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NEW TETRAHYDRONAPHTHALENE DERIVATIVES AS COMBINED THROMBOXANE RECEPTOR ANTAGONISTS AND THROMBOXANE SYNTHASE INHIBITORS[1]

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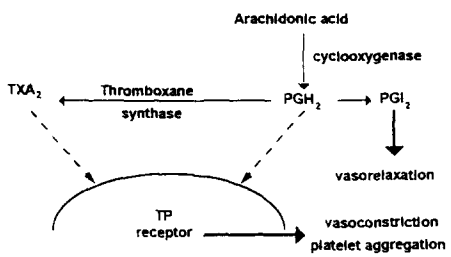
Abstract: A pyridine group was linked to the tetrahydronaphthalene moiety of the derivatives described in the preceding paper, to afford new combined thromboxane receptor (TP-receptor) antagonists and synthase inhibitors. The most interesting compound **2f** inhibits TXA2 synthase with an IC50 value of 0.64 μM and the aggregation of human platelets with an IC50 value of 0.063 μM and shows a long duration of action in different species after oral administration.

Arachidonic acid is converted by the enzyme cyclooxygenase to the unstable prostaglandine endoperoxide PGH_2 which is in turn the precursor of numerous metabolites (Fig 1). PGH_2 is rearranged into thromboxane A_2 (TXA_2) by the enzyme TXA_2 synthase. Binding of TXA_2 to its receptor leads to vasoconstriction and platelet aggregation while PGI_2, another metabolite of PGH_2 has vasodilating and platelet aggregation inhibition properties. PGH_2 is itself an agonist of the TP-receptor, causing also platelet aggregation and vasoconstriction[2].

Fig. 1



Both TP-receptor antagonists[3] and inhibitors of TXA_2 synthase (TxSI)[4] have been developped as specific antiplatelet drugs. Clinical results with TxSI's have been disappointing. The lack of clinical efficacy of these compounds was attributed to the accumulation of the PGH_2 which activates the TP-receptor. A combined TP-receptor antagonist/TxSI drug would be a cure of choice in a range of thrombotic diseases, because the action of both TXA_2 and PGH_2 would be blocked by the TP-receptor antagonist component while the metabolism of PGH_2 would be shunt to the beneficial PGI_2 by the TxSI component[5].

Several compounds which combine both activities in one molecule[6, 7] have been reported. The key structural feature of a potent TxSI is the presence of a ligand for heme iron, such as the 3-pyridyl group, and a carboxylic acid at a distance of approximately 10 Å[8, 9].

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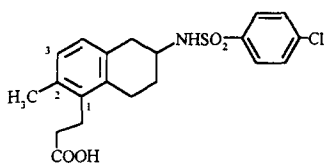
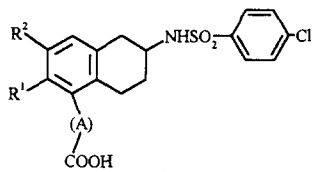
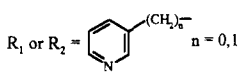
In this report we describe the synthesis and pharmacological evaluation of new compounds combining both activities, in which the 3-pyridyl group was introduced on appropriate positions of the very potent TP-receptor antagonist **1**[10]. Examination of molecular models suggested that the 3-pyridyl moiety should be grafted on position 2 or 3 of the tetrahydronaphthalene framework to lead to potentially active compounds **2**.



1



2



R_1 or R_2 = H, alkyl, phenyl

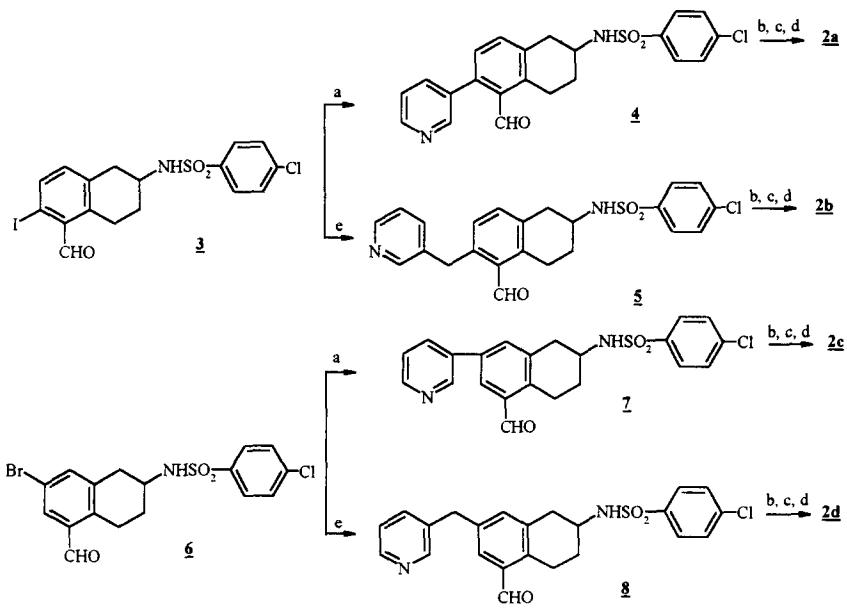
A = $(CH_2)_2$-, -CH=CH-$(CH_2)_p$- p = 2 or 3

Chemistry:

The different compounds **2** were obtained following the same type of reactions which has been described in the preceding paper. The main features of the synthesis are the use of Diels-Alder reaction and Stille coupling.

Compounds **2a-d** were prepared following the sequence depicted in Scheme I. The iodoaldehyde **3**[10] was coupled under Stille conditions either with 3-(tributylstannyl)pyridine or with 3-(tributylstannylmethyl) pyridine[11] to give aldehydes **4** and **5** respectively. In a same manner, aldehydes **7** and **8** were obtained starting from bromoaldehyde **6**[10]. Then the resulting aldehydes were submitted to a chain elongation reaction which led to the final acidic compounds **2a-d** (overall yield 70 - 80% from substituted aldehydes).

Scheme I

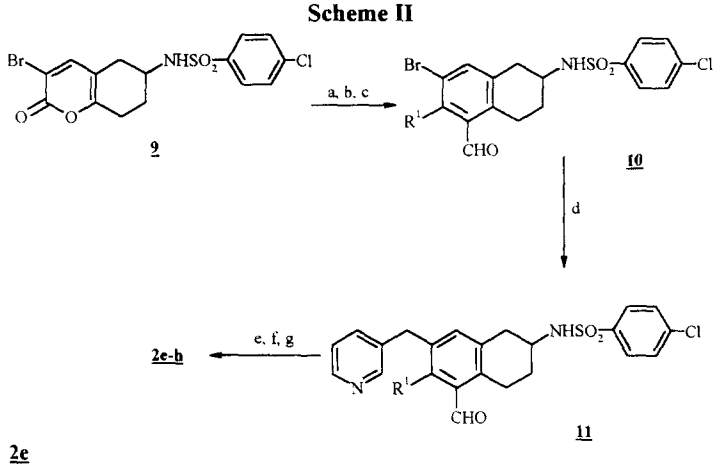


a: 3-(tributylstannyl)pyridine, $Pd(PPh_3)_4$, NMP, 110°C, 16 h, 80%; b: Ph_3P=CH-$COOCH_3$, toluene, reflux; c: $NaBH_4$, $CoCl_2$, MeOH, 20°C; d: NaOH, MeOH/H_2O, reflux and then CH_3COOH; e: 3-(tributyl-stannyl-methyl)pyridine, $Pd(PPh_3)_4$, NMP, 110°C, 16 h, 80%.

Compounds where R^1 is alkyl or phenyl were obtained starting from the 3-bromopyrone **9**[10] (Scheme II). **9** was heated at reflux of a five fold excess of an appropriate acetylenic ester for at least 12 hours. The 2-alkyl-3-bromo-5,6,7,8 tetrahydronaphthalenic esters obtained in a yield varying from 30 % to 70 % were transformed into aldehydes **10**. The latter were reacted with the tributylstannane derivative of the 3-methylpyridine[11] (yield 50 - 80%). Then **11** were transformed in compounds **2e-h** (overall yield 30 - 70% from the substituted aldehyde).

Finally the compounds depicted in Table II bearing a longer acidic chain than the compounds shown in Table I were obtained starting from the different aldehydes **5**, **8** and **11e** ($R^1 = CH_3$) (Scheme III). Reaction of these aldehydes and (ω-carboxypropyl) or (ω-carboxybutyl) triphenylphosphonium halides which were treated with potassium tertbutoxide in tetrahydro-furan at -10°C to room temperature led to the formation of a mixture of *E* and *Z* isomers in good yields. The resulting two geometrical *E* and *Z* isomers were separated by chromatography[12] except in the case of reactions with the (ω-carboxypropyl) triphenylphosphonium bromide where the *Z* derivatives were formed in proportion less than 10%. Such anomalous *E*-stereoselectivity in the reaction of "non stabilized" triphenylphosphorus ylides bearing anionic groups with aromatic aldehydes were previously reported by Marianoff[13]. In contrast the (ω-carboxybutyl) triphenylphosphonium chloride used in the same experimental conditions gave rise to much higher proportions of *Z* isomers (40 to 60%). This difference in the *E/Z* ratio could be explained by the capability of the butylanionic chain, but not the propyl, to form an hydrogen bond or a salt bridge with the sulfonamide residu[14].

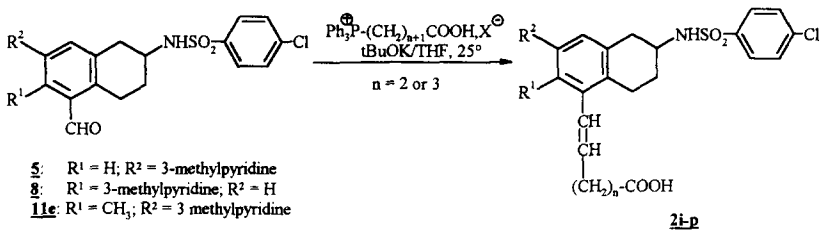
Scheme II



R^1 = CH_3- **2e**
= $CH_3(CH_2)_2$- **2f**
= CH_3-$(CH_2)_4$- **2g**
= Ph- **2h**

a: R^1-C≡C-$COOCH_3$, reflux, 12-24 h; b: $LiAlH_4/AlCl_3$, THF/Et_2O, 20°C; c: 4-benzylpyridinium-dichromate, CH_2Cl_2, 20°C; d: 3-(tributylstannylmethyl)pyridine, $Pd(PPh_3)_4$, NMP, 110°C, 16 h ; e: Ph_3P=CH-$COOCH_3$, toluene, reflux; f: $NaBH_4/CoCl_2$-$6H_2O$, MeOH, 20°C; g: NaOH, $MeOH/H_2O$, reflux, then CH_3COOH

Scheme III



5: $R^1 = H$; R^2 = 3-methylpyridine
8: R^1 = 3-methylpyridine; $R^2 = H$
11e: $R^1 = CH_3$; R^2 = 3 methylpyridine

2i-p

Biological Results:

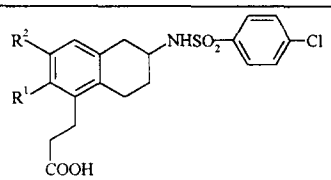
The TP-receptor antagonistic activities of the compounds were evaluated in a racemic form, using the techniques described in the preceding paper[10]. The compounds were also tested for TxSI activity in human whole blood following the method described by Watts[15]. The *in vitro* biological profile of compounds **2a-p** is summarized in Tables I and II. One reference dual TXA_2/TxSI compound, Samixogrel, was tested for comparison.

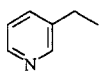
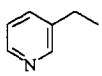
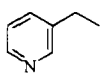
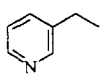
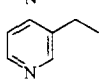
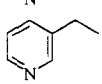
All the compounds described in the tables, except **2e**, are potent TXA_2 antagonists on the isolated tissues ($PA_2 \geq 8$). The result obtained for **2e** is difficult to interpret since compounds bearing no substituent (**2d**) or longer alkyl chain on position 2 (**2f** and **2g**) are much more potent antagonists. Previously we have found the best activities for compounds having a benzyl substituent[10]. In this paper, the best antagonistic activities are obtained when the benzyl is replaced by a pyridine moiety linked by a methylene to the tetrahydronaphthalene ring (**2b** → **2a**; **2d** → **2c**). The length of the carboxyalkyl chain has been varied and the compounds possessing a pentenoic acidic chain appear to be the most potent (**2i**, **2l**). The configuration *E* or *Z* did not influence greatly on the antagonistic activity (**2m** → **2n**; **2o** → **2p**). A moderate inhibition of aggregation of human platelets observed with certain compounds which exhibited good PA_2 values may be due to a high plasma-protein binding (**2k**, **2m**).

Two different conclusions can be made concerning the enzymatic activity. Firstly, compounds bearing a propanoic acidic chain (Table I) are inhibitors of the TXA_2 synthase only when the pyridine ring is grafted on position 3. Secondly, an increase of the length of the acidic chain allows both derivatives substituted on position 2 or 3, to be inhibitors of the synthase (Table II).

The purpose of our work was to select compounds possessing potent TP-receptor antagonistic activities with additionnal TxSI properties, differing from Samixogrel which is a potent TXA_2 synthase inhibitor (Table I). The best compromise was obtained for compounds **2d**, **2f** and **2k** because of their powerfull antiplatelet activity. These compounds have been tested *in vivo* in different species. Oral administration of **2f** (10 mg/kg) to conscious rats produced long lasting (> 6 h) and complete TXA_2 synthase inhibition and TP receptor blockade (as measured by inhibition of *ex vivo* U46619 induced platelet aggregation).

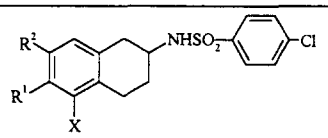
TABLE I: Biological activities of compounds 2



Compound[a]	R^1	R^2	Inhibition of U46619 induced: contraction of isolated rabbit saphenous vein (pA_2)[b]	Inhibition of U46619 induced: aggregation of human platelets (IC_{50} µM)[b]	Anti-synthase activity (IC_{50}µM)[b]
2a		H	9.7	0.14	> 10
2b		H	9.5	0.02	> 10
2c	H		7.9	0.67	> 5
2d	H		9.7	0.007	1.1
2e	CH_3		6.8	0.61	0.85
2f	CH_3-$(CH_2)_2$-		8.4	0.063	0.64
2g	CH_3-$(CH_2)_4$		8.8	0.270	6.6
2h	Ph		9.1	0.180	>10
Samixogrel			7.8	1.76	0.19

a: all compounds had satisfactory IR,MS and ^1H, ^{13}C-NMR analysis; b: values represent at least three determinations

TABLE II: Biological activities of compounds 2



Compound[a]				Stereo chemistry	Inhibition of U46619 induced		Anti-synthase activity ($IC_{50}\mu M$)[b]
	R^1	R^2	X		contraction of isolated rabbit saphenous vein (pA_2)[b]	aggregation of human platelets (IC_{50} μM)[b]	
2i		H	$CH{=}CH(CH_2)_2COOH$	E	11.1	0.047	1.4
2j	"	"	$CH{=}CH\text{-}(CH_2)_3COOH$	E	8.9	0.450	1.1
2k	"	"	"	Z	9.7	0.160	0.35
2l	H		$CH{=}CH(CH_2)_2COOH$	E	9.4	0.009	> 10
2m	"	"	$CH{=}CH\text{-}(CH_2)_3COOH$	E	8.7	1.200	> 5
2n	"	"	"	Z	8.6	0.090	4.2
2o	CH_3	"	"	E	8.1	0.460	2.9
2p	"	"	"	Z	8.0	1.000	0.96

a: all compounds had satisfactory IR,MS and ^1H, ^{13}C-NMR analysis; b: values represent at least three determinations

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