New Synthetic Route to Granulatimide and Its Structural Analogues

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The Stille coupling reaction of stannylindole 12 with 4-iodoimidazole 13 (or 24) in the presence of $PdCl_2(PPh_3)_2$ gave the corresponding indole–imidazole coupling product 14 (or 25), thereby affording a new synthetic approach to the alkaloid granulatimide (7), isolated from the Brazilian ascidian *Didemnum granulatum*, as well as its structural analogues, 10-methylgranulatimide (23), 17-methylgranulatimide (30), 10,17-dimethylgranulatimide (31).

Key words alkaloid; indole; maleimide; imidazole; Stille coupling reaction; synthesis

Bisindolylmaleimides represent an important class of antitumor antibiotics.[1,2] Rebeccamycin (**5**), a weak inhibitor of topoisomerase I, and staurosporin (**3**), a non-specific protein kinase C (PKC) inhibitor, are representative compounds of this family.

It is noteworthy that, of two classes of G2 checkpoint inhibitors that have been discovered serendipitously, one class includes the purine alkaloids caffeine (**1**) and pentoxifylline (**2**),[3—5] while the other includes the bisindolylmaleimides staurosporine (**3**) and UCN-01 (**4**).

Recently it was reported that an extract of the Brazilian ascidian *Didemnum granulatum* showed strong activity as a G2 checkpoint inhibitor due to the presence of two compounds, granulatimide (**7**) and isogranulatimide (**8**)[6—9] (Chart 1). These compounds lack the second indole unit of bisindolylmaleimides such as staurosporine (**3**) and UCN-01 (**4**), having an imidazole moiety in its place. The indole/maleimide/imidazole-containing aromatic heterocyclic skeletons of **7** and **8** are without precedent among natural products, although they are related the purine alkaloids caffeine (**1**) and pentoxifylline (**2**).

Total syntheses of **7**, **8** and related analogues have already been reported by several groups.[6,10,11]

Recently, we reported the synthesis and protein kinase C inhibitory activity of arcyriacyanin A (**6**),[12,13] an unsymmetrically substituted green-blue indole pigment of the slime mould *Arcyria obvelata* ONSBERG (*Arcyria nutans* GREV.).

The method used to construct the unsymmetric bisindolylmaleimide employed the reaction of bisindolyl Grignard reagents with dibromomaleimides. Our strategy for the synthesis of granulatimide (**7**) and its analogues is illustrated in Chart 2. The application of our method for the synthesis of arcyriacyanin A[13] should allow the synthesis of **7** by reaction of the bromomagnesium salt of the indole–imidazole **10** with 3,4-dibromomaleimide.

We are interested in the syntheses and biological activities of indole maleimide compounds, and in this paper we would like to report a new synthetic route to granulatimide (**7**), 10-methylgranulatimide (**23**), 17-methylgranulatimide (**30**) and 10,17-dimethylgranulatimide (**31**).

Results and Discussion

The new synthesis of **7** and its analogues consists of the Stille coupling reactions of stannylindole **12** with 4-iodo-1-(methoxymethyl)imidazole (**13**)[14] and 4-iodo-1-methylimidazole (**24**)[15] (Chart 3). The stannyl derivative **12** was itself prepared from 1-methoxyindole (**11**) by regioselective lithiation with *n*-BuLi and subsequent reaction with chlorotributylstannane.[16] The Stille coupling reaction of **12** with imidazoles such as **13** (or **24**) in the presence of $PdCl_2(PPh_3)_2$ afforded the corresponding indole–imidazole coupling product **14** (48% yield) or **25** (58% yield), respectively.

Subsequent deprotection of the 1-methoxy group in **14** and **25** was readily achieved with Mg–methanol[13] in tetrahydrofuran (THF) to give, in 75 and 93% yields, 4-(1*H*-indol-2-yl)-1-(methoxymethyl)-1*H*-imidazole (**15**) and 4-(1*H*-indol-2-yl)-1-methyl-1*H*-imidazole (**26**), a key intermediate for the syntheses of granulatimide and its analogues.

To confirm the coupling reaction, compounds **15** and **25** were subjected to heteronuclear multiple bond connectivity (HMBC) study. As shown in Fig. 1, **15** was demonstrated to be the 2,4′-coupling product, since a correlation between the methylene protons of the methoxymethyl (MOM) group and C(2′) as well as C(5′) was observed. The HMBC spectrum of **25** was similar to that of **15**, except for the long-range correlation of methyl protons to (C2′) and (C5′).

The next stage in the syntheses of **7** and its analogues was carried out by the reaction of the maleimide **17** (or **18**) with the Grignard reagent **16** (or **27**) prepared from the coupling product **15** (or **26**) according to our previous synthesis[12,13] with some modifications. The reaction of **15** (or **26**) with ethylmagnesium bromide in absolute THF gave the MgBr salt **16** (or **27**). The condensation of **16** (or **27**) with maleimide **17** (or **18**) in THF to afforded the corresponding synthon condensation product (**19**, **20**, **28**, or **29**) in a yield of 42, 71, 43, or 68%, respectively.

We have carried out the photocyclization of **19** (or **20**) according to the Piers procedure[10] with some modification. Thus, when **19** (or **20**) was irradiated with an external light source (60 W, low-pressure mercury lamp) in MeCN, we obtained the granulatimide derivative **21** or **22** in 80 or 96% yield, respectively. Deprotection of the MOM group was performed with 10% HCl either on **21** or **22** (Chart 3). Granulatimide (**7**) and 10-methylgranulatimide **23** were obtained in 72 and 92% yields, respectively. All physical data for granulatimide (**7**) were identical with those reported.[6] The structural assigment of the new analogue **23** was based on the NMR spectrum and high resolution (HR)-MS. As expected,

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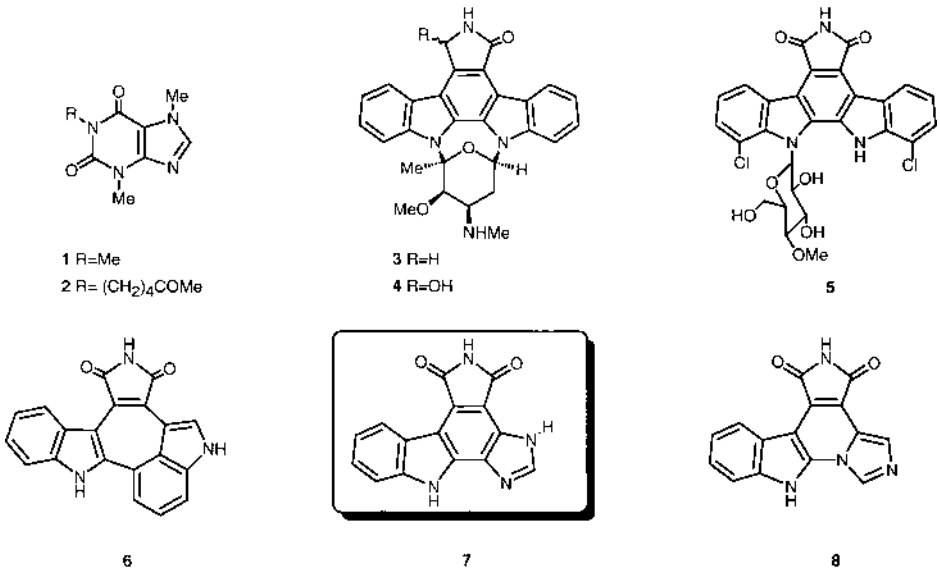


Chart 1

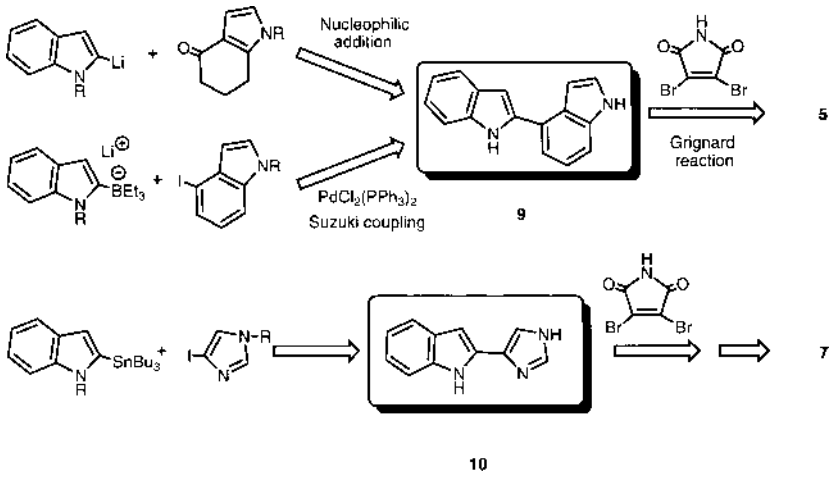


Chart 2

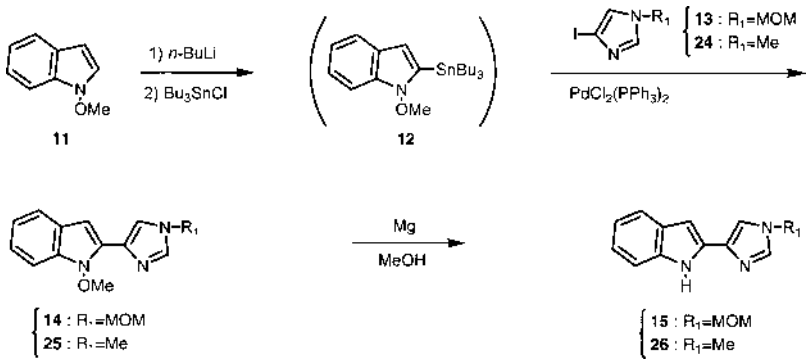


Chart 3

the ^{1}H-NMR spectrum of **23** is very similar to that of granulatimide (**7**), except that the resonance due to the maleimide *N*-Me function in **23** (δ 3.12) replaces the corresponding N–H signal (δ 10.96) of **7**. Thus, a straightforward and efficient synthesis of granulatimide (**7**) and its analogue **23** has been developed.

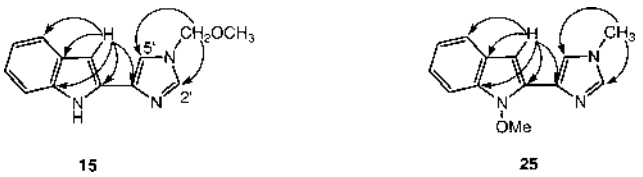
We then turned to the syntheses of 17-methylgranulatimide (**30**) and 10,17-dimethylgranulatimide (**31**). A similar

sequence of reactions to that described above for the preparation of granulatimide provided readily access to 17-methylgranulatimide (**30**) and 10,17-dimethylgranulatimide (**31**) from **28** and **29**, *via* photocyclization[6] in MeCN, affording **30** and **31** in 50 and 70% yields, respectively. The synthetic 17-methylgranulatimide (**30**) was identical in all respects to synthetic products reported previously.[10] As expected, the ^{1}H-NMR spectrum of **31** is very similar to that of **30**, except that the resonance due to the maleimide *N*-Me function in **31** (δ 3.08) replaces the corresponding N–H signal (δ 11.04) of **30**. Furthermore, the ^{1}H–^{1}H and ^{1}H–^{13}C correlation spectroscopy (COSY) data substantiated the structure of **31**. Consequently, this product was confirmed to be 10,17-dimethylgranulatimide (**31**). As anticipated, granulatimide (**7**) and its analogues **23**, **30**, and **31** are extremely insoluble in most common organic solvents.

Thus, a new synthetic route to granulatimide (**7**) and its analogues **23**, **30**, and **31** has been established by the construction of the indole–imidazole nucleus **15** (or **26**) based on the Stille coupling reaction involving the indole–imidazole (2,4′-) bond. An evaluation of the biological activity of these materials will be reported elsewhere.

Experimental

All melting points (mp) were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JNM-AL300 and JMN-α500 spectrometers. The chemical shifts were given in ppm (δ) values with tetramethylsilane as an internal standard (DMSO-d_6 and $CDCl_3$). Mass spectra were recorded on JEOL JMS-D300, JMS-HX110 and Shimadzu QP-5000 spectrometers. Wako silica gel C-200 (200 mesh) was used for column chromatography. Merck Kieselgel 60F_{254} was used for thin-layer chromatography (TLC), and spots were detected by ultraviolet (UV) illumination and by spraying 1% $Ce(SO_4)_4$ in 10% H_2SO_4 followed by heating. The organic extract was dried over Na_2SO_4. THF was distilled from sodium-benzophenone under nitrogen atmosphere before use. Low pressure mercury lamp (EL-120) was used for irradiation.



15 **25**

Fig. 1. Long-Range Correlations (^{1}H ^{13}C) in the HMBC Spectrum

4-(1-Methoxy-1*H*-indol-2-yl)-1-(methoxymethyl)-1*H*-imidazole (14) *n*-BuLi in *n*-hexane (2.5 mol/l, 0.5 ml, 1.2 mmol) was added to the stirred solution of **11** (147 mg, 1 mmol) in THF at −78 °C under nitrogen atmosphere, and the mixture was stirred for 30 min. Then, Bu_3SnCl (488 mg, 1.5 mmol) in THF was added dropwise, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was worked up with H_2O, extracted with Et_2O, dried and concentrated. The residue was treated with **13** (280 mg, 1.2 mmol) and $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) in toluene (10 ml), and the mixture was refluxed overnight. Then, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with AcOEt, washed with brine, dried and concentrated. The residue was subjected to silica gel chromatograph (AcOEt) to give 123 mg (48%) of **14** as an oil. IR (KBr) cm^{-1}: 3110, 2936, 1505, 1445, 1397, 1346, 1218, 1105, 737. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.34 (3H, s, O–Me), 3.98 (3H, s, N–O–Me), 5.29 (2H, s, –CH_2–), 6.83 (1H, s, indole H-3), 7.11 (1H, t, J=7.4 Hz, indole Ar-H), 7.23 (1H, t, J=7.2 Hz, indole Ar-H), 7.43 (1H, d, J=8.0 Hz, indole Ar-H), 7.56 (1H, d, J=1.1 Hz, imidazole H-5), 7.60 (1H, d, J=7.9 Hz, indole Ar-H), 7.70 (1H, d, J=1.3 Hz, imidazole H-2). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ: 56.3, 64.1, 77.9, 96.2, 108.1, 116.2, 120.3, 120.9, 122.1, 124.3, 130.5, 132.9, 133.7, 137.7. HR-MS Calcd for $C_{14}H_{15}N_3O_2$: 257.1163. Found: 257.1184. MS *m/z*: 257 (M^+).

4-(1*H*-Indol-2-yl)-1-(methoxymethyl)-1*H*-imidazole (15) The mixture of **14** (129 mg, 0.5 mmol) and Mg (1.2 g, 50 mmol) in THF (10 ml)–MeOH (20 ml) was refluxed under nitrogen atmosphere for 4 h. Then, the reaction mixture was worked up with aq. NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried and concentrated. The residue was recrystallized with AcOEt to give 85 mg (75%) of **15** as white powder. mp 103—104 °C. IR (KBr) cm^{-1}: 3196, 3100, 1343, 1321, 1107, 905, 784, 729. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.32 (3H, s, O–Me), 5.23 (2H, s, –CH_2–), 6.66 (1H, s, indole H-3), 7.08 (1H, t, J=7.3 Hz, indole Ar-H), 7.13 (1H, t, J=7.5 Hz, indole Ar-H), 7.34 (1H, d, J=7.9 Hz, indole Ar-H), 7.37 (1H, d, J=1.2 Hz, imidazole H-5), 7.58 (1H, d, J=7.9 Hz, indole Ar-H), 7.63 (1H, d, J=1.2 Hz, imidazole H-2), 9.73 (1H, br, N–H). ^{13}C-NMR ($CDCl_3$, 125.65 MHz) δ: 56.3, 78.0, 97.2, 110.9, 114.9, 119.8, 120.2, 121.6, 129.2, 132.2, 135.9, 136.4, 137.3. HR-MS Calcd for $C_{13}H_{13}N_3O$: 227.1058. Found: 227.1087. MS *m/z*: 227 (M^+).

3-Bromo-4-[2-(1-methoxymethyl-1*H*-imidazol-4-yl)-1*H*-indol-3-yl]pyrrole-2,5-dione (19) Compound **15** (114 mg, 0.5 mmol) in THF (4 ml) was added dropwise to the solution of EtMgBr prepared from Mg (24 mg, 1 mmol) and EtBr (218 mg, 2 mmol) in THF (2 ml), and the resulting solution was stirred at ambient temperature under nitrogen atmosphere for 30 min. Then, **17** (127 mg, 0.5 mmol) in THF (2 ml) was added dropwise and the mixture was stirred overnight. The reaction mixture was worked up with aq. NH_4Cl, extracted with AcOEt, washed with brine, dried and concentrated. The residue was subjected to silica gel chromatograph (acetone : $CHCl_3$=1 : 2) to give 84 mg (42%) of **19** as a red powder (from AcOEt–*n*-

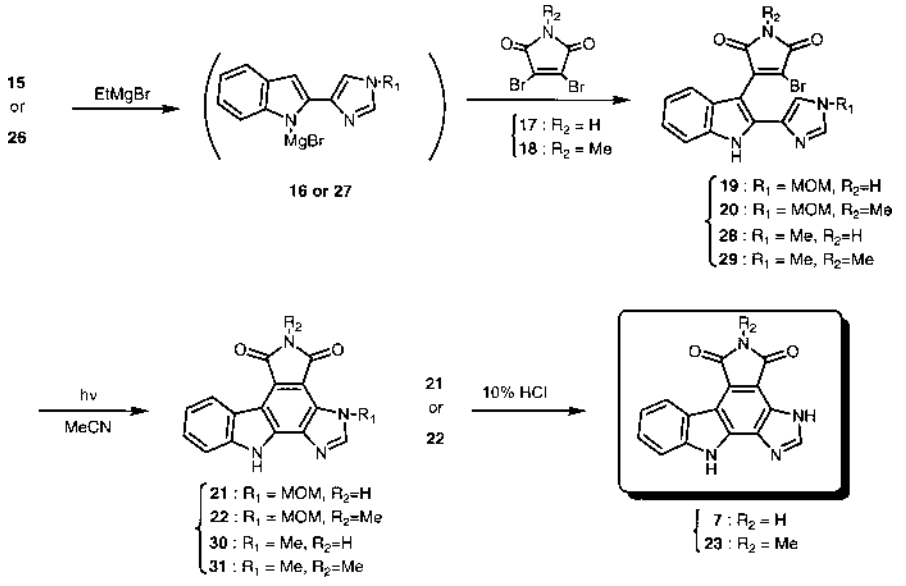


Chart 4

hexane). mp 230 °C (decomp.). IR (KBr) cm^{-1}: 3458, 1765, 1717, 1625, 1335, 1110, 1028, 735. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.23 (3H, s, O–Me), 5.34 (2H, s, –CH_2–), 7.04 (1H, t, J=7.5 Hz, indole Ar-H), 7.14 (1H, t, J=7.5 Hz, indole Ar-H), 7.36 (1H, d, J=7.9 Hz, indole Ar-H), 7.44 (1H, d, J=8.1 Hz, indole Ar-H), 7.66 (1H, d, J=1.3 Hz, imidazole H-5), 7.90 (1H, d, J=1.3 Hz, imidazole H-2), 11.24 (1H, s, CO–NH–CO), 11.90 (1H, s, N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 50.6, 76.9, 98.2, 111.6, 118.7, 119.7, 119.8, 121.8, 122.6, 126.5, 133.6, 133.7, 135.9, 138.4, 140.7, 167.1, 169.2. HR-MS Calcd for $C_{17}H_{13}{}^{79}BrN_4O_3$: 400.0169. Found: 400.0144. Calcd for $C_{17}H_{13}{}^{81}BrN_4O_3$: 402.0149. Found: 402.0103. MS *m/z*: 400(M^+), 402 (M^++2).

3-Bromo-4-[2-(1-methoxymethyl-1*H*-imidazol-4-yl)-1*H*-indol-3-yl]-1-methylpyrrole-2,5-dione (20) Compound **15** (56 mg, 0.25 mmol) was treated with EtMgBr, followed by **18** (67 mg, 0.25 mmol) as described for **19** to give 74 mg (71%) of **20** as a red powder (from AcOEt–*n*-hexane). mp 210 °C (decomp.). IR (KBr) cm^{-1}: 3352, 3150, 2934, 1770, 1707, 1627, 1433, 1380, 1105, 730. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.19 (3H, s, N–Me), 3.29 (3H, s, O–Me), 5.18 (2H, s, –CH_2–), 7.06 (1H, d, J=1.3 Hz, imidazole H-5), 7.16 (1H, t, J=7.5 Hz, indole Ar-H), 7.22 (1H, t, J=7.5 Hz, indole Ar-H), 7.39 (1H, d, J=7.5 Hz, indole Ar-H), 7.48 (1H, d, J=7.5 Hz, indole Ar-H), 7.62 (1H, d, J=1.3 Hz, imidazole H-2), 10.19 (1H, br, N–H). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ: 24.9, 56.4, 78.0, 99.2, 111.5, 118.1, 120.5, 120.9, 122.3, 123.0, 127.1, 133.1, 134.2, 135.6, 137.2, 139.9, 166.3, 168.6. HR-MS Calcd for $C_{18}H_{15}{}^{79}BrN_4O_3$: 414.0325. Found: 414.0325. Calcd for $C_{18}H_{15}{}^{81}BrN_4O_3$: 416.0305. Found: 416.0330. MS *m/z*: 414 (M^+), 416 (M^++2).

17-(Methoxymethyl)granulatimide (21) The solution of **19** (30 mg, 0.075 mmol) in MeCN (6 ml) was irradiated with low-pressure mercury lamp (60 W) for 7 h. Then, resulting solid material was filtered to give 20 mg (80%) of **21** as a yellow solid (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3256, 2948, 2716, 1740, 1705, 1324, 1221, 1104, 793, 734. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.26 (3H, s, O–Me), 6.15 (2H, s, –CH_2–), 7.31 (1H, t, J=7.5 Hz, indole Ar-H), 7.50 (1H, t, J=7.5 Hz, indole Ar-H), 7.62 (1H, d, J=8.1 Hz, indole Ar-H), 8.70 (1H, s, imidazole H-2), 8.95 (1H, d, J=8.1 Hz, indole Ar-H), 11.09 (1H, s, CO–NH–CO), 12.65 (1H, s, N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 55.2, 77.5, 109.5, 111.7, 113.6, 120.2, 121.2, 124.1, 124.2, 126.5, 127.5, 133.6, 135.7, 140.7, 147.0, 169.0, 170.6. HR-MS Calcd for $C_{17}H_{12}N_4O_3$: 320.0909. Found: 320.0893. MS *m/z*: 320 (M^+).

10-Methyl-17-(methoxymethyl)granulatimide (22) Compound **20** (42 mg, 0.1 mmol) was irradiated as described for **21** to give 32 mg (96%) of **22** as a yellow powder (from MeOH). mp >300°C. IR (KBr) cm^{-1}: 3106, 1758, 1694, 1594, 1376, 1252, 1114, 733. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.05 (3H, s, N–Me), 3.25 (3H, s, O–Me), 6.05 (2H, s, –CH_2–), 7.29 (1H, t, J=7.0 Hz, indole Ar-H), 7.50 (1H, t, J=7.0 Hz, indole Ar-H), 7.61 (1H, d, J=8.1 Hz, indole Ar-H), 8.66 (1H, s, imidazole H-2), 8.88 (1H, d, J=7.9 Hz, indole Ar-H), 12.58 (1H, br, N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 23.5, 55.2, 77.3, 108.3, 111.7, 113.7, 120.2, 121.0, 122.9, 124.0, 126.5, 127.3, 133.2, 135.4, 140.7, 146.9, 167.4, 169.0. HR-MS Calcd for $C_{18}H_{14}N_4O_3$: 334.1065. Found: 334.1053. MS *m/z*: 334 (M^+).

Granulatimide (7) The solution of **21** (16 mg, 0.05 mmol) in 10% aq. HCl (2 ml) was heated at 100 °C for 2 h. After cooling, the reaction mixture was basisity with aq. $NaHCO_3$. The resulting solid was corrected to give 9.9 mg (72%) of **7** as a yellow solid (from MeOH).

10-Methylgranulatimide (23) Compound **22** (17 mg, 0.05 mmol) was treated with 10% aq. HCl (10 ml) for 16 h as described for **7** to give 13.3 mg (92%) of **23** as a yellow solid (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3306, 1749, 1690, 1378, 804, 736. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.12 (3H, s, N–Me), 7.30 (1H, t, J=7.9 Hz, indole Ar-H), 7.49 (1H, t, J=7.5 Hz, indole Ar-H), 7.62 (1H, d, J=8.1 Hz, indole Ar-H), 8.52 (1H, s, imidazole H-2), 8.90 (1H, d, J=7.7 Hz, indole Ar-H), 12.54 (1H, br, indole N–H), 13.56 (1H, br, imidazole N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 23.5, 108.7, 111.7, 113.2, 120.1, 121.3, 121.8, 123.7, 126.2, 135.1, 140.5, 144.6, 168.1, 169.6. HR-MS Calcd for $C_{16}H_{10}N_4O_2$: 290.0803. Found: 290.0783. MS *m/z*: 290 (M^+).

4-(1-Methoxy-1*H*-indol-2-yl)-1-methyl-1*H*-imidazole (25) *n*-BuLi in *n*-hexane (2.5 mol/l, 2.0 ml, 4.8 mmol) was added to the stirred solution of **11** (592 mg, 4 mmol) in THF at −78 °C under nitrogen atmosphere, and the mixture was stirred for 30 min. Then, Bu_3SnCl (1.96 g, 6.0 mmol) in THF was added dropwise, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was worked up with H_2O, extracted with Et_2O, dried and concentrated. The residue was treated with **24** (1.0 g, 4.8 mmol) and $PdCl_2(PPh_3)_2$ (280 mg, 0.4 mmol) in toluene (80 ml), and the mixture was refluxed overnight. Then, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with AcOEt, washed with brine, dried and concentrated. The residue was subjected to silica gel chromatograph (AcOEt) to give 529 mg (58%) of **25** as white powder (from AcOEt–*n*-hexane). mp 91—92 °C. IR (KBr) cm^{-1}: 3114, 2922, 1641, 1517, 1462, 1416, 1231, 1206, 1101, 937, 612. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.74 (3H, s, N–Me), 3.96 (3H, s, O–Me), 6.78 (1H, s, indole H-3), 7.10 (1H, t, J=7.9 Hz, indole Ar-H), 7.21 (1H, t, J=7.9 Hz, indole Ar-H), 7.39 (1H, s, imidazole H-5), 7.42 (1H, d, J=7.9 Hz, indole Ar-H), 7.51 (1H, s, imidazole H-2), 7.58 (1H, d, J=7.9 Hz, indole Ar-H). ^{13}C-NMR ($CDCl_3$, 125.65 MHz) δ: 33.5, 64.1, 95.7, 108.1, 117.8, 120.3, 120.8, 121.9, 124.5, 131.0, 132.8, 133.1, 138.1. HR-MS Calcd for $C_{13}H_{13}N_3O$: 227.1058. Found: 227.1084. MS *m/z*: 227 (M^+).

4-(1*H*-Indol-2-yl)-1-methyl-1*H*-imidazole (26) The mixture of **25** (454 mg, 2 mmol) and Mg (4.8 g, 200 mmol) in THF (40 ml)–MeOH (80 ml) was refluxed under nitrogen atmosphere for 5 h. Then, the reaction mixture was worked up with aq. NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried and concentrated. The residue was recrystallized from AcOEt to give 365 mg (93%) of **26** as white powder. mp 222—224 °C. IR (KBr) cm^{-1}: 3144, 3100, 1522, 1414, 1335, 1292, 788, 736. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.70 (3H, s, N–Me), 6.56 (1H, s, indole H-3), 6.93 (1H, t, J=7.5 Hz, indole Ar-H), 7.01 (1H, t, J=7.4 Hz, indole Ar-H), 7.35 (1H, d, J=7.9 Hz, indole Ar-H), 7.45 (1H, d, J=7.7 Hz, indole Ar-H), 7.52 (1H, s, imidazole H-5), 7.67 (1H, s, imidazole H-2), 11.24 (1H, s, N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz): 33.1, 96.0, 111.0, 117.1, 118.9, 119.4, 120.4, 128.7, 133.9, 134.9, 136.2, 138.3. HR-MS Calcd for $C_{12}H_{11}N_3$: 197.0952. Found: 197.0979. MS *m/z*: 197 (M^+).

3-Bromo-4-[2-(1-methyl-1*H*-imidazol-4-yl)-1*H*-indol-3-yl]pyrrole-2,5-dione (28) Compound **26** (197 mg, 1 mmol) was treated with EtMgBr, followed by **17** (255 mg, 1 mmol) as described for **19** to give 158 mg (43%) of **28** as a red powder (from AcOEt–*n*-hexane). mp 240 °C (decomp.). IR (KBr) cm^{-1}: 3332, 1710, 1620, 1435, 1340, 1037, 618. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.75 (3H, s, N–Me), 7.09 (1H, t, J=7.5 Hz, indole Ar-H), 7.18 (1H, t, J=7.5 Hz, indole Ar-H), 7.39 (1H, d, J=7.9 Hz, indole Ar-H), 7.49 (1H, d, J=7.9 Hz, indole Ar-H), 7.55 (1H, d, J=1.1 Hz, imidazole H-5), 7.73 (1H, d, J=0.9 Hz, imidazole H-2), 11.29 (1H, s, CO–NH–CO), 11.88 (1H, s, N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 33.1, 97.6, 111.5, 119.5, 119.7(×2), 121.6, 122.6, 126.6, 133.1, 134.1, 135.8, 138.4, 140.9, 167.1, 169.2. HR-MS *m/z*: Calcd for $C_{16}H_{11}{}^{79}BrN_4O_2$: 370.0063. Found: 370.0066. Calcd for $C_{16}H_{11}{}^{81}BrN_4O_2$: 372.0043. Found: 372.0068. MS *m/z*: 370 (M^+), 372 (M^++2).

3-Bromo-4-[2-(1-methyl-1*H*-imidazol-4-yl)-1*H*-indol-3-yl]-1-methylpyrrole-2,5-dione (29) Compound **26** (49 mg, 0.25 mmol) was treated with EtMgBr, followed by **18** (67 mg, 0.25 mmol) as described for **19** to give 65 mg (68%) of **29** as a red powder (from AcOEt–*n*-hexane). mp >300 °C. IR (KBr) cm^{-1}: 3328, 1773, 1708, 1630, 1438, 1380, 840, 810, 736. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.01 (3H, s, CO–N–Me), 3.68 (3H, s, N–Me), 7.03 (1H, t, J=7.0 Hz, indole Ar-H), 7.13 (1H, t, J=7.0 Hz, indole Ar-H), 7.35 (1H, d, J=7.9 Hz, indole Ar-H), 7.44 (1H, d, J=7.9 Hz, indole Ar-H), 7.52 (1H, d, J=1.3 Hz, imidazole H-5), 7.68 (1H, d, J=0.9 Hz, imidazole H-2), 11.88 (1H, s, N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 24.5, 33.1, 97.5, 111.5, 119.6, 119.7, 119.9, 121.6, 121.8, 126.6, 132.9, 134.2, 135.8, 138.3, 140.2, 166.2, 168.2. HR-MS Calcd for $C_{17}H_{13}{}^{79}BrN_4O_2$: 384.0220. Found: 384.0259. Calcd for $C_{17}H_{13}{}^{81}BrN_4O_2$: 386.0199. Found: 386.0244. MS *m/z*: 384 (M^+), 386 (M^++2).

17-Methylgranulatimide (30) Compound **28** (28 mg, 0.075 mmol) was irradiated as described for **21** to give 11 mg (50%) of **30** as a yellow powder (from MeOH).

10,17-Dimethylgranulatimide (31) Compound **29** (39 mg, 0.1 mmol) was irradiated as described for **21** to give 21 mg (70%) of **31** as a yellow powder (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3122, 3064, 1756, 1701, 1431, 1381, 1255, 800, 734. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.08 (3H, s, CO–N–Me), 4.28 (3H, s, N–Me), 7.27 (1H, t, J=7.4 Hz, indole Ar-H), 7.49 (1H, t, J=7.4 Hz, indole Ar-H), 7.61 (1H, d, J=7.9 Hz, indole Ar-H), 8.52 (1H, s, imidazole H-2), 8.91 (1H, d, J=7.7 Hz, indole Ar-H), 12.55 (1H, br, N–H). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 23.0, 34.5, 108.3, 111.2, 113.0, 119.7, 121.0, 122.3, 123.6, 126.0, 128.1, 132.8, 135.1, 140.4, 146.5, 167.2, 168.8. HR-MS Calcd for $C_{17}H_{12}N_4O_2$: 304.0959. Found: 304.0941. MS *m/z*: 304 (M^+).

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