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NOVEL PROSTANOID THROMBOXANE A_2 ANTAGONISTS

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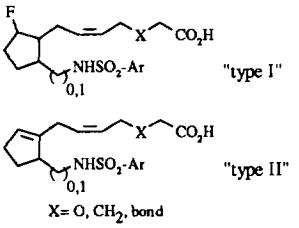
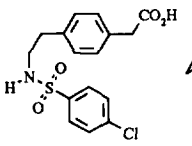
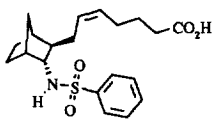
ABSTRACT: The chemistry and *in vitro* pharmacology of novel prostanoid TXA_2(TP)-receptor antagonists is described. (5Z)-(9R)-12-(4-Chlorobenzenesulfonamido)-9-fluoro-13,14,15,16,17,18,19,20-octanor-5-prostenoic acid was identified as a potent TP-receptor antagonist.

INTRODUCTION: In a former publication[1] we demonstrated that $\Delta^{8,9}$- or 9-fluoro prostanoids possess a remarkable affinity to the TP-receptor. Because we did not succeed to synthesize TP-receptor antagonists in this series having a prostanoid ω-side chain, we envisaged compounds of type I and type II possessing sulfonamides in the lower side chain, which seem to introduce or increase thromboxane antagonistic qualities into a variety of different structural classes. Examples for representative TP-antagonists containing sulfonamide moieties are BM 13505[2], S-145[3] and Bay-u-3405[4].

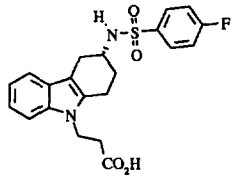




BM 13505 (Daltroban)



S-145 (rac.)



Bay-u-3405

SYNTHESIS[5]: The synthesis started with the optically active Corey lactone **1**, which was readily deoxygenated via the tosylate[6]. DIBAL reduction followed by Wittig reaction with either carboxybutyltriphenylphosphonium bromide (n = 1) or carboxypropyltriphenylphosphonium bromide (n = 0) and subsequent esterification furnished the key compound **6**. Reaction with (diethylamino)sulfur trifluoride (DAST) gave an 1:1-mixture of the 9-fluoro- and $\Delta^{8,9}$-prostanoid precursors **7** and **8** which was separated by column chromatography on silica gel after deprotection[7]. A nitrogen atom in position 14 was introduced by a multistep sequence which led, after reaction with several aromatic sulfonyl chlorides, to the target compounds **14** and **20** (figure 1).

To prepare the analogous 13-aza derivatives we benzoylated the 9-hydroxyl group in **6**, removed the silyl group and oxidized the primary alcohol **22** to the carboxylic acid **23**. The corresponding acid azide **25** underwent a Curtius-rearrangement to give a mixture of **26** and **27**. The amine **27** was sulfonylated and finally the benzoate removed to yield **29** (figure 2).

Reaction of **29** with DAST, separation of the 9-fluoro- and the $\Delta^{8,9}$-compounds and saponification of the esters led to **31** and **33**. Interestingly, in this case the DAST reaction yielded the 9-fluoro- and the $\Delta^{8,9}$-compounds **30** and **32** in a ratio of 7:3. Intermediate **29** was also used to invert the configuration at position 9 by an oxidation-reduction sequence. **35** was transformed into the 9α-fluoro compounds **37** as already described (figure 3).

Dedicated to Professor Dr. Helmut Vorbrüggen on the occasion of his 65th birthday.

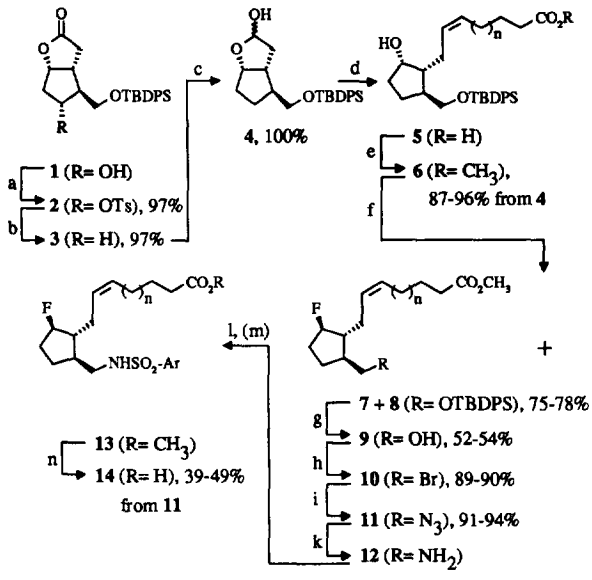


figure 1

figure 2

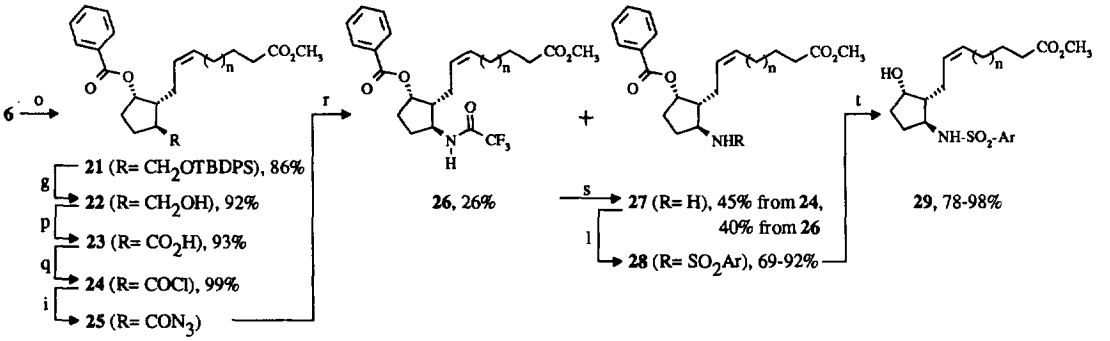
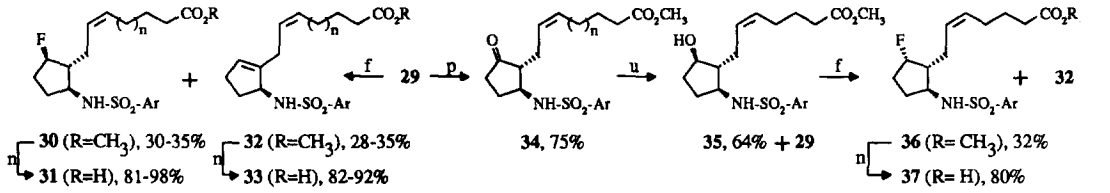


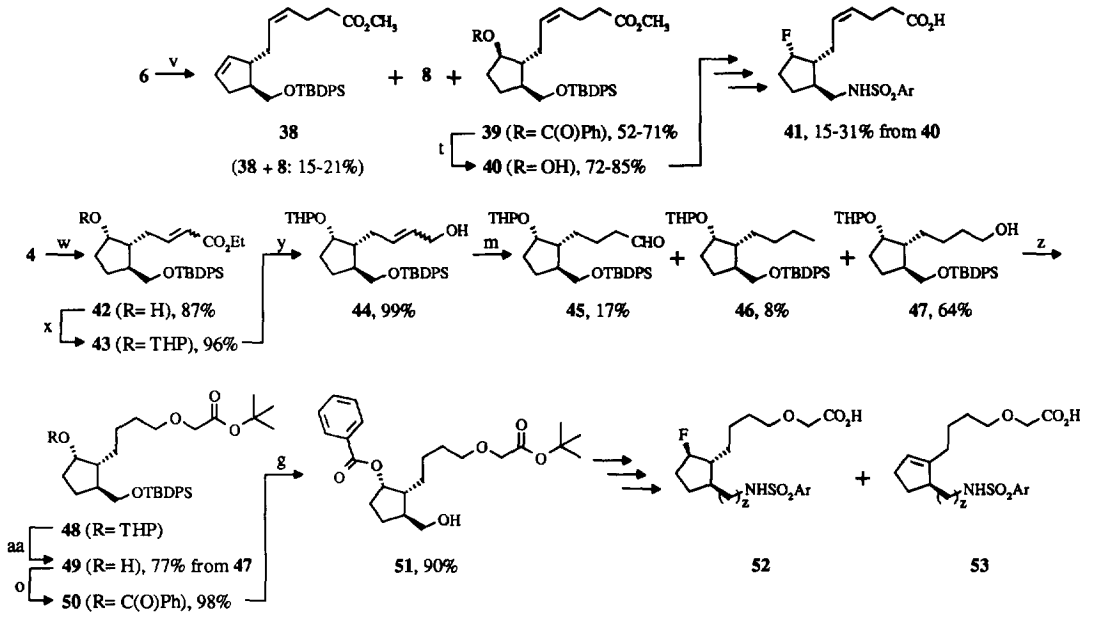
figure 3



The 9α-fluoro-14-aza derivatives **41** were synthesized by another route. A Mitsunobu reaction of **6** with benzoic acid gave **39** together with a 4:1 mixture of elimination products **8** and **38**. Debenzoylation of **39** and subsequent reaction with DAST yielded the 9α-fluoro compound together with a 1:1 mixture of **8** and **38**. The introduction of the sulfonamides followed the sequence already described for the 9β-fluoro analogues **14**.

In order to introduce a 3-oxa moiety into the α-chain we performed a Wittig reaction on lactol **4** and obtained the unsaturated ester **42** as a mixture of E/Z-isomers with a ratio of 91:9. After protection of the 9-hydroxyl

group and reduction of the ester, the resulting allylic alcohol **44** was hydrogenated catalytically to **47**, whereupon we obtained as side products the butyl-derivative **46** and the aldehyde **45**, the latter being formed by isomerisation of the double bond prior to hydrogenation as depicted in the following scheme.



Etherification of the primary alcohol under phase-transfer conditions with bromo tert.-butylacetate[8] completed the synthesis of the α-chain. After exchanging the protecting group at position 9 (**48** → **50**) and cleavage of the silylether in **50** we obtained **51** as key intermediate for the preparation of the 13-aza and 14-aza sulfonamides **52** and **53** as already described for the compounds with the natural α-chain.

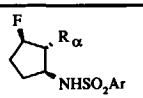
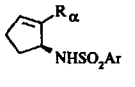
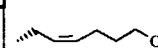
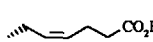
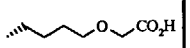
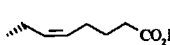
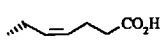
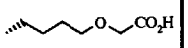
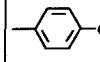
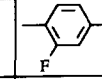
CONDITIONS: a: TsCl, pyridine, 50°C, 4-8h; SiO_2; **b:** NaI, Zn-dust, H_2O, DME, rf, 10-15h; SiO_2; **c:** DIBAL, toluene, -70°C, 1h; **d:** LiHMDS, carboxybutyl- or carboxypropyltriphenylphosphonium bromide, THF, 30-60°C, 2-6h; **e:** CH_2N_2, CH_2Cl_2, 0°C, 30min; SiO_2; **f:** DAST, pyridine, toluene, -60°C→-20°C, 2.5h; SiO_2; **g:** 1M TBAF, THF, rt, 2-4h; SiO_2; **h:** CBr_4, Ph_3P, collidine, CH_3CN, rt, 2-8h; SiO_2; **i:** NaN_3, cat. Bu_4NHSO_4, CH_2Cl_2, H_2O, 5°C, 1h; **k:** Ph_3P, THF, rt, 16h; H_2O, rf, 1h; SiO_2; **l:** $ArSO_2Cl$, Et_3N, CH_2Cl_2, rt, 5h; SiO_2; **m:** 1at H_2, cat. Pd/C (5%), ethyl acetate, rt; **n:** 5% LiOH, MeOH, rt, 2-16h; SiO_2; **o:** PhCOCl, pyridine, rt, 1.5h; SiO_2; **p:** Jones-ox., -10°C, 3h; SiO_2; **q:** $SOCl_2$, CH_2Cl_2, rt, 5h; **r:** CF_3CO_2H, H_2O, CH_2Cl_2, rf, 6h; SiO_2; **s:** $NaBH_4$, EtOH, rt, 5h; SiO_2; **t:** K_2CO_3, MeOH, rt, 1h; SiO_2; **u:** $NaBH_4$, MeOH, -40°C, 1h; SiO_2; **v:** DEAD, Ph_3P, $PhCO_2H$, toluene, rt, 5h; SiO_2; **w:** Ph_3P=CH-CO_2Et, toluene, 80°C, 48h; SiO_2; **x:** dihydropyrane, cat. p-TsOH, CH_2Cl_2, rt, 1h; SiO_2; **y:** DIBAL, toluene, 0°C, 1h; **z:** Br-CH_2CO_2-t-Bu, 50% KOH, cat. Bu_4NHSO_4, 2.5h; SiO_2; **aa:** cat. PPTs, EtOH, 55°C, 4h; SiO_2.

RESULTS AND DISCUSSION: Structure-activity-relationships for selected compounds will be discussed in detail based upon the biological results given in the following tables.

In the compounds described in *table 1* we varied the substitution pattern of the aryl-sulfonamide for three different α-chains. On studying the biological data it is not possible to deduce a consistent structure-activity-relationship which can be demonstrated at three examples:

- There is a good correlation between the receptor binding and the functional activity for the compound of entry 6a, while the corresponding $\Delta^{8,9}$-analogue (entry 6d) shows the same receptor binding affinity as 6a,

Influence of the aryl-sulfonamide substitution pattern for three different α-chains on the TP-receptor binding and the inhibition of platelet aggregation.

table 1													
R_α:													
		a		**b**		**c**		**d**		**e**		**f**	
entry	**-Ar**	**C_F**[9]	**IC_{50}**[10]	**C_F**	**IC_{50}**	**C_F**	**IC_{50}**	**C_F**	**IC_{50}**	**C_F**	**IC_{50}**	**C_F**	**IC_{50}**
1		4.0	1.1 (0.0005)	10	2.0	9.1 np	1.7	3.5	2.3	12	2.2	26	2.0
2		1.5 2.0[11]	0.26 0.6[11]	5.1	1.9	3.5 np	1.8	1.5	0.25 (0.0006)	7.4	1.8	11	1.9
3		1.5	0.54 (0.006)	4.3	0.75	2.7 np	1.8	1.5	4.4	5.5	1.3	13	2.0
4		1.1	0.2	6.6	1.6	30	1.8	1.5	ne	14	20	22	1.8
5		10	1.8	370	0.56	330	5.5	6.6	0.68	40	0.6	130	1.9
6		0.3	0.07	1.3	0.21	0.8	ne	0.3	ne	2.8	1.9	2.6	ne
7		0.5	0.63	1.4	1.7	2.3 np	ne	1.1	ne	13	1.9	7.6	1.9
8		0.3	0.2	not synthesized				0.3	1.9	not synthesized			
9		340	2.0	not synthesized				560	2.0	not synthesized			

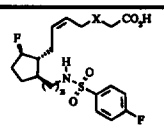
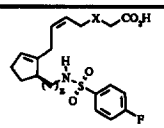
but does not inhibit platelet aggregation.

- In contrast to this finding, the two structures of entries 5b and 5d are equally effective in inhibiting platelet aggregation, although the first compound does not show the expected affinity to the TP-receptor.
- Even more pronounced is the discrepancy between the receptor binding and the functional activity in the compounds of entries 8 and 9. The C_F-values differ by a factor of 1000 to 2000 whereas the change in potency is only 10-fold at maximum.

In all cases where the inhibition of platelet aggregation has been determined using gel filtered platelets, the antiaggregatory potency increased 100 to 2000 fold.

At higher concentrations, some compounds show a partial agonistic behaviour which was expressed either by an amplification of the ADP induced aggregation or a by induction of aggregation.

In *table 2* the influence of the distance between the carboxylic acid and the sulfonamide concerning the TP-receptor binding and the inhibition of platelet aggregation is shown

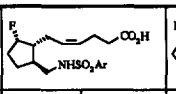
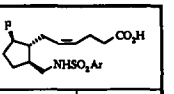
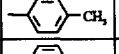
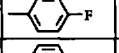
table 2							
entry	**z**	**X**	**Δ[5]**	**C_F[9]**	**IC_{50}[10]**	**C_F**	**IC_{50}**
1	1	CH_2	Z	50	2.0	17	1.7 (0.16)
2	1	CH_2	sat.	260	6.0	not synthesized	
3	1	O	sat.	6.7 np	0.65	0.5 np	0.2
4	1	bond	Z	300	1.9	21	0.6
5	1	bond	sat.	380	4.7	not synthesized	
6	0	CH_2	Z	1.5	0.54 (0.006)	1.5	4.4
7	0	CH_2	sat.	7.5	2.4	2.7	0.62 (0.04)
8	0	O	sat.	2.7 np	1.8	13	2.0
9	0	bond	Z	4.3	0.75	5.5	1.3

- Shortening the natural α-chain by one methylene group does not have a significant influence (compare entries 1 with 4 and 6 with 9) on the biological activities.
- The saturation of the double bond slightly reduces the affinity to the TP-receptor (compare entries 1 with 2 and 6 with 7), while the inhibition of platelet aggregation is enhanced for the $\Delta^{8,9}$-compound of entry 7.
- In the case of the 14-aza compounds (z = 1) the introduction of a 3-oxa moiety improves both qualities (compare entry 2 with 3), whereas in the 13-aza series (z = 0) this is only true for the 9-fluoro derivatives (compare entry 7 with 8).
- The inhibition of platelet aggregation is similar for all these compounds, with the IC_{50}-values in the range $0.2\text{-}6.0 \cdot 10^{-6}$M. For most compounds, the receptor binding affinity also lay within a relatively narrow range with the exception of the 9-fluoro-analogues of entries 1, 2, 4 and 5, in which the receptor binding affinity is considerably lower.

- Keeping the distance between the 1-carboxyl group and the sulfonamide nitrogen constant (z = 1, X = bond versus z = 0, X = CH_2), the influence of the position of the five membered ring can be deduced comparing entries 4 with 6 and 5 with 7[11].

Comparing the 9α- with the 9β-fluoro-compounds we found that the TP-receptor affinities for the former ones are higher in all cases, whereas this tendency again does not correlate with the platelet data (*table 3*).

Influence of the configuration at carbon 9 for differently substituted aryl-sulfonamides concerning the TP-receptor binding and the inhibition of platelet aggregation.

table 3					
entry	-Ar	C_F[9]	IC_{50}[10]	C_F	IC_{50}
1		6.0 np	ne	154	1.9
2		11 np	0.65	300	1.9
3		1.8 np	ne	40	1.8

ACKNOWLEDGEMENT: We thank Drs. F. McDonald, K.-H. Thierauch and P.F.J. Verhallen for providing us with the biological data.

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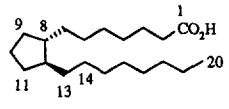
3. Ohtani M.; Matsuura T.; Watanabe F.; and Narisada M. *J. Org. Chem.* **1991**, 56, 2122.
4. Perzborn E.; Boberg M.; Bühner K. et al. *Drugs Future* **1991**, 16, 701.
5. The structures of all synthesized compounds were at least confirmed by high resolution NMR-spectroscopy.
6. Pradhan S.K.; Kolhe J.N.; and Mistry J.S. *Tetrahedron Lett.* **1982**, 23, 4481.
7. To simplify the discussion, the prostaglandin numbering concerning the five membered ring will be maintained throughout this paper regardless of the changes made in the side chains.



8. Skuballa W.; Schillinger E.; Stürzebecher C.-St.; and Vorbrüggen H. *J. Med. Chem.* **1986**, 29, 313.
9. The TP-receptor affinities in the tables are given as competition factors C_F= (IC_{50}-test)/(IC_{50}-standard); C_F -U46619 = 36. In the binding assay the standard ^{3}H-SQ 29548 is used as standard TP-receptor antagonist at 5 nM. The K_D-value for ^{3}H-SQ 29548 on platelet membranes is 20 nM. Unlabelled SQ 29548 or test compounds are added at concentrations up to 10 µM; nc means no competition; np not parallel. A detailed experimental description is given in Klar U.; Pletsch A.; Rehwinkel H.; Schreyer R. Biomed. Chem. Lett., submitted for publication.
10. Platelet aggregation was assessed turbidimetrically in citrated human platelet rich plasma (PRP; treated with acetylsalicylic acid $5 \cdot 10^{-3}$ M and diluted 1:1 with Tyrode buffer); stirred continuously at 1000 rpm; where the optical density of unstimulated platelets was taken to represent 0% aggregation and that of platelet poor plasma to represent 100% aggregation. Test substances were added to PRP to investigate pro-aggregatory activity; in the absence of pro-aggregatory activity; the effects of test substance on aggregation induced by the stable TP-mimetic U 46619 (1 µM) were assessed following pre-incubation with test substance for 1 minute. All values are given in micromolar concentrations and represent a single determination; ne means not effective at concentrations up to 10 µM. Data given in brackets are determined using gel-filtered platelets.
11. These values correspond to the 9α-fluoro-epimer.

(*Received in Belgium* 14 *March* 1995)