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SYNTHESIS OF NEW 3,4-DISUBSTITUTED PYRROLIDINES AS THROMBOXANE A_2/PROSTAGLANDIN H_2 (TP) RECEPTOR ANTAGONISTS[1]

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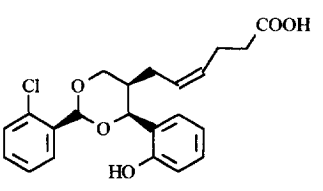
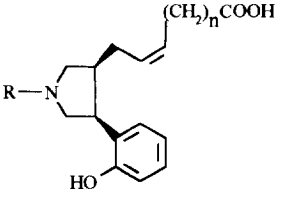
Abstract: The synthesis and TP-receptor antagonistic activity of a series of 3,4-disubstituted pyrrolidines is described. The sulfonamide **1h** was the most potent TP-receptor antagonist in this series with a pA_2 value of 9.5 in isolated guinea pig trachea.

Thromboxane A_2 (TxA_2), an unstable metabolite of arachidonic acid, has been implicated in the pathogenesis of numerous circulatory disorders[2]. To prevent these disorders, different structural classes of TxA_2/Prostaglandin H_2 (TP) receptor antagonists have been developed[3,4]. The structures of the majority of the known TP-receptor antagonists are characterized by an alkenoic acid α-chain and an ω-chain, the latter exhibiting a wide array of structural variations. ICI 192605 possessing an o-hydroxyphenyl group instead of a ω-side chain, was described as a very potent and pure TP-receptor antagonist[5]. It has been shown that the presence of a phenolic hydroxyl group markedly increased the TP-receptor antagonistic activity, suggesting that this group interacts with the TP-receptor. According to this concept, we decided to synthesize new N-substituted pyrrolidines **1** having an o-hydroxyphenyl group.



ICI 192605



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This communication describes the synthesis and biological activity of new pyrrolidine derivatives bearing different types of substituent on the nitrogen atom.

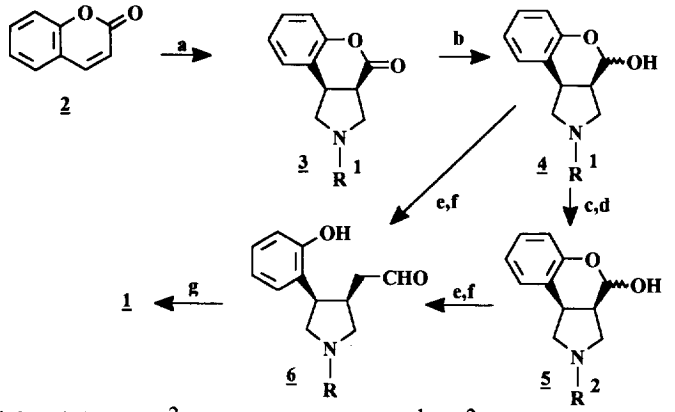
Chemistry:

The target compounds were synthesized via a 1,3-dipolar cycloaddition using a non-stabilized azomethine ylide and an activated double bond[6].

Synthesis of the cis compounds 1. The coumarin **2** was chosen as a starting material for the synthesis of pyrrolidines **3** which had key substituents in a good setting (Scheme I). The cycloaddition gave **3** in 90% yield when R^1 is benzyl. Then, the partial reduction of lactones **3** resulted in the lactols **4** in 70% yield. At this stage, various substituents were introduced on the nitrogen atom. Debenzylation of **4** was done on its hydrochloride form in a quantitative yield and then sulfonylation or acylation were performed by usual manner. The lactols **4** and **5** were then transformed into the final compounds **1** by a sequence which involved two successive Wittig reactions, respectively. The first homologation reaction using

methoxymethylenetriphenylphosphorane prepared in situ from the corresponding phosphonium salt gave the enol ethers which were hydrolyzed to give the aldehydes **6**. During these homologation reactions (**4** to **6** and **5** to **6**), a partial epimerisation was observed[7]. Finally, the cis aldehyde **6** was transformed directly into the ethylenic acid **1**[8].

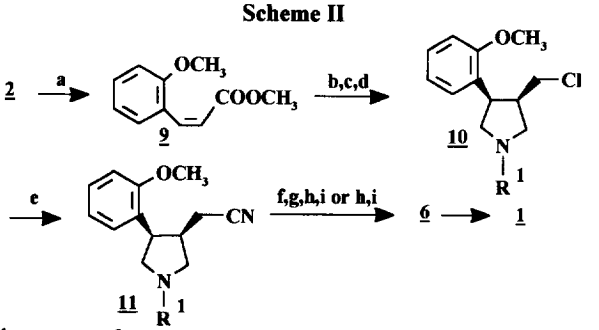
Scheme I



R^1 = benzyl; 3-methylpyridyl, R^2 = $ArylSO_2$; AlkylCO, R = R^1 or R^2
a: $Me_3SiCH_2N(CH_2OCH_3)R^1/CF_3COOH$ cat/EtOAc, 5°C to 50°C; b: DIBAL /toluene, -78°C; c: HCl/ EtOH then H_2-Pd/C, 25°C; d: $R^2X/Et_3N/CHCl_3$, 0°C; e: $Ph_3P^+CH_2OCH_3,Cl^-$/tBuOK/THF, 25°C; f: $CF_3COOH/H_2O/CH_3CN$, g: $Ph_3P^+(CH_2)_{n+1}$ $COOH,X^-$/tBuOK/THF, 25°C (n = 2 or 3).

To avoid the partial formation of trans isomer **8** and to assign unambiguously the stereochemistry on the pyrrolidine ring, we prepared the cis isomer **1** according to the route shown in Scheme II. Coumarin **2** was opened by treatment with barium dihydroxide in dimethylformamide in the presence of methyl iodide to give the Z o-methoxycinnamate **9**[9].

Scheme II



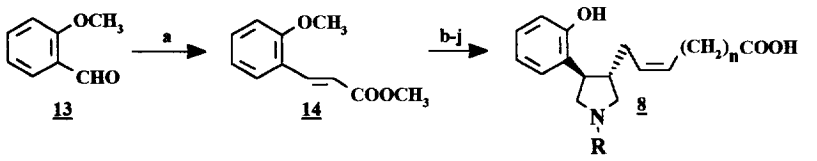
R = R^1 or R^2, R^1 = CH_2Ph, R^2 = $ArylSO_2$, AlkylCO
a: $Ba(OH)_2 \cdot 8H_2O$/MeI/DMF, 40°C; b: $Me_3SiCH_2N(CH_2OCH_3)R^1/CF_3COOH$ cat./EtOAc, 5°C to 50°C; c: $LiAlH_4$/THF, 10°C; d: $CHCl_3$/HCl gas, 25°C then $SOCl_2$, reflux; e: $nBu_4N^+CN^-$/DMF, 80°C; f: HCl/ EtOH then H_2-Pd/C, 25°C; g: $R^2X/Et_3N/CHCl_3$, 0°C; h: BBr_3/CH_2Cl_2,-80°C to 20°C; i: DIBAL/CH_2Cl_2/ -50°C; j: $Ph_3P^+(CH_2)_{n+1}$ $COOH,X^-$/tBuOK/THF, 25°C, (n = 2 or 3)[8].

The 1,3-dipolar cycloadditon of **9** gave the cis pyrrolidine with an ester function. Reduction of ester followed by the chlorination of the resulting alcohol gave the chloride **10** in 50% overall yield. Treatment of chloride **10** with tetrabutylammonium cyanide in dimethylformamide gave the nitrile **11**[10]. Then, various substituents were introduced on the nitrogen atom as described before. Finally, aldehydes **6** were obtained

by the demethylation of **11** with boron tribromide and the partial reduction of the nitrile with DIBAL in 60% overall yield.

Synthesis of the trans compounds 8. The trans compounds were prepared as outlined in Scheme III. The 2-methoxybenzaldehyde **13** was transformed into cinnamate using the Horner-Emmons reaction. The E isomer was obtained by chromatography. Then, the sequence described in Scheme II was applied.

Scheme III



a: $(CH_3O)_2P(O)CH_2COOCH_3$/NaH/THF; b: $Me_3SiCH_2N(CH_2OCH_3)R^1/CF_3COOH$ cat./EtOAc, 5°C to 50°C; c: $LiAlH_4$/THF, 10°C; d: $CHCl_3$/HCl gas, 25°C then $SOCl_2$, reflux; e: $nBu_4N^+CN^-$/DMF, 80°C; f: HCl/EtOH then H_2-Pd/C, 25°C; g: $R^2X/Et_3N/CHCl_3$, 0°C; h: BBr_3/CH_2Cl_2,-80°C to 20°C; i: DIBAL/CH_2Cl_2/ -50°C; j: $Ph_3P^+(CH_2)_{n+1}$ $COOH,X^-$/tBuOK/THF, 25°C (n = 2 or 3).

Biological results. The TP-receptor antagonistic activities of compounds **1a-i**, **8c** and **8h** were evaluated in a racemic form. Table I represents the *in vitro* and *in vivo* results of the compounds.

The antagonistic properties on TP-receptors were first evaluated using the isolated tissue technique[12]. Isolated guinea pig tracheal rings were contracted with increasing concentrations of the TP-receptor agonist, U46619, in the absence or presence of compounds; the antagonistic activity was measured by calculating the pA_2 values. The *in vivo* activity of the compounds was evaluated after their *i.v.* administration to guinea pigs in which an increase in the tracheal pressure was evoked with U46619 using the technique originally described by Konzett and Rossler[13]; the IC_{50} values were expressed in μg/kg. The anti-platelet activity of the compounds was measured by studying their inhibitory effects on human platelet rich plasma (PRP) aggregated with U46619; the IC_{50} values were expressed in μM.

Finally, compound **1b** and **1h** were tested for TxA_2-synthase inhibitory activity in human whole blood and no TxA_2-synthase inhibitory effect was observed for these substances[14].

The new pyrrolidines bearing an o-hydroxyphenyl group were very potent TP-receptor antagonists. The lengths of side chain containing a carboxyl group (**1f**, **1g**) and the stereochemistry on the pyrrolidine ring (**1c**-**8c** and **1h**-**8h**) strongly influenced on activity. The most active compounds were the sulfonamide derivatives of the pyrrolidine, showing the crucial role of the sulfonyl group for the activity. Like ICI 192605, compound **1h** neither caused aggregation nor shape change of human platelets demonstrating the absence of platelet agonist activity. The cis compound **1h** was selected for further evaluations.

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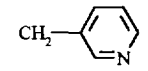
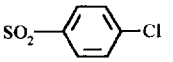
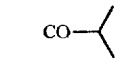
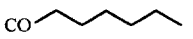
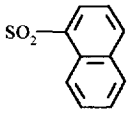
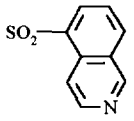
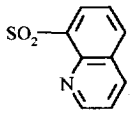
Table I: Biological activities of pyrrolidine derivatives

Compound[a]	R	n	Inhibition of U 46619 induced: contraction of isolated guinea pig trachea (pA_2)	increase in tracheal pressure of guinea pigs ($ID_{50}\mu g/kg$)[b]	aggregation of human platelets ($IC_{50}\mu M$)[b]
1a	CH_2Ph	2	6.6	170	NT
1b		"	5.8	1000	NT
1c		"	9	30	4.7
8c	"	"	7.9	120	NT
1d		"	6.7	110	"
1e		"	7.7	430	"
1f		"	8.8	7.5	0.6
1g	"	3	8.2	80	3.6
1h[11]		2	9.5	11	1.3
8h	"	"	NT	56	NT
1i		"	NT	25	3
ICI 192605			9.4	0.7	0.013

a: All compounds had satisfactory IR,MS and ^1H, ^{13}C-NMR analysis; b: values represent single determinations
NT: not tested

References and notes

1. Presented in part at the 23rd American Chemical National Medicinal Chemistry Symposium, Buffalo N.Y., Poster 48, June 14-18, **1992**.
2. Cross P.E.; Dickinson R.P.; *Chemistry in Britain* **1991**, 911.
3. For a comprehensive review of TxA_2 antagonists see: Hall S.E.; *Med. Res. Review* **1991**, *11*, 503.
4. For more recent reports see: a) Misra R.N.; Brown B.R.; Sher P.M.; Patel M.M.; Hall S.E.; Han W.C.; Barrish J.C.; Kocy O.; Harris D.N.; Goldenberg H.J.; Michel I.M.; Schumacher W.A.; Webb M.L.; Monshizadegan H.; Ogletree M.L. *J. Med. Chem.*, **1993**, *36*, 1401. b) Komiotis D.; Pananookooln S.; Zaw K.; Dieter J.P.; Le Breton G.C.; Venton D.L.; *Eur. J. Med. Chem.*, **1995**, *30*, 321.
5. Brewster A.G.; Brown G.R.; Foubister A.J.; Jessup R., Smithers M.J.; *Prostaglandins* **1988**, *36*, 173.
6. Terao Y.; Kotaki H.; Imai N.; Achiwa K.; *Chem. Pharm. Bull.* **1985**, *33*, 2762.
7. The cis/trans ratio was dependent on the nature of the substituent on the nitrogen atom and fluctuated from 63/35 (R = n-hexCO) to 85/15 (R = benzyl). The two aldehydes were separated by flash column chromatography (cyclohex/EtOAc), and **6** were obtained on 40 to 60% overall yield.
8. The Z/E ratio for the two isomers formed during the Wittig reaction varied from 80/20 (R = benzyl) to 95/5 (R=n-hexCO). The Z isomer was isolated after HPLC.
9. Kuhn R.; Trischmann H.; *Chem. Ber.* **1961**, 2258.
10. Use of KCN for the preparation of **11** led to a partial epimerisation at the benzylic carbon atom.
11. Spectral data for compound **1h**: I.R.: 3400-2500, 1709 cm^{-1}; ^1H NMR (DMSO-d6)δ 9.55 (s,1H), 8.8 (d,1H), 8.6 (d,1H), 8.5 (d,1H), 8.45 (d,1H), 7.9 (t,1H), 7.05 (t,1H), 6.75 (2d,2H), 6.5 (t,1H), 5.2 (m,J = 11, 1Hz, 1H), 5.1 (m,1H), 3.7 (m,2H), 3.6 (m,1H), 3.5-3.1 (dd,2H), 2.55 (m,1H), 2.1 (t,2H), 1.85 (m,2H), 1.6-1.45 (m,2H).
12. Verbeuren T.J.; Simonet S.; Herman A.G.; *Eur. J. Pharmacol.* **1994**, *270*,27.
13. Konzett, H. and Rossler R.; *Arch. Exp. Pathol. Pharmacol.* **1940**, *195*, 71.
14. Watts I.S.; Wharton K.A.; While B.P. and Lumley P.; *Br. J. Pharmacol.* **1991**, *102*, 497

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