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BM-520, an original TXA_2 modulator, inhibits the action of thromboxane A_2 and 8-iso-prostaglandin $F_{2\alpha}$ *in vitro* and *in vivo* on human and rodent platelets, and aortic vascular smooth muscles from rodents

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Abstract

Thromboxane A_2 (TXA_2) and 8-iso-$PGF_{2\alpha}$ are two prostanoid agonists of the thromboxane A_2 receptor (TP), whose activation has been involved in platelet aggregation and atherosclerosis. Agents able to counteract the actions of these agonists are of great interest in the treatment and prevention of cardiovascular events. Here, we investigated *in vitro* and *in vivo* the pharmacological profile of BM-520, a new TP antagonist. In our experiments, this compound showed a great binding affinity for human washed platelets TP receptors, and prevented human platelet activation and aggregation induced by U-46619, arachidonic acid and 8-iso-$PGF_{2\alpha}$. The TP receptor antagonist property of BM-520 was confirmed by its relaxing effect on rat aorta smooth muscle preparations precontracted with U-46619 and 8-iso-$PGF_{2\alpha}$. Further, its TP antagonism was also demonstrated *in vivo* in guinea pig after a single intravenous injection (10 mg kg^{-1}). We conclude that this novel TP antagonist could be a promising therapeutic tool in pathologies such as atherosclerosis where an increased production of TXA_2 and 8-iso-$PGF_{2\alpha}$, as well as TP activation are well-established pathogenic events.

Keywords: Thromboxane A2; Antiplatelet agent; Isoprostanes

1. Introduction

Thromboxane A_2 (TXA_2) is a short-lived cellular lipid mediator mainly produced by activated platelets and macrophages via the arachidonic acid metabolism (Fig. 1). First, arachidonic acid is metabolized by cyclooxygenase to give unstable prostaglandin H_2 which is then transformed by the thromboxane synthase into TXA_2 [1]. Both

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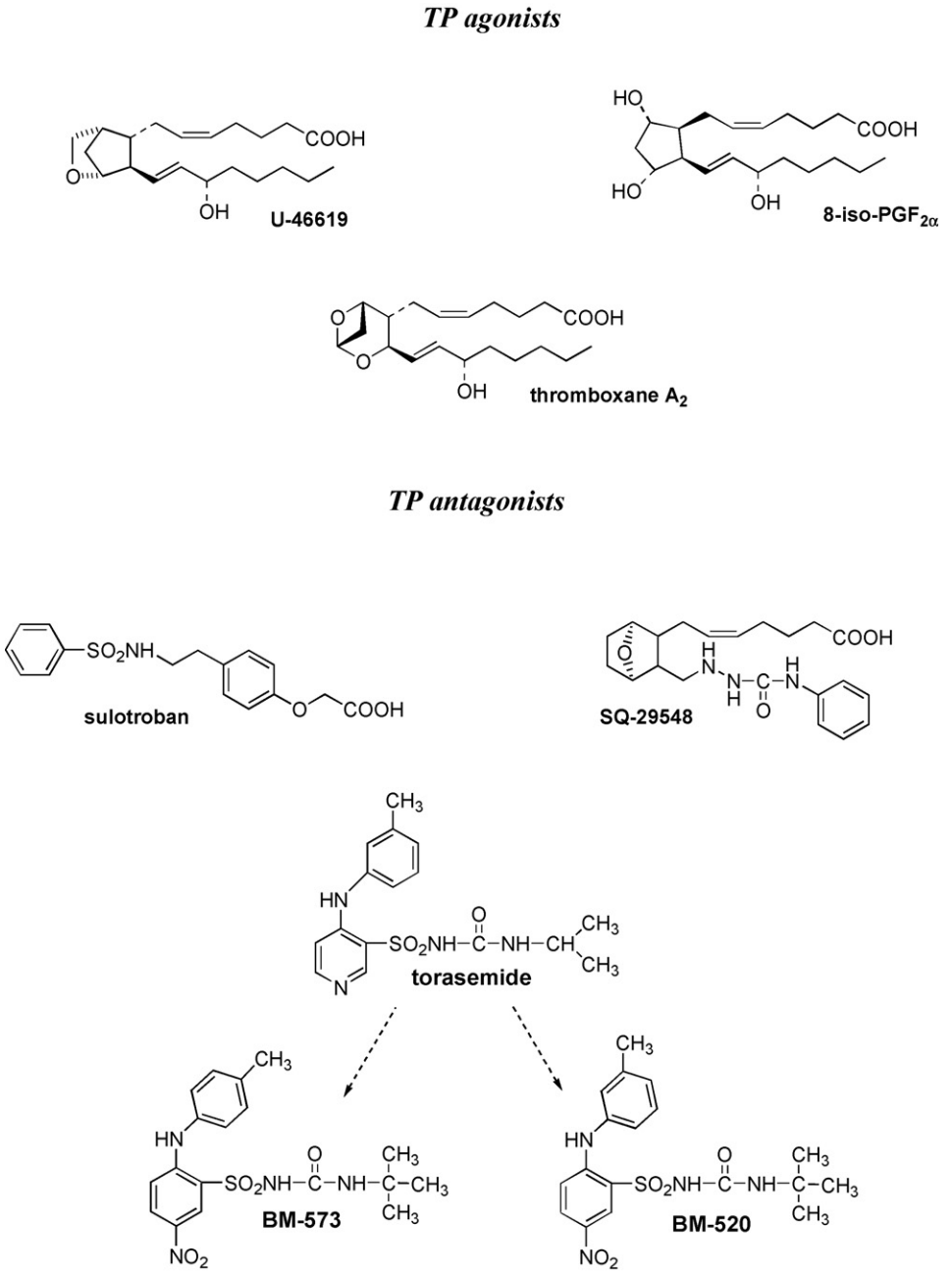

Fig. 1. Chemical structures of TXA_2 receptor (TP) agonists (U-46619, 8-iso-$PGF_{2\alpha}$), of reference TP antagonists (sulotroban, SQ-29548) and of torasemide and its original chemically related compounds (BM-573 and BM-520).

PGH_2 and TXA_2 bind a specific receptor, TXA_2 receptor (TP), which is a member of the seven-transmembrane G-protein-coupled receptor super family [2]. TP receptors are widely distributed in different cells types and systems [3]. Their activation leads to different biological effects such as platelet aggregation and constriction of vascular smooth muscles [4]. Due to these biological properties, TXA_2 has been implicated in the pathogenesis of ischemic cardiovascular diseases such as myocardial infarction and stroke [5]. Furthermore, due to its bronchoconstrictor properties, TXA_2 has also been involved in bronchial asthma [6]. Consequently, TP receptors represent an attractive therapeutic target in such pathological states [7,8]. As a result, TXA_2 synthase inhibitors and TP antagonists have been developed to reduce