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Synthesis of pyridino[3',2':4,5]pyrrolo[3,2-g]pyrrolo-[3,4-e]indolizin-1,3-dione and pyrrolo[3,2-c]pyrazole skeletons

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Abstract—A three step synthesis of an isogranulatimide analogue, in which the imidazole moiety is replaced by a pyrrole unit and the indole heterocycle is replaced by a 7-azaindole moiety is described. Moreover, a novel synthetic pathway to the pyrrolo[3,2-c]pyrazole skeleton is reported.

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1. Introduction

Granulatimide and isogranulatimide are aromatic alkaloids isolated from the brazilian ascidian *Didemnum granulatum* (Fig. 1).^{1–3} These compounds have been identified as cell cycle G2 checkpoint inhibitors. In response to DNA damage, cell cycle checkpoints are activated. Their role consists in blocking the cell cycle to allow time for DNA repair. In more than 50% of cancer cells, the *p53* gene is mutated. The G1 checkpoint is dependent on the *p53* protein. Therefore, in the *p53*-mutated cells, the G1 checkpoint is lacking. These cells will be more sensitive to DNA damaging agents in the presence of a G2 checkpoint inhibitor, than healthy cells in which G1 checkpoint remains intact.^{4–13} Granulatimide and isogranulatimide, as well as staurosporine and UCN-01, are G2 checkpoint inhibitors. Compounds structurally related to granulatimide and isogranulatimide have been recently synthesized by our group.^{14–17} A series of compounds related to isogranulatimide, in which the imidazole moiety was replaced by a pyrrole heterocycle has been described (Fig. 1).¹⁴

In this letter, we report the synthesis of an isogranulatimide analogue bearing a pyrrole moiety instead of the imidazole heterocycle, and a 7-azaindole unit instead of an indole heterocycle. Azaindoles are bioisosters of

indole. They are found in many natural and synthetic compounds of biological interest. The replacement of a carbon atom by a nitrogen atom may modify the affinity for the binding site of the target enzyme(s), due to the modification of the electronic distribution on the aromatic framework and also due to the presence of a supplementary lone electron pair, which may induce additional hydrogen bonds. Moreover, a novel two-step synthesis of a pyrrolo[3,2-c]pyrazole is reported.

2. Chemistry

The preparation of compound **5** is outlined in Scheme 1. In indole series, 2,2'-pyrrolylindole was prepared from 3-bromoindole and pyrrole in an acidic medium.^{14,18} In these conditions, the coupling between 3-bromo-7-azaindole and pyrrole did not occur. For the preparation of 7-azaindoles, acid-catalyzed Fischer indolization from pyridylhydrazones is not favored.^{19,20} 7-Azaindole framework could be built by thermal cyclization from the hydrazone prepared from 2-hydrazinopyridine and the appropriate ketone.^{21,22} Heating 2-acetylpyrrole in 2-hydrazinopyridine at 160 °C allowed the isolation of hydrazone **1** in 94% yield (Scheme 1).²³ Unfortunately, the 7-azaindole derivative **3** could not be obtained by thermal indolization. Heating **1** at 245 °C in diethylene glycol²² led to decomposition of starting material. When the reaction was performed in nitrobenzene at 200 °C, pyrazole **2** was isolated in 40% yield after purification by flash chromatography.²⁴ Only few methods are described in the literature for the synthesis of

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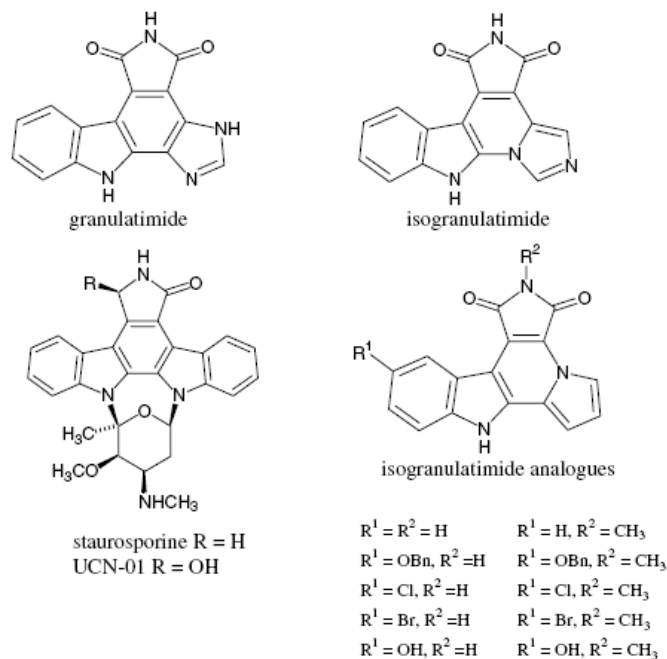
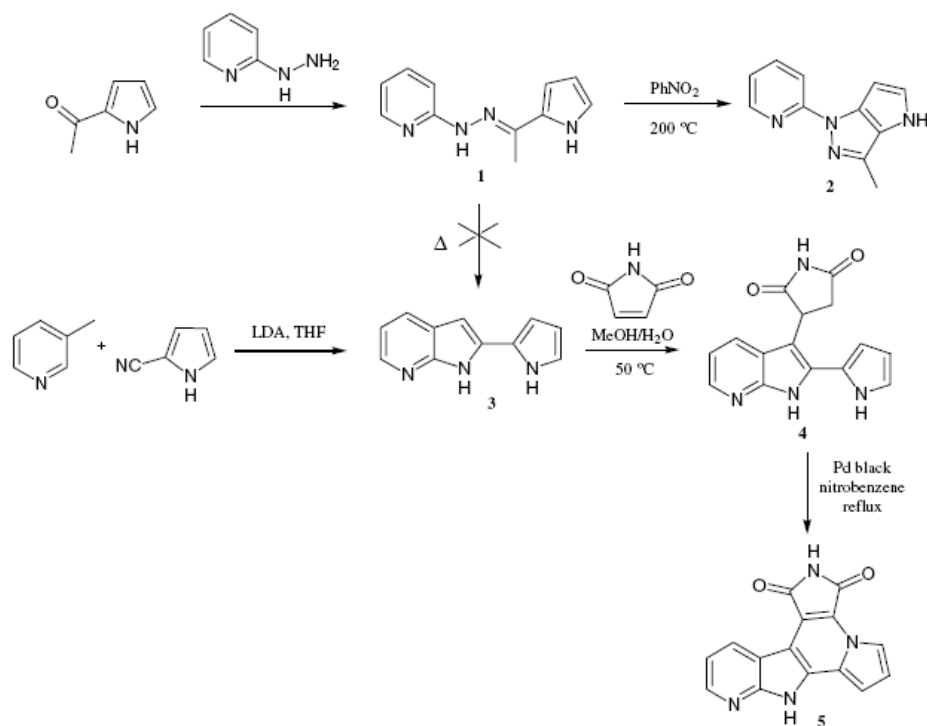


Figure 1.



Scheme 1.

pyrrolo[3,2-*c*]pyrazoles.^{25,26} The pyrrolo[3,2-*c*]pyrazole nucleus is found in more complex or related structures^{27–33} or condensed aromatic systems of biological interest.^{34,35} However, to our knowledge, this synthetic pathway has never been described previously. The structure of compound **2** has been confirmed from

NMR spectroscopic data (¹H–¹H COSY, ¹³C–¹H HSQC, ¹³C–¹H HMBC, ¹⁵N–¹H HMBC correlations), which allowed the assignments of the signals (Fig. 2). A possible mechanism for the formation of compound **2** could involve an azomethine imine intermediate, which would undergo electrocyclicization.^{36,37}

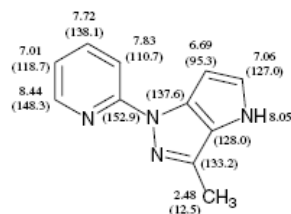


Figure 2. NMR chemical shifts in CDCl_3 of ^1H and ^{13}C (in brackets) for compound **2**.

Compound **3** was obtained in 42% yield by coupling 3-picoline and 2-cyanopyrrole in the presence of LDA.^{38–40} A Michael addition between compound **3** and maleimide in refluxing toluene in the presence of SnCl_2 ¹⁴ allowed the obtention of compound **4** in poor yield. As previously observed, a Michael addition could not be performed from 7-azaindole and maleimide in acetic acid.¹⁷ Finally, coupling of compound **3** with maleimide was successfully carried out in a mixture $\text{MeOH}/\text{H}_2\text{O}$ 1:2 at 50 °C giving the Michael adduct **4** in 54% yield.⁴¹ Compound **5** was obtained in 14% yield by cyclization of **4** in refluxing nitrobenzene in the presence of Pd black followed by filtration and purification by flash chromatography.^{14,42} This step probably involves the oxidation of the succinimide to maleimide prior to the cyclization.

In summary, a new isogranulatimide analogue was prepared in three steps via a 2,2'-pyrrolyl-7-azaindole intermediate. In parallel, the synthesis of a pyrrolo[3,2-*c*]pyrazole derivative was performed in two steps. This method could be applied to obtain analogues bearing various substituents. The pyrrolo[3,2-*c*]pyrazole nucleus is found in structures of biological interest. The biological activities of the new compounds are under investigation.

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- Procedure for the preparation of **1** and spectral data: a solution of 2-acetylpyrrole (100 mg, 0.92 mmol) in 2-hydrazinopyridine (1.4 g, 12.8 mmol) was heated at 160 °C for 24 h. Compound **1** was isolated after purification by chromatography on silica gel (eluent EtOAc) as a pale yellow solid (172.6 mg, 0.86 mmol, 94% yield). Mp 134–135 °C. IR (KBr) 1440, 1570, 1600, 3200, 3300 cm^{-1} . HRMS (FAB+) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{12}\text{N}_4$ 201.1140, found 201.1145. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 2.21 (3H, s), 6.09 (1H, m), 6.40 (3H, m), 6.76 (1H, ddd, $J_1 = 7.0$ Hz, $J_2 = 5.0$ Hz, $J_3 = 1.0$ Hz), 6.86 (1H, m), 7.54 (1H, pd, $J = 9.0$ Hz), 7.64 (1H, ddd, $J_1 = 9.0$ Hz, $J_2 = 7.0$ Hz, $J_3 = 2.0$ Hz), 8.12 (1H, ddd, $J_1 = 5.0$ Hz, $J_2 = 2.0$ Hz, $J_3 = 1.0$ Hz), 9.44 (1H, s, NH), 11.08 (1H, br s, NH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): 13.0 (CH_3), 107.2, 108.2, 108.6, 114.5, 120.4, 137.5, 147.3 (CH), 131.2, 138.6, 158.0 (C).
- Procedure for the preparation of **2** and spectral data: a mixture of **1** (60 mg, 0.30 mmol) in nitrobenzene (10 mL) was heated at 200 °C for 39 h. The reaction mixture was purified by flash chromatography (eluent cyclohexane/ CH_2Cl_2 1:1 then EtOAc/ CH_2Cl_2 1:1) to obtain **2** (23.5 mg, 0.119 mmol, 40% yield) as a brown solid. Mp 159–162 °C. IR (KBr) 1475, 1540, 1590, 3380 cm^{-1} . HRMS (FAB+) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4$ 199.0984, found 199.0967. ^1H NMR (400 MHz, CDCl_3): 2.48 (3H, s), 6.69 (1H, dd, $J_1 = 3.0$ Hz, $J_2 = 1.5$ Hz), 7.01 (1H, ddd, $J_1 = 7.0$ Hz, $J_2 = 5.0$ Hz, $J_3 = 1.0$ Hz), 7.06 (1H, t, $J = 3.0$ Hz), 7.72 (1H, ddd, $J_1 = 8.5$ Hz, $J_2 = 7.5$ Hz, $J_3 = 2.0$ Hz), 7.83 (1H, dt, $J_1 = 8.5$ Hz, $J_2 = 1.0$ Hz), 8.05 (1H, br s), 8.44 (1H, ddd, $J_1 = 5.0$ Hz, $J_2 = 2.0$ Hz, $J_3 = 1.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3): 12.5 (CH_3), 95.3, 110.7, 118.7, 127.0, 138.1, 148.3 (CH arom.), 128.0, 133.2, 137.6, 152.9 (C).
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40. Procedure for the preparation of **3** and spectral data: a solution of LDA was prepared at 0 °C from a 2.0 M solution of butyllithium in cyclohexane (8.1 mL) and diisopropylamine (2.26 mL) in THF (20 mL). The solution was stirred at 0 °C for 10 min before addition of 3-picoline (522 μ L, 5.38 mmol). The mixture was stirred at 0 °C for 10 min then cooled to –78 °C before addition of 2-cyanopyrrole (455 μ L, 5.38 mmol). The mixture was stirred at 0 °C for 1.5 h. A solution of LDA was added (9 mmol—prepared from 2.0 M butyllithium in cyclohexane (4.5 mL) and diisopropylamine (1.26 mL) in THF (10 mL)) and the reaction mixture was heated at 45 °C for 5 h. After cooling and addition of brine, the mixture was extracted with EtOAc. The organic phase was dried over MgSO₄, filtered, and evaporated. Compound **3** was isolated after purification by flash chromatography (eluent EtOAc/cyclohexane 6:4) as a salmon-colored solid (410 mg, 2.24 mmol, 42% yield). Mp > 150 °C (decomposition). IR (KBr) ν_{NH} 3420 cm⁻¹. HRMS (FAB+) [M+H]⁺ calcd for C₁₁H₉N₃ 184.0875, found 184.0872. ¹H NMR (400 MHz, DMSO-*d*₆): 6.18 (1H, m), 6.64 (1H, d, *J* = 2.0 Hz), 6.77 (1H, m), 6.95 (1H, m), 7.03 (1H, dd, *J*₁ = 8.0 Hz, *J*₂ = 5.0 Hz), 7.86 (1H, dd, *J*₁ = 8.0 Hz, *J*₂ = 1.5 Hz), 8.13 (1H, dd, *J*₁ = 5.0 Hz, *J*₂ = 1.5 Hz), 11.41 (1H, br s, NH), 11.81 (1H, br s, NH). ¹³C NMR (100 MHz, DMSO-*d*₆): 93.0, 107.0, 108.9, 115.6, 119.8, 126.5, 141.3 (CH), 121.2, 124.3, 133.1, 149.1 (C).
41. Procedure for the preparation of **4** and spectral data: a mixture of **3** (100 mg, 0.546 mmol) and maleimide (530 mg, 5.46 mmol) in H₂O/MeOH (2:1 v/v, 30 mL) was heated at 50 °C for 48 h. Methanol was evaporated and after addition of brine, the aqueous mixture was extensively extracted with EtOAc. The organic phase was dried over MgSO₄, filtered, and evaporated. Compound **4** was isolated after purification by flash chromatography (eluent EtOAc/cyclohexane from 5:5 to 8:2) as an off-white solid (82.6 mg, 0.295 mmol, 54% yield). Mp > 200 °C (decomposition). IR (KBr) $\nu_{\text{C=O}}$ 1700, 1770 cm⁻¹, ν_{NH} 3300–3600 cm⁻¹. HRMS (FAB+) [M+H]⁺ calcd for C₁₅H₁₂N₄O₂ 281.1039, found 281.1037. ¹H NMR (500 MHz, DMSO-*d*₆): 2.77 (1H, dd, *J*₁ = 18.0 Hz, *J*₂ = 5.5 Hz), 3.32 (1H, dd, *J*₁ = 18.0 Hz, *J*₂ = 10.0 Hz), 4.60 (1H, dd, *J*₁ = 10.0 Hz, *J*₂ = 5.5 Hz), 6.26 (1H, m), 6.57 (1H, br s), 7.05 (1H, br s), 7.07 (1H, dd, *J*₁ = 8.0 Hz, *J*₂ = 4.5 Hz), 7.59 (1H, d, *J* = 7.5 Hz), 8.21 (1H, d, *J* = 4.5 Hz), 11.11 (1H, br s, NH), 11.50 (1H, br s, NH), 11.64 (1H, br s, NH). ¹³C NMR (100 MHz, DMSO-*d*₆): 37.2 (CH₂), 38.9 (CH), 109.1, 109.4, 115.6, 120.3, 125.4, 142.3 (CH arom.), 104.2, 118.7, 122.2, 130.9, 148.3 (C), 177.9, 179.9 (C=O).
42. Procedure for the preparation of **5** and spectral data: a mixture of **4** (82 mg, 0.295 mmol) and Pd black (31.4 mg) in nitrobenzene (5 mL) was refluxed for 7 h. The reaction mixture was filtered over flash silica gel (eluent dichloromethane then THF). Compound **5** was isolated after purification by flash chromatography (eluent THF/CH₂Cl₂ 1:9 then 2:8) as a purple solid (11.5 mg, 0.042 mmol, 14% yield). Mp > 300 °C. IR (KBr) $\nu_{\text{C=O}}$ 1720, 1760 cm⁻¹, ν_{NH} 3150–3300 cm⁻¹. HRMS (FAB+) [M+H]⁺ calcd for C₁₅H₈N₄O₂ 277.0726, found 277.0718. ¹H NMR (400 MHz, DMSO-*d*₆): 7.16 (1H, dd, *J*₁ = 4.0 Hz, *J*₂ = 2.5 Hz), 7.23 (1H, dd, *J*₁ = 4.0 Hz, *J*₂ = 1.0 Hz), 7.40 (1H, dd, *J*₁ = 8.0 Hz, *J*₂ = 4.5 Hz), 8.30 (1H, dd, *J*₁ = 2.5 Hz, *J*₂ = 1.0 Hz), 8.49 (1H, dd, *J*₁ = 4.5 Hz, *J*₂ = 1.5 Hz), 8.76 (1H, dd, *J*₁ = 8.0 Hz, *J*₂ = 1.5 Hz), 11.17 (1H, br s, NH), 13.24 (1H, br s, NH). ¹³C NMR (100 MHz, DMSO-*d*₆): 101.1, 114.7, 116.4, 117.2, 130.0, 145.3 (CH), 101.3, 114.4, 116.8, 122.2, 124.2, 133.3, 151.2 (C), 166.4, 169.1 (C=O).