Bioorganic & Medicinal Chemistry Letters, Vol.2, No.9, pp. 937-940, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

INTERPHENYLENE PHENYL OXAZOLES: NOVEL, POTENT THROMBOXANE RECEPTOR ANTAGONISTS

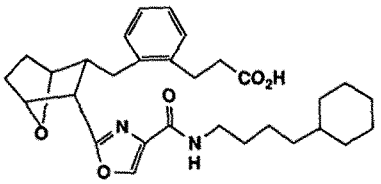
Raj N. Misra, Don N. Harris, Inge M. Michel,
Harold J. Goldenberg, Maria L. Webb, Baerbel R. Brown*

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, N. J. 08543-4000

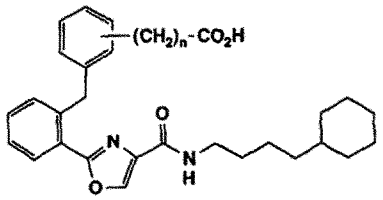
(*Received* 15 *May* 1992)

Abstract: The synthesis and in vitro evaluation of a novel series of structurally simple interphenylene phenyl oxazoles **2** is described. The optimal interphenylene substitution pattern and carboxyl side chain length were determined and from this series **2b** (SQ 34,942) was identified as a potent TxA_2 antagonist (AAIPA I_{50}=31 nM, K_d=19 nM).

The potent platelet and vascular activities of thromboxane A_2 (TxA_2),[1] a labile arachidonic acid metabolite, has resulted in efforts to develop TxA_2 receptor antagonists for the potential treatment of cardiovascular, renal and pulmonary diseases.[1-3] We previously reported interphenylene 7-oxabicycloheptane oxazole **1** (SQ 33,961) as a potent and long-acting TxA_2 receptor antagonist.[4] Due to the synthetic complexity required in assembling chiral



1 (SQ 33,961)



2

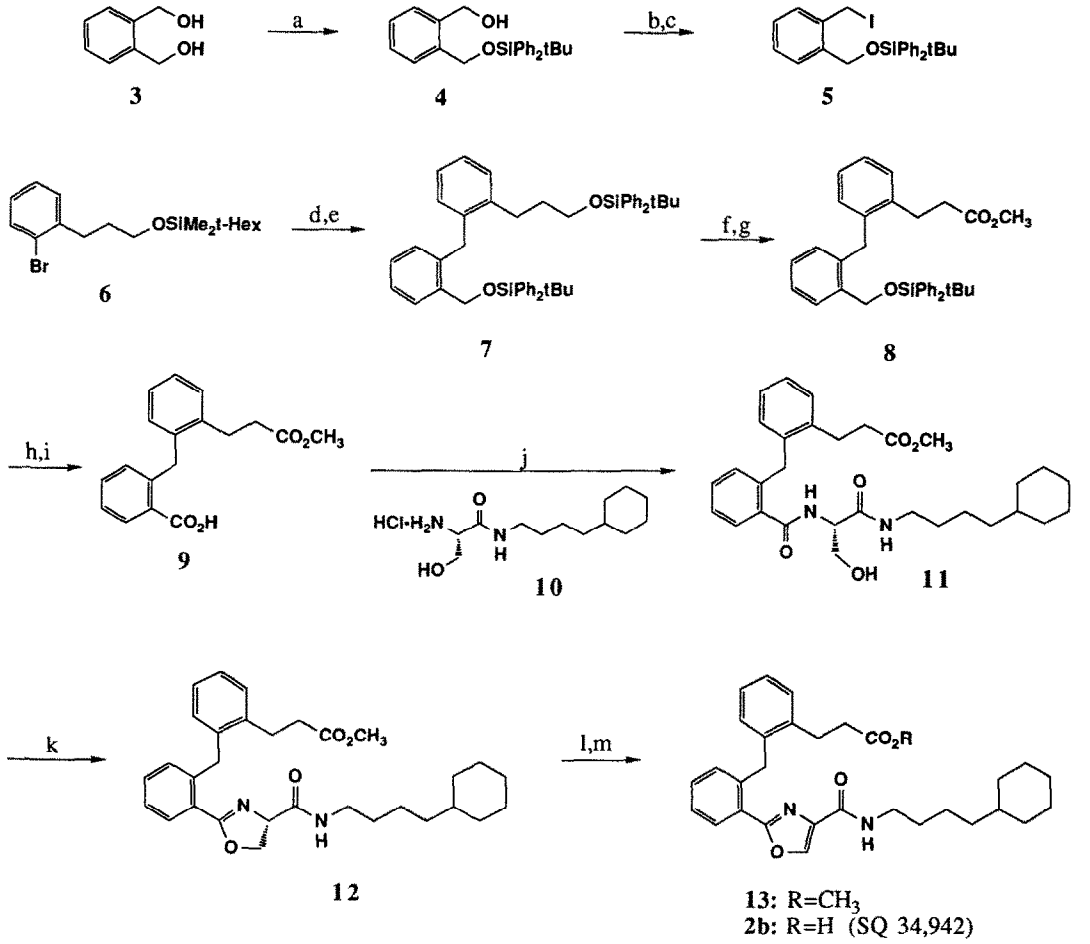
7-oxabicycloheptanes we have been involved in a program to identify antagonists related to SQ 33,961 with ring systems of simplified structure. In particular we targeted analogs of general structure **2** in which the 7-oxabicycloheptane ring has been replaced by a simple phenyl ring. In addition to providing relatively easily accessible synthetic targets, we anticipated that comparision of the TxA_2 antagonistic activity of analogs **2** with the antagonistic activity of SQ 33,961 would provide an indication of the importance of the 7-oxabicycloheptane ring of SQ 33,961 to antagonistic activity. We describe here our preliminary results on the synthesis of interphenylene phenyl oxazoles **2** and report the effect of interphenylene substitution pattern and carboxyl sidechain length on TxA_2 antagonistic activity.

Synthesis

Interphenylene phenyl oxazoles **2** were prepared by a lithium tetrachlorocuprate catalyzed coupling of benzyl iodide **5** with an appropriately substituted aryl Grignard reagent followed by construction of the oxazole ring as exemplified in Scheme I for the synthesis of **2b**. Benzyl iodide **5** was prepared by the monosilylation of 1,2-benzenedimethanol,[5] followed by mesylation of the unprotected alcohol and subsequent iodide displacement

of the mesylate. Coupling of iodide **5** with the Grignard reagent derived from aryl bromide **6**[6] was accomplished in the presence of catalytic lithium tetrachlorocuprate[7] in THF at 0°. The crude coupling product **7** was selectively oxidized by treatment with Jones reagent and then esterified with diazomethane to afford methyl ester **8**. The overall yield of ester **8** from aryl bromide **6** was 60%. Elaboration of the ω-chain proceeded by initial alcohol deprotection of **8** with tetrabutylammonium fluoride, followed by treatment of the resulting alcohol with

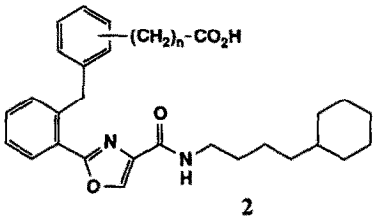
Scheme I: Preparation of Interphenylene Phenyl Oxazole SQ 34,942



a. NaH/THF, 50° then $ClSiPh_2tBu$ /THF, 25°, 100%; b. $MsCl/Et_3N/CH_2Cl_2$, -20°; c. NaI/acetone, 25°, 94% from **5**; d. Mg/THF/I_2, reflux; e. Li_2CuCl_4/0° then **5**, 0-25° f. Jones, 0°; g. CH_2N_2/Et_2O, 0°, 60% from **6**; h. nBu_4NF/THF, 25°, 88%; i. Jones, 0-25°, 97%; j. WSC/ HOBT/Et_3N/DMF, 0-25°, 76%; k. Ph_3P/ DIPEA/CCl_4/MeCN/CH_2Cl_2,25°, 96%; l. $CuBr_2$ /DBU/EtOAc/$CHCl_3$, 25°, 46%; m. LiOH/aq THF, 25°, 92%.

Jones reagent to give the acid-ester **9**. Coupling (WSC/HOBT) of acid-ester **9** with L-serine cyclohexylbutyl amide hydrochloride **10**[8] afforded amide **11**. Serine amide **11** was converted to oxazoline **12** by treatment with triphenylphosphine/carbon tetrachloride which was oxidized to oxazole **13** employing a mixture of copper(II) bromide/DBU as described previously.[9] Base hydrolysis of ester **13** gave **2b** (SQ 34,942) as a white solid.[10]

Table I: In Vitro Pharmacological Evaluation of Interphenylene Phenyl Oxazoles 2[11]



2

Compound	Substitution	n	AAIPA I_{50} (μM)	U-IPA I_{50} (μM)
1	-	-	0.002	0.006
2a	ortho	1	67	330
2b	ortho	2	0.031	0.11
2c	ortho	3	0.058	0.63
2d	meta	1	2.0	6.0
2e	meta	2	0.47	2.0

Structure-Activity Studies and Discussion

Interphenylene phenyl oxazoles **2** were evaluated for their ability to inhibit platelet aggregation induced by arachidonic acid (AAIPA) and U-46,619 (U-IPA) in human platelet rich plasma.[11] The results are shown in Table 1. In the ortho substituted series (**2a-c**), the propionic acid derivative, **2b**, (n=2) exhibited the most potent antagonistic activity in both AAIPA and U-IPA studies; the propionic acid analog **2e** was also the most potent in the meta substituted series. Comparision of the the ortho and meta substituted analogs showed that maximal potency was obtained with the ortho substituted analogs. The most potent ortho substituted analog, **2b**, was 15-fold more active than its meta substituted counterpart **2e**. In the interphenylene 7-oxabicycloheptane series, ortho substitution also produced significantly more active compounds than meta substitution with the propionic acids exhibiting maximal potency.[6,12] A striking difference in the SAR of the interphenylene 7-oxabicycloheptane oxazoles and interphenylene phenyl oxazoles was the greater sensitivity to carboxyl chain length variations displayed by the interphenylene phenyl oxazole series. The ortho substituted interphenylene phenyl oxazoles exhibited a >1000-fold difference in activity for chain lengths of n=1-3 while the interphenylene 7-oxabicycloheptane oxazoles exhibited only a 10-fold difference in activity for comparable analogs. A final comparison of the most potent compounds from the interphenyelene phenyl oxazole and interphenylene 7-oxabicycloheptane oxazole series showed that although **2b** (SQ 34,942) was a relatively potent TxA_2 antagonist, it

was 15-fold less active than SQ 33,961 indicating that the 7-oxabicycloheptane ring system provides a significant enhancement in potency relative to a phenyl ring. In support, radioligand binding studies in human platelet membranes using TxA_2 receptor radioligand [^{3}H]-SQ 29,548[13] showed K_d values for **2b** (SQ 34,942) of 19 nM and for SQ 33,961 of 0.1 nM indicating that SQ 33,961 also exhibited significantly enhanced receptor binding.

In summary, interphenylene phenyl oxazoles **2** have demonstrated that potent TxA_2 antagonistic activity can be achieved with structurally simple analogs of interphenylene 7-oxabicycloheptane oxazoles. The potency of interphenylene phenyl oxazoles **2** was found to be highly sensitive to the substitution pattern and length of the carboxyl side chain with ortho substitution and propionic acid side chain length optimal. From this series **2b** (SQ 34,942) was identified as a relatively potent TxA_2 antagonist in vitro exhibiting an AAIPA I_{50} = 31 nM and K_d = 19 nM.

Acknowledgements: We thank the Bristol-Myers Squibb Pharmaceutical Research Institute Analytical Research Department for elemental combustion and mass spectral analyses, Dr. Anders Hedberg for radioligand bindings studies on SQ 33,961 and Dr. Steven E. Hall for helpful discussions.

Notes and References

1. Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994-2998.
2. (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.
   (c) Oglctree, M. L. *Federation Proc.* **1987**, *46* (1), 133-138.
3. Hall, S. E. *Med Res. Rev.* **1991**, *11* (5), 503-579.
4. Misra, R.N.; Brown, B. R.; Sher. P. M.; Patel, M. M.; Goldenberg, H. J.; Michel, I. M.; Harris, D. N. *BioMed. Chem. Lett.* **1991**, *1* (9), 461-464.
5. McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388-3390.
6. 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), 2882-2891.
7. Lithium tetrachlorocuprate was used as a 0.1M solution in THF and was prepared as described by Tamura, M.; Kochi, J. *Synthesis*, **1971**, 303.
8. Serine amide **10** (white solid, mp 200° (dec)) was prepared in 2 steps from BOC-L-serine by coupling with cyclohexylbutyl amine (WSC/HOBT/Et_3N/DMF, 0 to 25°, 70%) followed by BOC-deprotection and HCl salt formation (excess 4N HCl in dioxane, 71%).
9. Misra, R. N.; Brown, B. R.; Sher, P. M.; Patel, M. M.; Hall, S. E.; Han, W.-C.; Barrish, J. C.; Floyd, D. M.; Sprague, P. W.; Morrison, R. A.; Ridgewell, R. E.; White, R. E.; DiDonato, G. C.; Harris, D. N.; Hedberg, A.; Schumacher, W. A.; Webb, M. L.; Ogletree, M. L. *BioMed. Chem . Lett.* **1991**, *2* (1), 73-76.
10. Characterization of **2b** (SQ 34,942): white solid, mp 117-119°; IR(KBr): 3431 (broad), 2924, 1726, 2851, 1713, 1656, 1604, 1523, 1212 cm^{-1}; 270 MHz ^{1}H NMR ($CDCl_3$) δ 0.82-1.68 (m, 17H), 2.58 (dd, *J* =7, 7, 2H), 2.94 (dd, *J* =8 , 8, 2H), 3.38 (q, *J* =7, 2 H), 4.52 (s, 2H), 6.93 (crude d, *J*=7, 2H), 7.14 (m, 4H), 7.35 (m, 2H), 7.99 (m, 1H), 8.22 (s, 1H); 67.8 MHz ^{13}C NMR ($CDCl_3$) δ 24.2, 26.4, 26.7, 27.7, 29.9, 33.3, 34.4, 36.9, 37.1, 37.5, 39.2, 125.7, 126.6, 126.8, 128.8, 129.4, 129.9, 130.8, 130.9, 137.0, 138.3, 138.4, 139.7, 140.6, 160.8, 161.1, 176.9; MS(CI): *m/z* 489 $(M+H)^+$.
11. Assay as described by Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Heikes, J. E.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22* (2), 295-307; the AAIPA and U-IPA I_{50} of BM 13,505 were 730 nM and 1600 nM and those of GR 32,191 were 33 nM and 59 nM, respectively, under identical assay conditions.
12. Misra, R. N.; Brown, B. R.; Hall, S. E.; Han, W.-C., unpublished results.
13. Assay 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.