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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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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**

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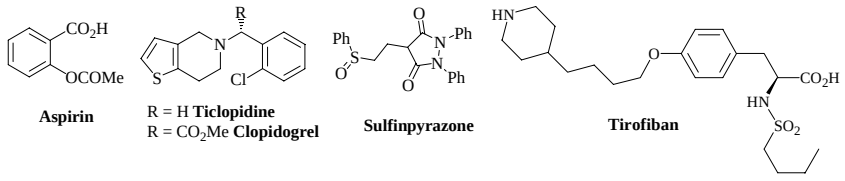


Figure 1. Structure of the most prominent antiplatelet agents currently employed.

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

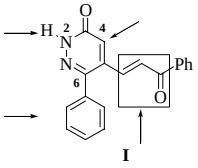
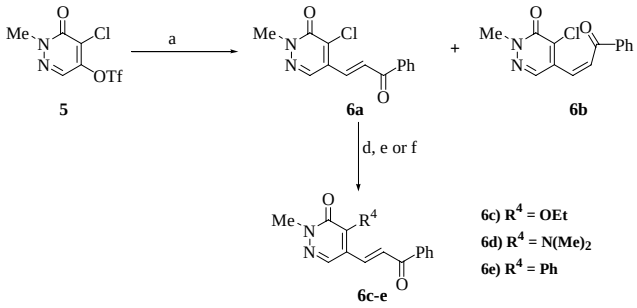


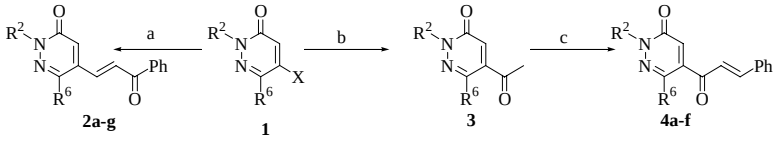
Figure 2. Structure of the lead compound **I** and points modified during lead optimization.



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.

Table 1. Structure[11] and antiplatelet activity[13] of pyridazin-3(2*H*)-ones **2**, **4**, **6** and reference compounds

Compound	R^2	R^6	R^4	R^5	Mp (°C)	Yield (%)	IC_{50} (μM)
2a	H	Ph	H	CH=CH–CO–Ph	230–231	69[a]	25.9 ± 1.7
2b	Me	Ph	H	CH=CH–CO–Ph	209–210	70	[b]
2c	MOM	Ph	H	CH=CH–CO–Ph	177–178	80	[b]
2d	Bn	Ph	H	CH=CH–CO–Ph	180–182	75	[c]
2e	H	H	H	CH=CH–CO–Ph	193–194	60	19.7 ± 0.8
2f	Me	H	H	CH=CH–CO–Ph	192–194	89	15.7 ± 0.7
2g	Bn	H	H	CH=CH–CO–Ph	174–175	70	4.2 ± 0.3
2h	Ph	H	H	CH=CH–CO–Ph	156–157	77	3.3 ± 0.3
4a	H	Ph	H	CO–CH=CH–Ph	175–177	60	35.5 ± 2.0
4b	MOM	Ph	H	CO–CH=CH–Ph	152–153	70	38.5 ± 1.6
4c	Me	Ph	H	CO–CH=CH–Ph	134–136	67	43.0 ± 8.2
4d	H	H	H	CO–CH=CH–Ph	188–190	64[a]	[c]
4e	Me	H	H	CO–CH=CH–Ph	212–214	62	[c]
4f	Bn	H	H	CO–CH=CH–Ph	73–75	76	[d]
6a	Me	H	Cl	CH=CH–CO–Ph	167–168	30	14.4 ± 1.8
6b	Me	H	Cl	CH=CH–CO–Ph	109–111	[e]	31.3 ± 4.9
6c	Me	H	OEt	CH=CH–CO–Ph	120–121	43	48.5 ± 5.6
6d	Me	H	$N(Me)_2$	CH=CH–CO–Ph	96–97	91	221.3 ± 2.2
6e	Me	H	Ph	CH=CH–CO–Ph	159–160	55	18.9 ± 0.7
Sulfinpyrazone							509.1 ± 49.0
Milrinone							4.7 ± 0.5

[a] Overall yield of coupling and deprotection.
[b] IC_{50} > 150 μM (precipitate at higher concentrations).
[c] Precipitate under test conditions.
[d] Stimulates platelet aggregation above 100 μM.
[e] Attempts to separate the 48/52 (*E*/*Z*) mixture yielded only a small fraction of pure *Z*.

Analysis of the data obtained for the 5-(3-oxo-3-phenylprop-1-en-1-yl)pyridazin-3(2*H*)-ones (**2a**–**h**) suggests that removal of the phenyl group at C-6 increases the antiplatelet activity (Table 1, compare **2a** and **2e**, **2b** and **2f**). Furthermore, in this series the introduction of substituents at *N*-2 produces a different effect depending on the presence or not of the phenyl ring at C-6. Thus, for those derivatives containing a 6-phenyl group, alkylation of the heterocyclic lactam led to a decreased activity (Table 1, compare **2a** with **2b** and **2c**). On the contrary for compounds **2e**–**h**, the activity is increased by substitution at *N*-2. Interestingly, a substantial increase in potency (4-fold) is associated with the incorporation of bulky groups at *N*-2 (benzyl (**2g**) or phenyl (**2h**)) independently of the rigidity of their structure.

Regarding the positional isomeric pyridazin-3(2*H*)-ones **4** in the 6-phenyl series it is evident that the group at *N*-2 (H, Me and MOM) does not substantially affect the antiplatelet activity (Table 1, see **4a**–**c**). Unfortunately, the low solubility of compounds **4d** and **4e** did not allow us to obtain information about the effect of the removal of the C-6-phenyl ring. Comparison of the available data for the 6-phenyl derivatives suggests that the 5-(3-phenylprop-2-enoyl)pyridazin-3(2*H*)-ones **4a**–**c** are generally slightly more potent than their corresponding isomers **2a**–**c** (Table 1). These results reveal that isomerism of the oxopropenyl system does not produce significant differences in the antiplatelet activity of the prepared series. Importantly, analysis of the pharmacological data of the isomeric derivatives **2g** and **4f** (Fig. 3) clearly indicates that such a modification could produce severe consequences for the activity either at the quantitative but also at the qualitative level since the former is a potent

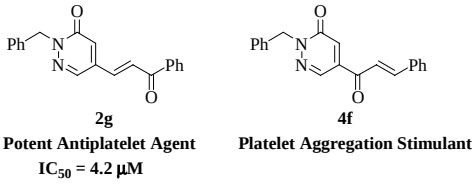


Figure 3. Different pharmacological profile of the isomeric derivatives **2f** and **4f**.

antiplatelet agent (IC_{50} = 4.2 μM), while its positional isomer **4f** stimulates platelet aggregation at relatively high concentrations (100 μM).[15]

One interesting but not unexpected result coming from the evaluation of compounds **6** is the slight difference in activity (2-fold) observed for the geometric isomers **6a** and **6b**. Although at this stage of the research programme there are only a limited number of compounds available, a preliminary comparison of the activity of enones **6a**–**e** with their parent compound **2e** reveals that replacement of the 4-H atom by a substitutent had only a modest effect on the antiplatelet activity, with the dimethylamino group (**6d**) as the only exception. These observations suggest a pharmacophoric tolerance that could be judiciously employed to improve the pharmaco-kinetic profile in further pyridazin-3(2*H*)-one series. Although derivatives **6** did not retain the excellent activity observed for some compounds of the series (**2g** and **2h**), it should be noted that they are 2-methylpyridazin-3(2*H*)-ones. It can be expected that introduction of a benzyl or a phenyl group at this position will increase their activity.

In summary, we prepared a focussed library of diversely substituted pyridazin-3(2*H*)-ones containing the 3-oxo-3-phenylprop-1-en-1-yl or 3-phenylprop-2-enoyl fragments as key pharmacophoric elements. The biological evaluation of these compounds allowed the identification of several new, potent antiplatelet agents but also the establishment of relevant features of the SAR in this series. Further studies are in progress in our laboratories to exploit these preliminary results for the synthesis of a larger library incorporating substitution on/and bioisosteric replacement of the phenyl group in the enone system.

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