Bioorganic & Medicinal Chemistry Letters, Vol 2, No.12, pp. 1623-1626, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

THROMBOXANE RECEPTOR ANTAGONISM COMBINED WITH THROMBOXANE SYNTHASE INHIBITION. 7. PYRIDINYLALKYL-SUBSTITUTED ARYLSULFONYLAMINO ARYLALKANOIC ACIDS.

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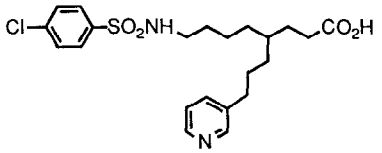
(*Received* 14 *July* 1992)

Abstract: Arylsulfonylamino arylalkanoic acids substituted with a pyridinylalkyl group on the arylalkanoic acid portion of the molecule were synthesized and found to behave as thromboxane receptor antagonists (TxRAs) and thromboxane synthase inhibitors (TxSIs). One of these compounds (**11**), with a 1,3,5-trisubstituted central aromatic ring was demonstrated to have good functional bioavailability and efficacy as a platelet inhibitor in guinea pigs.

Our research program for the discovery of compounds that inhibit the actions of thromboxane A_2 (TxA_2) by simultaneous inhibition of thromboxane synthase and antagonism of the receptors for TxA_2, has led to the discovery of several classes of compounds that are thromboxane receptor antagonists (TxRAs) and thromboxane synthase inhibitors (TxSIs) (TxRA/TxSI)[1]. Arylsulfonylamino-octanoic acids such as **1**, with a pyridinylalkyl group at the 4-position of the chain, comprise one such class[2]. With the goal of eliminating the only chiral center in these molecules and simultaneously changing their physicochemical as well as pharmacokinetic profile, we decided to synthesize analogs of the type **I** shown below with an aromatic ring in the middle of the chain. In this letter we disclose our efforts which have led to the identification of one lead compound which has a 1,3,5-trisubstituted aromatic ring with arylsulfonylaminoalkyl, pyridinylalkyl and alkanoic acid substituents.



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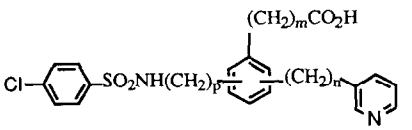
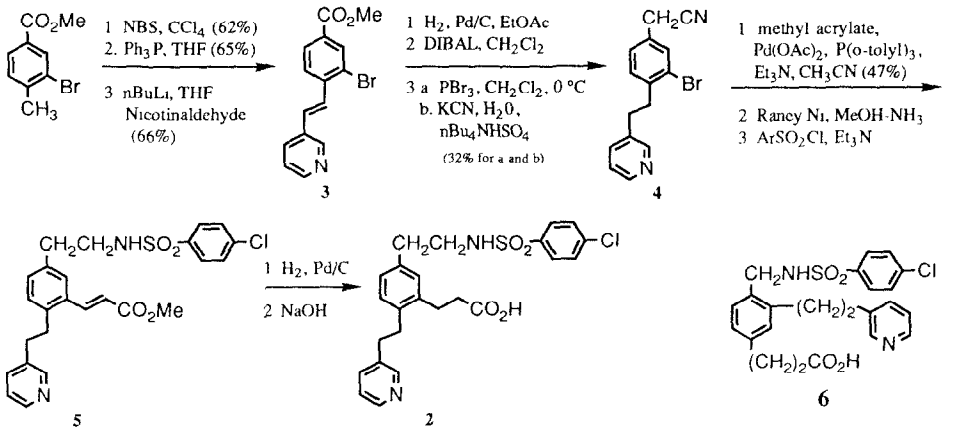


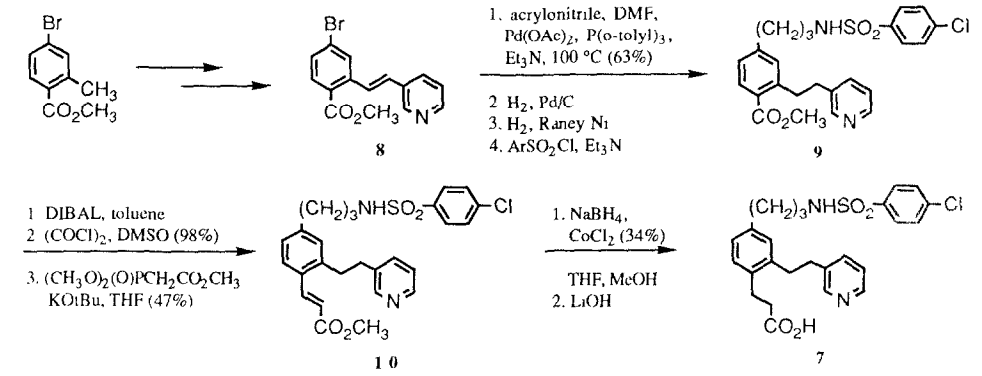
I

Compound **2** with the propionic acid and pyridinylethyl side chain was synthesized as shown in Scheme I. The methyl ester of commercially available 3-bromo-4-methylbenzoic acid was brominated using NBS to give the benzylic bromide which was converted to the corresponding phosphonium salt. Wittig reaction of the phosphorane with nicotinaldehyde gave **3**. Hydrogenation of the double bond of **3** followed by reduction of the ester gave the alcohol

Scheme I

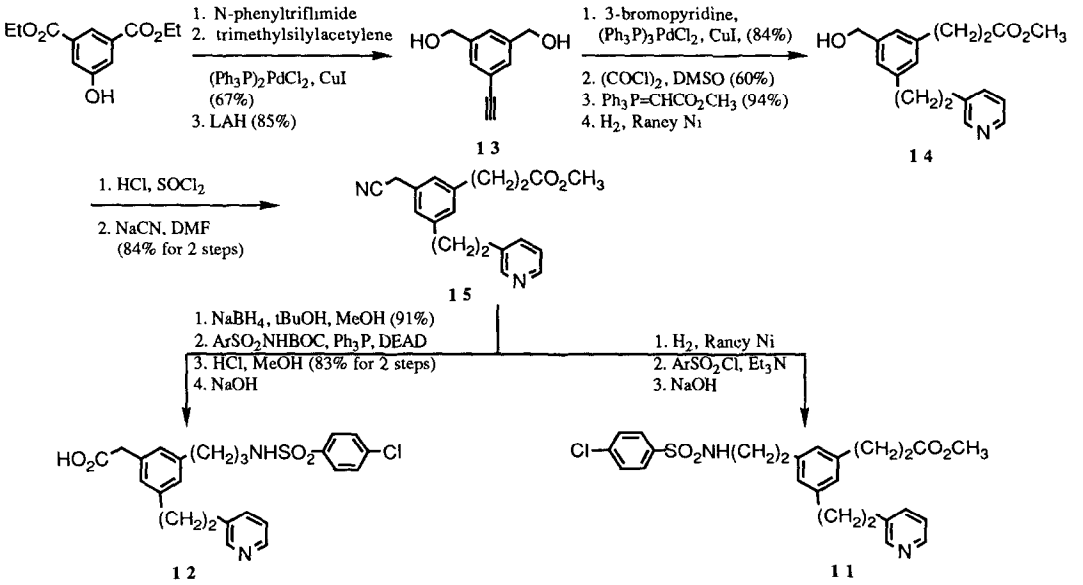


Scheme II



which was converted to the corresponding bromide and treated with KCN to give **4** Coupling of **4** with methyl acrylate under Heck reaction conditions[3] followed by reduction of the nitrile and sulfonylation of the resulting amine gave **5** Hydrogenation of the double bond of **5** followed by saponification gave **2** Compound **6** was synthesized using an essentially identical sequence of reactions starting from 5-bromo-2-cyanotoluene. Compound **7** was synthesized as shown in Scheme II Intermediate **8**, which is an isomer of **3**, was synthesized using the same sequence of reactions shown in Scheme I Heck reaction of **8** with acrylonitrile followed by hydrogenation of the double bonds, reduction of the nitrile and sulfonylation of the resulting amine gave **9** Homologation of **9** using DIBAL reduction, Swern oxidation of the resulting alcohol and Horner-Emmons reaction gave **10** Reduction of the conjugated double bond followed by saponification gave **7**.

Scheme III



The 1,3,5-trisubstituted aromatic compounds, **11** and **12**, were synthesized as shown in Scheme III. Diethyl 5-hydroxyisophthalate was coupled via its triflate with trimethylsilyl-acetylene using catalytic amounts of Pd (II) and Cu (I) salts[4a,b] and then reduced with LAH to give **13**. The reduction was accompanied by protodesilation. Coupling[4b] of **13** with 3-bromopyridine followed by Swern oxidation, Wittig reaction and hydrogenation gave **14**. Conversion of the alcohol to the corresponding chloride followed by displacement with NaCN gave the key intermediate **15**. Reduction of the nitrile followed by sulfonylation of the resulting amine and hydrolysis gave **11**[5] Reduction of the ester group of **15** followed by a one step conversion to the BOC-protected arysulfonamide[6] under Mitsunobu reaction conditions[7], hydrolysis of the nitrile to the ester and saponification gave **12**.

The target compounds **2**, **6**, **7**, **11** and **12** were tested for their ability to inhibit thromboxane synthase from a human microsomal platelet preparation and to antagonize the TxA_2-receptor mediated U 46619 induced aggregation of human platelets[8]. The IC_{50} values for the TxRA and TxSI activities are given in Table I.

Of the three 1,2,4/1,3,4-trisubstituted aromatic compounds shown here, **2** was the most potent as a TxRA [IC_{50}=15 nM (washed platelets, WP) and 300 nM (platelet rich plasma, PRP)] and a TxSI (IC_{50}=15 nM). The weaker activity in PRP relative to WP is probably due to protein binding and this behavior has been observed for other sulfonamide type TxRA[2]. Compound **7** was found to be fairly potent as a TxSI and both **6** and **7** were weakly active as a TxRA. Of the two 1,3,5-trisubstituted aromatic compounds, **11** was the more potent TxRA/TxSI In fact, **11** is one of the most potent TxRA we have tested with IC_{50}=3 nM (WP) and 170 nM (PRP).

Table I. TxRA and TxSI activities of the compounds

Compound[a]	mp, °C	Thromboxane Synthase Inhibition IC_{50}[b], μM	Inhibition of U 46619 induced aggregation of human WP IC_{50}[b], μM	aggregation of human PRP IC_{50}[b], μM
2	140-146	0.015	0.015	0 3
6	196-198	0.043	0 38	-
7	132-135	0 026	0.23	-
11	146-147	0.009	0 003	0 17
12	58-60	0 007	1 13	10 7

[a] All compounds had satisfactory IR and ^{1}H-NMR and the elemental analyses were within ±0.4% [b] Values represent single determination

Due to the superior *in vitro* "dual inhibitory" activity of **11**, it was tested for its functional bioavailability in guinea pigs using the procedures described in an earlier publication[2] Upon oral administration (10 mg/kg) to guinea pigs (n=6), the concentration ratio (CR, the ratio of the EC_{50} for drug treated animals over that for control) for the U 46619 induced *ex vivo* platelet aggregation 1 h post dosing, was >100. The CR is an indication of the relative increase in the concentration of the agonist needed for aggregating the platelets from drug treated animals. At the dose indicated above, we could not elicit a response to up to a 40 μM concentration of U 46619, indicating that **11** has good bioavailability and efficacy as a platelet inhibitor in guinea pigs. Compound **2** was much less active in this assay with CR=5 2±1.1 (10 mg/kg p o dose, n=6) Further work is needed to evaluate the pharmacological efficacy of **11** in animal models

Acknowledgement: We are grateful to Ms Lia Raabis and Mr Karl Gunderson for some of the ^{1}H NMR spectra and Ms Natalie Cahoon and Mr Michael Hatolski for IR spectra.

References

(1) For part 6 see. Bhagwat, S S ; Boswell, C.; Gude, C , Contardo, N., Cohen, D. S., Mathis, J., Dotson, R.; Lee, W. *Bio. Med Chem. Lett.*, preceding paper in this issue. (2) Bhagwat, S S.; Gude, C.; Boswell, C ; Contardo, N., Cohen, D. S , Dotson, R ; Mathis, J.; Lee, W ; Furness, P., Zoganas, H *J. Med. Chem.*, **1992**, 35, 0000 (3) Heck, R F *Org. Reactions*, **27**, 345-390 (1982). (4) (a) Sonogashira, K., Tohda, Y,; Hagihara, N. *Tetrahedron Lett.*, **1975**, 4467-4470. (b) Ames, D E ; Bull, D ; Takundwa, C. *Synthesis*, **1981**, 364-365. (5) Spectral data for compound **11:** IR($CDCl_3$) 3689, 3283 (br), 2930, 1720, 1602, 1478, 1335, 1163, 1096 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 8 38 (br s, 1H), 8.11 (s, 1H), 7.75 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7 24 (m, 1H), 6.81 (s, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 4 67 (br, 2H), 3 15 (t, J = 7 Hz, 2H), 2 86 (m, 6H), 2 68 (t, J = 7 Hz, 2H), 2.57 (t, J = 7 Hz, 2H). (6) Henry, J R.; Marcin, L R ; McIntosh, M C , Scola, P M ; Harris, G D., Weinreb, S. M *Tetrahedron Lett.*, **1989**, 5709-5712. (7) Bhagwat, S S , Gude, C , Cohen, D , Dotson, R.; Mathis, J , Lee, W ; Furness, P *J. Med. Chem.*, submitted for publication. (8) Bhagwat, S S., Gude, C , Cohen, D S ; Lee, W.; Furness, P., Clarke, F. H *J. Med. Chem.*, **1991**, 34, 1790-1797