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Tetrahedron Letters 44 (2003) 4607–4611

TETRAHEDRON LETTERS

Synthesis of isogranulatimides A and B analogues possessing a 7-azaindole unit instead of an indole moiety

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Received 25 March 2003; revised 7 April 2003; accepted 8 April 2003

Abstract—The synthesis of a new family of isogranulatimides analogues is described in which a 7-azaindole replaces the indole moiety. The key step is the photocyclization of the aza didemnimide intermediates which leads to two isomeric analogues of isogranulatimides A and B. A derivative bearing a carbohydrate part linked to the azaindole via a β-*N*-glycosidic bond was also prepared.

In the search for antitumor compounds, the ultimate goal is to develop drugs that are highly efficient against tumor cells and without effect on normal cells. A recent approach consists in the development of drugs able to inhibit the G2 checkpoint of the cell cycle. In the cell cycle, two main checkpoints in the G1 and G2 phases are activated in response to DNA damage. Their role is to stop temporarily the progression of the cell cycle to allow DNA repairing. In most tumor cells, the G1 checkpoint is inactive due to mutations of several genes, moreover the G2 checkpoint is usually weaker than in normal cells. Accordingly, combination of a DNA damaging agent with a G2 checkpoint inhibitor should lead to a lethal mitosis.[1–4] To date, few G2 checkpoint inhibitors have been identified.[5–9] Among them, granulatimide and isogranulatimide, natural compounds isolated from the ascidian *Didemnum granulatum*, were reported to inhibit the G2 checkpoint with IC_{50} values of 1.3 and 1.8 μM, respectively.[10–12] These results have triggered synthetic efforts to prepare analogues. In this connection, several synthetic pathways have been investigated to prepare granulatimides and isogranulatimides A–C and the didemnimide intermediates.[13–15] The heterocyclic chromophores of granulatimides and isogranulatimides are structurally related to that of the staurosporine aglycone (Fig. 1). Staurosporine is a microbial metabolite well known to inhibit kinases without selectivity.[16] Staurosporine inhibits also the G2 checkpoint with an IC_{50} value of 0.2 nM.[11] It has been shown that the sugar moiety is necessary for the G2 checkpoint inhibition since the staurosporine aglycone is not active.

Azaindole biosters of indole present considerable biological importance.[17] In 7-aza-isogranulatimide analogues, the replacement of a carbon atom by a nitrogen atom may contribute to reinforce the hydrogen bond net which stabilizes the drug in the active site of the target enzyme(s).[18,19]

In this paper, we report the synthesis of isogranulatimides A and B analogues possessing a 7-azaindole moiety instead of the indole moiety. Moreover, to investigate the influence of the presence of a carbohydrate unit, an analogue bearing a glucopyranose linked to the azaindole part via a β-*N*-glycosidic bond was synthesized. In other natural products such as the microbial metabolite rebeccamycin (Fig. 1), which is not a kinase inhibitor but a topoisomerase I inhibitor, a sugar part is also attached to one of the indole moieties via a β-*N*-glycosidic bond.[18]

The synthetic strategy is outlined in Scheme 1. Reaction of 7-azaindole magnesium bromide with *N*-methyldibromomaleimide, followed by protection of the azaindole NH with a Boc group has already been reported.[20] Coupling with imidazole magnesium bromide led to compound **1**[22] with concomitant removal of the Boc

Keywords: G2 checkpoint inhibitors; isogranulatimide; rebeccamycin.
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0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00924-9

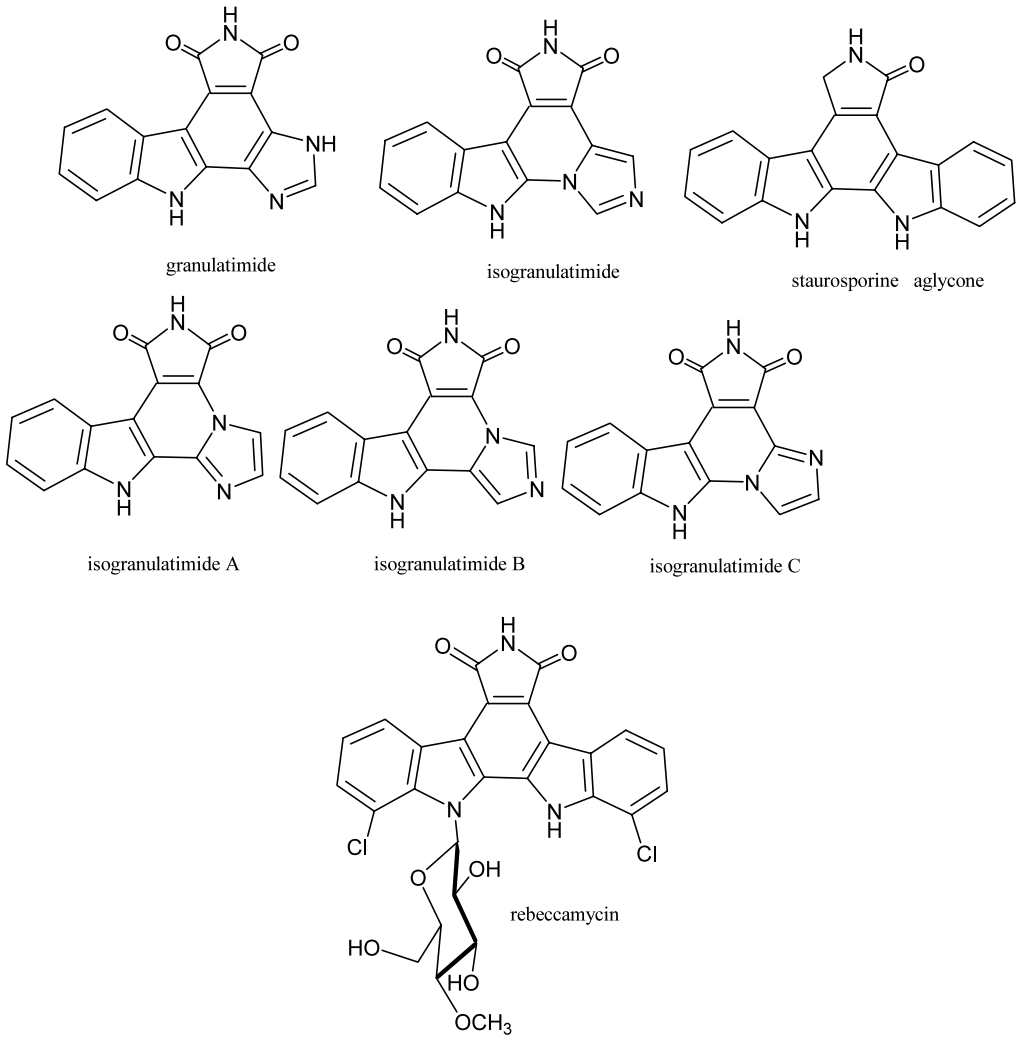
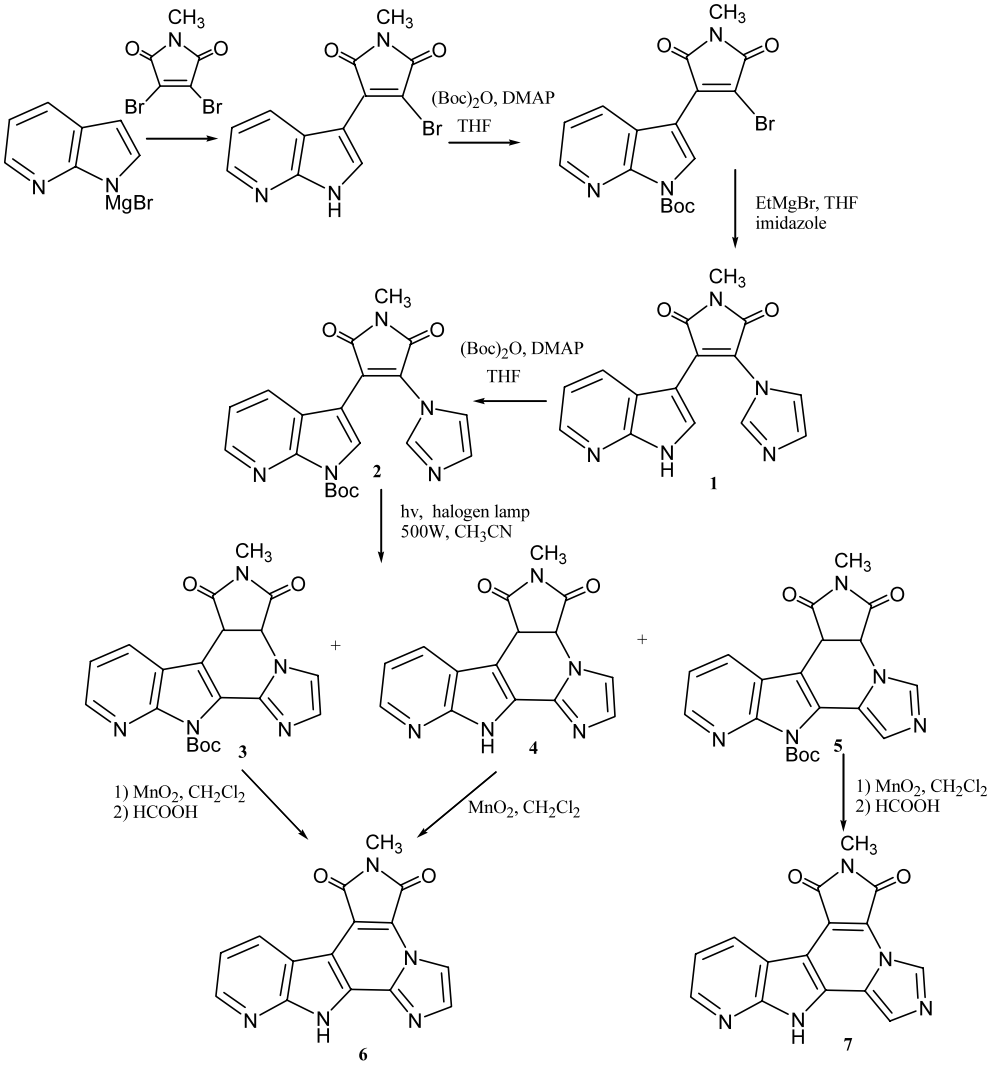


Figure 1.

protective group. Due to the insolubility of compound **1** in acetonitrile, the azaindole NH was protected with a Boc group for the further cyclization step. Compound **2** was irradiated with a halogen lamp in acetonitrile according to the method described par Terpin et al.[15] for the non-aza analogues. Two isomers **3** and **5** were obtained in 21% and 19% yields respectively, together with a deprotected compound **4** (24% yield). Oxidation with MnO_2 followed by removal of the Boc group using formic acid, led to compound **6**,[23] an isogranulatimide A analogue, in 77% yield and to compound **7**,[24] an isogranulatimide B analogue, in 47% yield. The identification of isomers **3** and **5** has been achieved by NOE 1D experiments. Irradiation of compound **1** without the Boc protective group led only to the formation of compound **6**. To introduce the sugar moiety, a Mitsunobu method was chosen using 2,3,4,6-tetra-*O*-acetyl-α-glucopyranose to get a β-*N*-glycosylic bond in the coupling product. This method, largely used in rebeccamycin series,[18,19,21] allowed the formation of the required compound **8** as the major product of the reaction in 65% yield. Photocyclization was then carried out leading to compounds **9**, **10** and **11** in 5, 50 and 18% yields, respectively. Oxidation of **10** and **11** followed by deprotection of the hydroxyl protective groups of the sugar part gave compounds **12**[25] and **13**[26] in 40 and 30% yields, respectively (Scheme 2).

In summary, the synthesis of isogranulatimides A and B analogues in which the indole unit is replaced by a 7-azaindole is described. Another derivative bearing a glucopyranosyl moiety has also been prepared. The synthesis of analogues with a 5- and 6-azaindole parts is in progress. The biological activities of the new isogranulatimides analogues are being evaluated.



Scheme 1.

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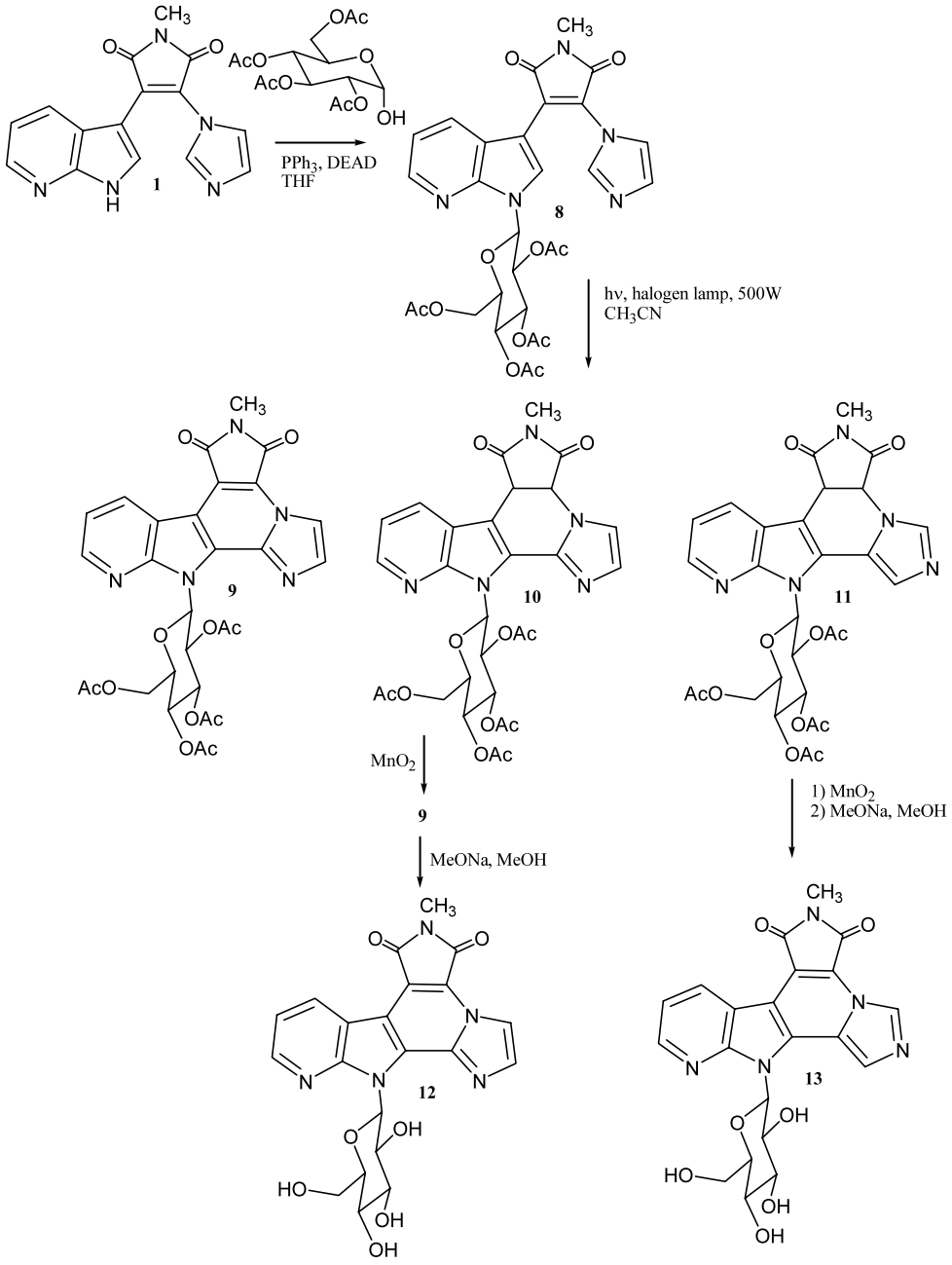

Scheme 2.

19. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Joubert, A.; Bailly, C.; Renard, P.; Hickman, J.; Prudhomme, M. *J. Med. Chem*. **2003**, *46*, 609–622.
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22. Data of **1**: Mp 246–248°C. IR (KBr): $\nu_{C=O}$ 1710 cm^{-1}, ν_{NH} 3320–3500 cm^{-1}. HRMS (FAB+) ($M+2H^+$) calcd for $C_{15}H_{13}N_5O_2$, 296.1148, found, 296.1143. ^1H NMR (400 MHz, DMSO-d_6): 3.09 (3H, s, NCH_3), 6.57 (1H, dd, $J_1=8$ Hz, $J_2=2$ Hz), 6.96 (1H, dd, $J_1=8$ Hz, $J_2=5$ Hz), 7.14 (1H, s), 7.37 (1H, s), 7.89 (1H, s), 8.18 (1H, s), 8.28 (1H, dd, $J_1=5$ Hz, $J_2=2$ Hz), 12.68 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 24.1 (NCH_3), 101.1, 124.9, 137.9 (C quat arom), 116.9, 128.1, 129.2, 131.9, 132.0, 144.0 (C tert arom), 167.2, 169.2 (C=O).
23. Data of **6**: Mp 258°C (decomposition). IR (KBr): $\nu_{C=O}$ 1710, 1760 cm^{-1}, ν_{NH} 3400–3450 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{15}H_{10}N_5O_2$, 292.0834, found, 292.0842. ^1H NMR (400 MHz, DMSO-d_6): 3.14 (3H, s, NCH_3), 7.47 (1H, dd, $J_1=8$ Hz, $J_2=5$ Hz), 7.97 (1H, s), 8.53 (1H, s), 8.59 (1H, dd, $J_1=5$ Hz, $J_2=2$ Hz), 8.89 (1H, dd, $J_1=8$ Hz, $J_2=2$ Hz), 13.75 (1H, s, NH).
24. Data of **7**: Mp 304–307°C. IR (KBr): $\nu_{C=O}$ 1710, 1760 cm^{-1}, ν_{NH} 3450 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{15}H_{10}N_5O_2$, 292.0835, found, 292,0834. ^1H NMR (400 MHz, DMSO-d_6): 3.13 (3H, s, NCH_3), 7.44 (1H, dd,

$J_1 = 7$ Hz, $J_2 = 5$ Hz), 8.01 (1H, s), 8.53 (1H, d, $J = 5$ Hz), 8.73 (1H, d, $J = 8$ Hz), 8.92 (1H, s), 13.56 (1H, s, NH).

25. Data of **12**: Mp 298–300°C. HRMS (FAB+) ($M+H^+$) calcd for $C_{21}H_{20}N_5O_7$, 454.1363, found, 454.1371. IR (KBr): $\nu_{C=O}$ 1710, 1720 cm^{-1}, $\nu_{NH,OH}$ 3200–3600 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 3.47–3.76 (6 H, m), 4.59 (1H, t, $J = 6$ Hz), 5.15 (1H, d, $J = 6$ Hz), 5.22 (1H, d, $J = 6$ Hz), 5.26 (1H, d, $J = 6$ Hz), 7.35 (1H, d, $J = 9$ Hz, $H_{1'}$), 7.59 (1H, dd, $J_1 = 8$ Hz, $J_2 = 5$ Hz), 8.06 (1H, d, $J = 1$ Hz), 8.63 (1H, d, $J = 1$ Hz), 8.65 (1H, dd, $J_1 = 5$ Hz, $J_2 = 1$ Hz), 9.04 (1H, dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz).
26. Data of **13**: Mp >300°C. IR (KBr): $\nu_{C=O}$ 1710, 1720 cm^{-1}, $\nu_{NH,OH}$ 3240–3600 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{21}H_{20}N_5O_7$, 454.1363, found, 454.1370. ^1H NMR (400 MHz, DMSO-d_6): 3.18 (3H, s, CH_3), 3.49–3.85 (6H, m), 4.85 (1H, m, OH), 5.13 (1H, d, $J = 5$ Hz, OH), 5.30 (1H, d, $J = 4$ Hz, OH), 5.35 (1H, d, $J = 4$ Hz, OH), 6.52 (1H, d, $J = 9$ Hz), 7.55 (1H, m), 8.32 (1H, s), 8.60 (1H, br s), 8.96 (1H, d, $J = 8$ Hz), 9.05 (1H, s).