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CONFORMATIONALLY-RESTRICTED ANALOGS OF TXA_2 ANTAGONIST SQ 33,961: RECEPTOR BINDING CONFORMATION OF THE CARBOXYL SIDECHAIN

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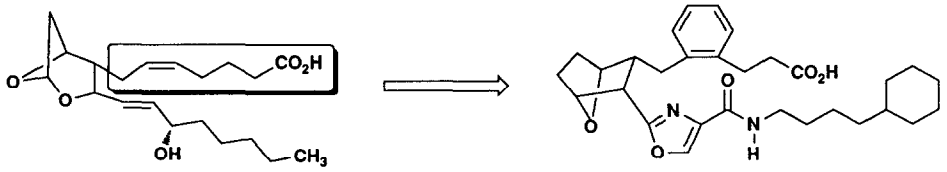
Abstract: Two distinct conformational families, exemplified by **1** and **2**, of thromboxane A_2 (TxA_2) receptor antagonist SQ 33,961 have been determined by molecular modeling. Synthesis and biological evaluation of conformationally-restricted mimic **3Z** suggested that the hairpin conformer, **1**, is the bioactive conformation.

Since the discovery and structure elucidation of thromboxane A_2 (TxA_2)[1] a number of prostanoid-like TxA_2 receptor antagonists have been reported.[2] A common structural feature among these molecules, which has hindered definitive elucidation of their receptor binding conformation, has been a flexible *cis*-olefin carboxyl sidechain which is also present in TxA_2.[3] We recently described a novel prostanoid-like TxA_2 antagonist



TxA_2 **SQ 33,961**

SQ 33,961 in which the olefin carboxyl sidechain is replaced by an interphenylene sidechain.[4] We anticipated that sufficient constraints would be imposed by the interphenylene modification such that the carboxyl sidechain would be limited to a small number of low energy conformations and thus facilitate modeling of probable binding conformations. Preparation of analogs of defined structure which mimic these conformations and examination for TxA_2 antagonistic potency would then presumably determine a definitive receptor binding conformation.

The molecular modeling protocol we employed included systematic conformational searches, using MMP2[5,6], with the α-chain truncated to *o*-Me at the phenyl and the ω-chain to N-Me at the amide, followed by selective sampling of conformations with the full side chains. Low energy representatives of the resulting conformational families are shown in Figures 1 and 2, top, as conformers **1** and **2**[7]. In conformer **1** the interphenylene phenyl ring lies nearly orthogonal to the oxazole ring. The overall orientation of the sidechains resembles the hairpin structure proposed for a number of prostaglandins; in the case of SQ 33,961 a phenyl ring has been formally annulated on the α-chain double bond. In contrast, in conformer **2** the interphenylene phenyl ring and oxazole ring adopt a stacked orientation. Overlaying of conformers **1** and **2** indicated that their respective interphenylene phenyl rings and carboxyl groups occupy different volumes of space, thus providing two distinct α-chain orientations. MMP2 calculations showed that conformer **1** was 4.3 kcal/mol lower in steric energy than

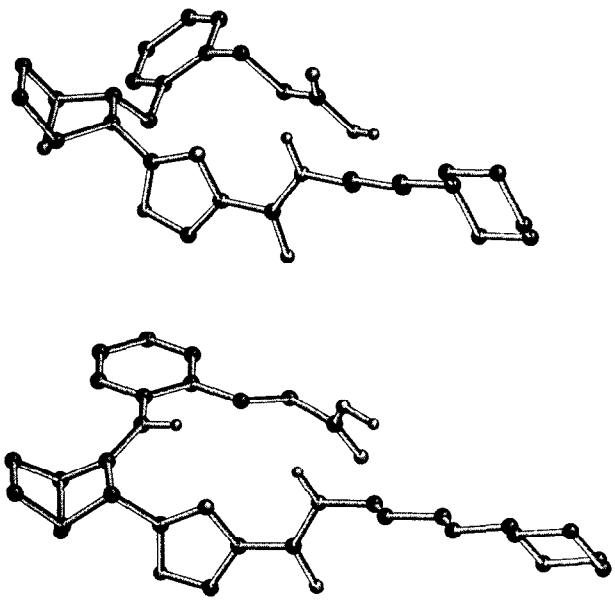


Figure 1. Top: Conformer **1**, MMP2 minimized structure of SQ 33,961 (38.0 kcal/mol). Bottom: MMP2 minimized structure of **3Z** (41.8 kcal/mol).

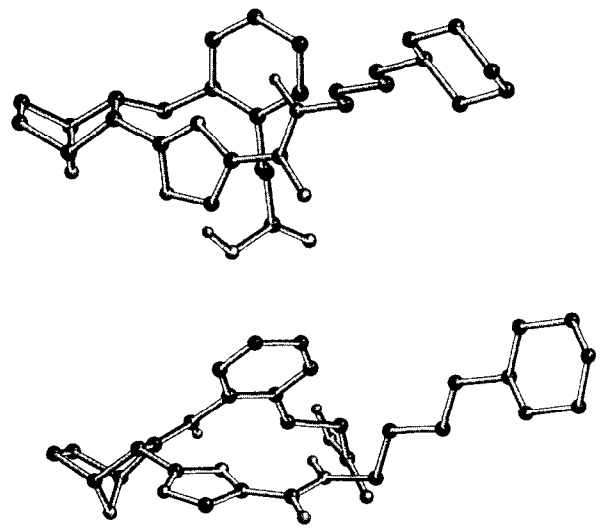
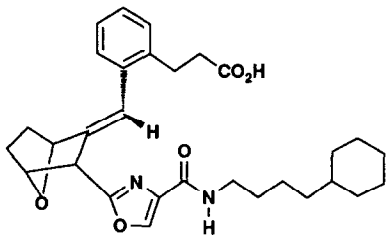
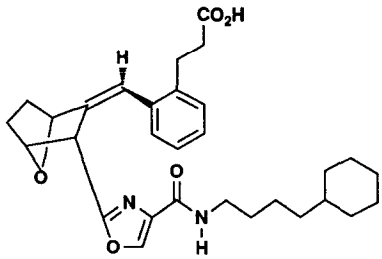


Figure 2. Top: Conformer **2**, MMP2 minimized structure of SQ 33,961 (42.3 kcal/mol). Bottom: MMP2 minimized structure of **3E** (46.3 kcal/mol).

conformer **2**. After examination of molecular models we anticipated that the two *exo*-methylene analogs **3Z** and **3E** would provide conformationally-restricted mimics of conformers **1** and **2**, respectively. MMP2 energy minimization of *exo*-methylene analog **3Z** and examination of the resulting structure indicated that it was a suitable mimic of conformer **1**. Comparison of the two energy minimized structures is shown in Figure 1. In contrast to **3Z**, although isomer **3E** was able to adopt a conformation which represented conformation **2**, energy minimiz-



3Z

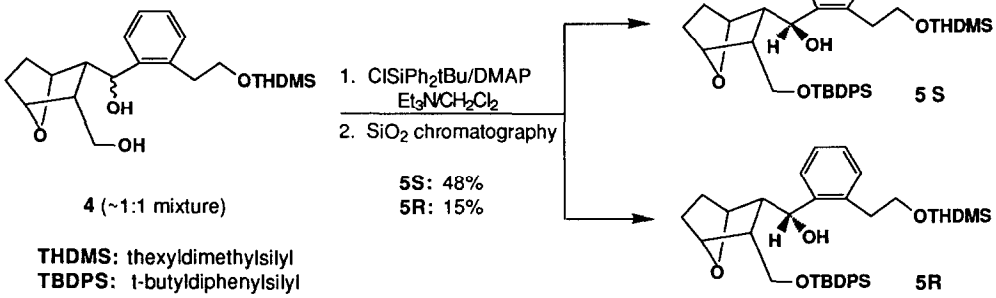


3E

ation indicated that the interphenylene phenyl ring prefers a nearly planar, styrene-like orientation in which it is conjugated with the *exo*-methylene double bond. The resultant steric congestion between the two aromatic rings is alleviated by twisting of the oxazole ring as shown in Figure 2, bottom. Comparison of the two energy minimized structures indicated that **3E**, unfortunately, is likely not a suitable mimic for conformer **2**. Isomer **3E** was calculated as 4.5 kcal/mol higher in steric energy than **3Z**. In order to determine if conformer **1** was in fact the receptor binding conformation of SQ 33,961 we prepared conformationally-restricted analog **3Z**. The synthesis of **3Z** is shown in Schemes I and II. In addition, we prepared isomer **3E** by an analogous route.

Olefins **3Z** and **3E** were prepared employing a Chugaev elimination[8] to stereospecifically introduce the key

Scheme I

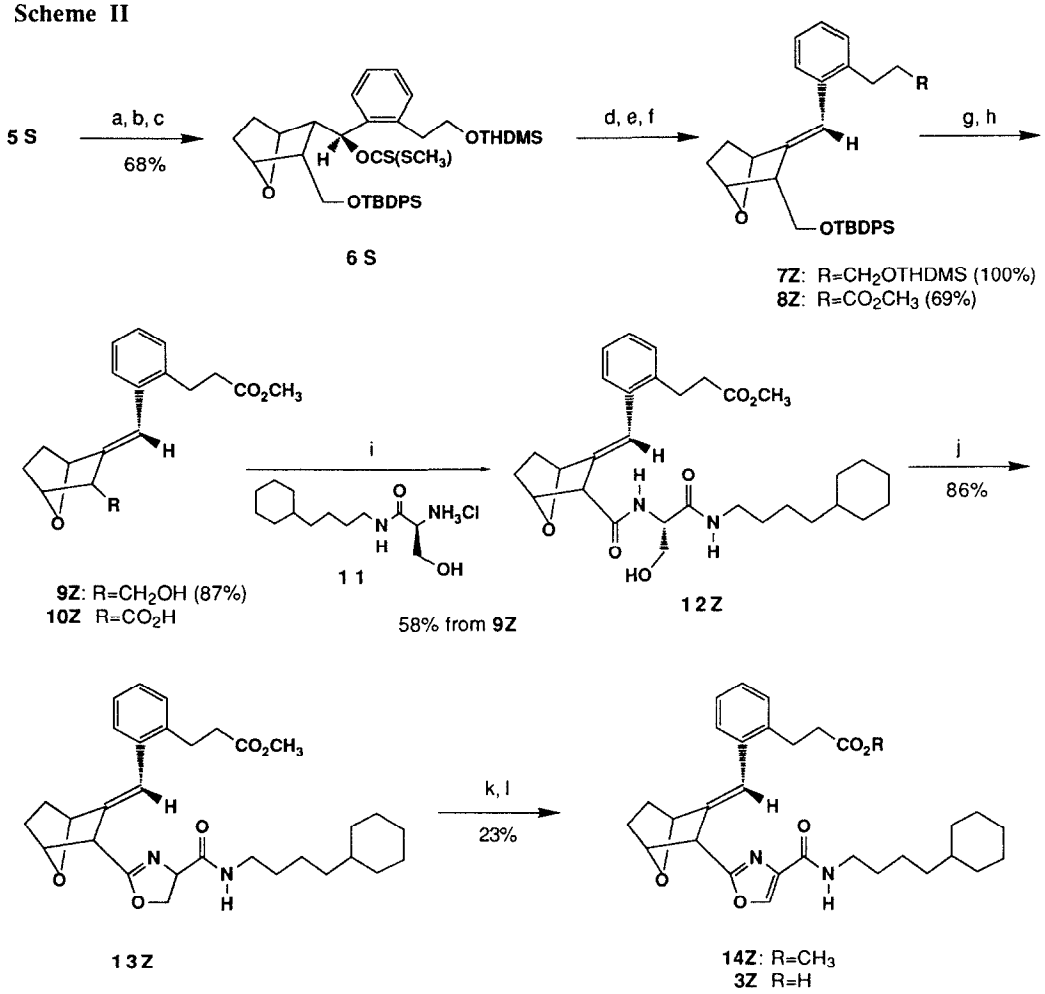


THDMS: thexyldimethylsilyl
TBDPS: t-butyldiphenylsilyl

exo-methylene double bond. Isomers **3Z** and **3E** were prepared from diastereomers **5S** and **5R**, respectively. The individual diastereomers were available from the known epimeric diol mixture **4**[9] after selective silylation of the 1° alcohol as the t-butyldiphenylsilyl (TBDPS) ether[10,11] (Scheme I).

As shown in Scheme II, diastereomer **5S** was converted to **3Z** by derivatization of the benzylic hydroxyl as the methyl xanthate by treatment with sodium hydride then excess carbon disulfide and quenching with iodomethane.[8] The resulting xanthate, **6S**, was heated in toluene (110°) to cleanly afford olefin **7Z** which

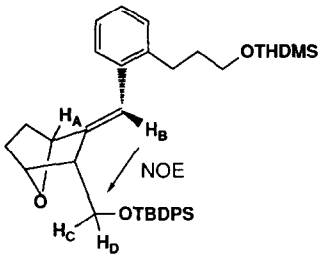
Scheme II



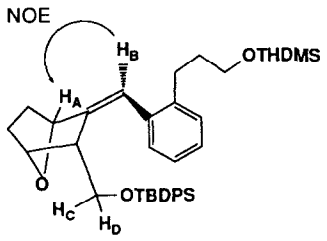
a. NaH/THF, 60°, b. CS_2 (2.2eq), 25°, 20h; c. CH_3I (2 1eq), 25°; d. toluene, 110°, 2.5 h; e. Jones, 0°; f. CH_2N_2/ether, 0°; g. nBu_4NF/THF, 25°, 2 h; h Jones, 0°, i WSC/HOBT/Et_3N/DMF, 0 to 25°; j. PPh_3(2eq)/DIPEA(3eq)/CCl_4(2eq)/ CH_3CN/CH_2Cl_2, 25°, 18 h; k. NiO_2(4 wt eq)/CH_2Cl_2, 25°; l LiOH(2eq)/aq THF, 25°, 3 h.

showed a characteristic ^1H NMR ($CDCl_3$) olefin singlet at δ 6.09. The α-chain thexyldimethylsilyl (THDMS) ether was selectively cleaved and oxidized upon treatment with Jones reagent.[12] Diazomethane esterification of the resulting crude acid gave methyl ester **8Z**. The ω-chain hydroxyl was deprotected by exposure to tetra-n-butyl

ammonium fluoride[13] to afford alcohol-ester **9Z**. Jones oxidation of **9Z** followed by standard WSC/HOBT mediated coupling of the resulting acid with L-serine amide derivative **11**[14] gave hydroxyamide **12Z**. Cyclization of **12Z** using PPh_3/CCl_4 conditions followed by nickel peroxide oxidation[15] of the resulting oxazoline **13Z** gave oxazole **14Z**.[16] Hydrolysis of **14Z** afforded desired *exo*-methylene isomer **3Z**. Isomer **3E** was prepared from diastereomer **5R** by a similar sequence. In this case $NaH/CS_2/CH_3I$ derivatization of the benzylic alcohol proceeded poorly. Alternatively, the methyl xanthate was obtained in good yield employing a recently reported two-phase procedure (CS_2/aq NaOH/CH_3I/cat nBu_4NHSO_4, 25°, 48 h, 89%).[17] In contrast to the clean elimination of **6S**, pyrolysis of the *R*-isomer (toluene, 110°, 2.5 h) afforded only a 40% yield of *E*-isomer product **7E** which showed a characteristic ^1H NMR ($CDCl_3$) olefin singlet at δ 6.38. Importantly however, among the several products obtained only a single olefin product was formed. The remainder of the sequence proceeded as described in Scheme II to afford **3E**. The crucial double bond geometries of isomers **3Z** and **3E** were established with the aid of 400 MHz ^1H NMR NOE data on intermediate precursors **7Z** and **7E**. Isomer **7Z** showed a strong NOE between H_B and $H_{C,D}$ and the absence of an NOE between H_B and H_A. In contrast, a strong NOE was observed between H_A and H_B in **7E**.



7Z



7E

Both **3Z** and **3E** were evaluated for their ability to inhibit arachidonic acid induced platelet aggregation (AAIPA)[18] and the results are shown in Table I. Examination of the results indicates that *exo*-methylene oxabicycloheptane analog **3Z** which mimics conformer **1** exhibited comparable antagonistic activity to SQ 33,961. This suggests that the receptor binding conformation of SQ 33,961 resembles conformer **1** in which the sidechains lie in an extended hairpin conformation.

Table I. *In Vitro* Evaluation of *Exo*-Methylene Oxabicycloheptanes[18]

Compound	Inhibition of AAIPA (I_{50})
SQ 33,961	2 nM
3Z	8 nM
3E	12700 nM

Acknowledgement: We thank the Bristol-Myers Squibb Analytical Research Department for assistance in obtaining spectral and elemental combustion data, Ms. Alicia D. Kahle for NOE studies, Mr. Harold J. Goldenberg and Ms. Inge M. Michel for pharmacological data and Drs. Philip M. Sher and Steven E. Hall for

helpful discussions. In addition, we thank one of the referees for alerting us to the preferred rotameric conformation of the oxazole amide.

Notes and References

1. Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A* **1975**, *72*, 2994-2998.

2. For a comprehensive review of TxA_2 antagonists see: Hall, S. E. *Med.Res. Rev.* **1991**, *11* , in press.

3. See discussion and references cited in: Andersen, N. H.; Hartzell, C. J.; De, B. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1985**, *14*, 1-43

4. Misra, R. N.; Brown, B. R.; Sher, P. M.; Patel, M. M.; Harris, D. N. *BioMed Chem. Lett.* preceeding communication.

5. Sprague, J. T.; Tai, J. C.; Yuh, Y.; Allinger, N. L. *J. Comput. Chem.* **1987**, *8*, 581-603.

6. Some non-standard MM2 parameters were needed to carry out the MMP2 calculations reported here. These were either adapted from existing MM2 parameters for chemically analogous atom types, or were derived from least squares fits to semiempirical quantum chemical results. (See Hopfinger, A. J.; Pearlstein, R. A. *J. Comput. Chem.* **1984**, *5*, 486-499.) In our case, the quantum chemical method was AM1 (Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909). The full parameter set is available on request from one of the authors (A.T.P.).

7. Analogous conformers were also examined, in which the oxazole sidechain was rotated 180° as a rigid unit and the resulting geometry was reoptimized. These were only very slightly higher in steric energy than the pictured conformers, and were not further considered. Note that this study does not attempt to select a definitive binding conformation for the oxazole ring. Note also that Figures 1 and 2 show the oxazole amide moiety in its preferred rotameric state, *i.e.*, carbonyl O *anti* to oxazole N, as opposed to the structural formulas in the text, which do not convey conformational details.

8. Review: Nace, H. R. *Org. React.* **1962**, *12*, 57-100.

9. Misra, R. N.; Brown, B. R.; Han, W.-C.; Harris, D. N.; Hedberg, A.; Webb, M. L.; Hall, S. E. *J. Med. Chem.* **1991**, *34* (9), 0000, in press.

10. All compounds exhibited spectral data (IR, MS, ^1H and/or ^{13}C NMR) consistent with their proposed structures. In addition, satisfactory elemental combustion analyses were obtained for acids **3Z** and **3E**.

11. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99-102.

12. See Djerassi procedure in Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* ; Vol. 1; Wiley: New York, 1967; pp 142-144.

13. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975-2977.

14. Amide **11** was prepared in 70% yield from BOC-(L)-serine by coupling with 4-cyclohexylbutylamine (WSC/HOBT/NMM/DMF, 0 to 25°) followed by BOC-cleavage (TFA/CH_2Cl_2, 25°) and chromatography.

15. Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L. Jr.; Meyers, A. I. *J Org Chem* **1979**, *44*, 497-501.

16. The sequence for elaborating the omega chain was similar to that described in reference 4.

17. Lee, A. W. M.; Chan, W. H.; Wong, H. C.; Wong, M. S. *Syn. Comm.* **1989**, *19*, 547-552.

18. Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22*, 295-307.