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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 1080–1083

Pyridazines part 41: Synthesis, antiplatelet activity and SAR of 2,4,6-substituted 5-(3-oxo-3-phenylprop-1-en-1-yl)- or 5-(3-phenylprop-2-enoyl)pyridazin-3(2*H*)-ones☆

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Received 14 September 2005; revised 19 October 2005; accepted 20 October 2005
Available online 14 November 2005

Abstract—As part of the optimization process of the lead compound **I** a focussed library of diversely substituted pyridazin-3(2*H*)-ones containing a 3-oxo-3-phenylprop-1-en-1-yl or 3-phenylprop-2-enoyl fragment at position 5 has been obtained and evaluated as antiplatelet agents. The structural modification at positions 2, 6 and 4 of the heterocyclic moiety allowed us to obtain preliminary information on the structure–activity relationship in this family.

Platelets constitute the primary cellular component of haemeostasis in mammalian organisms, being their primary physiologic role to survey the integrity of the circulatory system and respond rapidly and robustly at sites of vascular injury.[2] Platelet activity must be exquisitely regulated since inadequate activity leads to bleeding and excessive activity leads to deleterious thrombosis[3] which causes myocardial and cerebral infarction, the leading cause of morbidity and mortality in the industrialised world.

In the past decades, major progress has been made in the knowledge of platelet function. Nonetheless, the number of antiplatelet agents available as drugs (Fig. 1) is still insufficient and deleterious side effects are associated with most of the currently used agents.[4] The need to prevent thrombus formation without impairing haemeostasis has spurred large research aimed at the development of new antithrombotic agents and platelet aggregation inhibitors. Despite the extensive search and increasing investment in this important research field, aspirin remains the standard antiaggregatory medication to prevent thrombotic events. Other currently employed antiplatelet agents are ticlopidine, clopidogrel, sulfinpyrazone and tirofiban.

As a part of our research programme aiming at the discovery of novel pyridazin-3(2*H*)-one-based antiplatelet agents[5] we recently reported[6] the potent antiaggregatory effect (IC_{50} = 25 μM) of the lead compound **I** which contains a 3-phenyl-3-oxoprop-1-en-1-yl fragment as a key structural element in the heterocyclic core. Encouraged by this result and taking into account the well-documented[7] pharmacological properties associated with this pharmacophoric unit and especially their antiplatelet activity,[8] we present in this communication the synthesis and preliminary results of the structure–activity relationship studies obtained during the lead optimization process performed on **I**.

In order to determine the most salient features of the SAR in this series, a small focussed library having different substitution patterns at positions 2, 6 and 4 (**2a**–**e**

Keywords: Platelets; Antiplatelet agents; Pyridazinones; Palladium.
☆ See Ref. 1.
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doi:10.1016/j.bmcl.2005.10.073

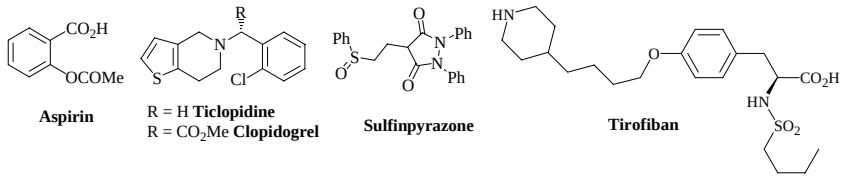


Figure 1. Structure of the most prominent antiplatelet agents currently employed.

and **6a**–**e**) of the scaffold was prepared. In addition, 3-phenylprop-2-enoyl positional isomers of the 3-oxo-3-phenylprop-1-en-1-yl system (**4a**–**f**) were synthesised (Fig. 2). Further work will be devoted to evaluate the effect of substitution on the phenyl group of the enone system.

Schemes 1 and 2 illustrate the synthetic methods developed to access the target compounds **2**, **4** and **6**. Sonogashira coupling of *N*-2-blocked 5-halopyridazinones **1** with 1-phenylprop-2-yn-1-ol, under previously reported conditions,[1,9] afforded the *trans*-configured enones **2** (Scheme 1). The transformation involves alkynylation followed by a base-promoted isomerisation of the initially formed 5-(3-hydroxy-3-phenylprop-1-yn-1-yl)pyridazin-3(2*H*)-one. The isomeric enones **4** were prepared by a Claisen–Schmidt condensation of the easily accessible methyl ketones **3**[1,10] with benzaldehyde dimethyl acetal in the presence of anhydrous aluminium chloride as a catalyst (Scheme 1).[11]

An effective and divergent approach based on the different reactivities of the triflate group and chlorine atom in the previously reported precursor **5**[12] was developed to access the targeted 4-substituted enones **6** (Scheme 2). Regioselective Sonogashira coupling on the triflate

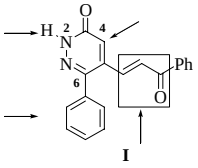
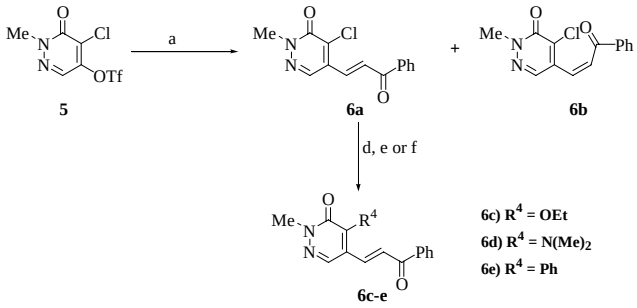


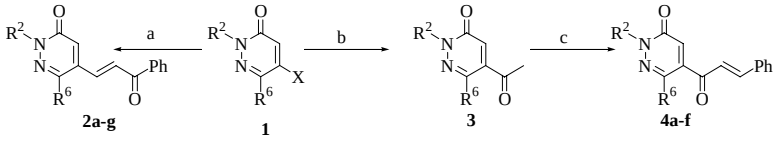
Figure 2. Structure of the lead compound **I** and points modified during lead optimization.



Scheme 2. Synthesis of 4-substituted 2-methyl-5-(3-oxo-3-phenylprop-1-en-1-yl)pyridazin-3(2*H*)-ones **6**.[11] Reagents and conditions: (a) CH≡CH(OH)Ph, $PdCl_2(PPh_3)_2$, CuI, Et_3N, Bu_4NI, DMF, rt; (d) EtOH, K_2CO_3, reflux; (e) $HN(Me)_2$, EtOH, rt; (f) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, H_2O, reflux.

group at C-5, based on chemoselective oxidative addition, afforded a 48/52 mixture of the *E*/*Z* enones **6a** and **b**. The *E*/*Z* mixture could be isomerised to a 92/8 ratio using triethylamine in dioxane at reflux for 24 h. Introduction of diversity at position 4 of **6a** (Scheme 2) was easily performed by exploiting the reactivity of the chlorine atom in nucleophilic substitution reactions (**6c**,**d**) or palladium-catalysed reactions (Suzuki–Miyaura coupling) (**6e**).

Table 1 shows the antiplatelet activity of compounds **2**, **4**, **6** and two reference compounds evaluated by the turbidimetric method of Born[14] employing thrombin as platelet aggregation inductor. Although the limited number of compounds precludes a detailed structure–activity relationship study, a few general features can be deduced and will be taken into account for further work.



Scheme 1. Synthesis of isomeric 5-(3-oxo-3-phenylprop-1-en-1-yl)pyridazin-3(2*H*)-ones **2** and 5-(3-phenylprop-2-enoyl)pyridazin-3(2*H*)-ones **4**.[11] Reagents and conditions: (a) CH≡CH(OH)–Ph, $PdCl_2(PPh_3)_2$, Et_3N, DMF, rt for X = I, 60 °C for X = Br; (b) (1) CH_2=C(OEt)Sn(Bu_3), $PdCl_2(PPh_3)_2$, DMF, Et_3N, reflux; (2) N HCl, reflux; (c) $PhCH(OMe)_2$, $AlCl_3$, dioxane, reflux.