Bioorganic & Medicinal Chemistry Letters, Vol.2, No.12, pp. 1619-1622, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

THROMBOXANE RECEPTOR ANTAGONISM COMBINED WITH THROMBOXANE SYNTHASE INHIBITION. 6. 4-SUBSTITUTED 3-PYRIDINYLALKANOIC ACIDS.

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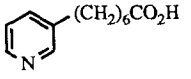
(*Received* 30 *June* 1992)

Abstract: (3-Pyridinyl)alkanoic acids substituted at the 4-position with an (arylsulfonamido)alkyl group were synthesized and found to behave as platelet thromboxane receptor antagonists (TxRAs) and thromboxane synthase inhibitors (TxSIs). The compounds behaved as **agonists** at the vascular receptor for thromboxane A_2.

Thromboxane A_2 (TxA_2), a potent platelet aggregating and vasoconstricting agent, has been implicated in the pathogenesis of circulatory disorders[1]. Thromboxane synthase inhibitors (TxSIs) and thromboxane receptor antagonists (TxRAs) have been developed to treat such disorders[2,3]. While the efficacy of TxRAs has yet to be established, the TxSIs have performed poorly in the clinic. The lack of efficacy of TxSIs has been ascribed to PGH_2 which accumulates due to the inhibition of thromboxane synthase[4,5]. The accumulated PGH_2, which has activity similar to that of TxA_2, nullifies the benefits of reducing the levels of TxA_2. We have undertaken a program to develop compounds which behave both as a TxRA and a TxSI[6a,b], because combining the two activities is proposed to be better than either one alone[7,8].

It is well established that (3-pyridinyl)alkanoic acids and (arylsulfonylamino)alkanoic acids of the type **1** and **2** represent the basic structural features required for TxSI and TxRA activities respectively[9]. Examination of the literature indicated that placing a substituent at the 4-position of the pyridine ring of a TxSI is tolerated by the enzyme[10] In view of these structure activity relationship (SAR) considerations, we decided to synthesize pyridinyl-alkanoic acids of the type **I** with an arylsulfonamido group at the 4-position of the ring in order to obtain compounds with TxRA and TxSI activities.



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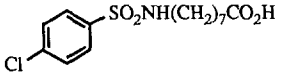

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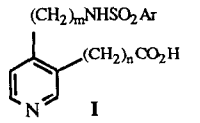
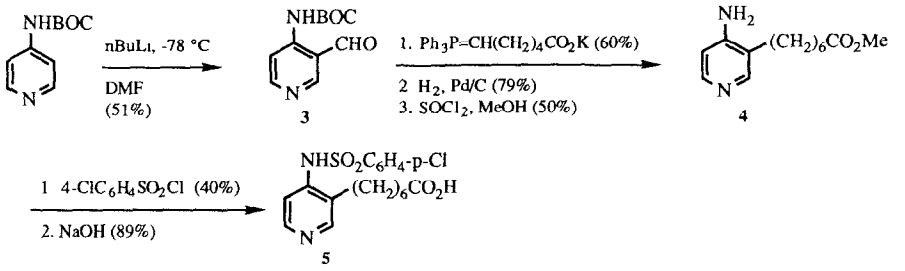


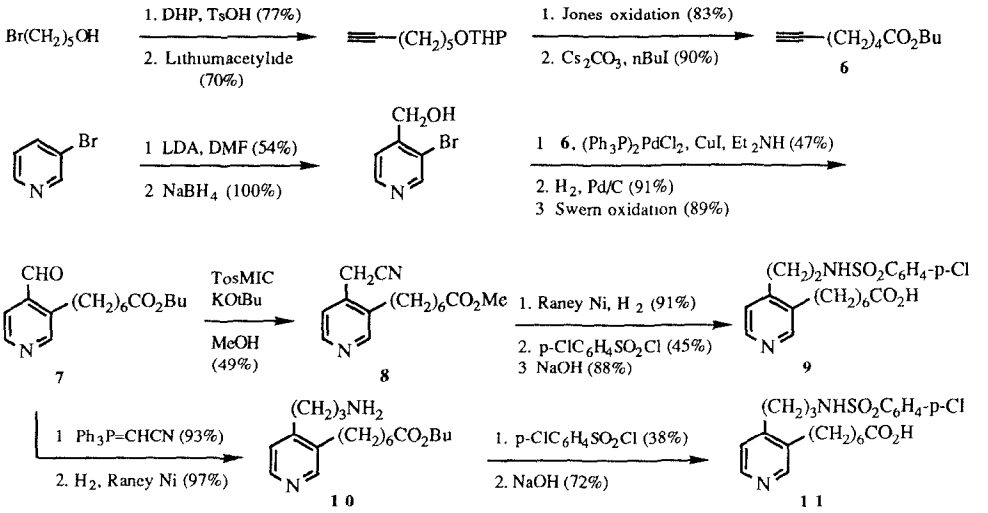
I

Compound **5** with the 4-chlorophenylsulfonylamino group attached directly to the 4-position of the pyridine ring was synthesized as shown in Scheme I. The BOC-protected 4-aminopyridine was lithiated[11] with nBuLi at -78 °C and quenched with DMF to give **3** Wittig reaction of **3** with the phosphorane derived from 4-carboxypentyltriphenyl-phosphonium bromide followed by reduction of the double bond and esterification gave the aminoester **4**. Sulfonylation of the amine followed by saponification of the ester gave the target compound **5**.

Scheme I



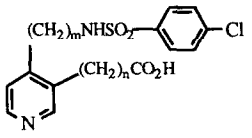
Scheme II



The homologs of **5**, with two or three methylenes between the pyridine ring and the sulfonamide nitrogen, were synthesized as shown in Scheme II. Formylation of 3-bromopyridine via the corresponding lithium derivative gave 3-bromopyridine-4-carboxaldehyde[12]. Reduction of the aldehyde to the corresponding alcohol followed by palladium (II) and Cu (I) catalyzed coupling[13] of this compound with the alkynoate **6**, hydrogenation and Swern oxidation gave **7** Reaction of **7** with the anion of (p-tolylsulfonyl)methylisocyanate (TosMIC)[14] gave the nitrile **8**. Conversion of the nitrile to the amine followed by sulfonylation and saponification gave **9** Wittig reaction of **7** with (triphenylphosphoranylidine)-acetonitrile followed by hydrogenation with Raney nickel gave the primary amine **10** Sulfonylation of **10** and hydrolysis gave **11** which has three methylenes connecting the pyridine ring and the sulfonylamino group Compounds **12**, **13** and **14** were synthesized similarly from n-butyl 5-hexynoate. In the preparation of **12**, the hydroxymethyl group at the 4-position was converted first to the corresponding chloride-hydrochloride salt ($SOCl_2$, reflux) which was then displaced with

the sodium anion of di-t-butyliminodicarboxylate. Deprotection of the amine followed by sulfonylation and saponification gave **12** Compounds **13** and **14** were synthesized using the reaction sequence used for **9** and **11**.

Table I. TxRA and TxSI activities of the compounds



Compound[a]	m	n	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
5	0	6	152-154	inactive	inactive	inactive
9	2	6	166-167	0.08	0.094	0.44
11	3	6	99-103	0.015	1.44	7.97
12	1	5	135-136	0.066	0.22	1.08
13	2	5	98-100	0.043	0.195	0.61
14	3	5	138-139	0.1	0.036	0.67

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

The target compounds **5**, **9**, **11**, **12**, **13** and **14** were tested for their ability to inhibit the thromboxane synthase enzyme and antagonize the platelet and vascular receptors for TxA_2 as per the procedures described earlier[15]. The inhibition of TxB_2 formation from human microsomal platelet preparation incubated with [^{14}C]-arachidonic acid was measured as an indicator of TxSI activity. The inhibition of U 46619 induced aggregation of aspirinated, washed human platelets (WP) and platelet rich plasma (PRP) were measured as indicators of platelet TxRA activity. The IC_{50} values for the TxSI and TxRA activities are given in Table I

Compound **5** was inactive both as a TxSI and TxRA. The reason for this lack of activity could possibly be due to the highly acidic sulfonamide proton which may make the pyridine ring exist in the dihydropyridine tautomeric form. Placing one or more methylenes between the pyridine ring and the sulfonylamino group gives both TxSI and TxRA activities to the compounds. Thus compounds **9**, **11**, **12**, **13** and **14** were found to be fairly active TxSI with IC_{50} values in the range 15-100 nM. We decided to choose n=5,6 for the compounds in Table I because these values are established to be optimal for the TxSI activity[9]. The variation in the TxSI activity of these compounds appears to be due to the change in the length of the sidechain at the 4-position of the pyridine ring.

We have observed that a separation of 6-8 methylenes between the arylsulfonylamino group and the carboxylic acid is optimal for TxRA activity in WP (data not shown) Introducing a cis-arrangement, as in the case of the compounds in Table I, enables one to increase the separation of these groups to 8-10 atoms without losing much activity (IC_{50} = 36-220 nM) Compound **11** with 11 atoms between the two groups is much less active. The TxRA activity of these compounds in PRP is lower than that in WP by 3-20 fold probably because of protein binding Such loss of activity has previously been observed for sulfonylaminoalkanoic acid types of TxRA[16]

The compounds in Table I were tested further for their ability to antagonize the vascular receptor for TxA_2 because it has been observed that the platelet receptor is different from that on vascular bed[17]. To our surprise, at concentrations of 10^{-6}-10^{-9} M, compounds **9**, **11**, **12**, **13** and **14** were all found to be **agonists** on the dog saphenous vein Therefore, at the concentrations specified, these compounds contracted the dog saphenous vein This result is surprising since in our earlier work[16] it was clear that the agonist activity on the dog saphenous vein is observed only when a pyridinylalkyl group is substituted at the carbon atom α- or β- to the sulfonylamino group. Further work is needed to determine the structural features that would dissociate the undesired agonist activity from these compounds.

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

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