New Developments on Thromboxane Modulators

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Abstract: Thromboxane A_2 (TXA_2) is a labile product formed from arachidonic acid by cyclooxygenase. The pathogenesis of numerous cardiovascular, pulmonary, and thromboembolic diseases can be related to this metabolite. Therefore, TXA_2 modulators have been developed for 20 years. This review will highlight the evolution in the field of TXA_2 modulators.

Keywords: Thromboxane A_2, Arachidonic acid, Thromboxane synthase, Prostanoids

INTRODUCTION

Arachidonic acid (AA) (**1**) metabolites play a fundamental role in a large number of physiological processes. In particular, thromboxane A_2 (TXA_2) (**5**), which is a potent inducer of platelet aggregation, vasoconstriction and bronchoconstriction [1-4], is implied in the proliferation of vascular smooth muscle cells and mitogenesis [5-8]. TXA_2 is formed by the action of thromboxane synthase on the prostaglandin endoperoxide H_2 (PGH_2) (**3**) [9, 10] mainly in activated platelets [11] and macrophages [12] where this enzyme is highly expressed (Fig. (**1**) and Fig. (**2**)) [13]. In platelets, PGH_2 is the result of enzymatic action of the constitutive form of cyclooxygenase (COX-1) on AA released from the cell membrane phospholipids by phospholipase A_2. In endothelial cells, prostacyclin synthase can convert PGH_2 into prostacyclin or prostaglandin I_2 (PGI_2) (**4**) (Fig. (**2**)). Blood cells and vessel blood cells cooperate in the biosynthesis of these eicosanoids. Indeed, prostaglandin endoperoxide G_2 (PGG_2) (**2**) and PGH_2 can be transferred from platelets to endothelial cells where they are converted into prostacyclin. A new synthetic pathway of TXA_2 and PGI_2 via the inducible form of the cyclooxygenase (COX-2) has also been reported [13, 14-16]. Moreover, it seems that platelet-derived TXA_2 can act in a paracrine manner to upregulate endothelial COX-2 expression and PGI_2 synthesis [17, 18]. TXA_2 rapidly breaks down non-enzymatically (half-life of 30 seconds at 37°C) to its more stable but biologically inactive blood metabolite thromboxane B_2 (TXB_2) [1]. The major urinary metabolite of circulating TXB_2 was identified as 2,3-dinor-TXB_2 [19]. An overproduction of TXA_2 has been revealed by an increase of these metabolites in patients with various disease states whereby this eicosanoid is assumed to contribute to the underlying pathomechanisms by its potent stimulation of platelet aggregation and smooth muscle contraction [20]. Indeed, it is well recognized that TXA_2 plays an important role in pathophysiological states such as myocardial infarction [21, 22], unstable angina [23], pregnancy-induced hypertension and preeclampsia [24-26], thrombosis and thrombotic disorders [27-29], pulmonary hypertension [30], asthma [31], septic shock [32], atherosclerosis [33-35], lupus nephritis [36, 37] and Raynaud's phenomenon [38]. Therefore, TXA_2 receptor antagonists, thromboxane synthase inhibitors and drugs combining both properties have been developed by several pharmaceutical companies. Several compounds have been launched on the market and others are under clinical evaluation. Moreover, since TXA_2 is not the only mediator implicated in the disease states cited above, original thromboxane modulators which combine another pharmacological activity such as platelet activating factor antagonism, angiotensin II antagonism, or 5-lipoxygenase inhibition have been recently developed. These drugs will also be presented at the end of this article.

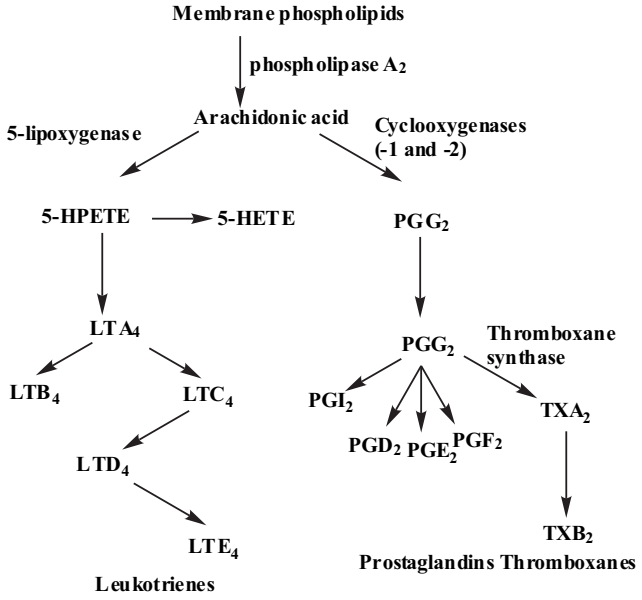

Fig. (1). Two major ways of metabolism of arachidonic acid: 5-lipoxygenase pathway leads to 5- hydroperoxyeicosatetraenoic acid (5-HPETE) and subsequent leukotrienes (A_4, B_4, C_4, D_4, E_4), whereas cyclooxygenase pathway leads to cyclic endoperoxides (PGG_2 and PGH_2) and the subsequent metabolic products: prostaglandins (D_2, E_2, $F_{2\alpha}$), prostacyclin (PGI_2) and thromboxanes A_2 (TXA_2) and its main blood metabolite, thromboxane B_2 (TXB_2).

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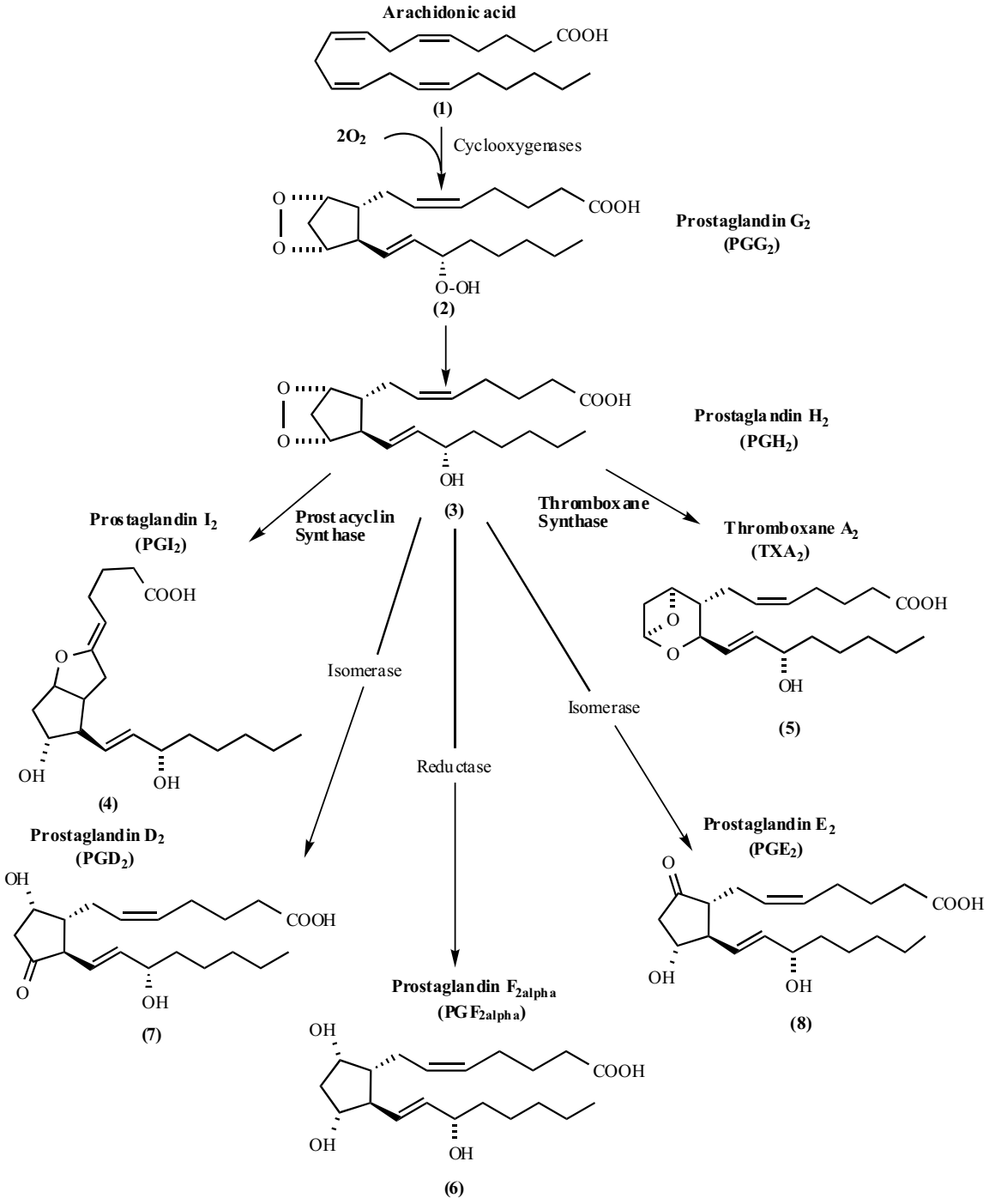


Fig. (2). Cyclooxygenase pathway and chemical structures of arachidonic acid, prostaglandins endoperoxides (PGG_2 and PGH_2), prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$), prostacyclin (PGI_2) and thromboxane A_2 (TXA_2).

THROMBOXANE SYNTHASE MODULATORS

The Thromboxane Synthase Inhibitors (TXSIs)

The selective inhibition of thromboxane synthase prevents the conversion of PGH_2 to TXA_2 [3, 21]. This has the advantage that other arachidonic acid metabolites can still be produced and is of particular interest in the prevention of platelet aggregation. Indeed, in the setting of platelet activation, as would occur locally at a vascular injury site, the platelet-produced endoperoxides can be taken by other cells such as smooth muscle cells and endothelial cells. In these cells, PGH_2 can be metabolised by the prostacyclin synthase in PGI_2, which is the most effective inhibitor of platelet aggregation and a potent vasodilator. Therefore, with a thromboxane synthase inhibitor, the antithrombotic effect due to the presence of locally-produced prostacyclin could exceed that is expected by blocking the cyclooxygenase, as does aspirin. Moreover, the conversion of PGH_2 to E-type prostaglandins could help reduce thrombus formation due to their vasodilatory action [39].

On the basis of this hypothesis, a series of TXSIs have been developed. Several compounds such as dazoxiben (UK 37248) (**9**), dazmagrel (UK 38485) (**10**), pirmagrel (CGS

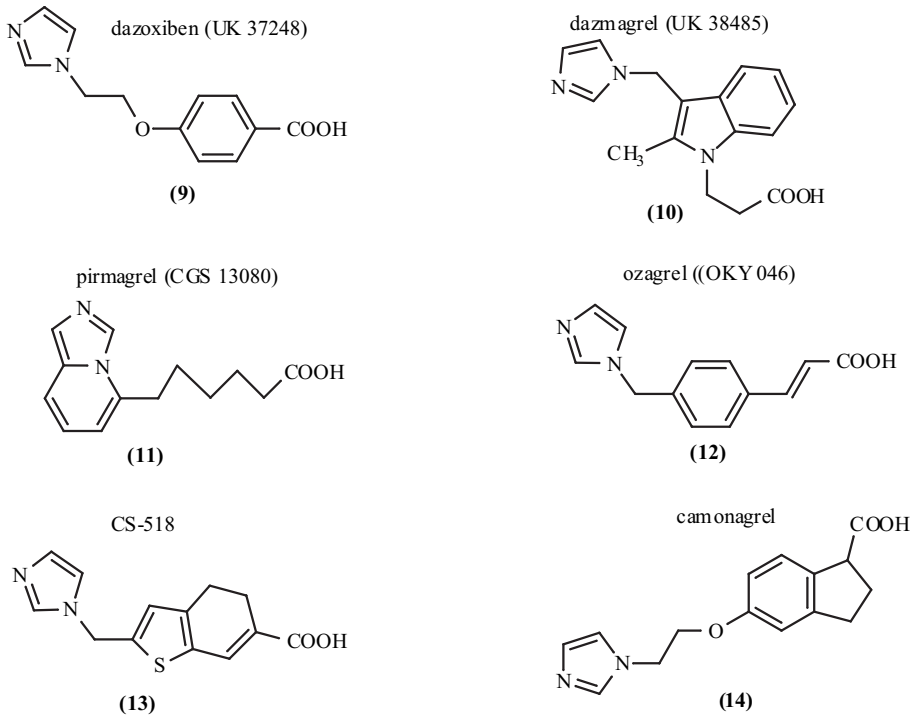


Fig. (3). Chemical structures of TXSIs characterized by an imidazol ring: dazoxiben, dazmagrel, pirmagrel, ozagrel, CS-518, and camonagrel.

13080) (**11**), ozagrel (OKY 046) (**12**), CS-518 (**13**), OKY 1581 (**15**), isbogrel (CV 4151) (**16**) and furegrelate (U63557A) (**17**) have undergone clinical testing. Others, such as camonagrel (**14**), are still under preclinical development (Fig. (**3**) and Fig. (**4**)). Unfortunately, these compounds were found less active than expected or sometimes ineffective although reducing the biosynthesis of TXA_2. Indeed, they failed to produce consistent effects in clinical conditions where an overproduction of TXA_2 has been detected [20]. The disappointing clinical results with this class of drugs can be explained by an incomplete blockage of thromboxane synthase with the dosage used and mainly by the fact that TXSIs provoke an accumulation of the TXA_2 precursor, PGH_2, which is chemically more stable and exerts similar biological effects by acting at common receptors [40-45]. As a consequence, few pharmaceutical companies have continued the clinical development of TXSIs as single drugs (only one patent has been deposited since January 1998, describing the synthesis and the use of a novel TXSI). It is nonetheless important to note that ozagrel hydrochloride was the first thromboxane modulator released onto the market (in Japan, 1992) for the treatment of adult bronchial asthma. Nevertheless, some TXSIs cited above are mainly used as pharmacological tools in a series of recent *in vitro* and *in vivo* studies with the aim of evaluating the influence of TXA_2 in physiologic or pathophysiologic states [20].

THROMBOXANE RECEPTORS MODULATORS

Thromboxane A_2 receptor, officially called TP receptor [46] or sometimes still named TXA_2/PGH_2 receptor, belongs to the G protein-coupled receptors superfamily which is characterised by 7 transmembrane domains [47]. The endogenous ligands for this receptor are TXA_2 and PGH_2. Several synthetic agonists, including (with growing order of affinity) STA2 (**18**), I-BOP (**19**), U-46619 (**20**), are used as pharmacological tools, because of the instability of TXA_2 (Fig. (**5**)) [48]. It is present in many cell types and

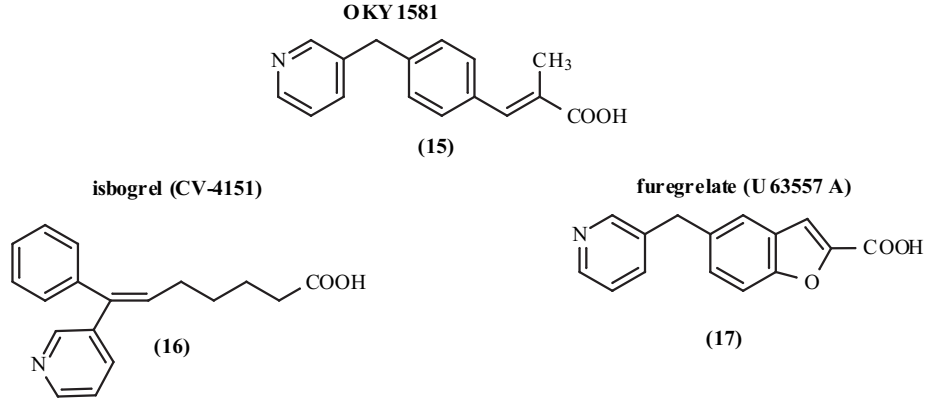


Fig. (4). Chemical structures of TXSIs characterized by a pyridine ring: OKY 1581, isbogrel and furegrelate.

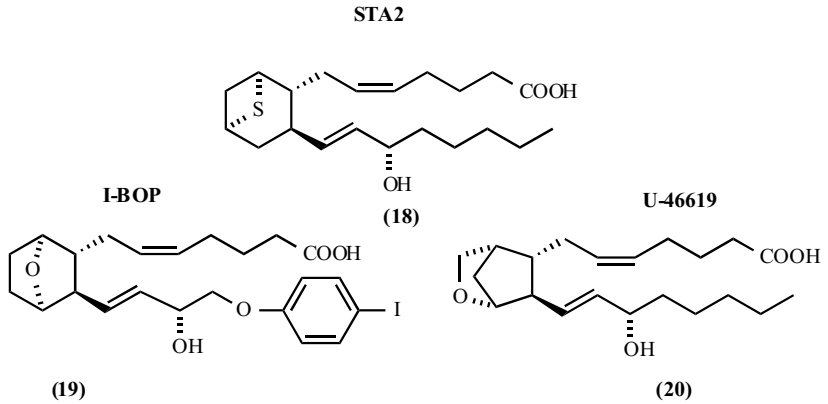


Fig. (5). Chemical structures of TXA_2 receptor ligands STA2, I-BOP, and U-46619.

tissues, with particular abundance in platelets, endothelial cells, vascular smooth muscle, kidney, brain, spleen, monocytes, thymus, uterus, and placenta [47, 49-55]. Early pharmacological studies in the eighties have shown that some compounds can discriminate between endothelial and platelet receptors, suggesting the existence of at least two different subtypes [56, 57]. Moreover, in platelets, it was demonstrated that some agonists bind to platelet TP with different affinity states: one that induces shape change and the other aggregation [58-60], giving strong evidence that heterogeneity existed among those platelet receptors. Since the discovery in 1991 by Hirata et al. of a cDNA coding for the human TP [47], active researches were conducted to find a molecular explanation for the apparent heterogeneity of this receptor. It was then shown that one gene was coding for the receptor [61], although two isoforms could be generated by alternative splicing [62].

THE THROMBOXANE RECEPTOR ANTAGONISTS

Thromboxane receptor antagonists (TXRAs) block the action of TXA_2 and PGH_2 at a receptor level. Consequently, in contrast to TXSIs, TXRAs do not affect the synthesis of prostacyclin and other prostaglandins. The development of this class of thromboxane modulators continues to be an active area of research. Thus, TXRAs are becoming an established method for treating asthma and various cardiovascular diseases in the clinic. Indeed, since the development of sulotroban (**24**) in 1980 [63-67], a large variety of prostanoid and non-prostanoid TXA_2 receptor antagonists have been patented. Some of these compounds are still being clinically evaluated and, one of them, seratrodast (**36**), a TXRA developed by Takeda Company® has been approved in Japan for the treatment of asthma (Bronica® 80 mg/day per os).

From a chemical point of view, TXRAs can be classified in two groups: the prostanoid TXRAs structurally related to the bicyclic physiological TP receptors ligands: PGH_2 and TXA_2 (Fig. (**6**)) and the non-prostanoid TXRAs of which the majority is characterized by a phenylsulfonamido moiety (Fig. (**7**)) [20].

Prostanoid Thromboxane A_2 Receptor Antagonists

All these compounds bear a carboxylic and a lipophilic side. The carboxylic and the ω-side chains of the PGH_2 ligands are fixed on a 5-atom ring (cyclopentyl or tetrahydrofuran) in contrast to the TXA_2 related compounds characterised by a 3,3-dimethyltetrahydropyren.

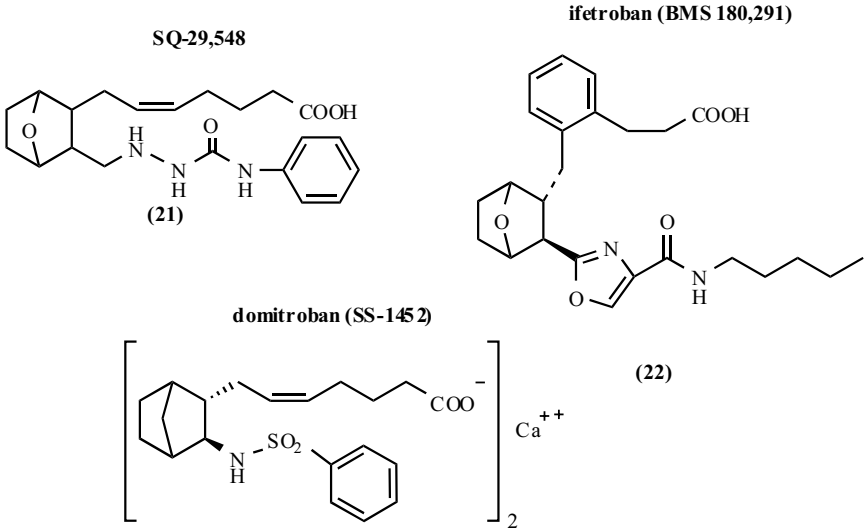


Fig. (6). Chemical structures of prostanoid TXRAs SQ-29548, ifetroban and domitroban.

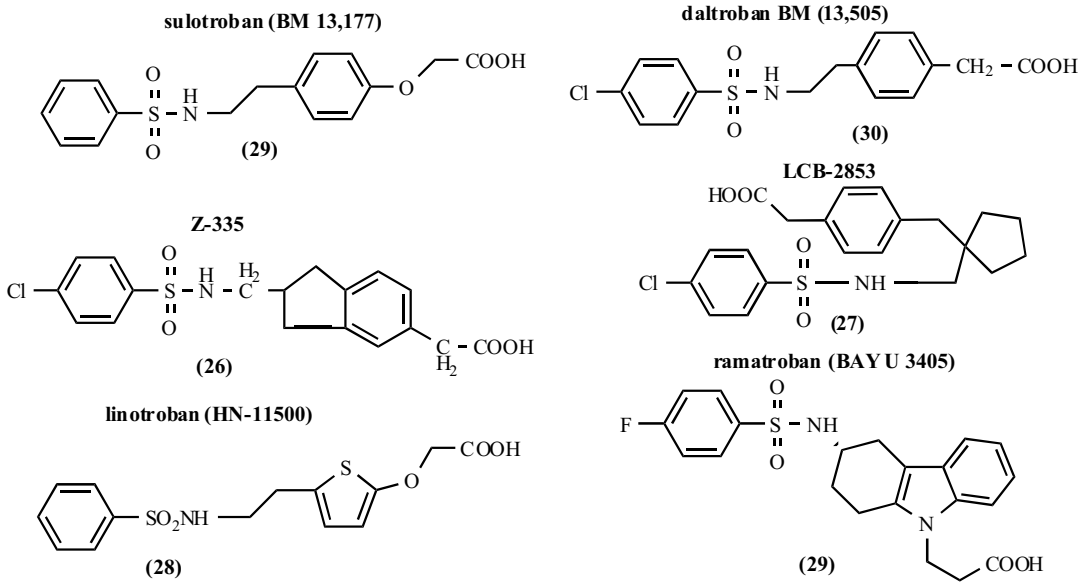


Fig. (7). Chemical structures of non-prostanoid TXRAs sulotroban, daltroban, Z-335, LCB-2853, linotroban and ramatroban.

SQ-29548 (**21**), ifetroban (**22**) and domitroban (**23**) are the most studied TXRAs derived from endoperoxide PGH_2. Semicarbazide SQ-29548 is considered as one of the most potent ligands and antagonist of the TXA_2 receptors [20, 68-71]. Thereby, it remains the major TXRA used as pharmacological tool in *in vitro* studies and *in vivo* experiments performed only in animals [72-75]. Indeed, its development as potential clinical candidate has been stopped because of its mutagenic potential revealed in the Ames screen when incubated with a rat liver microsome fraction [76]. Its labelled derivative [5,6-^{3}H]SQ-29548 is frequently used as a tracer in TXA_2 receptors binding studies [77, 78].

Another carboxamide derivative, ifetroban (BMS 180,291) (**22**), a proprietary Bristol-Myers Squibb, is a potent, long-acting, orally active TXA_2/PGH_2 receptor antagonist [79]. It was studied for treating leg ulcers in a prospective, randomised, double blind, placebo-controlled multicenter study in which 165 patients were randomised to ifetroban (n = 83, 250 mg daily) versus placebo (n = 82) for a period of 12 weeks. The results obtained were disappointing since complete ulcer healing was achieved after 12 weeks in 55% of patients receiving ifetroban and in 54% of those taking a placebo, with no significant difference [80, 81]. Nevertheless, other applications have been claimed for this TXRA.

Since Narisada opened the way to norbornane derivatives bearing a sulfonamide moiety [82], S-1452 (domitroban) (**23**) emerged as an original highly potent TXRA characterised by a long-lasting antiplatelet activity [83]. Currently, S-1452 is still being studied as an anti-asthma agent [84-86].

Non-Prostanoid Thromboxane A_2 Receptor Antagonists of the Phenylsulfonamide Type

Sulotroban (**24**) is the prototype of the "phenylsulfonamide" derivatives. Indeed, it was the first TXRA studied in clinical trials [63-67]. Its development was discontinued because of its moderate effects in several clinical situations such as angina. This lack of activity could be explained by an agonist activity revealed on vascular smooth muscle preparation. Moreover, sulotroban is a weak TXRA [78]. Consequently, a series of sulotroban derivatives have been developed with the aim of improving the antagonistic activity on TP receptors (Fig. (**7**)). Thus, daltroban (BM 13,505) (**25**), Z-335 (**26**), LCB-2853 (**27**), linotroban (HN-11500) (**28**) and ramatroban (BAY U 3405) (**29**) emerged as the most promising compounds of this class. From a chemical point of view, these compounds are characterized by a carboxylic acid, a phenylsulfonamide, and a "spacer" of these functional groups. The presence of a halogen atom on the benzene ring in the *para*-position of the sulfonamide moiety also characterized the majority of these compounds [20]. The structure of daltroban (**25**), which has a phenylethyl group as a spacer, is the simplest of these molecules. It has been shown to be ten times more potent than sulotroban in *in vitro* experiments and in healthy volunteers. Nevertheless, as observed for sulotroban, evidence for partial agonist properties at TP-receptors on vascular smooth muscle have also been reported [87]. Both sulotroban and daltroban are currently used as pharmacological tool [88, 89].

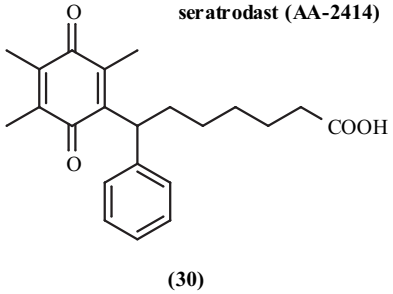


Fig. (8). Chemical structure of seratrodast, a non-prostanoid TXRA.

In 1999, Shinozaki and collaborators proposed the introduction of an indane ring as part of the structural rigid spacer in place of the phenylethyl group of daltroban. This modification led to Z-335 (**31**), which was found to be a

potent TXRA in oral administration [90]. It was studied as an antiplatelet and antithrombotic agent in rat and proved to be more active than cilostazol, a selective phosphodiesterase type III inhibitor [91, 92]. It is currently under clinical evaluation for its antithrombotic properties.

LCB-2853 (**27**) is another TXRA derived from daltroban and is under clinical evaluation for its antithrombotic properties. It is characterized by a cyclopentane ring as a spacer between the 4-chlorophenylsulfonamide group and the carboxylic acid. It was demonstrated to be a potent TXRA in *in vitro*, *ex vivo,* and *in vivo* experiments [93, 94].

Linotroban (**28**), developed by Nycomed company, is characterised by a thiophen ring as spacer in place of the benzene ring of sulotroban. It was early characterized as a potent antithrombotic agent [95].

Ramatroban (Bay-U-3405) (**29**) combines in its structure a 1,2,3,4,-tetrahydrocarbazole ring as spacer and a 4-fluorophenylsulfonamide group. It is a TXA_2/PGD_2 antagonist that has been launched in Japan for rhinitis in mid-2000 by Bayer Yakuhin (Baynas®, tablets of 75 and 150 mg) and is currently under phase III clinical evaluation as anti-asthmatic agent. It has also been patented for the treatment of allergy, atopic dermatitis and allergic dermatitis.

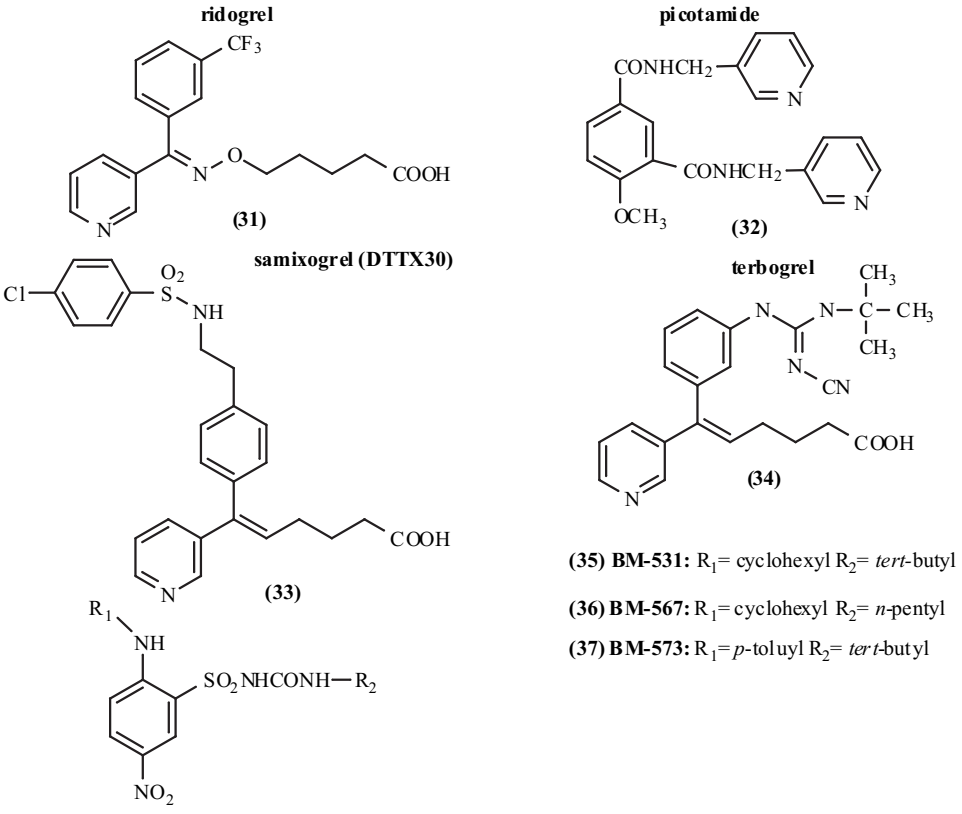
Miscellaneous Compounds

Seratrodast (AA-2414) (**30**) (Fig. (**8**)) is a orally active quinone derivative characterized by a potent thromboxane A_2 receptors antagonism [96-99]. Indeed, the lack of any carboxylic acid terminal group makes it original. Its crystal structure has been determined and served as starting point to docking studies with the modelled human TXA_2 receptor [100]. It is the first TXRA that is being developed as an anti-asthmatic drug. Indeed, it has also received marketing approval in Japan (1997) and is currently under phase III clinical trials in the United States.

COMBINED THROMBOXANE MODULATORS AND OTHER PHARMACOLOGICAL PROPERTIES

Combined Thromboxane Synthase Inhibitors and Thromboxane Receptor Antagonists

As reported above in this paper, both thromboxane receptor antagonists and thromboxane synthase inhibitors present interesting pharmacological characteristics. Thus, TXSIs can result in an increase of the synthesis of the antiaggregatory and vasodilatory prostacyclin and TXRAs can block the action of both TXA_2 and PGH_2 at a receptor level. Thereby, An apparent solution to optimise the therapeutical benefit of both thromboxane synthase inhibitors and thromboxane A_2 receptor antagonists used alone is to combine these properties in the same molecule. Indeed, to support this concept, the co-administration of the TXRA sulotroban and the TXSI dazoxiben has been demonstrated to prolong the bleeding time in man more than each drug used alone [101]. Therefore, a large variety of compounds associating both principles of action have been developed (Fig. (**9**)). Most of these drugs retain the pyridinic ring of the TXSI isbogrel. Thus, ridogrel (**31**), picotamide



(35) BM-531: R_1= cyclohexyl R_2= *tert*-butyl

(36) BM-567: R_1= cyclohexyl R_2= *n*-pentyl

(37) BM-573: R_1= *p*-toluyl R_2= *tert*-butyl

Fig. (9). Chemical structures of combined TXRAs and TXSIs ridogrel, picotamide, samixogrel, Terbogrel, and sulfonylureas BM-531, BM-567, and BM-573.

(**32**), and terbogrel (**34**) have been studied in clinical trials.

Ridogrel (**31**), a pyridinic derivative, was the first dual inhibitor of thromboxane A_2 to be studied in clinic but it yielded disappointing results. Nevertheless, this potent TXSI and weak TXRA is currently under clinical evaluation in the treatment of ulcerative colitis and in inflammatory bowel disease [102, 103].

Picotamide (**32**) is another combined TXRA and TXSI. It is characterised by two pyridine rings each fixed to a benzene by a carboxamide moiety. It was studied in man for the first time in 1978 [104] and evaluated in a series of clinical conditions [105-117]. It is currently marketed as antiplatelet and antithrombotic agent.

Terbogrel (**34**) is a close derivative of samixogrel (DTTX30) (**33**). Both were designed and synthesized as combined thromboxane A_2 receptor antagonists and thromboxane A_2 synthase inhibitors. Nevertheless, samixogrel which reflects structural elements of the synthase inhibitor isbogrel and the receptor antagonist daltroban showed only moderate plasma levels combined with an unexpected high variability after oral administration in human volunteers presumably due to its very low solubility in aqueous solution under physiological conditions. Thereby, the modification of the phenylsulfonamide of samixogrel led to the cyanoguanidine terbogrel. This drug showed a better pharmacokinetic profile [39]. It is currently under clinical evaluation as antithrombotic agent. Nevertheless, a recent study performed in patients suffering from primary pulmonary hypertension had to be halted because of the unforeseen side effect of leg pain, which occurred almost exclusively in patients with terbogrel treatment [118, 119].

Finally, a series of non-carboxylic combined TXRAs and TXSIs has been described. They derive from the high ceiling loop diuretic sulfonylurea torasemide which revealed a weak thromboxane receptor antagonistic activity. They are characterised by a nitrobenzenic ring bearing a N-alkylsulfonylurea moiety. These are represented by BM-531 (**35**), BM-567 (**36**) and BM-573 (**37**). Each compound was evaluated in preclinical development and presented a well-balanced effect on thromboxane synthase and TXA_2 receptors [120-124]. BM-573 is currently studied in pigs in prevention of a series of induced pathophysiological conditions, such as coronary thrombosis, septic shock and pulmonary thromboembolism.

Combined Thromboxane Synthase Inhibitors and Other Pharmacological Properties

Since TXA_2 is not the only mediator implicated in the disease states such as thrombosis, asthma and hypertension, original thromboxane modulators, which combine another pharmacological activity, have recently been developed. Thus, thromboxane modulators which antagonise LTD_4 receptors [125-129] or inhibit 5-lipoxygenase [130-134] have been described and proposed to be of great interest in the treatment of immunologic and/or inflammatory diseases and asthma. Moreover, the development of combined TXRAs and angiotensin II receptor antagonists and combined TXRAs has also been proposed in the prevention of hypertension [135]. Finally, a novel strategy for the treatment of mammary tumours has been developed with the design of combined TXSIs and aromatase [136]. Clinical studies are needed to evaluate the real interest of such compounds as new therapeutic agents.

CONCLUSIONS

Thromboxane A_2 is a potent inducer of platelet aggregation and smooth muscle contraction. It is implicated in many pathological processes, most notably thrombosis, pulmonary hypertension and asthma. Thereby, many thromboxane modulators have been developed to inhibit the effects of this eicosanoid. Thus, thromboxane synthase inhibitors suppress TXA_2 formation while increasing the synthesis of the antithrombotic and vasodilator prostacyclin by endothelial cells. However, clinical trials with these agents resulted in disappointing results because of the accumulation of endoperoxide prostaglandin H_2 which also binds to TP-receptors. Nevertheless, ozagrel hydrochloride was the first thromboxane modulator released onto the market (in Japan, 1992) for the treatment of adult bronchial asthma. In contrast to TXSIs, thromboxane A_2 receptor antagonists do not affect the synthesis of prostacyclin and other prostaglandins, but prevent TXA_2 and PGH_2 from activating platelets and inducing vaso- and bronchoconstriction. TXRAs are currently recognised as an established method for treating asthma and various cardiovascular diseases in the clinic. Non-prostanoid TXRAs characterized by a phenylsulfonamido moiety (derived from sulotroban) appear to be of great interest as proved by the number of compounds recently patented and studied in clinical trials. Moreover, Bayer Yakuhin has launched ramatroban in Japan for the treatment of rhinitis in mid-2000. This TXRA is also evaluated in clinical trials for the treatment of asthma. Seratrodast, a quinone derivative, is the only TXRA marketed so far in Japan as anti-asthmatic agent. Moreover, it is currently in clinical evaluation in the United States for the treatment of chronic obstructive pulmonary disease, asthma and cardiovascular disorders. Consequently, development of novel TXRAs is still an active area of research. Another interesting approach to modulate the action of thromboxane A_2 is to combine thromboxane synthase inhibition with thromboxane receptor antagonism in one drug. Picotamide, which is marketed as antiplatelet and antithrombotic agent, belongs to this class. It is commonly used with success in a series of pathophysiologic conditions in humans. Thereby, the development of such compounds continues to be a priority of different pharmaceutical companies. Other original thromboxane modulators, which combine another pharmacological activity, have also been developed recently. Thus, thromboxane modulators, which inhibit 5-lipoxygenase (such as E-3040) or antagonise LTD_4 receptors (such as YM158), combined TXRAs and angiotensin II receptor antagonists, combined TXRAs and PAF antagonists and combined TXSIs and aromatase inhibitors are current approaches in the thromboxane pharmacology.

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