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Synthesis of aminopyrimidylindoles structurally related to meridianins

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Abstract—The synthesis of new meridianin derivatives substituted at the C-5′ position of the 2-aminopyrimidine ring by various aryl groups and substituted or not by a methyl group on the indole nitrogen is described. The 2-aminopyrimidine ring was obtained via a Bredereck synthesis. Aryl groups were introduced by Suzuki cross-coupling after bromination of the 2-aminopyrimidine ring at the C-5′ position.

1. Introduction

Many kinase inhibitors from natural origin are sources of inspiration for the discovery of new biologically active compounds. A large number of nitrogen aromatic heterocycles containing an indole or a carbazole framework exhibit kinase inhibitory properties. Granulatimide and isogranulatimide, carbazoles isolated from the ascidian *Didemnum granulatum*, and structurally related analogs are Checkpoint kinase 1 (Chk1) inhibitors (Fig. 1).[1,2] Purine derivatives like roscovitine and olomoucine, two compounds isolated from starfish oocytes, are potent cyclin-dependent kinase inhibitors.[3] Indirubin, the active ingredient of the Chinese preparation Danggui Longhui Wan used to treat chronic diseases, indirubin derivatives,[4,5] as well as indolocarbazole bacterial metabolites staurosporine,[6,7] UCN-01,[8] and K252-c[9] are also described as potent kinase inhibitors. Synthetic compounds such as bisindolylmaleimides[10] and 4-aryl-3-indolylmaleimides[11,12] are known kinase inhibitors (Fig. 1).

Meridianin alkaloids, which were isolated and characterized from the south atlantic tunicate *Aplidium meridianum*,[13] are indole derivatives substituted at the C-3 position by a 2-aminopyrimidine ring. Meridianins A–G[13–15] (Fig. 1) were described as potent kinase inhibitors[15] and some derivatives displayed antitumor activity.[16]

In the course of the synthesis of new kinase inhibitors, we were interested in meridianin derivatives substituted at the C-5′ position of the 2-aminopyrimidine ring. Various 3-(2-aminopyrimidin-4-yl)-indoles substituted at the C-5′ and C-6′ positions and/or on the amino group of the 2-aminopyrimidine ring have been described in the literature.[16–37] Compounds substituted at C-5′ position by cyano, carbohydrazonamido, carboxy, and methyl groups or by a chlorine or a fluorine atom have previously been reported (Fig. 1).[16,17,19] These recent publications prompted us to report our own results. Substituent at the C-5′ position appeared to be important in terms of biological activity. Indeed, we observed a dramatic increase of kinase inhibitory properties when the C-5′ position of meridianin G was substituted by a bromine atom (Scheme 1 and Table 1). The kinase activities of compounds **3** (meridianin G) and **5** toward eight protein kinases were evaluated by Upstate's kinase profiler screening service (Dundee, Scotland). Both compounds were tested at a compound concentration of 10 μM under standard conditions determined by Upstate[38–40] for each selected kinase (MKK1, ERK2, RSK2, PKC-α, GSK3-β, CDK2/A, CK2, and MST2—Table 1). Compound **5** exhibited a significantly higher inhibitory activity than meridianin G (compound **3**) against all the kinases tested. Indeed, compound **5** inhibits all the kinases tested with percentages of inhibition over 80%, and is particularly potent toward MKK1 and MST2 (percentage of inhibition higher than 95%), whereas the inhibitory properties of compound **3** were found to be much lower, with percentages of inhibition from 9% (RSK2) to 66% (MKK1). These results encouraged us to synthesize meridianin derivatives bearing other substituents at the C-5′ position. Since the late 1980s[11,12] and recently,[41] it was reported that aryl groups at the C-4 position of 3-indolylmaleimides led to compounds exhibiting interesting kinase inhibitory properties. Therefore, we decided to introduce aryl rings at the C-5′ position of the pyrimidine ring of meridianin G. Compounds bearing an aryl group at the C-6′ position were reported,[22,25] but to our knowledge,

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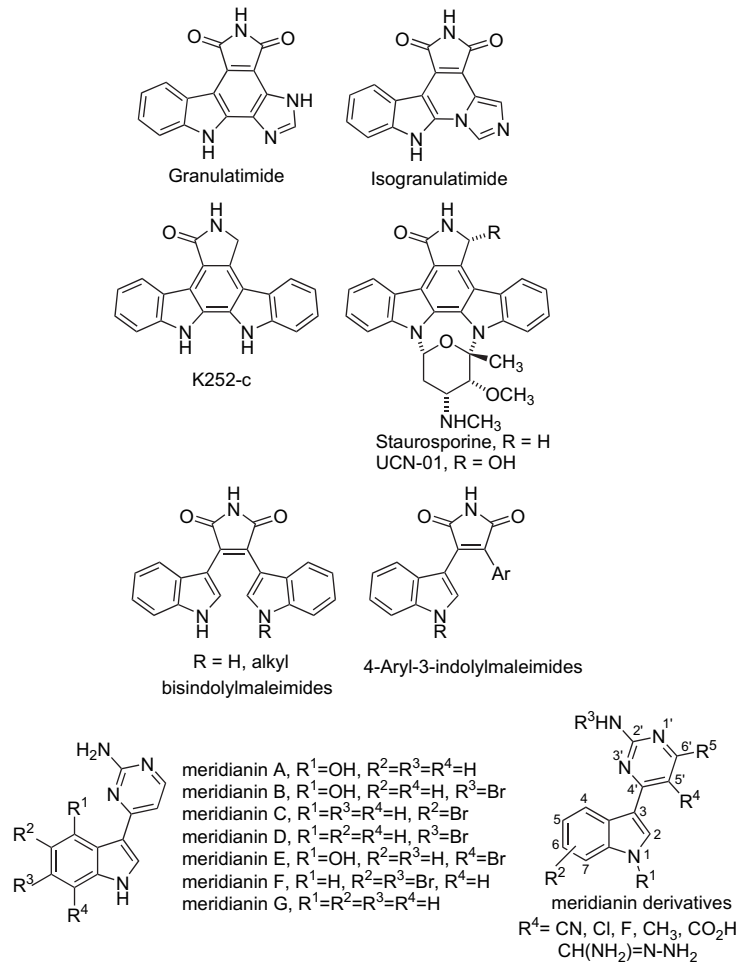
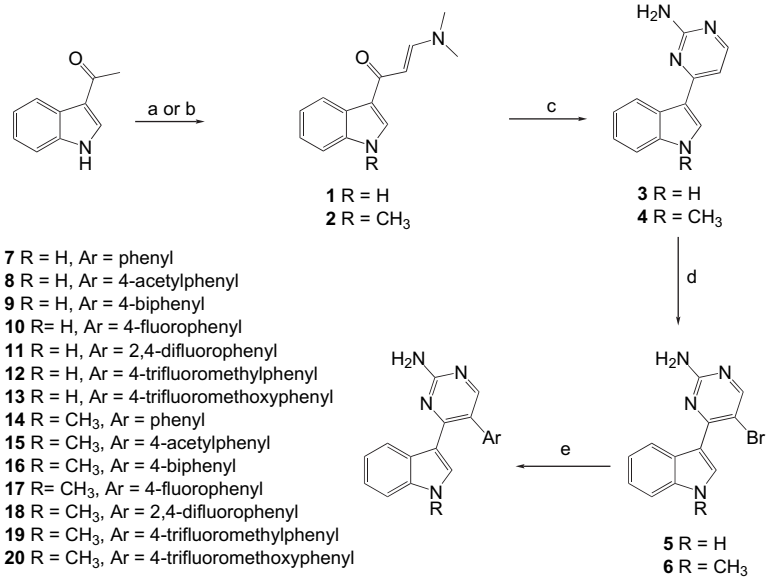


Figure 1. Kinase inhibitors and meridianin derivatives described in the literature.

meridianin derivatives with an aryl group at the C-5′ position have never been described. The replacement of the maleimide ring of 4-aryl-3-indolylmaleimides previously mentioned by the 2-aminopyrimidine ring could reinforce the interaction inside the ATP-binding pocket of the target kinase. To get an insight into the importance of the NH of the indole moiety, we also prepared derivatives substituted on the indole nitrogen with a methyl group. The introduction



Scheme 1. Synthesis of meridianin derivatives. (a) DMF/DMF-di-*tert*-butylacetal, reflux, R=H; (b) DMF/DMF-DMA, reflux, R=CH_3; (c) *iso*-propanol, guanidine, NaOMe, reflux; (d) NBS, THF, 0 °C; (e) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, EtOH/H_2O/toluene, reflux.