Synthesis of Granulatimide Positional Analogues

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The Stille coupling reaction of the stannylindole 13 with the 5-iodoimidazole derivative 14 (or 27) in the presence of $PdCl_2(PPh_3)_2$ gave the corresponding indole-imidazole coupling product 15 (or 28), thereby affording a synthetic approach to 10-methylgranulatimide (7), 15-methylgranulatimide (11), and 10,15-dimethylgranulatimide (12), as well as 10-methylisogranulatimide B (5).

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

Granulatimide (**1**) and isogranulatimide (**2**), isolated from the Brazilian ascidian *Didemnum granulatum*,[1—3] are without precedent among natural alkaloids having indole/maleimide/imidazole-containing aromatic heterocyclic skeletons, and they show strong activity as G2 checkpoint inhibitors.[4] Total syntheses of **1**, **2**, and their structural analogues, isogranulatimide A (**3**), isogranulatimide B (**4**), and isogranulatimide C (**6**) have already been reported by Piers and colleagues.[1,5] In a previous paper, we presented a new synthetic route to granulatimide (**1**), 10-methylgranulatimide (**7**), 17-methylgranulatimide (**8**) and 10,17-dimethylgranulatimide (**9**).[6] The latter analogues are congeners of the structural isomers **10**, **11** and **12** in the imidazole moiety (Fig. 1).

Previous syntheses of granulatimide and its analogues employed the Stille coupling reaction of stannylindole with 4-iodoimidazole in the presence of $PdCl_2(PPh_3)_2$, affording the 2,4′-indole-imidazole coupling product as a key intermediate. Subsequent reaction of indolyl Grignard reagents with 3,4-dibromomaleimide gave the condensation product, which was converted to granulatimide analogues by photocyclization (route A). Here we wish to report the preparation of new analogues of **1**, 10-methylgranulatimide (**10**), 15-methylgranulatimide (**11**), and 10,15-dimethylgranulatimide (**12**), as well as 10-methylisogranulatimide B (**5**), by the use of 5-iodoimidazole instead of 4-iodoimidazole in the same synthetic strategy (route B) (Chart 1).

Results and Discussion

To obtain the new granulatimide analogues **10**, **11**, **12** and the 2,5′-indole-imidazole coupling product for further structural manipulation, we needed to replace the 4-iodoimidazole moiety with a 5-iodoimidazole derivative. Thus, introduction of imidazole into compound **14** (or **27**) was carried out using 1-methoxy-2-tributylstannylindole (**13**) (Chart 2).

The 5-iodo-1-methyl-2-phenylthioimidazole (**14**) and 5-iodo-1-methoxymethyl-2-phenylthioimidazole (**27**) were synthesized from 1-methylimidazole (or imidazole) according to reported methods.[7] The stannyl derivative **13** was itself prepared from 1-methoxyindole[8,9] by regioselective lithiation with *n*-BuLi[10—12] and subsequent reaction with chlorotributylstannane.[13] The Stille coupling reaction[14,15] of **13** with the imidazole **14** in the presence of $PdCl_2(PPh_3)_2$ in toluene afforded the 2,5′-indole-imidazole coupling product **15** in 65% yield.

On the other hand, the reaction of **13** with the imidazole **27** under similar reaction conditions, but in benzene instead of toluene, afforded **28** in 64% yield. Subsequent deprotection of the 1-methoxy group in **15** and **28** was readily achieved with Mg–MeOH to give, in 92 and 76% yields, 5-(1*H*-indol-2-yl)-1-methyl-2-phenylthio-1*H*-imidazole (**16**) and 5-(1*H*-indol-2-yl)-1-methoxymethyl-2-phenylthio-1*H*-imidazole (**29**), key intermediates for synthesizing new analogues. To confirm the coupling reaction, compounds **15** and **29** were subjected to a heteronuclear multiple bond connectivity

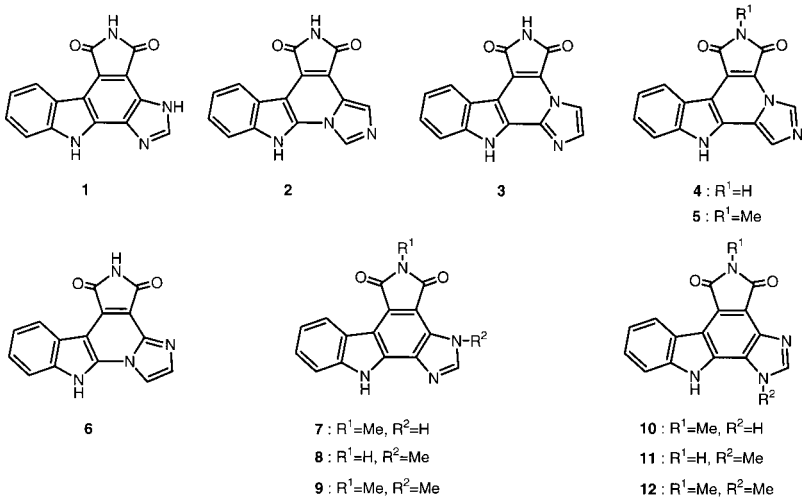

Fig. 1

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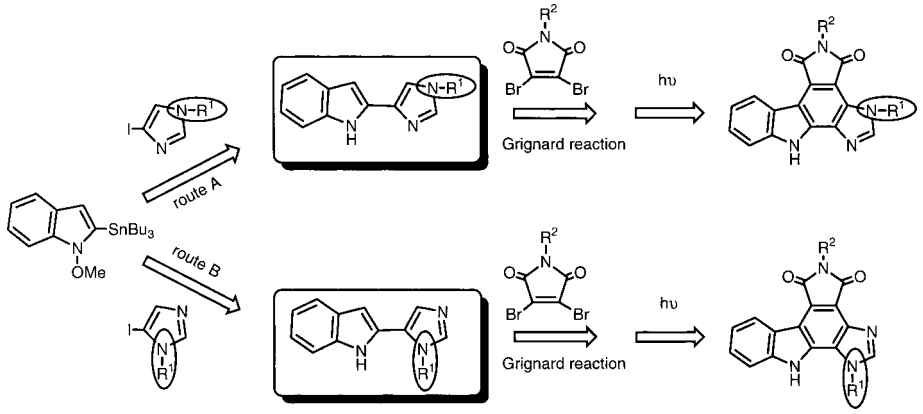

Chart 1

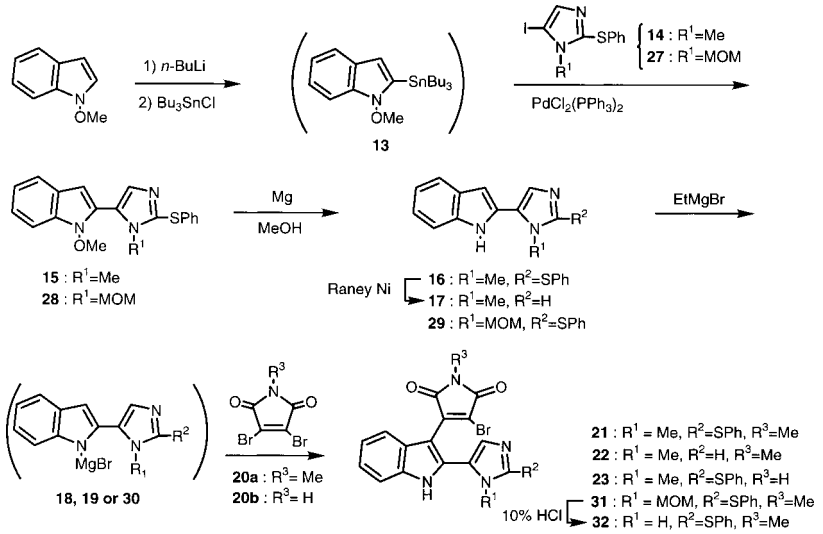

Chart 2

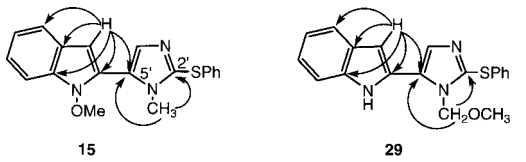

Fig. 2. Long-Range Correlations ($^{1}H \overset{\frown}{} ^{13}C$) in the HMBC Spectrum

(HMBC) study. As shown in Fig. 2, **15** was demonstrated to be the 2,5′-coupling product, since we observed a correlation between the methyl protons and C(2′), as well as C(5′). The HMBC spectrum of **29** was similar to that of **15**, except for the long-range correlations of methylene protons of the methoxymethyl (MOM) group to C(2′) and C(5′).

Removal of the phenylthio group in product **16** was performed by treatment with Raney Ni (W-2) in MeOH to give **17** in 71% yield.

The next stage in the syntheses of 15-methylgranulatimide (**11**) and its analogues was carried out by the reaction of the maleimide **20a** (or **20b**) with the Grignard reagent **18** (or **19**) generated from the coupling product **16** (or **17**) in the manner described previously.[16] The reaction of **16** (or **17**) with ethylmagnesium bromide in anhydrous tetrahydrofuran (THF) gave the MgBr salt **18** (or **19**). The condensation of **18** with the maleimide **20a** (or **20b**) in THF afforded the corresponding synthon condensation product (**21** or **23**) in a yield of 47% or 12%, respectively. Similar condensation reaction of **19** with **20a** afforded **22** in 37% yield.

We carried out the photocyclization of **21**, **22** or **23** according to the reported procedure.[1,5] Thus, when **21**, **22**, or **23** was irradiated with an external light source (60 W, low-pressure mercury lamp) in MeCN, we obtained the granulatimide derivative **24**, **12** or **26** in 85%, 70% or 71% yield, respectively. The structures of **24** and **26** were confirmed by ^{1}H- and ^{13}C-NMR, and high resolution (HR)-MS. The ^{13}C-NMR of **24** indicated that the imidazole C-4′ tertiary carbon signal (131.5 ppm) of **21** had disappeared, and a new quaternary carbon signal had appeared at 135.5 ppm, while the molecular ion peak at *m/z* 412 (M^{+}) was observed in the mass spectrum. Deprotection of the phenylthio group in **24** or **26** was performed with Raney Ni in MeOH (Chart 3). 10,15-Dimethylgranulatimide (**12**) and 15-methylgranulatimide (**11**) were obtained in 33% and 41% yields, respectively. Compound **12** was converted to **11** without isolation of the intermediate, according to Steglich's procedure.[16] The maleimide group was transformed into the anhydride (**25**) by alkaline hydrolysis followed by treatment with acid. Heating

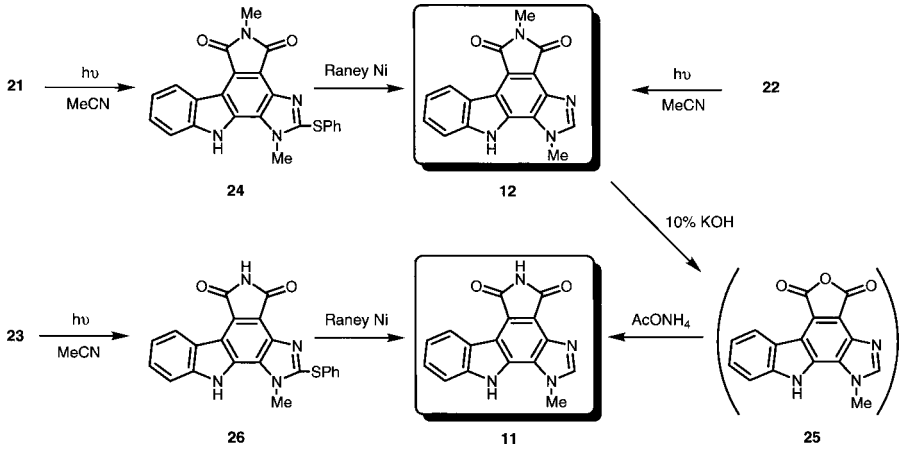

Chart 3

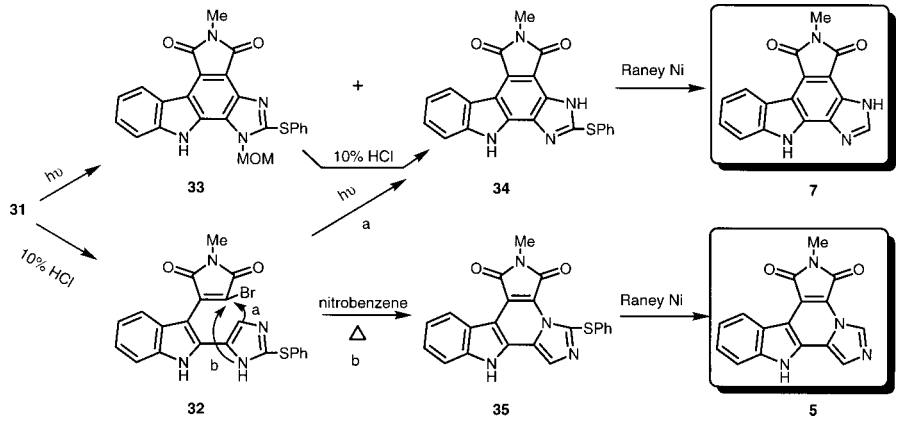

Chart 4

of the crude anhydride with ammonium acetate gave **11** in 17% overall yield. Thus, a straightforward and efficient synthesis of new granulatimide analogues, **11** and **12**, has been developed.

We then turned to the syntheses of 10-methylgranulatimide (**7**) (a tautomer of **10**) and 10-methylisogranulatimide B (**5**). A similar sequence of reactions to that described above for the preparation of **21** provided ready access to the condensation product of **29** with **20a**, *via* Grignard reaction in THF, affording **31** in 50% yield. Subsequent photocyclization reaction afforded a mixture of products. Flash chromatography of this material on silica gel provided **33** and **34** in 50 and 47% yields, respectively. It was considered that the leaving HBr reacted with the cyclization product **33** to remove the *N*-MOM protecting group, affording **34**.

As expected, the ^{1}H-NMR spectrum of **33** is very similar to that of **24**, except that the resonance due to the imidazole *N*-MOM function in **33** (δ 3.27) replaces the corresponding N–Me signal (δ 4.17) of **24**. Furthermore, the ^{1}H–^{1}H and ^{1}H–^{13}C COSY data substantiated the structure of **33**.

The conversion of **33** into **34** by refluxing in 10% HCl was clean and efficient. The phenylthio group of **34** was easily removed in moderate yield by the use of excess Raney Ni in refluxing MeOH to give **7**.

Based on the structural determination of **1** by Berlinck and co-workers,[1] the combination of an intramolecular hydrogen bond stabilizing the HN-17 tautomer and a severe steric interaction destabilizing the HN-15 tautomer may be responsible for suppressing the imidazole NH tautomerization in granulatimide (**1**). Direct comparison of **7** with a previously synthesized sample[6] confirmed the identity of the two in all respects [mp, TLC, MS, IR, ^{1}H- and ^{13}C-NMR spectra], supporting the HN-**17** tautomer structure of **7**.

When the order of the above reactions was changed, the removal of the MOM function from **31** by refluxing with 10% HCl led to **32**, and subsequent photocyclization reaction afforded **34** in 95% yield.

On the other hand, when a solution of **32** in nitrobenzene was heated at 200 °C, thermal cyclization proceeded to give **35** in 62% yield. In the ^{1}H-NMR spectrum of **35**, in comparison with that of **32**, the imidazole NH proton signal (δ 13.07) had disappeared, and the C-4 proton signal (δ 7.73) remained (δ 8.94), while HR-MS showed M^+ at *m/z* 398 and gave a molecular formula of $C_{22}H_{14}N_4O_2S$. Consequently, this product was confirmed to be 10-methyl-17-phenylthioisogranulatimide B (**35**).

Subsequent desulfurization with Raney Ni in MeOH gave isogranulatimide B (**5**) in 45% yield. As expected, the ^{1}H-NMR spectrum of **5** is very similar to that of **4**, except that the maleimide *N*-Me proton signal (δ 3.07) in **5** replaces the corresponding N–H signal of **4**, as reported previously.[5]

As anticipated for this analogues series, **35** and **5** were extremely insoluble in most common organic solvents.

Thus, a new synthetic route to positional analogues of

granulatimide, **11**, **12**, **7**, and to isogranulatimide B (**5**), has been established by the construction of the indole-imidazole (2,5′-) nucleus (route B) based on the same strategy as in the previous synthesis. Studies on the biological activity of these analogues are in progress.

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 JMN-AL 300 and JMN-α 500 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-D 300, JMS-HX 110 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. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under nitrogen atmosphere before use. Low pressure mercury lamp (EL-120) was used for irradiation.

5-(1-Methoxy-1*H*-indol-2-yl)-1-methyl-2-phenylthio-1*H*-imidazole (15) *n*-BuLi in *n*-hexane (1.5 mol/l, 8 ml, 12 mmol) was added to the stirred solution of 1-methoxyindole (1.47 g, 10 mmol) in THF (70 ml) at −78 °C under nitrogen atmosphere, and the mixture was stirred for 30 min. Then, Bu_3SnCl (4.88 g, 15 mmol) in THF (30 ml) was added dropwise, and the mixture was stirred for 30 min. The reaction mixture was allowed to warm to ambient temperature, and stirred additional 30 min. The reaction mixture was extracted with Et_2O, washed with brine, dried and concentrated. The residue was treated with **14** (3.16 g, 10 mmol) and $PdCl_2(PPh_3)_2$ (702 mg, 1 mmol) in toluene (50 ml). The reaction mixture was refluxed overnight. Then, solvent was removed *in vacuo*, and the residue was extracted with AcOEt, washed with brine, dried and concentrated. The residue was subjected with silica gel chromatograph (AcOEt : *n*-hexane = 1 : 4) to give 2.19 g (65%) of **15** as a white powder (from Et_2O–*n*-hexane). mp 73—74 °C. IR (KBr) cm^{-1}: 1577, 1476, 1440, 1365, 1324, 1303, 963, 845, 770, 736, 686. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.70 (3H, s, N–Me), 3.81 (3H, s, O–Me), 6.49 (1H, s, indole H-3), 7.16 (1H, t, J=7.9 Hz, indole Ar–H), 7.20—7.31 (6H, m, indole Ar–H and SPh–H), 7.46 (1H, d, J=8.2 Hz, indole Ar–H), 7.55 (1H, s, imidazole H-4), 7.60 (1H, d, J=7.9 Hz, indole Ar–H). ^{13}C-NMR ($CDCl_3$, 125.65 MHz) δ: 33.0, 64.7, 99.9, 108.6, 120.9, 121.1, 123.3, 123.8, 125.0, 126.1, 126.9, 128.5 (×2), 129.4 (×2), 131.3, 132.9, 134.4, 140.4. LR-MS *m*/*z*: 335 [M$^+$]. HR-MS *m*/*z*: 335.1083 [M$^+$] (Calcd for $C_{19}H_{17}N_3OS$, 335.1091).

5-(1*H*-Indol-2-yl)-1-methyl-2-phenythio-1*H*-imidazole (16) The mixture of **15** (167 mg, 0.5 mmol) and Mg (240 mg, 10 mmol) in MeOH (10 ml) was refluxed for 1 h. Then, the reaction mixture was worked up with aq. NH_4Cl, extracted with AcOEt, washed with brine, dried and concentrated. The residue was purified by silica gel chromatograph (acetone : *n*-hexane = 1 : 2) to give 140 mg (92%) of **16** as a colorless needls (from AcOEt–*n*-hexane). mp 158—159 °C. IR (KBr) cm^{-1}: 3100, 1576, 1476, 1456, 1439, 1371, 1343, 1325, 731. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.79 (3H, s, N–Me), 6.62 (1H, s, indole H-3), 7.10—7.27 (7H, m, indole Ar–H and SPh–H), 7.37 (1H, s, imidazole H-4), 7.40 (1H, d, J=7.9 Hz, indole Ar–H), 7.62 (1H, d, J=7.9 Hz, indole Ar–H), 9.19 (1H, br, indole NH). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ: 33.0, 101.8, 111.1, 120.3, 120.6, 122.9, 126.7, 126.9, 128.4 (×2), 128.5, 128.6, 129.4 (×2), 129.5, 134.3, 136.4, 140.0. LR-MS *m*/*z*: 305 [M$^+$]. HR-MS *m*/*z*: 305.1006 [M$^+$] (Calcd for $C_{18}H_{15}N_3S$, 305.0986).

5-(1*H*-Indol-2-yl)-1-methyl-1*H*-imidazole (17) The mixture of **16** (61 mg, 0.2 mmol) and Raney Ni (dissolved in EtOH) in MeOH (10 ml) was refluxed for 2 h. The reaction mixture was filtered through celite, and the filtrate was concentrated *in vacuo.* The residue was purified by silica gel chromatograph (AcOEt) to give 28 mg (71%) of **17** as a white powder (from MeOH). mp 178—180 °C. IR (KBr) cm^{-1}: 3462, 3102, 1623, 1574, 1515. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.84 (3H, s, N–Me), 6.67 (1H, s, indole H-3), 7.01 (1H, t, J=7.5 Hz, indole Ar–H), 7.11 (1H, t, J=7.5 Hz, indole Ar–H), 7.36 (1H, s, imidazole H-4), 7.38 (1H, d, J=8.1 Hz, indole Ar–H), 7.54 (1H, d, J=7.9 Hz, indole Ar–H), 7.80 (1H, s, imidazole H-2), 11.34 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 32.9, 99.0, 110.9, 119.2, 119.8, 121.5, 125.8, 127.4, 128.4, 136.3, 139.8. LR-MS *m*/*z*: 197 [M$^+$]. HR-MS *m*/*z*: 197.0964 [M$^+$] (Calcd for $C_{12}H_{11}N_3$, 197.2369).

3-Bromo-4-[2-(1-methyl-2-phenylthio-1*H*-imidazol-5-yl)-1*H*-indol-3-yl]-1-methyl-pyrrole-2,5-dione (21) Compound **16** (305 mg, 1 mmol) in THF (7 ml) was added to the solution of EtMgBr, prepared from Mg (48 mg, 2 mmol) and EtBr (436 mg, 4 mmol) in THF (4 ml), and the resulting mixture was stirred at ambient temperature under nitrogen atmosphere for 30 min. Then, **20a** (322 mg, 1.2 mmol) in THF (4 ml) was added dropwise, and the mixture was stirred for 1 h. The reaction mixture was worked up with aq. NH_4Cl, extracted with AcOEt, washed with brine, dried and concentrated. The residue was subjected with silica gel chromatograph (acetone : *n*-hexane = 1 : 4) to give 231 mg (47%) of **21** as an orange needles (from acetone–*n*-hexane). mp 245—247 °C. IR (KBr) cm^{-1}: 1768, 1711, 1626, 1591, 1431, 1379, 738. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.96 (3H, s, CO–N–Me), 3.65 (3H, s, N–Me), 7.15—7.20 (3H, m, indole Ar–H and SPh–H), 7.25—7.30 (3H, m, indole Ar–H, SPh–H and imidazole H-4), 7.37 (2H, t, J=7.6 Hz, SPh–H), 7.52 (1H, d, J=8.2 Hz, indole Ar–H), 7.59 (1H, d, J=7.9 Hz, indole Ar–H), 12.30 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 125.65 MHz) δ: 24.6, 32.5, 103.9, 112.0, 120.5, 121.1, 121.6, 123.1, 125.5, 126.7, 127.3 (×2), 128.0, 129.4 (×2), 129.6, 130.0, 131.5, 134.2, 136.6, 138.0, 165.9, 168.2. LR-MS *m*/*z*: 492 [M$^+$], 494 [M$^+$+2]. HR-MS *m*/*z*: 492.0237 [M$^+$] (Calcd for $C_{23}H_{17}{}^{79}BrN_4O_2S$, 492.0254), 494.0232 [M$^+$+2] (Calcd for $C_{23}H_{17}{}^{81}BrN_4O_2S$, 494.0233).

3-Bromo-4-[2-(1-methyl-1*H*-imidazol-5-yl)-1*H*-indol-3-yl]-1-methyl-pyrrole-2,5-dione (22) EtBr (218 mg, 2 mmol) was added dropwise to the mixture of **17** (98 mg, 0.5 mmol) and Mg (24 mg, 1 mmol) in THF at ambient temperature under nitrogen atmosphere, and the mixture was stirred until Mg was dissolved. Further, this mixture was stirred for 1 h. Then, **20a** (134 mg, 0.5 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred overnight. The reaction mixture was worked up with aq. NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried and concentrated. The residue was purified by silica gel chromatograph (MeOH : benzene = 3 : 20) to give 71 mg (37%) of **22** as a yellow powder. mp 254—256 °C. IR (KBr) cm^{-1}: 3210, 1710, 1694, 1665. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 2.95 (3H, s, CO–N–Me), 3.68 (3H, s, N–Me), 6.99 (1H, s, imidazole H-4), 7.13 (1H, t, J=7.5 Hz, indole Ar–H), 7.24 (1H, t, J=7.5 Hz, indole Ar–H), 7.48 (1H, d, J=8.1 Hz, indole Ar–H), 7.54 (1H, d, J=8.0 Hz, indole Ar–H), 7.79 (1H, s, imidazole H-2), 12.11 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 24.6, 32.0, 103.3, 111.8, 120.3, 120.8, 121.6, 122.8, 123.9, 125.8, 128.9, 130.8, 136.6, 138.5, 140.1, 166.0, 168.2. LR-MS *m*/*z*: 384 [M$^+$], 386 [M$^+$+2]. HR-MS *m*/*z*: 384.0259 [M$^+$] (Calcd for $C_{17}H_{13}{}^{79}BrN_4O_2$, 384.0220), 386.0220 [M$^+$+2] (Calcd for $C_{17}H_{13}{}^{81}BrN_4O_2$, 386.0199).

3-Bromo-4-[2-(1-methyl-2-phenylthio-1*H*-imidazol-5-yl)-1*H*-indol-3-yl]-pyrrole-2,5-dione (23) Compound **16** (76 mg, 0.25 mmol) was treated with EtMgBr, followed by **20b** (63 mg, 0.25 mmol) as described for **21** to give 14 mg (12%) of **23** as an orange powder (from AcOEt–*n*-hexane). mp 162—164 °C. IR (KBr) cm^{-1}: 3372, 3064, 1772, 1722, 1628, 1440, 1331, 1021, 734. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.60 (3H, s, N–Me), 7.13—7.38 (8H, m, indole Ar–H, SPh–H and imidazole H-4), 7.49 (1H, d, J=8.1 Hz, indole Ar–H), 7.56 (1H, d, J=8.1 Hz, indole Ar–H), 11.33 (1H, s, CO–NH–CO), 12.24 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 32.4, 103.8, 112.0, 120.4, 121.0, 122.6, 123.1, 125.5, 126.6, 127.2 (×2), 128.0, 128.1, 129.4 (×2), 131.7, 134.3, 136.6, 138.4, 138.6, 166.7, 169.2. LR-MS *m*/*z*: 478 [M$^+$], 480 [M$^+$+2]. HR-MS *m*/*z*: 478.0093 [M$^+$] (Calcd for $C_{22}H_{15}{}^{79}BrN_4O_2S$, 478.0096), 480.0064 [M$^+$+2] (Calcd for $C_{22}H_{15}{}^{81}BrN_4O_2S$, 480.0075).

10,15-Dimethyl-16-phenylthiogranulatimide (24) The solution of **21** (49 mg, 0.1 mmol) in MeCN (8 ml) was irradiated with low-pressure mercury lamp (60 W) for 12 h. Then, the resulting solid material was corrected to give 35 mg (85%) of **24** as a yellow solid (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3374, 1750, 1692, 1581, 1452, 1378, 1329, 747. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 3.01 (3H, s, CO–N–Me), 4.17 (3H, s, N–Me), 7.30 (1H, t, J=7.9 Hz, indole Ar–H), 7.37 (1H, t, J=7.0 Hz, SPh–H), 7.42 (2H, t, J=7.0 Hz, SPh–H), 7.47 (2H, d, J=7.3 Hz, SPh–H), 7.51 (1H, t, J=8.2 Hz, indole Ar–H), 7.66 (1H, d, J=8.2 Hz, indole Ar–H), 8.89 (1H, d, J=7.9 Hz, indole Ar–H), 12.10 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 125.65 MHz) δ: 23.3, 33.4, 111.7, 112.9, 114.1, 120.3, 120.4, 121.9, 123.8, 126.4, 126.5, 127.9, 128.5, 129.6 (×2), 130.0 (×2), 131.4, 135.5, 140.6, 149.7, 167.2, 169.2. LR-MS *m*/*z*: 412 [M$^+$]. HR-MS *m*/*z*: 412.0983 [M$^+$] (Calcd for $C_{23}H_{16}N_4O_2S$, 412.0993).

15-Methyl-16-phenylthiogranulatimide (26) Compound **23** (59 mg, 0.12 mmol) was irradiated as described for **24** to give 34 mg (71%) of **26** as a yellow solid (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3430, 3202, 1712, 1646, 1471, 1450, 1328, 993, 950, 746. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 4.24 (3H, s, N–Me), 7.31 (1H, t, J=7.9 Hz, indole Ar–H), 7.32—7.53 (6H, m, SPh–H and indole Ar–H), 7.69 (1H, d, J=8.3 Hz, indole Ar–H), 8.97 (1H, d, J=7.9 Hz, indole Ar–H), 10.88 (1H, s, CO–NH–CO),

12.18 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 33.5, 111.8, 114.1, 114.2, 120.4, 120.7, 123.1, 124.0, 126.5, 126.8, 128.0, 128.9, 129.7 (×2), 130.1 (×2), 131.4, 135.6, 140.7, 149.8, 168.7, 170.8. LR-MS *m/z*: 398 [M^+]. HR-MS *m/z*: 398.0821 [M^+] (Calcd for $C_{22}H_{14}N_4O_2S$, 398.1950).

10,15-Dimethylgranulatimide (12) From **24**: Compound **24** (41 mg, 0.1 mmol) was treated with Raney Ni as described for **17** to give 10 mg (33%) of **12** as a yellow powder (from MeOH).

From **22**: Compound **22** (39 mg, 0.1 mmol) was irradiated as described for **24** to give 21 mg (70%) of **12** as yellow powder (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3394, 1743, 1691, 1467, 1385, 1339, 1227, 807, 748, 736. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.07 (3H, s, CO–N–Me), 4.29 (3H, s, N–Me), 7.33 (1H, t, *J*=7.7 Hz, indole Ar–H), 7.52 (1H, t, *J*=7.7 Hz, indole Ar–H), 7.72 (1H, d, *J*=8.1 Hz, indole Ar–H), 8.44 (1H, s, imidazole H-2), 8.98 (1H, d, *J*=7.0 Hz, indole Ar–H), 12.20 (1H, br, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 23.4, 33.3, 111.8, 113.8, 113.9, 120.2, 120.7, 121.6, 123.8, 124.8, 126.4, 129.4, 137.1, 140.7, 147.3, 167.7, 169.6. LR-MS *m/z*: 304 [M^+]. HR-MS *m/z*: 304.0981 [M^+] (Calcd for $C_{17}H_{12}N_4O_2$, 304.0959).

15-Methylgranulatimide (11) From **12**: Compound **12** (30 mg, 0.1 mmol) in 10% aq. KOH (10 ml) was refluxed for 1 h. After cooling, the reaction mixture was acidified with 10% aq. HCl. The resulting yellow precipitate **25** was collected and dried. Then, **25** was heated with $AcONH_4$ (500 mg) at 140 °C for 30 min. After cooling, H_2O was added to the reaction mixture, and the resulting yellow material was collected, dried and purified by silica gel chromatograph (benzene : MeOH=20 : 3) to give 5 mg (17%) of **11** as a yellow powder (from MeOH).

From **26**: Compound **26** (20 mg, 0.05 mmol) was treated with Raney Ni as described for **17** to give 6 mg (41%) of **11** as a yellow powder (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3428, 1720, 1692, 1105, 1071. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 4.33 (3H, s, N–Me), 7.34 (1H, t, *J*=7.5 Hz, indole Ar–H), 7.53 (1H, t, *J*=7.0 Hz, indole Ar–H), 7.73 (1H, d, *J*=8.1 Hz, indole Ar–H), 8.47 (1H, s, imidazole H-2), 9.02 (1H, d, *J*=7.7 Hz, indole Ar–H), 10.85 (1H, s, CO–NH–CO), 12.16 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 37.6, 111.8, 114.7, 115.0, 120.5, 120.9, 121.8, 124.1, 124.5, 126.7, 129.0, 134.5, 140.1, 141.5, 167.3, 167.7. LR-MS *m/z*: 290 [M^+]. HR-MS *m/z*: 290.0781 [M^+] (Calcd for $C_{16}H_{10}N_4O_2$, 290.0802).

5-(1-Methoxy-1*H*-indol-2-yl)-1-(methoxymethyl)-2-phenylthio-1*H*-imidazole (28) *n*-BuLi in *n*-hexane (2.6 mol/l, 4 ml, 11 mmol) was added to the stirred solution of 1-methoxyindole (1.47 g, 10 mmol) in THF (10 ml) at −78 °C under nitrogen atmosphere, and the mixture was strried for 20 min. Then, the solution of Bu_3SnCl (3.9 g, 12 mmol) in THF (6 ml) was slowly added to the mixture, and the reaction mixture was warmed to ambient temperature, and stirred for 30 min. The reaction mixture was worked up with H_2O, extracted with Et_2O, washed with brine, dried and concentrated. The residue was treated with **27** (3.46 g, 10 mmol) and $PdCl_2(PPh_3)_3$ (70 mg, 0.1 mmol) in benzene (30 ml), and the mixture was refluxed under nitrogen atmosphere overnight. The solvent was removed *in vacuo*, and the residue was dissolved in AcOEt. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel chromatograph (AcOEt : *n*-hexane=1 : 10) to give 2.34 g (64%) of **28** as an oil. IR (KBr) cm^{-1}: 2938, 1581, 1443, 1219, 1107, 962, 746. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.27 (3H, s, N–OMe), 3.86 (3H, s, –OMe), 5.52 (2H, s, –CH_2–), 6.74 (1H, s, indole H-3), 7.15 (1H, t, *J*=7.5 Hz, indole Ar–H), 7.24—7.37 (6H, m, indole Ar–H and SPh–H), 7.46 (1H, d, *J*=8.2 Hz, indole Ar–H), 7.61 (1H, d, *J*=7.9 Hz, indole Ar–H), 7.66 (1H, s, imidazole H-4). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ: 56.2, 64.7, 75.4, 100.0, 108.5, 120.8, 121.2, 123.3, 123.8, 124.5, 125.8, 127.3, 129.1 (×2), 129.3 (×2), 131.4, 133.0, 133.9, 141.4. LR-MS *m/z*: 365 [M^+]. HR-MS *m/z*: 365.1197 [M^+] (Calcd for $C_{20}H_{19}N_3O_2S$, 365.1198).

5-(1*H*-Indol-2-yl)-1-(methoxymethyl)-2-phenylthio-1*H*-imidazole (29) The mixture of **28** (164 mg, 0.45 mmol) and Mg (216 mg, 9 mmol) in MeOH (10 ml) was refluxed under nitrogen atmosphere for 1 h. The reaction mixture was worked up with aq. NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried and concentrated. The residue was purified by silica gel chromatograph (AcOEt : *n*-hexane=1 : 2) to give 114 mg (76%) of **29** as a colorless needles (from AcOEt–*n*-hexane). mp 122—123 °C. IR (KBr) cm^{-1}: 3166, 1577, 1455, 1376, 1296, 1108, 914, 801, 736, 682. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.42 (3H, s, O–Me), 5.54 (2H, s, –CH_2–), 6.80 (1H, s, indole H-3), 7.13 (1H, t, *J*=7.9 Hz, indole Ar–H), 7.20—7.29 (6H, m, indole Ar–H and SPh–H), 7.40 (1H, d, *J*=8.2 Hz, indole Ar–H), 7.53 (1H, s, imidazole H-4), 7.63 (1H, d, *J*=7.9 Hz, indole Ar–H), 9.41 (1H, s, indole NH). ^{13}C-NMR ($CDCl_3$, 125.65 MHz) δ: 56.5, 75.4, 102.6, 111.2, 120.4, 120.7, 122.7, 126.5, 127.2, 128.4, 128.5 (×2), 129.4 (×2), 129.7, 130.2, 134.2, 136.7, 140.0. LR-MS *m/z*: 335 [M^+]. HR-MS *m/z*: 335.1088 [M^+] (Calcd for $C_{19}H_{17}N_3OS$, 335.1088).

3-Bromo-4-[2-(1-methoxymethyl-2-phenylthio-1*H*-imidazol-5-yl)-1*H*-indol-3-yl]-1-methyl-pyrrole-2,5-dione (31) Compound **29** was treated with EtMgBr, followed by **20a** (807 mg, 3 mmol) as described for **21** to give 788 mg (50%) of **31** as an orange solid (from AcOEt–*n*-hexane). mp 145—147 °C. IR (KBr) cm^{-1}: 3420, 1768, 1709, 1628, 1435, 1378, 1102, 981, 732. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.10 (3H, s, N–Me), 3.49 (3H, s, O–Me), 5.51 (2H, s, –CH_2–), 7.19 (1H, s, imidazole H-4), 7.22—7.35 (7H, m, indole Ar–H and SPh–H), 7.47 (1H, d, *J*=7.9 Hz, indole Ar–H), 7.61 (1H, d, *J*=8.1 Hz, indole Ar–H), 9.84 (1H, s, indole NH). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ: 24.9, 56.8, 75.5, 104.3, 111.9, 121.2, 121.5, 122.9, 124.0, 125.8, 127.2, 127.7, 128.1 (×3), 129.4 (×2), 133.1, 133.9, 136.4, 138.7, 140.9, 165.9, 168.2. LR-MS *m/z*: 522 [M^+], 524 [M^++2]. HR-MS *m/z*: 522.0361 [M^+] (Calcd for $C_{24}H_{19}{}^{79}BrN_4O_3S$, 522.0357), 524.0296 [$M^+$+2] (Calcd for $C_{24}H_{19}{}^{81}BrN_4O_3S$, 524.0336).

3-Bromo-4-[2-(2-phenylthio-1*H*-imidazol-5-yl)-1*H*-indol-3-yl]-1-methyl-pyrrole-2,5-dione (32) The mixture of **31** (261 mg, 0.5 mmol) and 10% aq. HCl (10 ml) in MeOH (6 ml) was refluxed for 3 h. After cooling, the reaction mixture was basified with aq. $NaHCO_3$, and extracted with CH_2Cl_2, washed with brine, dried and concentrated. The residue was purified by silica gel chromatograph (acetone : *n*-hexane=1 : 2) to give 228 mg (95%) of **32** as a red powder (from $CHCl_3$–*n*-hexane). mp 138—140 °C. IR (KBr) cm^{-1}: 3346, 1768, 1707, 1628, 1434, 1379, 988, 841, 807, 730. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 2.95 (3H, s, N–Me), 7.05 (1H, t, *J*=7.5 Hz, indole Ar–H), 7.15 (1H, t, *J*=7.5 Hz, indole Ar–H), 7.20—7.25 (3H, m, SPh–H), 7.30—7.36 (2H, m, SPh–H), 7.39 (1H, d, *J*=7.7 Hz, indole Ar–H), 7.45 (1H, d, *J*=7.9 Hz, indole Ar–H), 7.73 (1H, s, imidazole H-4), 11.99 (1H, s, indole NH), 13.07 (1H, br, imidazole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 24.5, 98.2, 111.7, 119.9, 121.9, 126.5, 127.5 (×2), 129.3 (×2), 133.5, 135.0, 135.6, 135.9, 139.9, 166.2, 168.3. FAB-MS *m/z*: 479 [M^++H], 481 [M^++H+2]. HR-FAB-MS *m/z*: 479.0178 [M^++H] (Calcd for $C_{22}H_{16}{}^{79}BrN_4O_2S$, 479.0174), 481.0152 [$M^+$+H+2] (Calcd for $C_{22}H_{16}{}^{81}BrN_4O_2S$, 481.0153).

15-Methoxymethyl-10-methyl-16-phenylthiogranulatimide (33) The solution of **31** (52 mg, 0.1 mmol) in MeCN (6 ml) was irradiated with low-pressure mercury lamp (60 W) for 17 h. The reaction mixture was concentrated, and the residue was purified by silica gel chromatograph ($CHCl_3$) to give 22 mg (50%) of **33** as a yellow powder (from MeOH) and 19 mg (47%) of **34** as a yellow powder (from acetone–*n*-hexane). mp 212—214 °C. IR (KBr) cm^{-1}: 3344, 1748, 1695, 1459, 1434, 1379, 1086, 1060, 805, 736. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.05 (3H, s, N–Me), 3.27 (3H, s, O–Me), 6.19 (2H, s, –CH_2–), 7.26 (1H, t, *J*=7.5 Hz, indole Ar–H), 7.42—7.51 (4H, m, SPh–H and indole Ar–H), 7.54 (1H, d, *J*=8.1 Hz, indole Ar–H), 7.67 (2H, dd, *J*=2.0, 7.8 Hz, SPh–H), 8.85 (1H, d, *J*=7.9 Hz, indole Ar–H), 12.53 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 23.6, 55.2, 76.6, 107.4, 111.7, 114.1, 120.2, 120.9, 122.7, 124.1, 126.7, 128.8, 129.6 (×2), 129.8, 130.1, 132.31 (×2), 132.33, 134.3, 140.9, 152.3, 167.6, 168.8. LR-MS *m/z*: 442 [M^+]. HR-MS *m/z*: 442.1118 [M^+] (Calcd for $C_{24}H_{18}N_4O_3S$, 442.1095).

10-Methyl-16-phenylthiogranulatimide (34) From **33**: The suspension of **33** (44 mg, 0.1 mmol) in 10% aq. HCl (6 ml) was heated at 100 °C for 4 h. After cooling, the reaction mixture was basified with aq. $NaHCO_3$, and then the resulting solid material was corrected to give 38 mg (95%) of **34** as a yellow powder (from acetone–*n*-hexane).

From **32**: Compound **32** (47 mg, 0.1 mmol) was irradiated as described for **24** to give 38 mg (95%) of **34** as a yellow powder (from acetone–*n*-hexane). mp 275—277 °C. IR (KBr) cm^{-1}: 3390, 3290, 1740, 1679, 1598, 1467, 1367, 1325, 1236, 1066, 984, 737, 638. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.09 (3H, s, N–Me), 7.26 (1H, dt, *J*=7.5, 1.1 Hz, indole Ar–H), 7.39—7.49 (4H, m, SPh–H and indole Ar–H), 7.55 (1H, d, *J*=8.1 Hz, indole Ar–H), 7.60—7.64 (2H, m, SPh–H), 8.85 (1H, d, *J*=7.9 Hz, indole Ar–H), 12.43 (1H, s, indole NH), 13.98 (1H, br, imidazole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 23.5, 111.6, 113.6, 120.1, 121.1, 121.4, 123.7, 126.3, 128.5, 129.5 (×2), 130.6, 132.1 (×2), 140.6, 151.0, 167.8, 169.4. LR-MS *m/z*: 398 [M^+]. HR-MS *m/z*: 398.0816 [M^+] (Calcd for $C_{22}H_{14}N_4O_2S$, 398.0834).

10-Methylgranulatimide (7)[6] Compound **34** (20 mg, 0.05 mmol) was treated with Raney Ni as described for **17** to give 8 mg (55%) of **7** as a yellow powder (from MeOH).

10-Methyl-17-phenylthioisogranulatimide B (35) The solution of **32** (96 mg, 0.2 mmol) in nitrobenzene (2 ml) was heated at 200 °C for 3 h. After cooling, the reaction mixture was purified by silica gel chromatograph (AcOEt : *n*-hexane=1 : 4) to give 49 mg (62%) of **35** as a red powder (from MeOH). mp 280—282 °C. IR (KBr) cm^{-1}: 3438, 1762, 1701, 1522, 1438, 1389, 1257, 1079, 977, 802, 728. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.12

(3H, s, N–Me), 7.15—7.27 (5H, m, SPh–H), 7.32 (1H, t, J=7.5 Hz, indole Ar–H), 7.44 (1H, t, J=7.5 Hz, indole Ar–H), 7.82 (1H, d, J=8.1 Hz, indole Ar–H), 8.55 (1H, d, J=7.7 Hz, indole Ar–H), 8.94 (1H, s, imidazole H-4), 12.11 (1H, s, indole NH). ^{13}C-NMR (DMSO-d_6, 75.45 MHz) δ: 23.2, 106.5, 112.9, 118.9, 120.4, 121.3, 121.9, 122.0, 125.1, 125.4, 125.7, 127.1 (×2), 128.6 (×2), 129.3, 129.4, 130.4, 136.8, 139.2, 163.7, 166.9. LR-MS m/z: 398 [M^+]. HR-MS m/z: 398.0874 [M^+] (Calcd for $C_{22}H_{14}N_4O_2S$, 398.0834).

10-Methylisogranulatimide B (5) Compound **35** (15 mg, 0.038 mmol) was treated with Raney Ni as described for **17** to give 5 mg (45%) of **5** as a red powder (from MeOH). mp >300 °C. IR (KBr) cm^{-1}: 3442, 3392, 3332, 2922, 2858, 1758, 1706, 1652, 1526, 1435, 1372, 1253, 1104, 1070, 934, 747. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.07 (3H, s, N–Me), 7.30 (1H, t, J=7.5 Hz, indole Ar–H), 7.41 (1H, t, J=7.5 Hz, indole Ar–H), 7.62 (1H, d, J=8.3 Hz, indole Ar–H), 7.89 (1H, s, imidazole H-2), 8.47 (1H, d, J=8.1 Hz, indole Ar–H), 8.82 (1H, s, imidazole H-4), 12.88 (1H, br, indole NH). LR-MS m/z: 290 [M^+]. HR-MS m/z: 290.0815 [M^+] (Calcd for $C_{16}H_{10}N_4O_2$, 290.0804).

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