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Bioorganic & Medicinal Chemistry Letters
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Bioorganic & Medicinal Chemistry Letters 14 (2004) 321–324

Pyridazines. Part 36: Synthesis and antiplatelet activity of 5-substituted-6-phenyl-3(2*H*)-pyridazinones☆

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Received 18 September 2003; revised 24 October 2003; accepted 7 November 2003

Abstract—A convenient and efficient palladium-catalysed retro-ene-assisted method has been developed to prepare a series of 5-substituted-6-phenyl-3(2*H*)-pyridazinones as potential antiplatelet drugs. The most active compounds were those that contain a 3-phenyl-3-oxo-propenyl fragment or a phenylthio group at position 5 of the heterocyclic ring.

Platelet-mediated thrombus formation in the coronary artery is a primary factor in the development of thrombotic disorders such as unstable angina, myocardial infarction, stroke and peripheral artery disease.[2,3] The clinical need for more efficacious antiplatelet agents and the growing understanding of the role of platelets in vascular injury have catalysed an extensive evaluation of novel approaches to control platelet function.

Aspirin, the primary antiplatelet therapy currently in use, has been shown to reduce the risk of arterial thrombosis in placebo-controlled clinical trials.[4] Despite the proved efficacy of aspirin, there are reasons to believe that substantial improvements in antiplatelet therapy can be made. Other therapeutic-based strategies to inhibit platelet function include the use of Clopidogrel, Ticlopidine or Sulfinpyrazone (Fig. 1)—although some of these drugs have a relatively low activity and up to one third of patients respond in a limited manner to treatment. Glycoprotein (GP) II_b/III_a receptor antagonists have recently been identified as a prominent target for drug development,[5] although several complications involving bleeding have been reported during the use of these compounds in clinical trials.[6] Thus, the search for new agents with other mechanisms of action is of great interest not only to be used as drugs but also because such compounds could be used as pharmacological tools to provide important information regarding platelet function.

For a number of years our group has been involved in a project concerning the synthesis and study of the antiplatelet activity of 3(2*H*)-pyridazinones.[7–9] Our initial target in this project was the general structure **I** (Fig. 2), which is structurally related to the two most important azinone PDE III inhibitors [2(1*H*)-pyridones (Amrinone and Milrinone) and 3(2*H*)-pyridazinones (Zardaverine)]. Pharmacological studies on these compounds revealed that both the mechanism of action and the

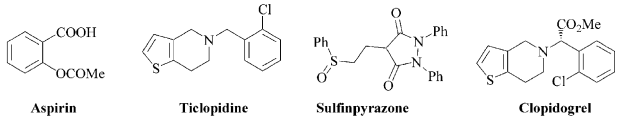

Figure 1.

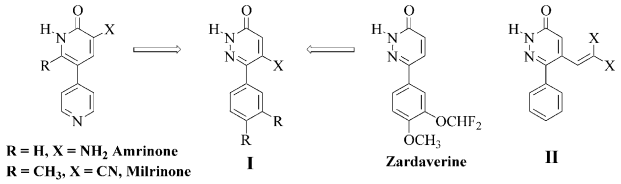

Figure 2.

Keywords: Pyridazinones; Antiplatelet agents.
☆See ref 1.
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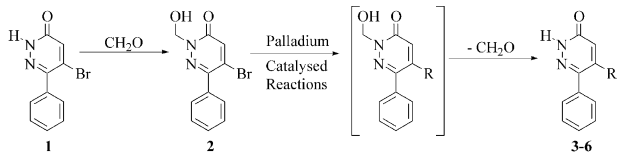
doi:10.1016/j.bmcl.2003.11.009



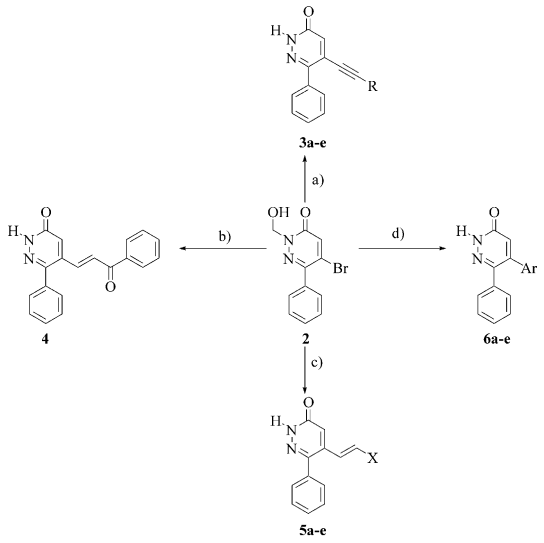
Scheme 1.

antiplatelet activity of this series are highly dependent on the nature of the chemical group present at the 5-position of the heterocyclic ring.[10]

The potent antiplatelet activity shown by 6-phenyl-3(2*H*)-pyridazinones that have alkylidene groups in the 5-position **II**[11] (Fig. 2) prompted us to prepare other pyridazinones with different carbon-based functions at this position in the heterocycle. The synthetic pathway selected to prepare these compounds involves the use of palladium-catalysed reactions (PCR) (Stille, Heck, Sonogashira and Suzuki) on precursor **1** (Scheme 1). During the course of these studies we observed that the NH group of the lactam function completely inhibits palladium-catalysed reactions.[12–14] Indeed, prior to submitting the 3(2*H*)-pyridazinone to the catalytic cycle it is essential to protect the NH group in **1**. The protection was initially achieved using the methoxymethyl (MOM) group,[12–14] but attending to the substituent at the 5-position several unexpected results were obtained during the cleavage.[15]

In a very recent paper, we briefly reported the use of the hydroxymethyl group as a protecting group for the NH group of pyridazinones[16] and described some of the advantages of its use in cross-coupling reactions (Scheme 1). We now describe the extensive exploitation of this new methodology to prepare 5-substituted-6-phenyl-3(2*H*)-pyridazinones and present the preliminary results of the antiplatelet activity and structure–activity relationships in this series.

The reaction sequences are outlined in Schemes 1 and 2. The readily obtainable 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1**[17] was converted into 5-bromo-2-hydroxymethyl-6-phenyl-3-pyridazinone **2** (89%) by hydroxymethylation using a 35% solution of formaldehyde (Scheme 1).[16] The straightforward preparation of this



Scheme 2. Reagents: (a) HC≡C-R/$Pd(PPh_3)_2Cl_2$/CuI/Et_3N/DMF/55 °C; (b) HC≡C–CH(OH)Ph/$Pd(PPh_3)_2Cl_2$/CuI/Et_3N/DMF/55 °C; (c) H_2C=CH-X/$PdCl_2[P(o\text{-tolyl})_3]_2$/DMF/110 °C/24 h; (d) $ArB(OH)_2$/$Pd(PPh_3)_4$/DME/H_2O (3:1)/90 °C.

compound represents a valuable advantage, although the most noteworthy aspect in terms of the synthetic applicability of this compound as a 2-blocked pyridazinone in cross-coupling reactions is derived from its chemical and thermal stability. Compound **2** is a 1-*O*, 3-*N*, 5-*O* ene-adduct,[18] which easily loses formaldehyde through a retro-ene reaction promoted by base and/or by heat once the PCR has occurred. This process yields the corresponding 3(2*H*)-pyridazinones **3–6** in a very efficient and short pathway (Scheme 1).

In order to rapidly achieve structural diversification at position 5 in this system, we proceeded to study several palladium-catalysed cross coupling reactions on **2** (Scheme 2).[16] As can be observed, these transformations give different 5-alkynyl, 5-alkenyl and 5-aryl-6-phenyl-3(2*H*)-pyridazinones in satisfactory to excellent yields (Table 1).[16]

The most significant result obtained during PCR on **2** was found with the Sonogashira coupling with 1-phenyl-2-propyn-1-ol. The expected 5-alkynylpyridazinone was

Table 1. 5-Substituted-6-phenyl-3(2*H*)-pyridazinones **3–6**

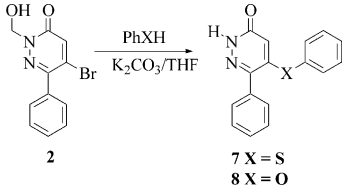
Compd	Substituent at position 5	Mp[a] (°C)	References	Yield (%)	Compd	Substituent at position 5	Mp[a] (°C)	References	Yield (%)
3a	C≡C–H[b]	202–203	21	58[c]	**5d**	CH=CH–CN	231–232	—	68
3b	C≡C–CH_2OH	200–201	13	87	**5e**	CH=CH–Ph	251–252	—	75
3c	C≡C–$(CH_2)_2$OH	167–169	21	78	**6a**	Ph	178–180	12	72
3d	C≡C–$(CH_2)_3$OH	199–201	21	82	**6b**	4-Cl–Ph	222–223	12	82
3e	C≡C–$CH(OEt)_2$	133–135	—	63	**6c**	4-CH_3–Ph	198–200	12	74
4	CH=CHCOPh	231–232	21	65	**6d**	4-CHO–Ph	172–173	12	72
5a	CH=CH–COOMe	203–204	—	52	**6e**	2-Furyl	235–236	12	88
5b	CH=CH–COOEt	189–190	—	50	**7**	S–Ph	162–164	10	90
5c	CH=CH–COO $(CH_2)_2$OMe	169–170	—	56	**8**	OPh	202–204	10	88

[a] All compounds were recrystallyzed from *i*-PrOH.
[b] Obtained by desilylation of 6-phenyl-5-trimethylsilylethynyl-3(2*H*)-pyridazinone employing KOH/MeOH.
[c] Overall yield from **2** (cross-coupling + desilylation).

not isolated but the isomeric *E*-chalcone **4**[19] was obtained in good yield (85%) (Scheme 2). The unusual formation of chalcone **4** is not dissimilar to results described in previous papers[20] and can be explained as a consequence of base-catalysed isomerisation of the 5-(3-hydroxy-3-phenylprop-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone intermediate—a process that is facilitated by the electron-deficient nature of the pyridazinone system.[21]

In order to study the reactivity of **2** in other transformations, and taking into account that several authors have previously described how the introduction of an alkyl or hydroxymethyl group at position 2 in the pyridazinone ring facilitates nucleophilic halogen substitution reactions,[22] we decided to study the reaction of **2** with mercaptobenzene and phenol (Scheme 3). These experiments confirmed that **2** is a more reactive precursor than **1** in this transformation[10] and gave, in a more efficient way, the previously obtained[10] phenylthio and phenyloxy derivatives **7** and **8**.

The platelet aggregation inhibitory activity of the 3(2*H*)-pyridazinone derivatives described above was examined on washed human platelets using thrombin as inducer of platelet aggregation. The turbidimetric method described by Born was used in this study.[23] The results of these experiments are summarised in Table 2. Most of the compounds studied inhibit platelet aggregation in a dose-dependent manner, with their antiplatelet effects being similar or superior to Sulfinpyrazone ($IC_{50} = 500$ μM).



2 **7 X = S** **8 X = O**

Scheme 3.

Table 2. Antiplatelet activity (IC_{50}) of compounds **3–6**[a]

Compd	Substituent at 5	IC_{50} μM	Compd	Substituent at 5	IC_{50} μM
3a	C≡C–H	500	**5d**	CH=CH–CN	>1000
3b	C≡C–CH_2OH	>1000	**5e**	CH=CH–Ph	—
3c	C≡C–$(CH_2)_2OH$	>2000	**6a**	Ph	[b]
3d	C≡C–$(CH_2)_4OH$	>1000	**6b**	4-Cl–Ph	[b]
3e	C≡C–$CH(OEt)_2$	>1000	**6c**	4-CH_3–Ph	152
4	CH=CHCOPh	25	**6d**	4-CHO–Ph	[b]
5a	CH=CH–COOMe	>1000	**6e**	2-Furyl	635
5b	CH=CH–COOEt	—	**7**	S-Ph	15
5c	CH=CH–COO $(CH_2)_2OMe$	>1000	**8**	OPh	[c]

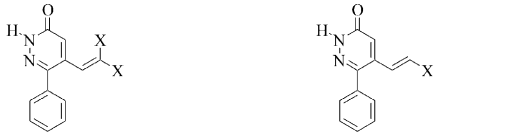
[a] The antiplatelet activities of the standards and the synthesised compounds were tested by the turbidimetric method in washed human platelets using thrombin as agonist. Methods for these assays have been published elsewhere.[10] Results shown are means of at least three experiments. The highest mean standard error of IC_{50} values was 10%. —Inactive.
[b] Precipitates under the conditions of the study.
[c] Promotes platelet aggregation.

A general view of the antiplatelet activities listed in Table 2 reveals the important effect of the substituent at position 5 on the antiplatelet activity. In the series of carbon-based 5-substituted-3(2*H*)-pyridazinones, 5-alkynyl **3** and 5-alkenyl **5** derivatives showed only a weak activity, but these derivatives were slightly more potent than their analogues without the multiple bonds (general structure **I**). Unfortunately, most of the 5-aryl derivatives **6** were either not sufficiently soluble to be tested or precipitated during the study. However, the data obtained for two compounds (**6c** and **6e**) are particularly interesting for further SAR studies.

Comparison of antiplatelet activities of the lead compounds **II**[10] and the acrylates **5a** and **5b** shows that the elimination of one of the ester groups in **II** causes a dramatic drop in activity (Fig. 3). Interestingly, the most sterically hindered derivative of the 5-alkenyl analogues (compound **4**) shows the highest efficacy as platelet aggregation inhibitor within these series and has an IC_{50} value in the micromolar range (25 μM). This fact demonstrates the importance of the steric effect.

Interestingly, the 5-styryl derivative **5d**, which can be considered a bioisoster of the previously described[10] potent antiplatelet agent 6-phenyl-5-phenylthio-3(2*H*)-pyridazinone **7**, proved to be inactive while the 5-(3-oxo-3-phenylpropenyl) derivative **4** had an antiplatelet activity comparable to **7**. These results, along with others from our group,[24] suggest that the 3-oxo-3-phenylpropenyl fragment may be a more effective bioisosteric group for the phenylthio radical than the styryl group in compounds where the activity is particularly influenced by both steric and electronic factors (Fig. 4).

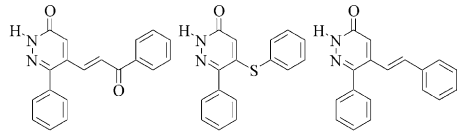
In conclusion, we have applied a short, efficient and versatile palladium-assisted synthetic approach to achieve structural diversification at the 5-position of 6-phenyl-3(2*H*)-pyridazinone system. The most significative features emerging from these preliminary studies have been taken into account for the design of more potent antiplatelet agents. Further studies are in progress in our laboratory and will be reported in detail in a series of forthcoming papers.



IIa X = COOMe $IC_{50} = 45\mu M$
IIb X = COOEt $IC_{50} = 20\mu M$

5a X = COOMe $IC_{50} = >1000\mu M$
5b X = COOEt **Inactive**

Figure 3.



4 $IC_{50} = 25\mu M$ **7** $IC_{50} = 15\ \mu M$ **5e** **Inactive**

Figure 4.

Acknowledgements

This work was supported in part by Xunta de Galicia PGYDT (TQ1PX20309PR). E. Sotelo thanks the University of Santiago de Compostela for his appointment as Post-doctoral fellow.

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