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INTERPHENYLENE 7-OXABICYCLO[2.2.1]HEPTANES. SQ 33,961: A NEW POTENT, LONG-ACTING THROMBOXANE ANTAGONIST[1]

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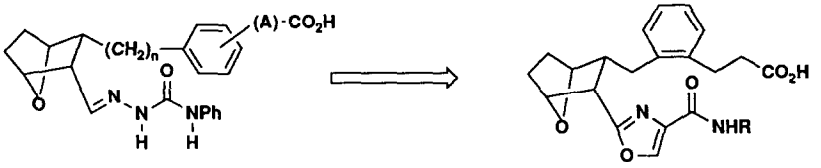
Abstract: The synthesis and initial biological evaluation of a novel series of chiral interphenylene 7-oxabicyclo-[2.2.1]heptane TxA_2 antagonists with 4-amido oxazole omega chains is described. Within this series SQ 33,961 has been identified as a highly potent TxA_2 antagonist with an exceptionally long *in vivo* duration of action.

Thromboxane A_2 (TxA_2)[2] is a potent, short-lived endogenous arachidonic acid derived mediator which induces platelet activation/aggregation and vasoconstriction and has been implicated as a contributor in cardiovascular disease.[3] As part of a program to develop clinically useful antagonists of TxA_2 we have been involved in the identification of compounds which are resistant to β-oxidation and exhibit a therapeutically useful *in vivo* duration of action in addition to potency, selectivity and oral activity.[4] We previously reported that interphenylene 7-oxabicyclo[2.2.1]heptanes with semicarbazone omega chains, **1**, were potent, orally-active TxA_2 antagonists with an extended duration of action.[5,11] Despite the favorable biological profile of these



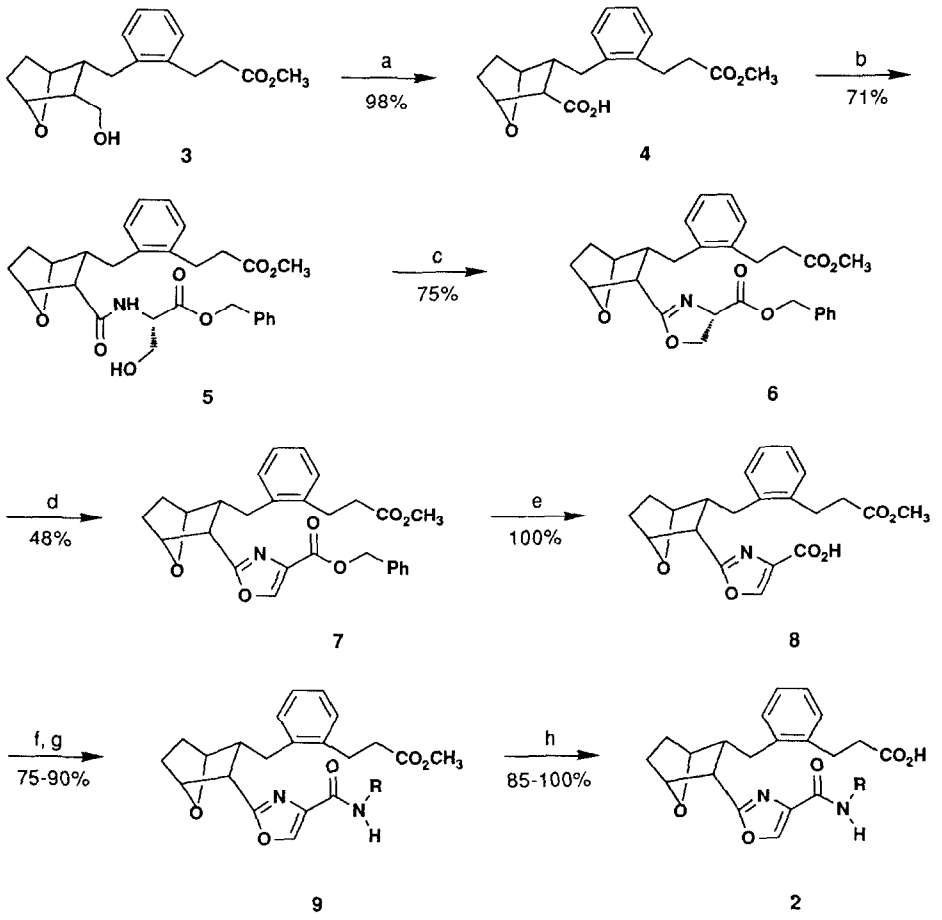
1 **2**

antagonists we were reluctant to pursue further development of this series due to concerns related to the possible toxicity of semicarbazones. Although we were unable to develop the semicarbazone series, it provided a novel interphenylene 7-oxabicycloheptane substructure with an established potential for potency, oral activity and duration of action which we anticipated could be employed in conjunction with a suitable semicarbazone surrogate. We report here in preliminary form the synthesis and initial biological evaluation of a novel series of very potent interphenylene 7-oxabicycloheptane TxA_2 antagonists, **2**, in which the semicarbazone omega chain of **1** has been replaced by a 4-amido oxazole, a recently reported semicarbazone surrogate which has been employed in a related series of TxA_2 antagonists.[6]

Oxabicycloheptane oxazoles **2** were prepared by elaboration[6] of the omega chain of known chiral interphenylene 7-oxabicycloheptane alcohol-ester **3**.[5] As shown in Scheme I, Jones oxidation of **3** afforded *exo*-acid **4**.[7] The requisite carbons for the 4-amido oxazole were introduced by coupling of acid **4** with L-serine benzyl ester hydrochloride using standard DCC/HOBT conditions to give hydroxyamide **5**. Oxazole formation was accomplished by a sequence which involved initial cyclization of hydroxyamide **5** using triphenylphosphine/carbon tetrachloride followed by oxidation of the resulting intermediate oxazoline **6**. It was

noted that the cyclization reaction proceeded at an appreciably faster rate in acetonitrile than in THF. In addition, an observed β-elimination side reaction to afford the corresponding acrylate was largely suppressed by employing the hindered base diisopropylethylamine rather than triethylamine. Acid sensitive oxazoline **6** was oxidized

Scheme I: Preparation of Interphenylene 7-Oxabicycloheptane Oxazoles



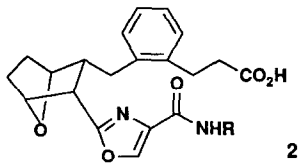
a. Jones, 0°; b. L-serine benzyl ester hydrochloride/DCC/HOBT/Et_3N/THF, 0 to 25°; c. Ph_3P/CCl_4/DIPEA/CH_3CN, 25°; d. NiO_2/CH_2Cl_2, 25°; e. 20% $Pd(OH)_2$-C/H_2(1 atm), EtOAc; f. $(COCl)_2$/cat DMF/CH_2Cl_2, 25°; g. $RNH_2/Et_3N/CH_2Cl_2$, 0°; h. LiOH/aq THF, 25°.

rapidly to oxazole **7** by addition of excess nickel peroxide (4-5x by weight).[8,9] The reactions were monitored by TLC adding nickel peroxide in portions until oxazoline **6** was consumed. Although the oxidation of **6** proceeded relatively cleanly to afford a major mobile product by TLC, the yield of **7** after silica gel purification was only 48%. The benzyl ester of **7** was selectively cleaved using Pearlman's catalyst to give oxazole acid **8**. Oxazole acid

8 was converted to the corresponding acid chloride, which was used to prepare, after reaction with the appropriate amine and base hydrolysis, amide modified analogs **2a-g.**[10] Interphenylene 7-oxabicycloheptanes **2a-g** were generally purified by recrystallization and isolated as stable, white solids.

Interphenylene 7-oxabicycloheptane oxazoles **2a-g** were evaluated for their ability to inhibit arachidonic acid and U-46,619 induced platelet aggregation (AAIPA and U-IPA) in human platelet-rich plasma.[11] The results are shown in Table I and expressed as I_{50} values. Examination of Table I indicates that oxazoles **2** are highly potent

Table I: *In Vitro* Evaluation of Interphenylene 7-Oxabicycloheptanes



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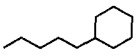
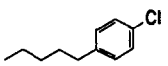
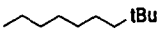
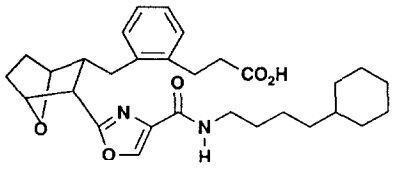
Compound	R	Inhibition of AAIPA I_{50} (nM)	Inhibition of U-IPA I_{50} (nM)
2a (SQ 33,961)		2	6
2b		3	25
2c		4	13
2d		3	5
2e	-$nC_{10}H_{21}$	1	6
2f	-nC_7H_{15}	2	13
2g	-CH_3	20	81

TxA_2 antagonists in which a variety of lipophilic groups, R, are tolerated as amide substituents. Surprisingly, even **2g** with simple N-methyl substitution exhibited potent TxA_2 antagonistic properties. In particular, SQ 33,961 (**2a**), was found to be an exceptionally potent TxA_2 antagonist in human platelets and was further evaluated for its *in vivo* duration of action. SQ 33,961 was examined for its ability to protect from U-46,619 induced lethality in mice as a function of time and was highly effective at 0.2 mpk/po, exhibiting a T_{50} value of 23 hr.[12] Receptor binding studies with TxA_2 receptor radioligand [^{3}H]-SQ 29,548 in human platelet membranes

showed a K_d = 0.1 nM establishing that SQ 33,961 was acting at the TxA_2 receptor.[13] In summary, SQ 33, 961 has been identified as a potent TxA_2 antagonist with an exceptionally long *in vivo* duration of action. Complete structure-activity studies and detailed pharmacological evaluation of SQ 33,961 will be the subject of future reports.



SQ 33,961

AAIPA I_{50} = 2 nM
U-46,619 IPA I_{50} = 6 nM
K_d = 0.1 nM
U-46,619 Mouse Lethality
T_{50} (0.2 mpk/po) = 23 hr

Acknowledgement: We thank the Bristol-Myers Squibb Analytical Research Department for assistance in obtaining spectral and elemental combustion data; Dr. Anders Hedberg for receptor binding studies and Drs. David M. Floyd, Steven E. Hall, Martin L. Ogletree and Peter W. Sprague for helpful discussions.

Notes and References

1. Presented at the 201st American Chemical Society National Meeting, Atlanta, GA, MEDI 73, April 14-19,1991.
2. Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A* **1975**, *72*, 2994-2998.
3. (a) Halushka, P. V.; Mais, D. E. *Drugs of Today* **1989**, *25* (6), 383-393.
   (b) Smith, E. F. III *Eicosanoids* **1989**, *2* (4), 199-212.
4. For an excellent review of TxA_2 antagonists see: Hall, S. E. *Med. Res. Rev.* **1991**, *11*, in press.
5. 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.
6. Sher, P. M.; Patel, M. M.; Stein, P. D.; Han, W.-C.; Hall, S. E.; Floyd, D. M.; Harris, D. N.; 201st American Chemical Society National Meeting, Atlanta, GA, MEDI 68, April 14-19,1991.
7. 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 **2a-g**.
8. Nickel peroxide prep: Nakagawa, K.; Konaka, R.; Nakata, T. *J. Org. Chem.* **1962**, *27*, 1597-1601.
9. Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L. Jr.; Meyers, A. I. *ibid.* **1979**, *44*, 497-501.
10. Characterization of SQ 33,961: white solid, mp 162-165° (CH_3CN); IR(KBr): 3420 (broad), 2923, 1724, 1648, 1603, 1520, 1107 cm^{-1}; 270 MHz ^1H NMR ($CDCl_3$) δ 0.70-1.90 (m, 21H), 2.21 (dd, *J* =2,9, 1H), 2.39 (dd, *J* =9,9, 1H), 2.55 (t, *J* =7, with overlapping 1 H m, 3H total), 2.91 (t, *J* =8, 2H), 3.38 (m, 3H), 4.39 (d, *J* =5, 1H), 4.98 (d, *J* =5, 1H), 7.05 (crude t, 1H), 7.14 (m, 4H), 8.12 (s, 1H); 67.8 MHz ^{13}C NMR ($CDCl_3$) δ 24.3, 26.4, 26.7, 27.5, 28.9, 29.9, 32.4, 33.4, 34.6, 37.1, 37.6, 39.2, 47.0, 50.0, 78.7, 79.7, 126.6, 126.7, 129.1, 129.7, 136.0, 137.8, 138.5, 140.9, 160.8, 163.9, 175.7; MS(CI): *m/z* 509 ($M+H^+$).
11. As described by Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22*, 295-307; the AAIPA and U-IPA I_{50} of BM13.505 were 730 nM and 1600 nM and those of GR 32,191 were 33 nM and 59 nM, respectively, under identical assay conditions; the I_{50} values for the semicarbazone analog of SQ 33, 961 (**1** where, n=1 and (A) = *o*-$(CH_2)_2$) were 3 nM and 12 nM, respectively.
12. The T_{50} value is defined as the calculated time from dosing that one half of the population survives U-46,619 challenge. For a description of the assay see: Kohler, C.; Wooding, W.; Ellenbogen, L. *Thromb. Res.* **1976**, *9*, 67-80. The T_{50} of BM13.505 was 7.1 hr and that of GR 32,191 was 0.5 hr, under identical assay and dosing conditions.
13. As described by Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Harris, D. N.; Liu, E. C.-K. *J. Pharmacol. Exp Ther.* **1988**, *245* (3), 786-792. We thank Dr. Anders Hedberg for receptor binding data on SQ 33,961