that they fit the two hydrophobic pockets identified in the receptor.

Some aryl sulfonamides (**2**) are potent TXA_2 receptor antagonists.[2] The lack of any carboxylic acid terminal group in these compounds, makes them original.[2] In this series, we suggest that the anionic form of the sulfonamido group (pKa around 6.0) could play a role similar to that of the essential carboxylic function of sertatrodast (**1**) and other antagonists (**3**). Starting from this correspondence, the conformation of the rest of the molecule, derived from conformational studies [8], is compatible with the pharmacophore associated to **1**. This is illustrated in Figure 2 for BM144 (**2** with R_1 = N-$(CH_2)_6$-, R_2 = 3-CH_3-C_6H_4-, and X= NCN). Information derived from the analysis of the relative position of BM144 in the binding site of the receptor will be used to further develop this series.

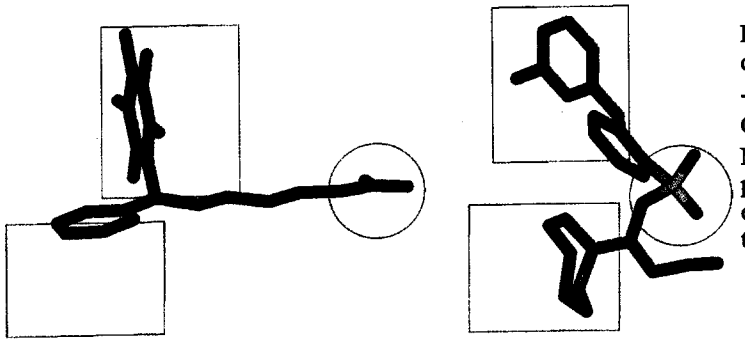


Figure 2. Conformation of BM144 (**2** with R_1 = -N-$(CH_2)_6$-, R_2 = 3-CH_3-C_6H_4-, and X= NCN) fitting the pharmacophore elements deduced from the study of seratrodast.

Conclusion. Pharmacophore elements were extracted from the crystal structure of seratrodast (**1**) that can be applied to other TXA2 antagonists (**3**). The proposed mode of binding of **1** to the TXA2 human receptor is compatible with SAR results associated to this series. Taken together, those structural elements will be useful in designing new molecules derived from aryl sulfonamides (**2**).

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References and Notes

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2. Masereel, B. et al. *J. Pharm. Pharmacol.* **1999**, *51*, 695-701.
3. $C_{22}H_{26}O_4$, triclinic, P-1, a = 8.089(2) Å, b = 8.415(2) Å, c = 15.254(4) Å, α = 99.84(3)°, β = 95.90(3)°, γ = 104.42(3)°, V = 979.2 $Å^3$, Z = 2, μ = 0.66 mm^{-1}, D_x = 1.202 g cm^{-3}, λ (Cu Kα) = 1.54178 Å, *F(000)* = 380, T = 290 K, 2042 unique reflections (R_{int} = 0.049), R_1 = 0.075 for 1397 $F_o > 4\sigma(F_o)$ and wR_2 = 0.234, *GooF* = S= 1.046. Full matrix least-squares on F^2 using the program Shelxl97 (Sheldrick, G. Univ Goettingen, Germany). Data have been corrected for absorption effects. The hydrogen of the terminal carboxylic acid has not been assigned.
Lists of atomic coordinates, displacement parameters, and complete geometry have been deposited with the IUCr.
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5. Yamamoto, Y.; Kamiya, K.; Terao, S. *J. Med. Chem.* **1993**, *36*, 820-825.
6. Energy calculations on receptor-ligand complexes were performed with the *Discover* program. Parameters (potential and charges) were taken from the cvff ForceField. The geometry of the binding site of the human TXA2 receptor was constructed with the Swiss-Model program (http://expasy.hcuge.ch/swissmod/SWISS-MODEL.htm) using the default parameters. The sequence of the seven putative transmembranar helices of the receptor were aligned with the sequence of bacteriorhodopsine that served as template for modeling of the structure, as described by Yamamoto *et al.*[5] The starting conformation for the ligand was taken from the crystallogarphic study of **1**. Both the *R* and the *S* isomers were studied. Manual docking of the ligand into the receptor placed the terminal carboxylic group of **1** in binding distance to the lateral chain of Arg_295 (distance between the two oxygen atoms of the carboxylate of the ligand and the two nitrogen atoms of the arginine residue close to 2.6Å) as suggested in the literature.[5] The rest of the antagonist was adjusted in the binding site of the receptor in order to minimize unfavorable steric contacts. The manual docking was followed by energy minimization (steepest descent and conjugated gradient procedure). All residues further than 6Å from the ligand were fixed. The solvent effect was approached by using a distance dependent dielectric constant (1*r). The complexes (receptor plus either the *R* or the *S* isomer) were energy minimized until the energy gradient dropped below 0.01 kcal/mol.
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