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Quantitative-Structure Activity Relationships on Thromboxane Receptor Antagonists

Dimitra Hadjipavlou–Litina and Christos A. Kontogiorgis

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, 54124, Greece

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Quantitative-Structure Activity Relationships on Thromboxane Receptor Antagonists[#]

Dimitra Hadjipavlou–Litina* and Christos A. Kontogiorgis

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, 54124, Greece

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Abstract

Motivation. TXA_2 is an unstable metabolite of arachidonic acid and a potent inducer of platelet aggregation, vasoconstriction and bronchoconstriction. TXA_2 receptor antagonists are effective for the treatment of circulatory disorders, angina and stroke. Some heptenoic acids synthesized as novel TXA_2 receptor antagonists were collected from the literature. For them, quantitative structure–activity relationships study were determined in order to provide a simple description of the physicochemical parameters which are involved in the (±)–(5Z)–7–[3–endo–[(phenylsulfonyl)amino]bicyclo[2.2.1]hept–2–exo–yl]heptenoic acids TXA_2 receptor site of action.

Method. The analysis was done by using the C–QSAR suite of programs (Biobyte).

Results. The evaluation of the quantitative structure–activity relationships (QSAR) revealed that the primary physicochemical feature influencing the in vitro TXA_2 receptor antagonists is the overall molar refractivity (CMR) of the molecule. The Swain–Lupton factor *F* was found to be also significant. A significant parabolic correlation was observed between the CMR of the studied compounds and the *in vitro* inhibition of the aggregation of washed platelets. The QSAR study also demonstrated that the inhibitory activity is affected by the Sterimol minimum width B_1.

Keywords. QSAR; quantitative structure–activity relationships; thromboxane receptor antagonists; heptenoic acids; lipophilicity; steric and electronic parameters.

Abbreviations and notations

CMR, calculated molar refractivity	QSAR, quantitative structure–activity relationships
PGH_2, prostaglandin H_2	TXA_2, thromboxane A_2
PRP, platelet–rich plasma	WP, washed platelets

1 INTRODUCTION

The basic molecular mechanisms involved in the formation and dissolution of thrombus are the subject of continuous research. Platelet aggregation is an important part of the process, and special attention is given to agents capable of interfering with platelet recruitment into forming thrombus and which can, therefore, play an important role in the treatment of arteriosclerosis, thrombosis and acute coronary syndromes [1].

[#] Dedicated to Professor Milan Randić on the occasion of the 70th birthday.

* Correspondence author; phone: +30310997627; fax: +30310997679; E–mail: hadjipav@pharm.auth.gr.

Thromboxane A_2 (TXA_2), an unstable endogenous metabolite of arachidonic acid, is one of the most potent inducers of platelet aggregation, vasoconstriction and bronchoconstriction [2,3,4,5], and is believed to play an important role in the pathogenesis of asthma and various circulatory disorders, including myocardial infraction, unstable angina and stroke [6,7,8]. Its function is counterbalanced with that of prostacyclin. Therefore, TXA_2 receptor antagonists are expected to be effective for the treatment of these diseases and a number of TXA_2 receptor antagonists have been clinically investigated [9].

A number of compounds of diverse structure have already been reported to be potent TXA_2 synthetase inhibitors with the basic structural requirements being a 1–imidazolyl or a 3–pyridyl moiety at one end of the molecule and a carboxylic acid group at the other [10]. However, 1–nonylimidazole has been reported to be a very potent inhibitor in spite of the absence of a carboxylic acid group [11]. Further, it was recently reported that heterocyclic compounds having a 1–imidazolylalkyl moiety without a carboxylic acid group have TXA_2 synthetase inhibitory activity [12].

However, the biosynthesis inhibitors have recently been recognized to be less effective than expected, probably because prostaglandin H_2 (PGH_2), and TXA_2 share a common receptor [13], and thus, the PGH_2 that accumulates with inhibition of the TXA_2 biosynthesis may act as an agonist of TXA_2. Several drugs with prostanoid, [14–23] *e.g.* SQ–29548 or ONO–3708, and non prostanoid [24,25] structures, *e.g.*, BM–13177, which possess the characteristics of TXA_2 receptor antagonists have been reported to be promising in preclinical evaluations [26–29].

Several QSAR equations modeling the activity of TXA_2 receptor antagonists have been reported [30,31,32]. Among them a QSAR study of 4–[2(4–substituted–phenylsulfonylamino)ethyl–thio]phenoxyacetic acids and related compounds has been performed [30]. In the parameterization of the structural features for the QSAR study Kawashima *et al.* [30] used physicochemical descriptors and indicator variables. The results obtained by regression analysis are given below:

$$-\log C = 1.06\ B_1 - 0.98\ L_{W-COOH} + 2.09\ \pi_{X+Y+W-COOH} + 3.04\ \Sigma Q_{1-6} + 10.12 \quad (1)$$
$$n = 36,\ r = 0.93,\ s = 0.27$$

$$-\log C = 0.61\ \pi_R + 1.1.4\ F_R - 9.33\ Qa–c + 4.99\ \Sigma Q_{1-6} + 3.93 \quad (2)$$
$$n = 36,\ r = 0.94,\ s = 0.25$$

$$-\log C = 0.78\ L_R - 0.12\ B_5^2 - 0.947\ Qa–c + 5.00\ \Sigma Q_{1-6} + 2.48 \quad (3)$$
$$n = 36,\ r = 0.94,\ s = 0.25$$

In Eqs. (1)–(3), π_R and $\pi_{X+Y+W-COOH}$ are lipophilicity parameters and F_R is the Swain–Lupton field constant for the substituent R from the compilation by Hansch and Leo [35]. The value of ΣQ_{1-6} is the total electronic charge of the benzene ring, and Qa–c is the electronic charge of the carbon atom adjacent to the carboxylate anion. The Sterimol parameters L, B_1 and B_5 represent the length, minimum width, and maximum width of the substituent R, and L_{W-COOH} is the length of the

W–COOH moiety. The positive coefficient for π_R and F_R in Eq. (2) suggested that a lipophilic and σ electron withdrawing substituent R at the *p*–position of the phenyl–sulfonyl moiety is required to improve the activity. Further, a substituent R, which is long and moderately wide, was suggested to be preferable for the activity. The positive coefficients for $\pi_{X+Y+W-COOH}$ and ΣQ_{1-6} may indicate that the introduction of a lipophilic and electron–withdrawing group on the benzene ring of the phenoxyacetic acid moiety enhances the activity. The length of the W–COOH moiety may also be important.

Kumar *et al*. [31] correlated quantitatively iodinated analogues of highly potent beta–2–adrenoreceptor ligands and site–selective Thromboxane A_2 – prostaglandin H_2 (TP) receptor–ligands. The receptor binding interactions associated with the varying sites of these compounds are developed. Significant QSAR correlation equations were obtained between the binding affinity pKi and the substituent physicochemical parameters, such as molar refraction (MR), hydrophobic constant π and the resonance parameter *R*.

A series of 39 7–oxabicyclo[2.2.1]heptane oxazole Thromboxane A_2 (TXA_2) receptor antagonists were studied using four–dimensional QSAR analysis [32]. Cubic grid cell sizes of 1 and 2 Å were considered, which then were used as independent variables in constructing three–dimensional (3D)–QSAR models after data reduction. The 3D–QSAR models were generated and evaluated by a scheme that combines a genetic algorithm (GA) optimization with partial least squares (PLS) regression and were evaluated by cross–validation using the leave–one–out–technique (Q^2 ranged from 0.27 to 0.86). The 3D–QSAR models provide detailed 3D–pharmacophore requirements in terms of atom types and corresponding locations needed for high TXA_2 inhibition activity. Specific sites in space that should not be occupied by an active inhibitor are also identified.

From the results of Kawashima [30], Kumar [31] and Albuquerque [32] the *in vitro* activity of various Thromboxane receptor antagonists was found to be predominantly controlled by the lipophilicity and the molar refractivity of the compounds. Because advances in QSAR studies have widened the scope of finding the mechanism of drug actions and the possibilities of having analogues of improved binding affinities in future synthetic efforts, a QSAR study on (±)–(5Z)–7–[3–endo–[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept–2–exo–yl]heptenoic acids, TXA_2 receptor antagonists [33], has been performed.

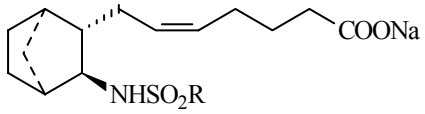
2 MATERIALS AND METHODS

The analysis was done by using the C–QSAR suite of programs (Biobyte) [34]. In the formulation of the QSAR we have used only calculated log *P* values, as well as CMR calculated molar refractivities, using the CLOGP Program. All clog *P* values are for the neutral forms.

The values of substituent constants MR, *F*, σ, L, B_1, B_5 have been taken from the literature [35,36,37,38,39,40]. In all equations *n* represents the number of data points, *r* is the correlation coefficient between observed values of the dependent and the values predicted from the equation, *s* is the standard deviation of the regression equation, q^2 defines the cross–validated r^2. Each regression equation also includes the 95% confidence limits for each term in the parentheses. In Tables 1 to 4 we have collected all of the reported experimental data [33] used in the derivation of Eqs (4)–(7). For drugs acting as antithrombotic and vasodilating agents, lipophilicity should be an important property. Lipophilicity is also a significant factor in the susceptibility of drugs to attack by the P–450 enzymes.

3 RESULTS AND DISCUSSION

The general structure of the studied compounds from Eqs (4)–(7) and Tables 1–4 is:



3.1 Inhibition of the Aggregation of Rabbit Platelet–Rich Plasma

The data in Table 1 were used to derive the quantitative structure–activity relationship (QSAR) given in Eq (4). The IC_{50} values referred to the inhibition of platelet–rich plasma (PRP) aggregation, which was induced by 500 μM of arachidonic acid. Platelet aggregation was examined by the method of Born [40].

$$\log 1/IC_{50}\ \text{PRP} = -1.056(\pm 0.269)\text{CMR} + 0.955(\pm 0.916)F_{-\text{Ph}} + 16.841(\pm 3.024)$$
$$n = 14,\ r = 0.953,\ q^2 = 0.830,\ r^2 = 0.909,\ s = 0.319,\ F_{2,11} = 37.263 \qquad (4)$$

In this expression CMR is the overall calculated molar refractivity of the molecule. It is primarily a measure of volume with a small component of polarizability. Its negative sign suggests steric hindrance either directly or through a conformational change in the receptor. The Swain–Lupton factor *F* for inductive field electronic effect refers to substituents in all positions of phenyl ring. Its positive sign suggests that electron withdrawing property of substituents in benzene ring is important and enhances activity as has already been shown in Eq (2) [30]. The electronic effects must be associated with reaction at an active site. The parameters are reasonably orthogonal. Two data points (**2** and **5**, Table 1) are omitted in the development of the above equation. Both compounds possess the same calculated CMR values (10.612). Compound **2** strongly deviates from the correlation being calculated 1.698 log units more potent than is observed. Compound **5** does not contain any unusual substitution moiety. Eq (4) seems unusual because it contains no π or clog P term. The reason is apparent from the correlation matrix, where it is seen that CMR and clog *P* are significantly collinear ($r = 0.838$).

Table 1. Inhibition of the Aggregation of Rabbit Platelet–Rich Plasma Induced by 500 μM of Arachidonic Acid. These Data are Used for the Derivation of Eq (4)

No	R	obs. log $1/IC_{50}$	calc. log $1/IC_{50}$	Δ log $1/IC_{50}$	clog P	CMR	F_{-Ph}
1	C_6H_5	6.0	6.127	–0.127	3.970	10.149	0
2	$C_6H_5CH_2$	3.940	5.138	–1.698	3.829	10.612	0
3	2–C_2H_5–C_6H_4	5.090	5.148	–0.058	4.278	11.076	0
4	3–C_3H_7–C_6H_4	4.850	4.658	0.192	4.657	11.540	0
5	4–CH_3–C_6H_4	6.30	5.599	0.701	4.469	10.612	–0.040
6	2–CH_3–C_6H_4	5.210	5.599	–0.389	4.469	10.612	–0.040
7	3–CH_3–C_6H_4	5.770	5.599	0.171	4.469	10.612	–0.040
8	4–C_2H_5–C_6H_4	5.340	5.100	0.240	4.998	11.076	–0.050
9	4–*n*–C_5H_{11}–C_6H_4	3.10	3.622	–0.522	6.585	12.468	–0.060
10	4–C_6H_5–C_6H_4	3.70	3.522	0.148	5.858	12.660	0.080
11	4–OH–C_6H_4	6.30	6.242	0.058	3.674	10.302	0.290
12	4–OCH_3–C_6H_4	5.770	5.724	0.046	4.248	10.766	0.260
13	4–NO_2–C_6H_4	5.850	6.121	–0.271	4.361	10.760	0.670
14	4–F–C_6H_4	6.220	6.521	–0.301	4.415	10.164	0.430
15	4–Cl–C_6H_4	6.520	6.000	0.520	4.985	10.640	0.410
16	4–N–$(CH_3)_2$–C_6H_4	5.150	4.854	0.296	4.348	11.445	0.100

Table 2. Inhibition of the Aggregation of Rabbit Platelet–Rich Plasma Induced by 500 μM of Arachidonic Acid. These Data are Used for the Derivation of Eq (5)

No	R	obs. log $1/IC_{50}$	calc. log $1/IC_{50}$	Δ log $1/IC_{50}$	CMR	B_{1-4}
1	C_6H_5	6.0	6.196	–0.196	10.149	1.000
2	$C_6H_5CH_2$	3.940	5.603	–1.663	10.612	1.000
3	2–C_2H_5–C_6H_4	5.090	5.010	0.080	11.076	1.000
4	3–C_3H_7–C_6H_4	4.850	4.418	0.432	11.540	1.000
5	4–CH_3–C_6H_4	6.30	6.046	0.254	10.612	1.520
6	2–CH_3–C_6H_4	5.210	5.603	–0.393	10.612	1.000
7	3–CH_3–C_6H_4	5.770	5.603	0.167	10.612	1.000
8	4–C_2H_5–C_6H_4	5.340	5.453	–0.113	11.076	1.520
9	4–n–C_5H_{11}–C_6H_4	3.10	3.675	–0.575	12.468	1.520
10	4–C_6H_5–C_6H_4	3.70	3.591	0.109	12.660	1.710
11	4–OH–C_6H_4	6.30	6.298	0.002	10.302	1.350
12	4–OCH_3–C_6H_4	5.770	5.705	0.065	10.766	1.350
13	4–NO_2–C_6H_4	5.850	6.010	–0.160	10.760	1.700
14	4–F–C_6H_4	6.220	6.474	–0.254	10.164	1.350
15	4–Cl–C_6H_5	6.520	6.249	0.271	10.640	1.800
16	4–COONa–C_6H_4	3.10	5.873	–2.773	10.801	1.600
17	4–N–$(CH_3)_2$–C_6H_4	5.150	4.837	0.313	11.445	1.350

In order to better delineate the physicochemical parameter that governs the effect of the substituent in the position 4, we derived Eq (5):

$$\log 1/IC_{50}PRP = -1.278(\pm0.244)CMR + 0.851(\pm0.643)B_{1-4ph} + 18.314(\pm2.568)$$
$$n = 15,\ r = 0.957,\ r^2 = 0.916,\ q^2 = 0.848,\ s = 0.303,\ F_{2,12} = 100.866 \qquad (5)$$

The B_{1-4ph} term (the Sterimol smallest width of the substituent) appears to confirm a positive steric effect for 4–substituents of the phenyl ring. This is in accordance with previous findings [30]. The larger the atom attached to the ring the more effective the acid derivative will be. The intercorrelation between CMR and B_{1-4ph} is not too high (0.4), which can give some more confidence in Eq (5). Of course, the term B_{1-4ph} covers also a lipophilic effect since the correlation matrix between clog *P* and B_{1-4ph} is 0.5. Two data points, compound **2** and **16**, are omitted.

Compound **2** is a benzyl–derivative with no substitution in position 4 or in any other position of benzene ring, while compound **16** is a sodium salt with different pharmacokinetic behavior.

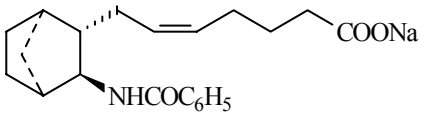
3.2 Inhibition of the Aggregation of Rat Washed Platelets

An attempt was made to develop a QSAR for the inhibitory activity of the same compounds on rat washed platelets (WP) aggregation, induced by 4 μg/ml of collagen.

$$\log 1/IC_{50}WP = 4.608(\pm1.784)CMR - 0.207(\pm0.084)CMR^2 - 20.257(\pm9.445)$$
$$n = 17,\ r = 0.859,\ r^2 = 0.738,\ q^2 = -0.197,\ s = 0.290,\ F_{2,14} = 19.69 \quad (6)$$

In Eq (6) the parabolic dependence of CMR provides an optimum at 11.447. No role for an electronic factor was found. The fact that only CMR has been used to develop Eq (6) implies that for all the parts where substituents have been entered, steric contacts have been made. No parameterization for R substituents has been performed.

Table 3. Inhibition of the Aggregation of Rat Washed Platelets by 4 μg/ml of Collagen. These Data are Used for the Derivation of Eq. 6.

No	R	obs. log $1/IC_{50}$	calc. log $1/IC_{50}$	Δ log $1/IC_{50}$	CMR
1	C_6H_5	5.540	5.218	0.322	10.149
2	$C_6H_5CH_2$	4.590	5.365	–0.775	10.612
3	2–C_2H_5–C_6H_4	5.430	5.423	0.007	11.076
4	3–C_3H_7–C_6H_4	4.960	5.392	–0.432	11.540
5	CH_3	3.430	3.507	–0.77	8.101
6	C_6H_{13}	4.720	5.315	–0.595	10.420
7	4–CH_3–C_6H_4	5.620	5.365	0.255	10.612
8	2–CH_3–C_6H_4	5.370	5.365	0.005	10.612
9	3–CH_3–C_6H_4	5.250	5.365	–0.115	10.612
10	4–C_2H_5–C_6H_4	5.480	5.423	0.057	11.076
11	4–n–C_5H_{11}–C_6H_4	4.840	5.063	–0.223	12.468
12	Naphthyl	5.570	5.326	0.244	11.837
13	4–C_6H_5–C_6H_4	5.220	4.951	0.269	12.660
14	4–OH–C_6H_4	5.40	5.376	0.124	10.302
15	4–OCH_3–C_6H_4	5.410	5.394	0.016	10.766
16	4–NO_2–C_6H_4	5.050	5.393	–0.343	10.760
17	4–F–C_6H_4	5.540	5.224	0.316	10.164
18	4–Cl–C_6H_4	5.540	5.371	0.169	10.640
19	4–N–$(CH_3)_2$–C_6H_4	4.280	5.406	–1.126	11.445
20		3.350	5.035	–1.685	9.776

Three data points, namely compounds **2**, **19** and **20** from Table 3, are poorly predicted, did not fit well the parabolic relationship and are omitted by use of the jack–knife procedure (C–QSAR, Biobyte). Compound **20** is a benzamide, with the lowest activity, whereas all the other compounds are sulfonyl derivatives. No correlation for a lipophilic effect was found. The main difficulty of Eq (6) is that, for the molecules on which it is based, there is a collinearity problem, lending to uncertainty as to whether the interaction occurs with the polar or the lipophilic space (Clog P vs CMR = 0.908). Previous QSAR [30,31] show that lipophilic and steric properties are important.

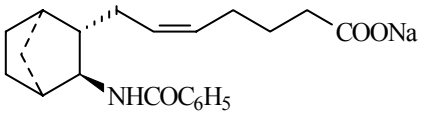
The importance of lipophilicity in cell penetration is not clear from Eqs (4) and (6). This is important because previous investigations [30,31] suggested that inhibition is related to lipophilicity with whole cells. It would be expected that there would be a lipophilic interaction with all parts of the compound because of its importance in membrane penetration. The calculated clog P values for compound **18** (the most potent congener in Table 1) was found to be 4.985, whereas for compound **7** (the most potent in Table 3) was found to be 4.469.

3.3 Inhibition of the Contraction of Rat Thoracic Aorta

In Eq (7) we tried to delineate the physicochemical parameters that are implicated to the inhibitory effect on rat thoracic aorta contraction, induced by 30 nM U–46619 [33].

$$\log 1/IC_{50} = 1.568(\pm0.819)CMR - 30.779(\pm16.402)F_{-Ph} - 12.506(\pm9.089)$$
$$n = 9,\ r = 0.901,\ q^2 = 0.488,\ r^2 = 0.811,\ s = 0.564,\ F_{2,6} = 0.977 \qquad (7)$$

Table 4. Inhibition of the Contraction of Rat Thoracic Aorta induced by 30 nM U–46619. These Data are Used for the Derivation of Eq (7)

No	R	obs. log $1/IC_{50}$	calc. log $1/IC_{50}$	Δ log $1/IC_{50}$	CMR	F_{-Ph}
1	C_6H_5	5.850	4.874	0.976	10.149	0
2	$C_6H_5CH_2$	3.950	4.874	–0.924	10.612	0
3	2–C_2H_5–C_6H_4	5.470	4.874	0.596	11.076	0
4	3–C_3H_7–C_6H_4	4.960	4.874	0.086	11.540	0
5	4–CH_3–C_6H_4	6.150	5.266	0.884	10.612	–0.040
6	2–CH_3–C_6H_4	5.430	5.266	0.164	10.612	–0.040
7	3–CH_3–C_6H_4	5.490	5.266	0.224	10.612	–0.040
8	4–C_2H_5–C_6H_4	5.820	5.364	0.456	11.076	–0.050
9	4–C_6H_5–C_6H_4	5.010	4.090	0.920	12.660	0.080
10		2.470	4.874	–2.404	9.776	0

Compound **1** (Table 4) with no substitution on the phenyl ring was omitted. The ratio number of data points/variables is low for Eq (7) and it might be insisted that little weight can be placed on this QSAR. The equation 7 is highly significant in terms of the F statistic, and account for 81% of the variation of the experimental data. Overall, CMR plays a very important role. In this QSAR, *F* is the Swain–Lupton parameter for the inductive field electronic effect. No significant results were obtained when the Es (the Taft's steric factor) or $\Sigma\pi$ (sum of π values for the substituents on the phenyl ring) were used.

4 CONCLUSIONS

The TXA_2 receptor belongs to the G–protein–coupled receptor class and its amino acid sequence in humans was determined from its cDNA sequence [41]. A model of the receptor has been constructed by Yamamoto *et al*. in 1993 [42]. According to the model, the ligand–binding pocket

includes Ser—201, Arg–295 and a large hydrophobic pocket between these two residues. Following our QSAR results, it is possible for the derivatives under study, to interact with Arg–295, through the [hept–2–exo–yl]–heptenoic moiety. If the sulfonylamino group of the antagonists interacts with the hydroxyl of Ser–201, the importance of lipophilicity of the phenyl group attached directly to the sulfonylamino group is obvious.

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5 REFERENCES

[1] W. Majerus, G. J. Broza, J. P. Miletich, and D. M. Tollesfsen, Anticoagulant, Thrombolytic and Antiplatelet Drugs. In *The Goodman and Gilman's Pharmacological Basis of Therapeutics*; L.S. Goodman, A.G. Gilman, J.G. Hardmann and L.E. Limbird, Eds.; McGraw–Hill: New York, 1996: pp. 1341–1359.

[2] M. Hamberg, J. Sbensson, and B. Samuelsson, Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides, *Proc. Natl. Acad. Sci. U.S.A*. **1975**, 72, 2994–2998.

[3] S. S. Bhagwat, P. R. Hamann, W. C. Still, S. Bunting, and F. A. Fitzpatrick, Synthesis and structure of the platelet aggregation factor Thromboxane A_2, *Nature* **1985**, 315, 511–513.

[4] S. S. Bhagwat, P. R. Hamann, and W. C. Still, Synthesis of Thromboxane A_2, *J. Am. Chem. Soc*. **1985**, 107, 6372.

[5] H. Arita, T. Nakano, and K. Hanasaki, Thromboxane A_2: its generation and role in platelet activation, *Prog. Lipid. Res*. **1989**, 28, 273.

[6] R. A. Coleman and R. L. G. Sheldrich, Prostanoid–induced contraction of human bronchial smooth muscle is mediated by TP–receptors, *Br. J. Pharmacol*. **1989**, 96, 688.

[7] S. Moncada and J. R. Vane, Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A_2, and prostacyclin, *Pharmacol Rev*. **1978**, 30, 293–331.

[8] P. W. Majerus, Arachidonate metabolism in vascular disorders, *J. Clin. Invest*. **1983**, 72, 1521–1525.

[9] E. Hall, Thromboxane A_2 receptor antagonists, *Med. Res. Rev.* **1991**,11, 503–579.

[10] K. Kato, S. Ohkawa, S. Terao, Z. Terashita, and K. Nishikawa, Thromboxane Synthetase inhibitors (TXSI). Design, Synthesis and Evaluation of a Novel Series of ω–Pyridylalkenoic Acids, *J. Med. Chem*. **1985**, 28, 287–294.

[11] H. H. Tai and B. Yuan, On the Inhibitory Potency of Imidazole and Its Derivatives of Thromboxane Synthetase, *Biochem. Biophys. Res. Commun*. **1978**, 80, 236–242.

[12] a) W. B. Wright Jr., J. B. Press, P. S. Chan, J. W. Marsico, M. F. Hang, J. Lucas, J. Tauber, and A. S. Tomcufcik, Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 1. N–[(1H–Imidazol–1–yl)alkyl]aryl Amides and N–[(1H–1,2,4–Triazol–1–yl)alkyl]aryl Amides, *J. Med.Chem.* **1986**, 29, 523–530; b) J. B. Press, W. B. Wright Jr., P. S. Chan, J. W. Marsico, F. M. Hang, J. Tauber, and A. S. Tomcufcik, Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 2. N–[(1H–Imidazol–1–yl)alkyl]–1H–isoidole–1,3(2H)–diones and N–[(1H–1,2,4–Triazol–1–yl)alkyl]–1H–isoidole–1,3(2H)–diones as Unique Antihypertensive Agents, *J. Med. Chem*. **1986**, 29, 816–819; c) J. B. Press, W. B. Wright Jr., P. S. Chan, J. W. Marsico, and A. S. Tomcufcik, Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 3. N–[(1H–Imidazol–1–yl)alkyl]heteroaryl Amides as Potent Enzyme Inhibitors, *J. Med. Chem*. **1987**, 30, 1036–1040; d) W. B. Wright Jr., A. S. Tomcufcik, P. S. Chan, J. W. Marsico, and J. B. Press, Thromboxane Synthetase Inhibitors and Antihypertensive Agents, 4. N–[(1H–Imidazol–1–yl)alkyl] Derivatives of Quinazoline–2,4 (1H,3H)–diones, Quinazolin–4(3H)–ones and 1,2,3–Benzotriazin–4(3H)–ones and 1,2,3–Benzotriazin–4(3H)–ones, *J. Med. Chem*. **1987**, 30, 2277–2283.

[13] a) M. E. Brezinski, A. Yanagisawa, and A. M. Lefer, Cardioprotective actions of specific thromboxane receptor antagonist in acute myocardial ischemia, *J Cardiovasc Pharmacol*. **1987**, 9, 65–71; b) M. L. Ogletree, Overview of physiological and pathophysiological effects of Thromboxane A_2. *Fed. Proc*., *Fed. Am. Soc. Exp. Biol*. **1987**, 46, 133–138; c) A. M. Lefer and H. Carius, A pharmacological approach to thromboxane receptor antagonism, *Fed. Proc*., *Fed. Am. Soc. Exp. Biol*.**1987**, 46, 144–148; d) P. V. Halushka, D. E. Mais, and D. L. Saussy Jr., Platelet and vascular smooth muscle Thromboxane A2/Prostaglandin H2 receptors, *Fed. Proc*., *Fed. Am. Soc. Exp. Biol*. **1987**, 46, 149–153.

[14] a) I. F. Charo, R. Feinman, T. Detwiler, J. B. Smith, C. M. Ingerman, and M. J. Silver, Prostaglandin

endoperoxides and thromboxane A2 can induce platelet aggregation in the absence of secretion, *Nature (London)* **1977**, 269, 66–69; b) R. A. Coleman, P. P. A. Humphrey, I. Kennedy, G. P. Levy, and P. Lumbley, Comparison of the actions of U–46619, a prostaglandin H_2–analogue, with those of prostaglandin H2 and thromboxane A2 on some isolated smooth muscle preparations, *Br. J. Pharmacol*. **1981**, 73, 773–778.

[15] K. C. Nicolaou, R. L. Magolda, J. B. Smith, D. Aharony, E. F. Smith, and A. M. Lefer, Synthesis and biological properties of pinane–thromboxane A2, a selective inhibitor of coronary artery constriction, platelet aggregation, and thromboxane formation, *Proc. Natl. Acad. Sci. U.S.A*. **1979**, 76, 2566–2570.

[16] S. E. Burke, A. M. Lefer, K. C. Nicolaou, G. M. Smith, and J. B.Smith, Responsiveness of platelets and coronary arteries from different species to synthetic thromboxane and prostaglandin endoperoxide analogues, *Br. J. Pharmacol*. **1983**, 78, 287–292.

[17] G. C. Le Breton, D. L. Venton, S. E. Enke, and P. V. Halushka, 13–Azaprostanoic acid: a specific antagonist of the human blood platelet thromboxane/endoperoxide receptor. *Proc. Natl. Acad. Sci. U.S.A*. **1979**, 76, 4097–101.

[18] P. W. Sprague, J. E. Heikes, J. Z. Gougoutas, M. F. Malley, D. N. Harris, and E. Greenberg, Synthesis and in vitro pharmacology of 7–oxabicyclo[2.2.1]heptane analogues of Thromboxane A_2/PGH_2, *J. Med. Chem*. **1985**, 28, 1580–1590.

[19] R. A. Armstrong, R. L. Jones, V. Peesapati, S. G. Will, and N. H. Wilson, Competitive antagonism at thromboxane receptors in human platelets, *Br J Pharmacol*. **1985**, 84, 595–607.

[20] R. T. Brittain, L. Boutal, M. C. Carter, R. A. Coleman, E. W. Collington, H. P. Geisow, O. Hallett, E. J. Hornby, P. P. A. Humphrey, D. Jack, I. Kennedy, P. Lumley, P. J. McCabe, I. F. Skidmore, M. Thomas, and J. C. Wallis, AH23848: a thromboxane receptor–blocking drug that can clarify the pathophysiologic role of Thromboxane A_2, *Circulation* **1985**, 72, 1208–1218.

[21] G. R. Brown and A. J. Foubister, ICI 180080, a novel selective thromboxane receptor antagonist: synthesis and relative activity, *J. Pharm. Pharmacol*. **1986**, 38, 706–708.

[22] R. M. Burch, D. E. Mais, D. L. Saussy Jr., and P. V. Halushka, Solubilization of a Thromboxane A_2/Prostaglandin H_2 antagonist binding site from human platelets, *Proc. Natl. Acad. Sci. U.S.A*. **1985**, 82, 7434–7438.

[23] M. L. Ogletree, D. N. Harris, R. Greenberg, M. F. Haslanger, and M. Nakane, Pharmacological actions of SQ 29,548, a novel selective thromboxane antagonist, *J. Pharmacol. Exp. Ther*. **1985**, 234, 435–441.

[24] Y. Yui, K. Sakaguchi, T. Susawa, R. Hattori, H. Takatsu, N. Yui, and C. Kawai, Thromboxane A_2 analogue induced coronary artery vasoconstriction in the rabbit, *Cardiovasc. Res*. **1987**, 21, 119–123.

[25] M. E. Brezinski, D. J. Lefer, B. Bowker, and A. M. Lefer, Thromboxane induced red blood cell lysis, *Prostaglandins* **1987**, 33, 75–84.

[26] C. C. Chan, D. J. Nathaniel, P. J. Yusko, R. A. Hall, and A. W. Ford–Hutchinson, Inhibition of prostanoid–mediated platelet aggregation in vivo and in vitro by 3–hydroxymethyl–dibenzo(b,f)thiepin 5,5–dioxide (L–640,035), *J Pharmacol Exp Ther*. **1984**, 229, 276–282.

[27] D. J. Fitzgerald, J. Doran, E. Jackson, and G. A. Fitzgerald, Coronary vascular occlusion mediated via Thromboxane A_2–prostaglandin endoperoxide receptor activation in vivo, *J. Clin. Invest*. **1986**, 77, 496–502.

[28] K. Schrör, E. F. Smith III, M. Bickerton J. Bryan–Smith, K. C. Nicolaou, R. Magolda, and A. M. Lefer, Preservation of ischemic myocardium by pinane Thromboxane A_2, *Am. J. Physiol*. **1980**, 238, H87–92.

[29] C. E. Hock, M. E. Brezinski, and A. M. Lefer, Anti–ischemic actions of a new thromboxane receptor antagonist, SQ–29, 548 in acute myocardial ischemia, *Eur. J. Pharmacol*. **1986**, 122, 213–219.

[30] Y. Kawashima, M. Sato, S. Yamamoto, Y. Shimazaki, Y. Chiba, M. Satake, C. Iwata, and K. Hatayama, Structure–Activity Relationship study of TXA_2 receptor antagonists 4–[2–(4–substituted phenylsulfonylamino)ethylthio] phenoxyacetic acids and related compounds, *Chem. Pharm. Bull*. **1995**, *43*, 1132–1136.

[31] R. Kumar and P. Singh, Quantitative structure–activity relationship study of iodinated analogues of trimetoquinol as highly potent beta 2–adrenoreceptor ligands, *Indian J. Biochem. Biophys*. **1998**, 35, 390–392.

[32] M. G. Albuquerque, A. J. Hopfinger E. J. Barreiro, and R. B. De Alencastro, Four–dimensional quantitative structure–activity relationship analysis of a series of interphenylene 7–oxabicycloheptane oxazole Thromboxane A_2 receptor antagonists, *J. Chem. Inf. Comput. Sci*. **1998**, 38, 925–938.

[33] M. Narisada, M. Ohtani, F. Watanabe, K. Uchida, H. Arita, M. Doteuchi, K. Hanasaki, H. Kakushi, K. Otani, and S. Hara, Synthesis and in Vitro Activity of Various Derivatives of a Novel Thromboxane Receptor Antagonist (±)–(5Z)–7–[3–endo–[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept–2–exo–yl]heptenoic Acid, *J. Med. Chem*. **1988**, 31, 1847–1854.

[34] C–QSAR and Clog *P*, Biobyte Corp., 201 W. Fourth Str. Suite 204 Claremont, CA 91711, USA.

[35] C. Hansch and A. J. Leo, *Substituent constants for correlation analysis in Chemistry and Biology*, Wiley, New York, 1979.

[36] C. Hansch, A. J. Leo, and W. R. Taft, *Chem Rev*. **1991**, 9, 165.

[37] C. Silipo and A. Vittoria *Comprehensive Medicinal Chemistry: Threee Dimensional Structure of Drugs*, Vol 4, Chap. 18.4, Eds. C. Hansch, P. G. Sammes, J. B. Taylor, and C. A. Ramsden, Pergamon Press, New York, 1990,

p.153.
[38] A. Verloop, Hoogenstraaten, and J. Tipker, *Drug Design*, Vol. 7, Ed. E. J. Ariens, Academic Press, New York, 1976, p.165.
[39] C. Hansch and A. Leo, *Exploring QSAR: Fundamentals and applications in Chemistry and Biology*, American Chemical Society, Washinghton, DC 1995.

Biographies

Dimitra Hadjipavlou-Litina received a B.S. and a Ph.D. in Pharmacy, for a synthetic and biological study of novel anti–inflammatory aminoketones. Following a postdoctoral year (1992–1993) with professor C. Hansch in the Chemistry Department of Pomona College, California, she returned as a lecturer of Pharmaceutical Chemistry, at the University of Thessaloniki, Greece. In 1998 she took her present position as an assistant Professor. Her research interests involve synthesis and biological studies on anti–inflammatory and antioxidant agents and the relationship between structure and activity of various drug classes.

Christos A. **Kontogiorgis** received a B.S. in School of Pharmacy, Aristotelian University of Thessaloniki in 2000. After that he joined the Department of Pharmaceutical Chemistry, School of Pharmacy as a Postgraduate student to receive his Ph.D.