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New platelet aggregation inhibitors based on pyridazinone moiety

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ABSTRACT

New series of pyridazinone derivatives (**4**, **5** and **6**) were synthesized in good yields following a synthetic strategy based on singlet oxygen oxidation of alkyl furans, in which a suitable $\beta(\alpha)$-substituted γ-hydroxybutenolide (**10** or **11**) or a bicyclic lactone (**12** or **13**) was the key intermediate. The synthesized compounds were tested in vitro as antiplatelet agents and some of them (compounds **4b**, **4d** and **5b**) exhibited potent inhibitory effects on collagen-induced platelet aggregation with IC_{50} values in the low μM range. Studies performed with the most active compound of these series (**4b**) demonstrated its lack of activity as inhibitor of platelet aggregation induced by other agonists as thrombin, ionomycin or U-46619 suggesting a selective action on the biochemical mechanisms triggered by collagen in the platelets.

1. Introduction

Cardiovascular diseases (CVDs), in particular coronary heart disease and stroke, are a leading cause of mortality in developed countries. According to the World Health Organization (WHO) 17 million people die every year by CVDs, accounting for almost one third of deaths worldwide per year [1]. In addition, CVDs are not only responsible for high morbidity and mortality, but negatively impact the quality of life of a huge amount of people across the world. Thrombus formation and hypertension are the most common risk factors for myocardial infarction and stroke. The pivotal role played by platelet activation in the physiopathology of thrombotic and ischemic diseases and the current limitations of antiplatelet therapy have prompted the search for new antiplatelet agents acting over novel therapeutic targets [2].

The 6-(aryl or heteroaryl)pyridazinone derivatives show a wide pharmacological profile that includes interesting properties on cardiovascular system, such as cardiotonic effects [3], antihypertensive activity [4] and platelet aggregation inhibition [5], being zardaverine, levosimendan and motapizone some characteristic drugs [5a,6] (Fig. 1).

The presence of the aryl (heteroaryl) group at C6 was considered essential when the cardiovascular effects are associated with phosphodiesterase III (PDE III) inhibition [5a,7]. Recently, several pyridazinone derivatives, in which the aryl or heteroaryl group at C6 was removed or replaced (compounds **1** and **2**, Fig. 2), were described as potential antihypertensive agents or platelet aggregation inhibitors whose activity is not related with inhibition of PDE [8,9].

In relation to cardiovascular drug research based on pyridazinone moiety we have recently reported a series of 2,6-disubstituted analogs with good antiplatelet properties. These pyridazinone derivatives have an alkyl chain of varying magnitude (1, 2, or 3 carbon atoms) functionalized with alcohol or ether groups in C6, and substituted or not with different lipophilic fragments in N2 (compounds **3**, Fig. 2). Most of the previously designed compounds inhibited platelet aggregation induced by collagen in the low μM range (1.80–69.6), being silyl ethers and N,O-dibenzyl derivatives the most active compounds. Many of them also showed a moderate vasorelaxant effect [10].

The interesting antiaggregatory properties showed by the 2,6-disubstituted pyridazinones **3** led us to continue with these studies in order to establish structure–activity relationships.

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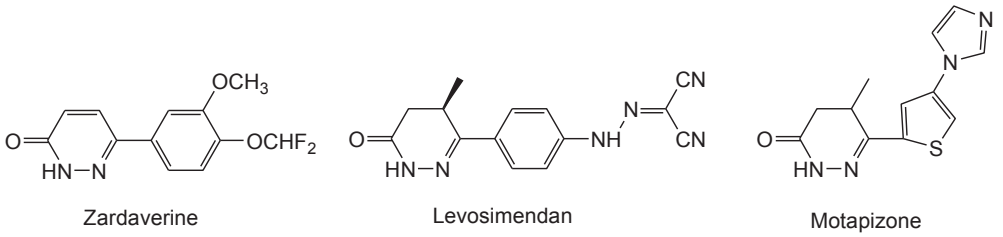

Fig. 1. Some cardiovascular drugs with the characteristic structure of 6-(aryl or heteroaryl)pyridazinone.

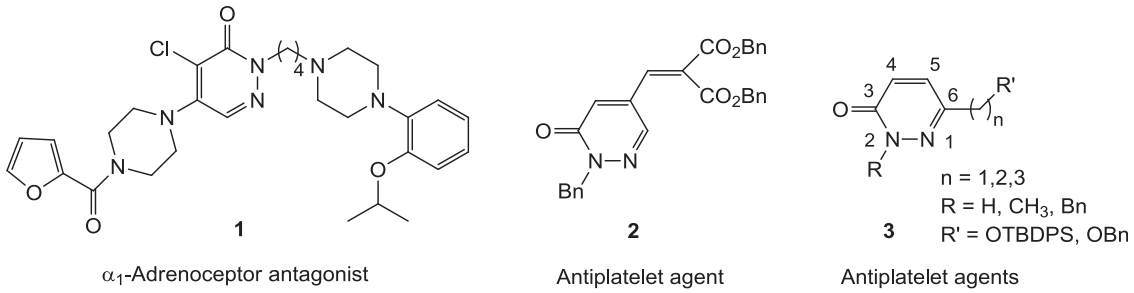

Fig. 2. Several pyridazinone derivatives with cardiovascular activity devoid of C6-(aryl or heteroaryl) group.

Therefore, we have synthesized and evaluated three new series of pyridazinone derivatives that have been designed considering two kinds of structural modifications, a positional change of the alkyl chain, which in the new analogs was placed at C5 or C4 of the pyridazinone ring (compounds **4** and **5** respectively, Fig. 3), and a reduction in conformational flexibility through the alkyl chain incorporation in different size rings resulting in bicyclic analogs **6** (Fig. 3).

2. Results and discussion

2.1. Chemistry

The pyridazinone derivatives studied in this work (compounds **4**, **5** and **6**) were synthesized according to the general procedures outlined in Schemes 1–3. Thus, the pyridazinone nucleus for monocyclic derivatives (**4** and **5**) was built by reaction of the $\beta(\alpha)$-substituted γ-hydroxybutenolide (**10** or **11**) with hydrazine or benzylhydrazine (Scheme 2), whereas for obtaining the fused pyridazinone core (**6**) a bicyclic lactone (**12** or **13**) was selected as the precursor suitable to react with hydrazine (Scheme 3).

The 4-hydroxybutenolides **10** and **11** were prepared in 3 steps from the commercially available ethyl 3-furoate (**7**) via oxidation with singlet oxygen, as shown in Scheme 1. Reduction of ester **7** with lithium aluminum hydride ($LiAlH_4$) in diethyl ether afforded alcohol **8** [11] (93% yield) which was protected as *tert*-butyldiphenylsilyl ether (compound **9** [12], yield 92%) in order to be submitted to singlet oxygen oxidation. Several protocols have been reported for the regioselective transformation of 3-substituted furans into α-substituted or β-substituted γ-hydroxybutenolides, via oxidation with singlet oxygen, in which a base-promoted regiocontrol was observed. In all cases, the oxidation was carried out in methanol or dichloromethane (DCM) at −78 °C in the presence of the suitable base. Thus, when the reaction is accomplished with some bulky bases, such as diisopropylethyl amine (DIPEA, Hünig's base), the β-substituted γ-hydroxybutenolides were the major products as a result of the sterically most favorable rearrangement [13,14]. The selective synthesis of the corresponding α-substituted γ-hydroxybutenolides is also possible by switching the base, for instance by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or tetrabutylammonium fluoride (TBAF). However, in this last strategy the reported results are extremely substrate-dependent [14,15]. In our case, oxidation of the alkylfuran **9** with singlet oxygen in the presence of the Hüning's base and methanol gave a mixture of regioisomers **10** and **11** in a 4:1 ratio and quantitative yield (Method A). Moreover, the proportion of the α-substituted γ-hydroxybutenolide **11** was increased with the use of DBU in DCM obtaining the mixture of **10** and **11** in 1:1.25 ratio and excellent yield (Method B, 96%). Purification by column chromatography afforded enough quantities of both regioisomers in order to identify them. Characterization of butenolides **10** and **11** was performed analyzing the differences found in their ^{1}H NMR data and specifically in the multiplicity of the methylene hydrogen atoms. These protons, which for the α-substituted butenolide **11** resonate as a multiplet centered at 4.48 ppm, appear fully differentiated for the β-substituted compound **10** as two doublet of doublets at 4.46 and 4.60 ppm, (J = 17.8 and 2.0 Hz) respectively. It is noteworthy that in the β-substituted butenolide (**10**) the oxygen atom of the side chain is close to the C5 hydroxyl group allowing the formation of a stable 6-membered ring through hydrogen bonding interactions which would explain the multiplicity differences observed.

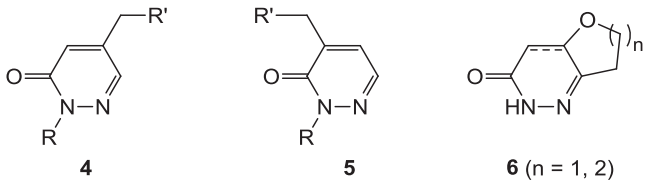

Fig. 3. General structure of pyridazinone analogs studied.

Treatment of a mixture containing **10** and **11** with hydrazine monohydrate in ethanol at reflux gave the pyridazinones **4a** and **5a** which were easily isolated and purified by column chromatography (Scheme 2). The structure of pyridazinone isomers **4a**–**5a** was established by the single crystal X-ray studies (Figs. 4 and 5) [16,17].