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Synthesis of isogranulatimide analogues possessing a pyrrole moiety instead of an imidazole heterocycle

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Abstract—An efficient four step synthesis from commercial indoles of isogranulatimide analogues is reported. In the new compounds, the imidazole moiety is replaced by a pyrrole unit, the indole part is substituted or not in 5-position and the nitrogen of the imide moiety bears or not a methyl substituent.

Granulatimide and isogranulatimide are natural compounds isolated from the ascidian *Didemnum granulatum* (Fig. 1).[1,2] Their biological activity is linked to their capacity to inhibit the G2 checkpoint, which represents a promising target for the development of new chemotherapeutic anticancer agents. DNA damage activates signal transduction pathways called checkpoints, which delay cell cycle progression and allow more time to repair DNA. Most of the cancer cells have mutations in genes involved in the G1 checkpoint such as the *p53*

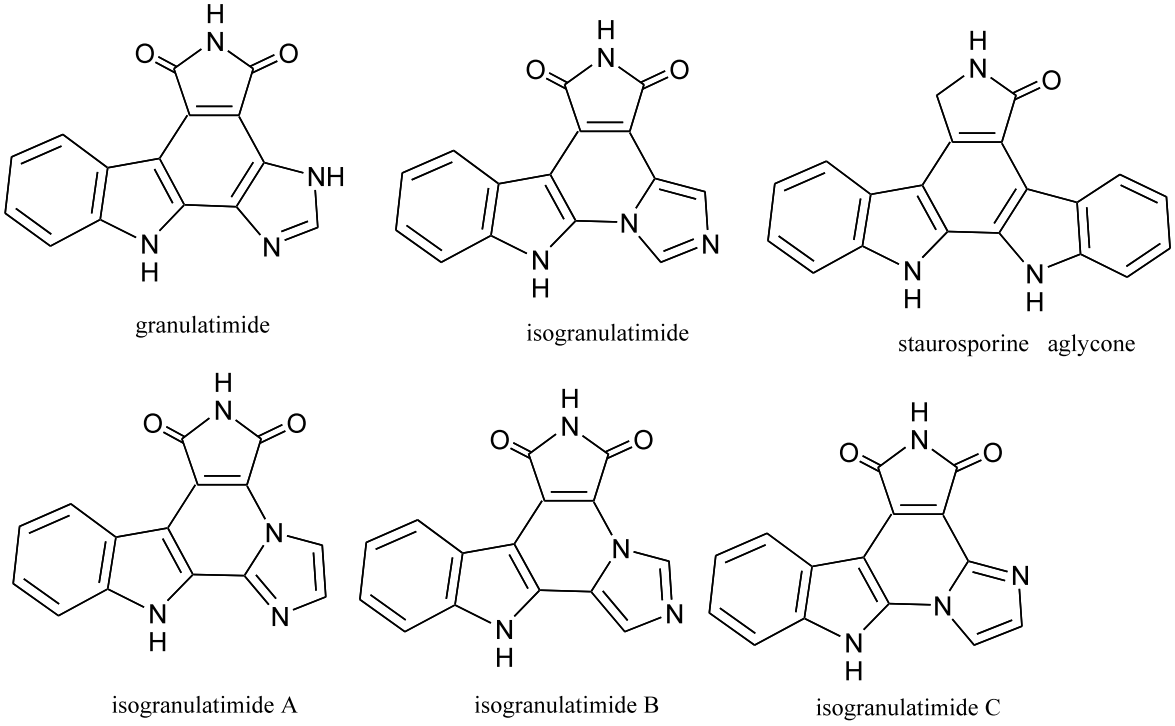

Figure 1.

Keywords: G2 checkpoint inhibitors; isogranulatimide; pyrrolo[3,4-*c*]carbazole.
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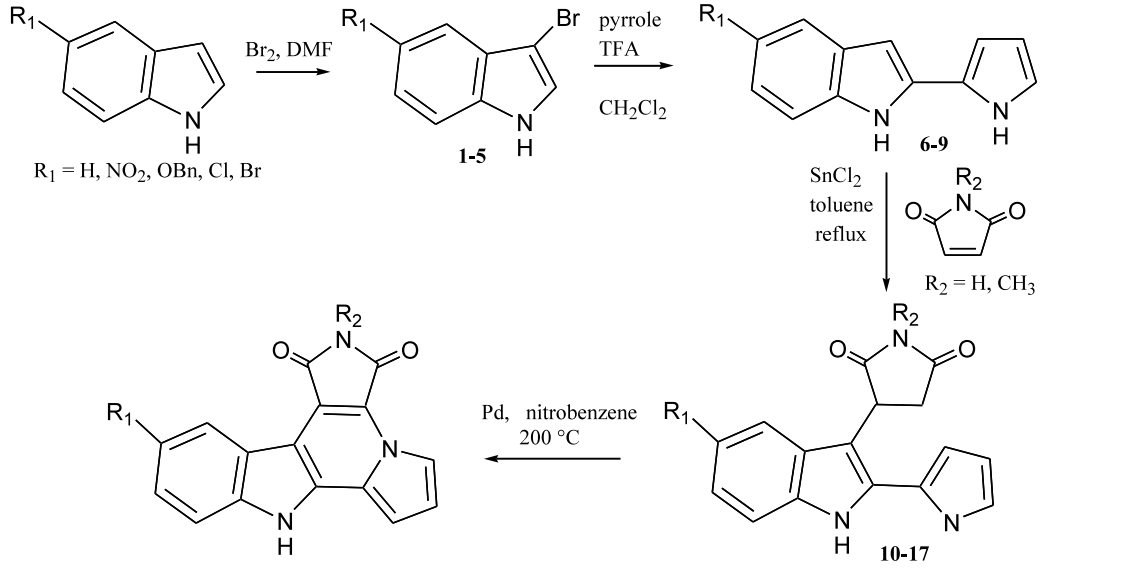
gene. If the G2 checkpoint is selectively disrupted, the cancer cells with the impaired G1 checkpoint will become more sensitive to a DNA-damaging treatment compared with normal cells because normal cells retain an intact G1 checkpoint.[3–8] Accordingly, the biological properties of granulatimide and isogranulatimide have triggered theoretical studies and synthetic efforts. Detailed computational studies were performed for granulatimide and isogranulatimide and structurally related didemnimides in order to initiate a quantitative structure–activity relationship study.[9] Various synthetic pathways have been investigated to prepare granulatimides and analogues and isogranulatimides A–C (Fig. 1).[1,10,11] Since, in contrast with granulatimide and isogranulatimide, staurosporine aglycone is completely inactive toward G2 checkpoint, it was deduced that the imidazole moiety could play a central role in their G2 checkpoint activity.[11]

Here we present the synthesis of a new family of isogranulatimide analogues in which the imidazole moiety is replaced by a pyrrole heterocycle. The first step consists in a selective bromination in 3-position of the indole.[12] Reaction of 3-bromoindole with pyrrole at room temperature in dichloromethane in the presence of trifluoroacetic acid led to the corresponding indolylpyrrole as described by Bocchi and Palla.[13] Cycloadditions between 2′,2′-bisindole and maleimides failed to give the formal [4+2] cycloadduct, only the fully aromatized product and the Michaël adduct were isolated in low yields.[14] Cycloaddition assays in acetic acid only led to the degradation of indolylpyrrole. Reaction of indolylpyrrole with maleimide in the presence of stannous chloride gave the Michaël adduct in a good yield (Scheme 1).

Various commercial 5-substituted indoles (5-chloro, 5-bromo, 5-nitro, 5-benzyloxy) and two maleimides (maleimide and *N*-methylmaleimide) were also used (Table 1). In the case of the electron withdrawing nitro group, coupling of the 5-nitroindole with pyrrole did not occur. To obtain 5-hydroxy analogues, hydrogenolysis of 5-*O*-benzyl compounds **12** and **13** using 10% Pd/C in EtOAc/MeOH led to **18** and **19** in 100% and 89% yields, respectively. Several conditions were tried for the cyclization of the Michaël adducts **10** and **11** with various catalysts[11,15,16] (Pd/C, Pd black, $Pd(OAc)_2$), several solvents (diphenyloxide, chlorobenzene, nitrobenzene, acetic acid) and different work-up. They are reported in Table 2. The best yields were obtained using Pd black and nitrobenzene and elimination of the solvent by filtration over silicagel. These optimal conditions were applied for the cyclizations of compounds **12**–**19**, the yields are reported in Table 3.[17–20] When $R_1 = OH$ degradation products were observed, the low yields could be due to the presence of a phenol function sensitive to oxidation.

In summary, in only four steps from commercial indoles, we have synthesized in good yields isogranulatimide analogues in which the imidazole part is replaced by a pyrrole moiety. This way was only possible with 5-substituted indoles bearing an electron donor group. The biological activities of the new isogranulatimide analogues are being evaluated.



Scheme 1.

Table 1. Yields obtained in the different steps from unsubstituted indole and 5-substituted indoles, and with maleimide and *N*-methylmaleimide for the synthesis of the Michaël adducts (mp in °C)

Indole	Bromation			Coupling with pyrrole			Michaël adduct					
							NH			NCH_3		
	Product	Mp (°C)	Yield (%)	Product	Mp (°C)	Yield (%)	Product	Mp (°C)	Yield (%)	Product	Mp (°C)	Yield (%)
5-H	**1**	65	83	**6**	216–218	83	**10**	67–69	90	**11**	142	89
5-NO_2	**2**	191–194	91									
5-OBn	**3**	89–92	92	**7**	178–182	69	**12**	103–107	68	**13**	89–94	82
5-Cl	**4**	84	65	**8**	223–227	72	**14**	138–144	56	**15**	92–102	79
5-Br	**5**	94	61	**9**	245	67	**16**	163	46	**17**	81	96

Table 2. Experimental conditions and yields for the cyclization of the Michaël adducts **10** and **11**

Starting product	Solvent	Catalyst	Temperature (°C)	Time of reaction (h)	Method for solvent elimination	Yield of cyclization (%)
11	Ph_2O	Pd/C 10%	180	48	Distillation under reduced pressure (5 mm Hg)	30
10	Ph_2O	Pd/C 10%	180	48	Filtration over silicagel	16
11	Chlorobenzene	Pd/C 10%	132	48	Evaporation under reduced pressure	Degradation
10	Nitrobenzene	Pd black	200	8	Filtration over silicagel	72
11	Nitrobenzene	Pd black	200	7	Filtration over silicagel	89
10	AcOH	$Pd(OAc)_2$	118	3	Evaporation under reduced pressure	Degradation

Table 3. Yields obtained in the cyclization of compounds **10**–**19** (mp in °C)

Substituent	Compounds	Yield (%)	Mp (°C)	Compounds	Yield (%)	Mp (°C)
H	**10→20**	89	218–220	**11→21**	89	226–228
OBn	**12→22**	35	275	**13→23**	75	120
Cl	**14→24**	52	298–304	**15→25**	81	249
Br	**16→26**	42	>300	**17→27**	92	>300
OH	**18→28**	16	>275	**19→29**	17	192

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17. Spectral data of **10**: IR (KBr) $\nu_{C=O}$ 1700, 1780 cm^{-1}, ν_{NH} 3100–3500 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{16}H_{13}N_3O_2$: 279.1007; found: 279.1004. ^1H NMR (400 MHz, DMSO-d_6): δ 2.80 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 3.32 (1H, dd, $J_1=18.0$ Hz, $J_2=10.0$ Hz), 4.56 (1H, dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz), 6.25 (1H, br s), 6.47 (1H, br s), 7.03 (2H, m), 7.14 (1H, d, $J=7.5$ Hz), 7.22 (1H, d, $J=8.0$ Hz), 7.42 (1H, d, $J=8.0$ Hz), 11.12 (2H, s, NH), 11.50 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.2 (CH_2), 39.0 (CH), 106.0, 122.9, 126.2, 130.6, 135.9 (C quat. arom.), 108.7, 108.9, 111.4, 117.5, 119.2, 119.7, 121.3 (C tert. arom.), 178.2, 180.3 (C=O).

18. Spectral data of **20**: IR (KBr) $\nu_{C=O}$ 1710, 1750 cm^{-1}, ν_{NH} 2900–3300 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{16}H_9N_3O_2$: 275.0694; found: 275.0698. ^1H NMR (400 MHz, DMSO-d_6): δ 7.11 (1H, s), 7.12 (1H, s), 7.30 (1H, t, $J=7.5$ Hz), 7.43 (1H, t, $J=7.5$ Hz), 7.62 (1H, d, $J=8.0$ Hz), 8.25 (1H, s), 8.55 (1H, d, $J=8.0$ Hz), 11.09 (1H, s, NH), 12.63 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.7, 113.2, 116.8, 120.8, 122.2, 122.4, 124.8 (C tert. arom.), 103.7, 117.0, 121.1, 121.6, 124.5, 133.6, 138.8 (C quat. arom.), 166.4, 169.2 (C=O).