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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW TETRAHYDRONAPHTHALENE DERIVATIVES AS THROMBOXANE RECEPTOR ANTAGONISTS[1]

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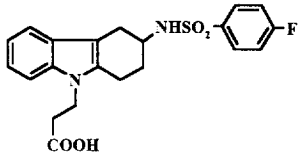
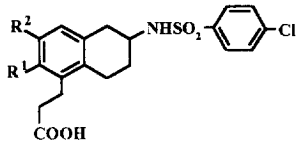
Abstract: New polysubstituted tetrahydronaphthalene derivatives were prepared as thromboxane receptor (TP-receptor) antagonists. Within this series of compounds **S 18886** has been identified as an orally active, highly potent antagonist with a very long duration of action in different species.

Thromboxane A_2 (TXA_2) is a potent, short-lived endogenous arachidonic acid metabolite which induces platelet aggregation and vasoconstriction and has been implicated in a wide range of cardiovascular, pulmonary and renal diseases[2]. As a consequence, the search for compounds to prevent the deleterious action of TXA_2 is currently very active[3,4]. As part of a program to develop potent, orally active TP-receptor antagonists, with a long duration of action, we have studied the synthesis of different series of compounds[5]. Numerous non-prostanoid TP-receptor antagonists have a carboxylic acid and a benzenesulfonamide group separated by a spacer as common structural features[6]. Ramatroban **1** is a good example of this type of compounds in which the spacer is a rigid polycycle, namely a carbazole derivative[7]. We report here the synthesis and the initial biological evaluation of a novel series of TP-receptor antagonists **2** where a substituted tetrahydronaphthalene was chosen as a rigid spacer.



1 Ramatroban

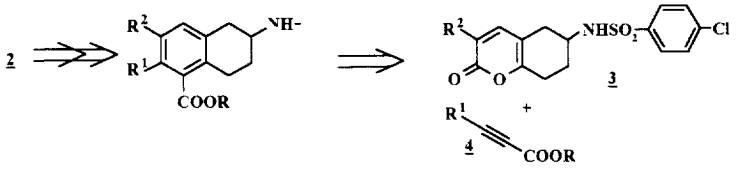


2

Chemistry:

The target compounds **2** were considered as polysubstituted benzenes instead of naphthalene derivatives and then the benzene ring was constructed via a Diels-Alder reaction between an appropriate 2-pyrone **3** and an acetylenic derivative **4**[8] (Scheme I).

Retrosynthetic Scheme I



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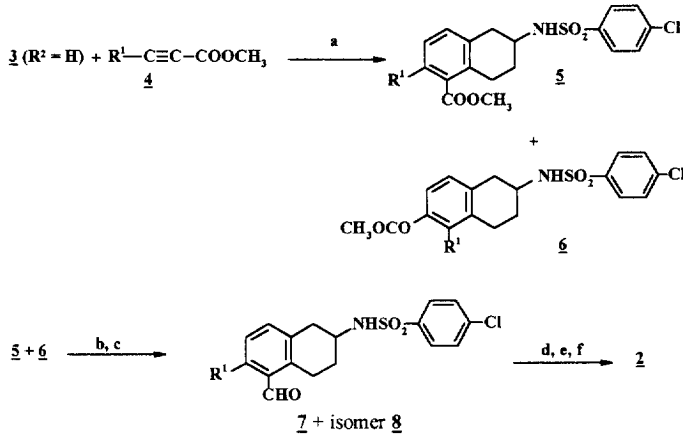
The 2-pyrone **3** (R^2 = H) was obtained via a new and very efficient route[9] and offers a general access to a wide range of compounds **2** where R^2 = H.

Synthesis of compounds 2 (R^2 = H). Compounds having no substituent on position 3 were prepared as outlined in Scheme II or III. The route shown in Scheme II was chosen when the acetylenic derivatives **4** were easily available. But in that case the Diels-Alder cycloaddition may lead to a mixture of two regioisomeric esters **5** + **6**[10]. Reduction of this mixture of esters followed by the oxidation of the resulting alcohols gave the aldehydes **7** + **8** in nearly quantitative yield. Separation of the regioisomers was done at this stage by preparative chromatography[11]. Treatment of aldehyde **7** with carbomethoxymethylene triphenylphosphorane followed by the reduction of the double bond of the resulting ethylenic ester with sodium borohydride added with 0.25 equivalent of cobaltous chloride[12] gave the propionic acid methyl ester which was saponified in the final acid **2**.

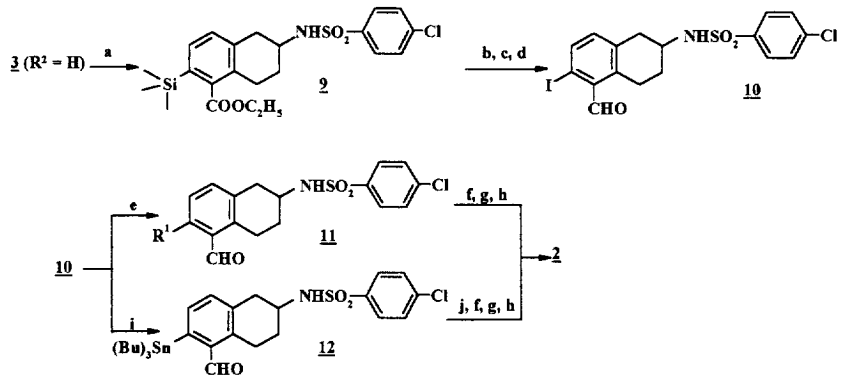
Scheme II



a: decaline, 200°C; b: $LiAlH_4/AlCl_3$/THF-Et_2O, 20°C; c: 4-benzylpyridinium-dichromate/ CH_2Cl_2, 20°C; d: Ph_3P = $CHCOOCH_3$/toluene/reflux; e: $NaBH_4/CoCl_2$/MeOH, 20°C; f: NaOH/MeOH/ H_2O, reflux

A short study of the regioselectivity of the Diels-Alder reaction showed that the introduction of a bulky R^1 substituent in **4** led to the selective synthesis of the desired isomer **5**. Then using the very bulky, commercially available ethyl 3-(trimethylsilyl)propiolate we developped a general and regioselective synthesis of compounds **2** (Scheme III). Compound **9** was isolated in 85% yield, after refluxing a solution of **3** (R^2 = H) with three equivalents of ethyl 3-(trimethylsilyl)propiolate during 16 hours. The transformation of **9** following two steps (b, c) previously described in Scheme II gave the corresponding aldehyde which was submitted to a iododesilylation reaction to yield the key iodoaldehyde **10** in 85% overall yield[13]. Introduction of different substituents on position 2 was achieved using a palladocatalysed Stille coupling. Then, the iodo derivative **10** was treated either with a tributylstannyl derivative or with the hexabutyldistannane to give **11** and **12** respectively. The choice between the two routes was dependent on the difficulty to synthesize the tin derivative or on the nature of the substituent to be transferred.

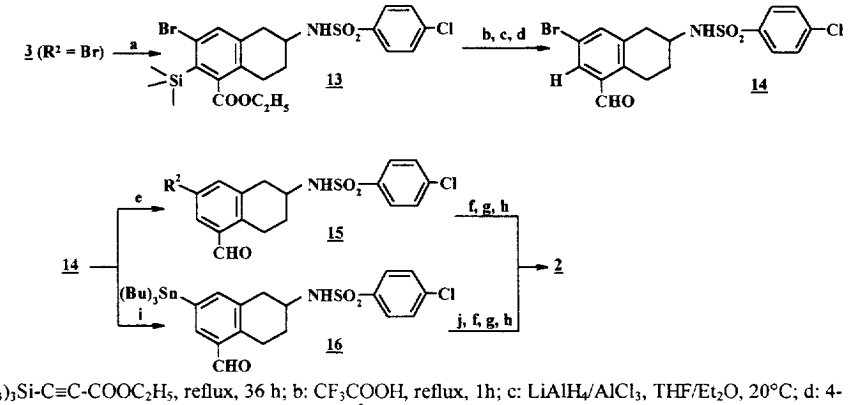
Scheme III



a: $(CH_3)_3SiC{\equiv}C\text{-}COOC_2H_5$, reflux; b: $LiAlH_4$/THF-Et_2O, 20°C; c: 4-benzylpyridinium dichromate, CH_2Cl_2, 20°C; d: ICl, CH_2Cl_2, 20°C; e: $R^1Sn(Bu)_3/Pd(PPh_3)_4$, NMP, 110°C, 1 h;
f: $Ph_3P{=}CHCOOCH_3$, toluene, reflux; g: $NaBH_4/CoCl_2$, MeOH, 20°C.; h: NaOH, MeOH/H_2O, reflux; i: $[(Bu_3)Sn]_2/Pd(PPh_3)_4$, NMP,110°C; j: R^1Br, $Pd(PPh_3)_4$, NMP, 110°C

Synthesis of compounds 2 ($R^2 \neq H$). 3-bromopyrone **3** (R^2 = Br) was the starting point of compounds where $R^2 \neq H$. **3** (R^2 = Br) was obtained in 50% yield (after recrystallization) by treatment of **3** (R^2 = H) with one equivalent of bromine in acetic acid at room temperature during 12 hours[14]. Then the sequence depicted in Scheme IV was applied. The Diels-Alder reaction using an excess of ethyl 3-(trimethysilyl)propiolate gave selectively the desired regioisomer **13** in 85% yield. The latter was protodesilylated in acidic medium[15] and then transformed in bromoaldhehyde **14** (overall yield 70%). **14** was treated with organostannane derivatives under Stille conditions to give **15** or **16** (30-90%).

Scheme IV



a: $(CH_3)_3Si\text{-}C{\equiv}C\text{-}COOC_2H_5$, reflux, 36 h; b: CF_3COOH, reflux, 1h; c: $LiAlH_4/AlCl_3$, THF/Et_2O, 20°C; d: 4-benzylpyridinium dichromate, CH_2Cl_2, 20°C; e: $R^2Sn(Bu)_3/Pd(PPh_3)_4$,NMP, 110°, 3 h; f: $Ph_3P{=}CHCOOCH_3$, toluene reflux; g: $NaBH_4/CoCl_2$, MeOH, 20°C; h: NaOH, MeOH/H_2O, reflux; i: $[(Bu_3)Sn]_2/Pd(PPh_3)_4$, NMP, 110°C; j: R^2Br, $Pd(PPh_3)_4$, NMP, 110°C

Disubstituted compounds **2p** ($R^1 = R^2 = CH_3$) and **2q** ($R^1 = R^2 = Ph$) were prepared from **3** ($R^2 = Br$) following a slightly modified sequence: 1) reaction of **3** with the methyl 2-butynoate or the methyl phenylpropiolate in 70% and 55% yield respectively; 2) substitution of the bromine under Stille conditions with tetramethyltin or phenyltributyltin (in 80% yield in both cases); 3) chain elongation.

Biological results: Table I and II represent the *in vitro* and *in vivo* results of the compounds.

The antagonistic properties on TP-receptors were first evaluated using the isolated tissue technique[16]. Isolated rabbit saphenous vein 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[17]; the ID_{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.

Examination of the tables indicates that the tetrahydronaphthalenes **2** are highly potent TP-receptor antagonists. However there is not always a good correlation between data obtained *in vitro* and *in vivo* or between those obtained on the rabbit saphenous vein and on human platelets. These could be due to differences in species and in receptor subtypes[18] or these may also be related to plasma-protein binding of some compounds. The influence of the nature of the substituent on position 2 on antagonistic activity was studied and results are shown in Table I. In general the alkyl groups gave the lowest activity and derivatives bearing phenyl or benzyl groups the highest: phenyl (**2f**) ≃ benzyl (**2g**, **2h**) > isopropyl (**2e**) ≃ straight alkyl (**2a**, **2d**). *In vitro*, the 2-hydroxymethyl derivative, which is a metabolite of **2a**, is ten time less potent than its parent compound. Comparison of Tables I and II, illustrates that compounds bearing their substituents on position 3 are generally more potent than their isomers on position 2. (**2i** > **2a**; **2j** > **2g** and **2l** > **2h**). Very potent derivatives were obtained by introducing different substituents on the benzyl group (Table II: **2k** - **2o**). It is remarkable that compound **2m** bearing a 4-phenyl substituent is still a potent antagonist, suggesting the possibility of grafting very bulky substituents on position 4 on the benzyl group. The disubstituted compounds are less active (**2p**) or inactive (**2q**).

The most active compounds have been tested *in vivo* in different species and special attention was payed to their oral absorption and their duration of action. Given orally in dogs, at the dose of 1 μg/kg **2a** inhibited completely the *ex vivo* platelet aggregation caused by U46619 for a period of at least four days. Compounds **2b**, **2g**, **2k** and **2o** tested orally in dogs were less long acting. Then the two enantiomers of **2a** were separated[19] and the (d) isomer (**S 18886**) was found to be the most active isomer in all species except in guinea pigs[18]. **S 18886** was therefore selected for further evaluation.

TABLE I: Biological activities of compounds 2 (R^2 = H)

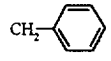
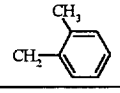
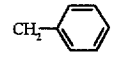
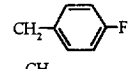
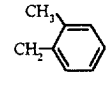
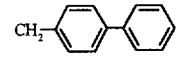
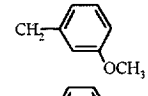
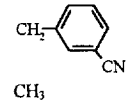
Compound [a]	R^1	R^2	Inhibition of U46619 induced contraction of isolated rabbit saphenous vein (pA_2)[b]	Inhibition of U46619 induced increase in tracheal pressure of guinea pigs[b] (ID_{50} µg/kg)	Inhibition of U46619 induced aggregation of human platelets (IC_{50} µM)[b]
2a racemic	CH_3	H	8.9	31	0.33
(l)	"	"	8.2	15	0.78
(d) S 18886	"	"	8.9	35	0.23
2b	H	"	9.4	7	0.11
2c	CH_2OH	"	7.9	23	1.1
2d	nC_3H_7	"	9	22	0.44
2e	iC_3H_7	"	9.2	32	1.3
2f	Ph	"	10.6	15	0.12
2g		"	9.9	4.8	0.086
2h		"	9.3	3.1	0.017

TABLE II: Biological activities of compounds 2 ($R^2 \neq$ H)

2i	H	CH_3	8.9	7.3	0.28
2j	"		10.1	4.8	0.006
2k	"		10.8	4.2	0.011
2l	"		11.0	2.4	0.008
2m	"		8.9	12	0.049
2n	"		9.6	4.7	0.035
2o	"		9.1	6.2	0.036
2p	CH_3	CH_3	8.1	55	1.7
2q	Ph	Ph	NT	500	NT
Ramatroban			7.9	17	0.38
ICI 192605			8.6	0.7	0.013

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

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10. For example the ratio **5**/**6** varied from 90/10 (R^1 = methyl) to 100/0 (R^1 = isopropyl).
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18. Simonet, S.; Descombes, J.J.; Vallez, M.O.; Dubuffet, T.; Lavielle, G.; Verbeuren, T.J. *Recent Advan. Prostagl. Thromb. Leuk. Res.* in press.
19. Separation was done by HPLC (Preparative DAICEL AS column; heptane, ethanol, TFAA; 70v/30v/0.2v). Analytical data for S 18886: $[\alpha]_D^{20}$ = 30.85 (DMSO, [c] = 1%); I.R.: 3400-2200, 3327, 1709, 1343-1160 cm^{-1}; ^{1}H-NMR (DMSO-d_6)δ: 12.5 (s,1H), 7.9 (s,1H), 7.8 (d,2H), 7.7 (d,2H), 6.9-6.7 (d,2H), 3.3 (m,1H), 3.0-2.5 (m,6H), 2.3 (m,2H), 2.2 (s,3H), 2.0-1.5 (m,2H).