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# Synthesis of granulatimide analogues bearing a maleimide instead of an imidazole heterocycle

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**Abstract**—A synthesis in a few steps of a new family of granulatimide analogues was performed. In the new compounds, the aromatic framework of granulatimide is modified by replacement of the imidazole unit by a maleimide moiety. The synthesis of a water-soluble analogue is also presented. 

Among the various strategies developed to inhibit tumor cell proliferation, a new approach targeting the checkpoints which control cell cycle progression seems especially promising.[1,2]

In the cell cycle of normal cells, two principal checkpoints can be activated in response to DNA damage in the G1 phase and in the G2 phase. These checkpoints control the ability of cells to arrest the cell cycle allowing time to repair the DNA. The G1 checkpoint allows DNA repair before DNA replication, and the G2 checkpoint allows DNA repair before mitosis. The G1 and G2 checkpoints are mainly activated by two kinases Chk1 and Chk2. The G1 checkpoint is dependent upon the activity of p53. The *p53* gene is mutated in nearly half of all human malignancies and in large proportions of premalignant precursor lesions.[3,4] In *p53* mutated cancer cells, the G1 checkpoint is lacking. Only the G2 checkpoint, although weaker than in normal cells, provides cancer cells with the opportunity to repair their DNA after damage. Therefore the combination of a DNA damaging agent with a G2 checkpoint inhibitor should force selectively cancer cells into a premature and lethal mitosis.

Few G2 checkpoints inhibitors are known, among them are caffeine, indolocarbazole compounds staurosporine and UCN-01, pyridopyrimidines, hymenialdisine, granulatimide and isogranulatimide (Fig. 1).[5–9]

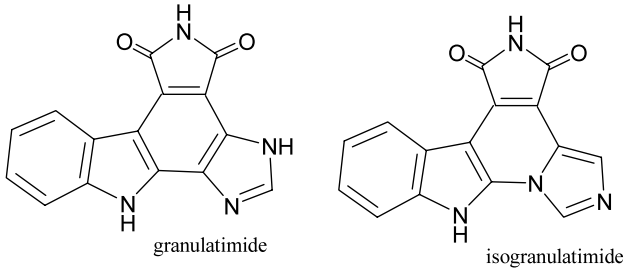


**Figure 1.**

In this paper, we report the synthesis of granulatimide analogues, in which the imidazole moiety is replaced by a maleimide unit.

The non-aromatized intermediates were prepared from monoindolylmaleimide according to the method described by Bergman et al.[10] Monoindolylmaleimide **1** can be synthesized via two routes: reaction of indolylmagnesium bromide with monobromomaleimide or oxidation of the Michaël adduct obtained from indole and maleimide by heating in glacial acetic acid.[11] Cycloaddition of compound **1** in refluxing xylene can lead to the two intermediates **2** and **3**. According to the method of isolation, either **2** or **3** were obtained. When the reaction mixture was filtered off, compound **2** was obtained in 84% yield as described by Bergman et al.[10] When the mixture was eluted on a silica gel chromatography column, only compound **3** was isolated in 49% yield. In our hands, refluxing compound **2** in dioxane for 24 h in the presence of trifluoroacetic acid gave compound **4** in 93% yield,[12] whereas Bergman et al.

*Keywords*: G2 checkpoint inhibitors; granulatimide; dipyrrolocarbazole tetraone.

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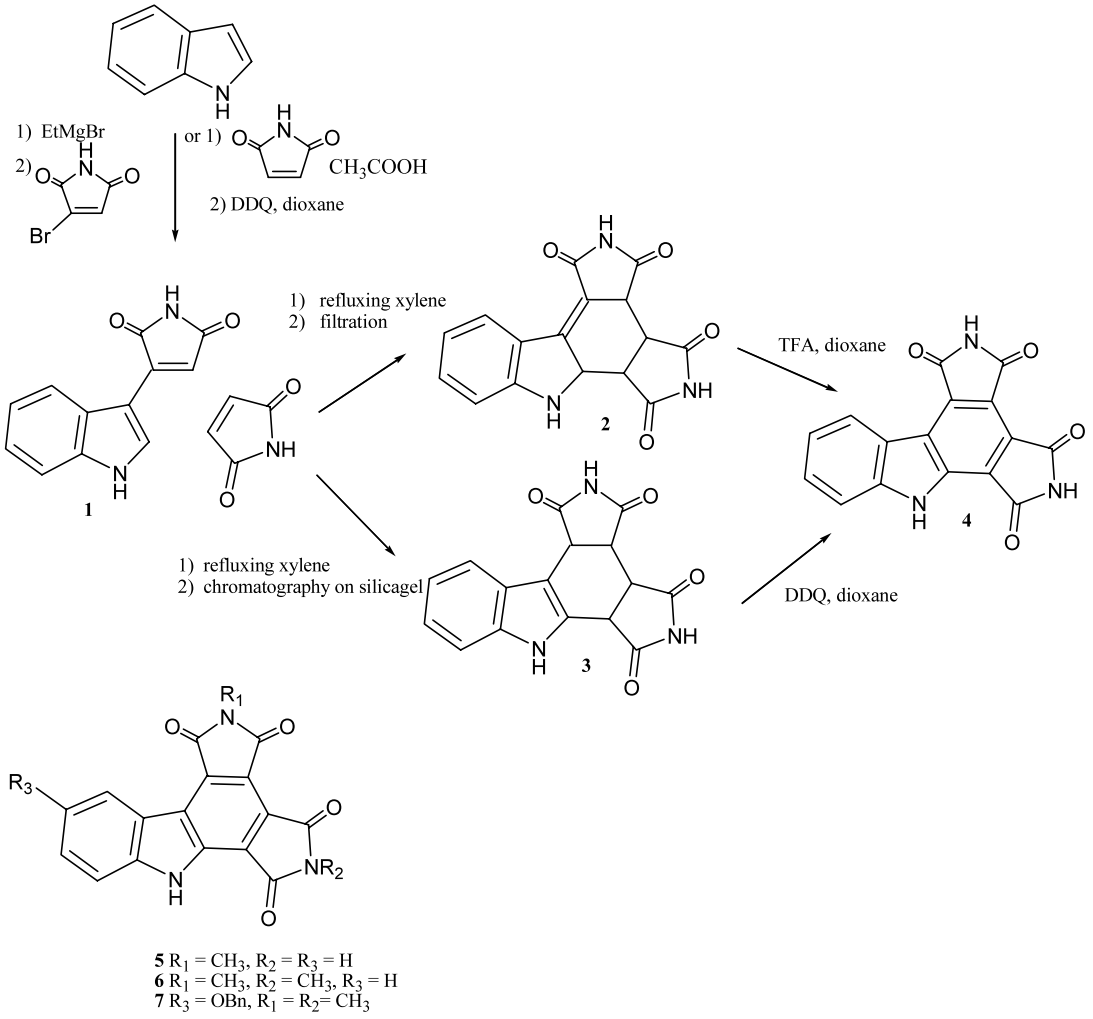
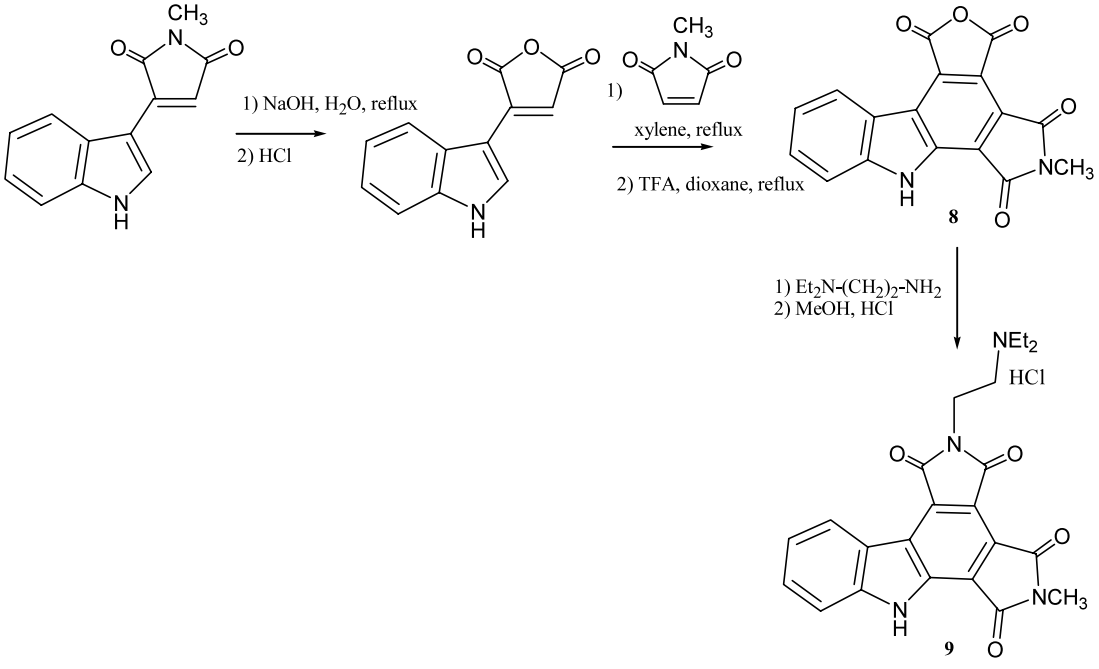



**Scheme 1.**




**Scheme 2.**

**Table 1.** Melting points (mp in °C) of compounds **4–9**

| Compound | Mp (°C) |
|---|---|
| **4** | >300 |
| **5** | >300 |
| **6** | >300 |
| **7** | >300 |
| **8** | 294 (decomposition) |
| **9** | 184 (decomposition) |

obtained only the isomer **3** by refluxing **2** in dioxane for 18 h. Oxidation of compound **3** with DDQ in dioxane for 24 h led to compound **4** in 60% yield (Scheme 1).[13]

Analogues **5** and **6** were obtained using identical sequences of reactions with one or two *N*-methyl maleimide moieties.

Compound **7** was synthesized from commercially available 5-benzyloxy-indole and two *N*-methyl maleimide units. Compounds **4–7** being highly insoluble, we investigated the possibility of obtaining a water-soluble analogue. In previous structure–activity relationship studies on rebeccamycin analogues, the solubility and the biological activity could be enhanced by introducing at the imide nitrogen a diethylaminoethyl chain.[14,15] Compound **9** was prepared from anhydride **8** as shown in Scheme 2.[16] Indolylmaleimide was transformed to the corresponding anhydride using aqueous sodium hydroxide. A Diels–Alder reaction was then carried out with *N*-methyl maleimide, followed by oxidation using TFA. Finally, the anhydride, which is more reactive than the imide toward amines, reacted with diethylaminoethylamine to give the *N*-substituted imide which was converted to hydrochloride **9**. The melting points of compounds **4–9** are reported in Table 1.

In summary, we have described the preparation of granulatimide analogues in which the aromatic framework is a dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone. Biological studies are in progress to evaluate the influence of the replacement of the imidazole heterocycle by a maleimide.

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12. Typical procedures for the preparation of **4**: **Method A**: compound **3** (86 mg, 0.277 mmol) was dissolved in dioxane (5 mL) and DDQ (138 mg, 0.610 mmol) was added. The mixture was refluxed for 3 days. After cooling to room temperature, water and EtOAc were added. The precipitate was filtered off, washed with water and EtOAc then dried to give **4** as an orange solid (51 mg, 0.167 mmol, 60% yield).
**Method B**: a mixture of compound **2** (120 mg, 0.388 mmol), dioxane (24 mL) and trifluoroacetic acid (400 μL) was refluxed for 24 h. After removal of the solvent, the solid residue was dissolved into EtOAc, washed with saturated aqueous $NaHCO_3$, and brine. Filtration of the solid formed at the interface gave **4** (110 mg, 0.360 mmol, 93% yield).
13. Spectral data of **4**: IR (KBr): $\nu_{C=O}$ 1690, 1730, 1745, 1780 $cm^{-1}$; $\nu_{NH}$ 3280–3380 $cm^{-1}$. HRMS (FAB+) $(M+H)^+$ calcd for $C_{16}H_8N_3O_4$, 306.0515, found, 306.0510. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.45 (1H, t, $J=7.5$ Hz), 7.71 (1H, t, $J=7.5$ Hz), 7.78 (1H, d, $J=8.0$ Hz), 9.01 (1H, d, $J=8.0$ Hz), 11.58 (1H, s, NH), 11.60 (1H, s, NH), 12.72 (1H, s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 112.9, 121.6, 125.5, 130.0 (C tert arom), 118.0, 119.4, 119.5, 124.3, 125.8, 131.5, 136.8, 144.1 (C quat arom), 166.4 (2C), 168.6, 169.3 (C=O).
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16. Spectral data of **9**: IR (KBr): $\nu_{C=O}=1710$, 1720, 1765, 1775 $cm^{-1}$, $\nu_{NH}=3300$–3600 $cm^{-1}$. HRMS (FAB+) $(M+H^+)$ calcd for $C_{23}H_{23}N_4O_4$, 419.1719, found, 419.1713. $^1H$ NMR (400 MHz, DMSO-$d_6$): 1.27 (6H, t, $J=7.0$ Hz), 3.18 (3H, s, $NCH_3$), 3.35 (4H, m), 3.50 (2H, m), 4.09 (2H, t, $J=6.5$ Hz), 7.51 (1H, t, $J=8.0$ Hz), 7.75 (1H, t, $J=8.0$ Hz), 7.84 (1H, d, $J=8.5$ Hz), 9.04 (1H, d, $J=8.5$ Hz), 9.43 (1H, br s), 12.95 (1H, s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): 8.2 (2C) ($CH_3$), 24.0 ($NCH_3$), 32.6, 46.1 (2C), 47.9 ($CH_2$), 113.0, 121.8, 125.4, 130.4 (C tert arom), 116.7, 118.2, 119.2, 124.5, 124.7, 130.1, 136.6, 144.3 (C quat arom), 164.8, 165.0, 167.1, 167.6 (C=O).