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Synthesis of two series of pyrazolic analogues of the marine alkaloids granulatimide and isogranulatimide as potent Checkpoint 1 kinase inhibitors

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ABSTRACT

Two series of regioisomeric pyrazolic analogues of the marine alkaloids granulatimide and isogranulatimide were prepared. The synthesis of the first series was based on the condensation reaction of diversely 5-substituted 3-bromoindoles with pyrazole followed by addition of the intermediates on dibromomaleimide, the so-obtained acyclic adducts being finally photochemically cyclised to the desired analogues. Compounds of the second series were obtained by reacting different 5-substituted-indole-3-glyoxylates with *N*-Boc-pyrazole-3-acetamide and subsequent photochemical cyclisation of the adducts.

1. Introduction

In the cell division cycle, G1 and G2 checkpoints are activated in response to DNA damage and consequently block the cycle progression to allow time for DNA repair. Interestingly, in more than 50% of cancer cells, the G1 checkpoint is lacking due to mutation of the p53 protein. Therefore, a combination of DNA damaging agent with a G2 checkpoint inhibitor should force selectively cancer cells into a premature and lethal mitosis, such a combination being currently envisaged as an original and particularly promising chemotherapeutic approach.[1–3]

In this biological context, granulatimide **1** and isogranulatimide **2**, natural alkaloids isolated from the ascidian *Didemnum granulatum*, have triggered considerable attention as cell cycle G2 checkpoint inhibitors (Fig. 1).[4–6] From a mechanistic point of view, they have been identified as selective inhibitors of the Chk1 kinase, a key enzyme involved in the G2 checkpoint regulation.[7] Since this pioneering result, intensive structure–activity relationship studies have been carried out to investigate the structural parameters required for the biological activity.[8,9] In this way, the importance of the maleimide moiety which establishes the two fundamental hydrogen bonds with Glu[85] and Cys[87] in the ATP binding pocket of the enzyme has been pointed out.

In this Letter, we describe the synthesis of two new classes **3** and **4** of potent Chk1 inhibitors. These compounds can be considered as analogues of the marine metabolites in which the imidazole ring has been replaced by a pyrazole ring.

2. Chemistry

The synthesis of compounds of the first series **3a–d** is outlined in Scheme 1. It was inspired by the route reported by Prudhomme and co-workers[10] to prepare pyrrolic analogues of isogranulatimide.

The two first steps, consisting in the regioselective bromination in 3-position of indoles **5a–c** and the subsequent reaction of the

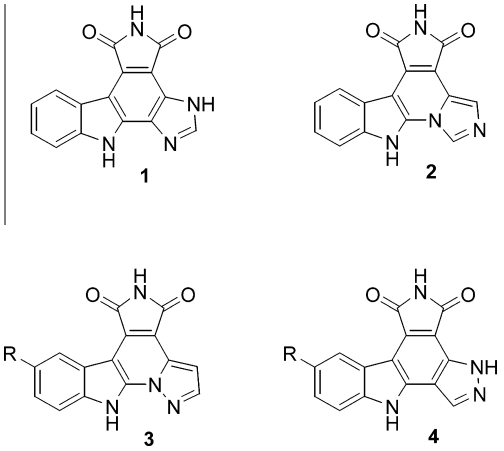

Figure 1.

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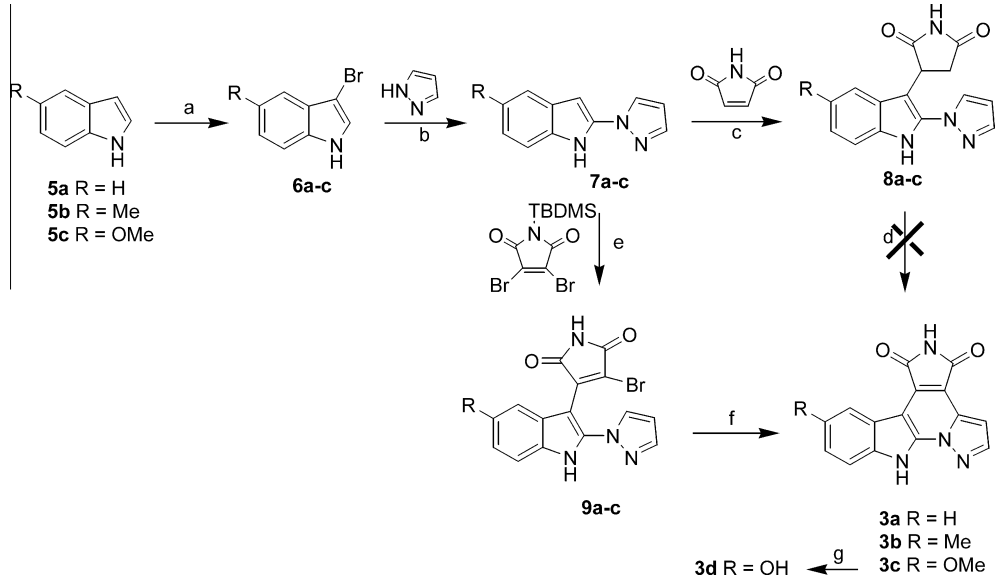
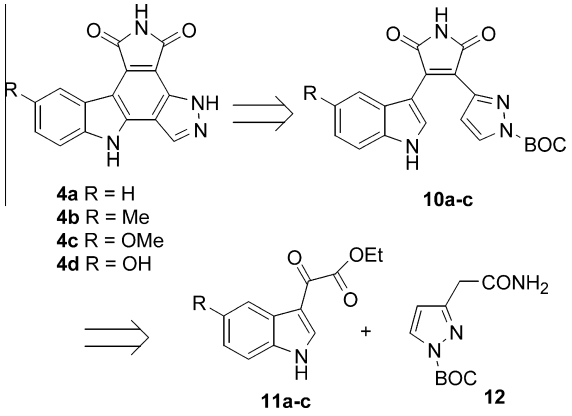


Scheme 1. Reagents and conditions: (a) Br_2, DMF, 2 h; (b) TFA, CH_2Cl_2, rt, 4 h (61%, 39%, 55%, respectively for the two steps); (c) $SnCl_2$, toluene, reflux, 24 h (17%, 28%, 11%, respectively); (d) Pd black, nitrobenzene, 200 °C, 5 h; (e) EtMgBr, THF, rt, 12 h (58%, 36%, 51%, respectively); (f) hν, CH_3CN, rt, 5 h (62%, 73%, 76%, respectively); (g) BBr_3, CH_2Cl_2, rt, 2 h (84%).

resulting bromo-derivatives **6a–c** with pyrazole, were realised according to the conditions previously described by Bocchi and Palla.[11,12] Noteworthy is that the acid-mediated installation of pyrazole onto the indole nucleus leading to the three *N*-indolylpyrazoles **7a–c** proceeded in modest to good yields through the formation of a C–N bond and not a C–C bond as previously observed with pyrrole and indole.[10] As in the case of the corresponding pyrolo-derivatives, the Michael addition of compounds **7a–c** on maleimide in the presence of tin(II) chloride, furnished the acyclic intermediates **8a–c** in low yields. The cyclisation of **8a–c** unexpectedly failed under the conditions used in the pyrrolic series (i.e., Pd black in nitrobenzene at 200 °C), no conversion of the acyclic precursor being observed even after prolonged time heating. Finally, the desired compounds **3a–c** could be prepared starting from *N*-indolylpyrazoles **7a–c**, by using an alternative two-step-sequence which consists in: (i) nucleophilic addition of the conjugated base of indolylpyrazoles (generated in situ) on *N*-TBDMS-dibromomaleimide with concomitant deprotection of the TBDMS protective group, (ii) photocyclisation of adducts **9a–c** to the desired pyrazolic analogues **3a–c**. Ultimately, the hydroxylated analogue **3d** was obtained by demethylation of the methoxy derivative **3c** with BBr_3.



Scheme 2.

The retrosynthetic scheme for accessing regioisomeric compounds **4a–c** of the second series was based on the methodology reported by Faul to prepare bisindolylmaleimides[13] and later on used by Piers et al. to publish an improved synthesis of isogranulatimide (Scheme 2).[14]

The different ethyl *N*-Boc-5-substituted-3-glyoxylates **11a–c**, readily obtained in two steps from the corresponding indoles **5a–c**,[15] were reacted in THF and in the presence of *t*BuOK with *N*-Boc-pyrazole-3-acetamide **12**, itself prepared from pyrazole-3-acetamide.[16] The final photochemical cyclisation of the so-obtained-indolylpyrazolylmaleimides **10a–c** to give the *N*-Boc-protected pentacyclic derivatives was effected in the same conditions as for the first series **3a–c** (around 6% overall yields for the two steps). The BOC group was finally cleaved to yield quantitatively compounds **4a–c** and the demethylation of **4c** under identical conditions as in the case of **3c** allowed the preparation of phenolic analogue **4d**.

In conclusion, this work reports on the preparation of the two novel series of compounds structurally related to granulatimide, in which a pyrazole heterocycle replaces the native imidazole moiety. The biological evaluation of these compounds both in terms of their Chk1 inhibition potential and their antiproliferative activities is currently in progress.

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