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Graphical Abstract

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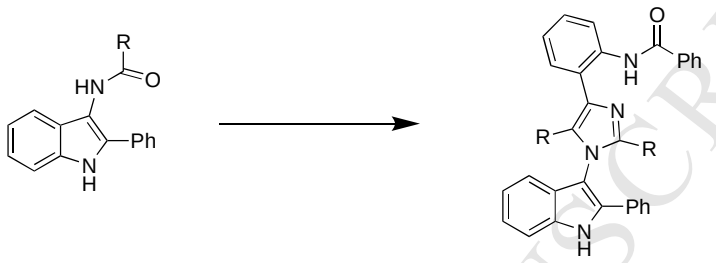

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Unusual formation of novel highly substituted *N*-(3-indolyl)-imidazoles

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Abstract— . © 2018 Elsevier Science. All rights reserved Treatment of 3-amidoindoles with phosphoryl chloride leads to a dimerization of the resulting iminochlorides to form tetrasubstituted imidazoles in moderate yield. One indole ring undergoes ring-opening to allow the formation of the imidazole ring. This strategically simple synthesis considerably expands the scope of delivering *N*-indolylimidazoles.

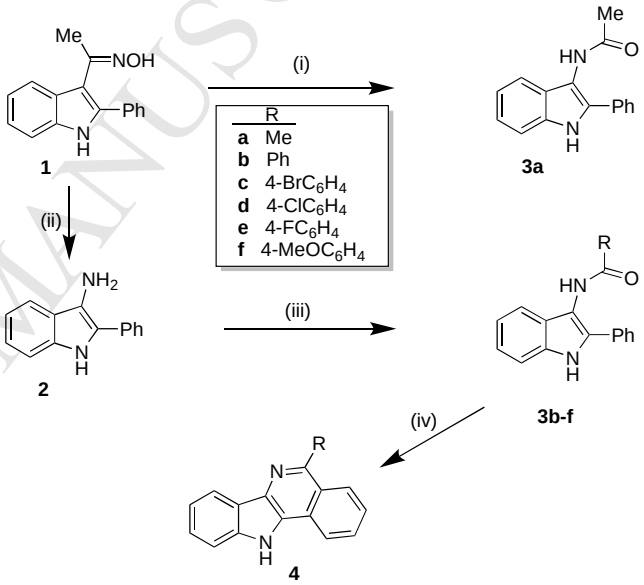
Keywords: indoles, 3-aminoindoles, 3-amidoindoles, imidazoles, *N*-indolylimidazoles

1. Introduction

Imidazoles are commonly synthesized from 1,2-dicarbonyl compounds and aldehydes in the presence of ammonia.[1,2] Tetraphenyl imidazoles can be synthesized from benzoin, aniline and benzaldehydes,[3] or from benzil, benzonitrile and aniline or related primary amines.[4-6]

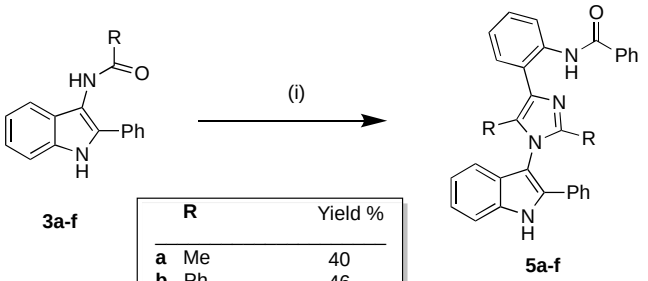
Although highly substituted imidazoles are well known in the literature, compounds linking indole and imidazole rings are not common. However, the indole-imidazole structure features in some bioactive alkaloids. Granulatimide and isogranulatimide, isolated from the Brazilian ascidian *Didemmum granulatum*,[7-9] are strong G2 checkpoint inhibitors,[10] and have been synthesized.[11] These link the indole through C2 to the imidazole C4 and N1 respectively. The bicyclic peptide moroidin, which shows potent inhibitory activity on tubulin assembly, has been isolated from the seeds of *Celosia argentea*[12] and the leaves of *Laportea moroides*,[13,14] and has also been synthesized.[15] The linkage in this case is also from the indole C2 to the imidazole N1. The nortopsentins and topsentins, isolated from deep-sea sponges, and which show potent anti-cancer activity, contain indole rings attached through their C3 positions to C2 and C4 positions of an imidazole ring. For example, topsentin A has been isolated from *Topsentia genitrix*[16] and nortopsentin A from *Spongosorites ruetzleri*.[17] The nortopsentins have also been synthesized.[18]

We now describe a completely new and unusual synthesis of *N*-indolylimidazoles. We have previously reported the synthesis of a range of 3-amido-2-arylindoles **3** from 2-phenylindole-3-acetoxime **1**[19]. The oxime **1** directly underwent the Beckmann rearrangement to give the 3-amidoindole **3a**. It was also converted by treatment with concentrated sulfuric acid into 3-amino-2-phenylindole **2**[2], which was then acylated with a range of benzoyl chlorides to yield the 3-amidoindoles **3b-f**. These amides were subsequently converted into a range of indoloquinolines **4**, by heating them overnight with P_2O_5 in toluene (Scheme 1).



Scheme 1. Conditions: (i) conc. H_2SO_4, MeCN, 64%; (ii) conc. H_2SO_4, 60%; (iii) RCOCl, 18-51%; (iv) P_2O_5, 26-67%.

During the course of the investigation of this Bischler-Napieralski cyclisation, the amides **3a-f** were heated in phosphoryl chloride for 3-5 h and unexpectedly gave the imidazoles **5a-f** in moderate yields (Scheme 2).



	R	Yield %
a	Me	40
b	Ph	46
c	4-BrC_6H_4	31
d	4-ClC_6H_4	52
e	4-FC_6H_4	44
f	4-MeOC_6H_4	52

Scheme 2. Conditions: (i) $POCl_3$, 110 ˚C, 3 h, 31-52%.

2. Results and Discussion

2.1. Synthesis of indolylimidazoles

The 3-amidoindoles **3a-f** were dissolved in phosphoryl chloride and heated under reflux for several hours and the red solutions were neutralised with sodium hydroxide. The yellow needle-like products were purified by chromatography and recrystallisation. The ^{1}H NMR spectrum of compound **5b** showed the amide NH signal at δ 11.76 ppm, which indicated that the amide group was different from that of the 3-amidoindole **3b**. Also, the integration of the protons in the aromatic region from 6.77-8.62 ppm was doubled, and indicated the presence of four aryl rings. The indolo-imidazole structure was confirmed by an X-ray crystal structure of compound **5b** (Figure 1).

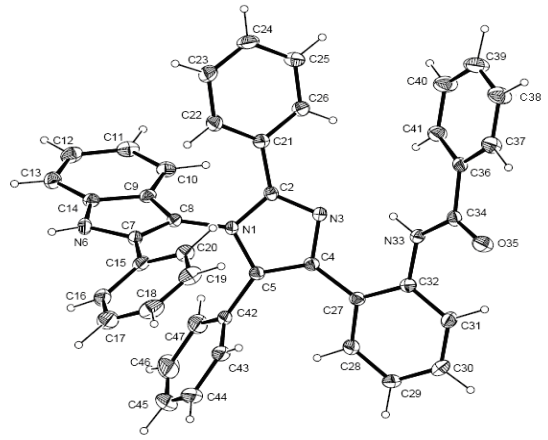
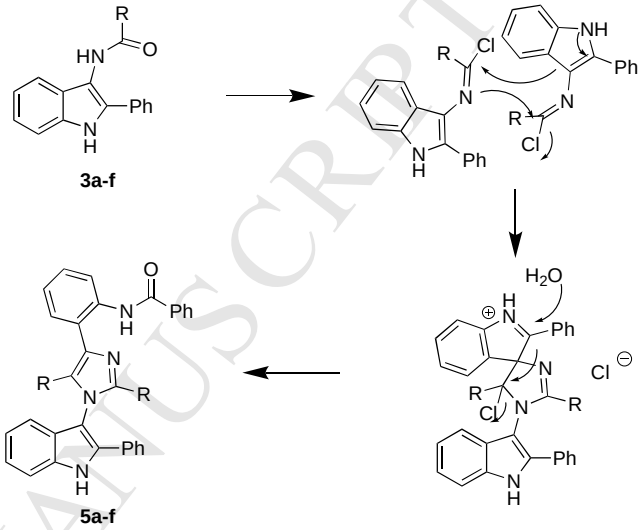


Figure 1. ORTEP diagram of the crystal structure of compound **5b**.

The new imidazole ring is fully substituted by an initial indole substituent at N1, the aryl amide at C4, and the two initial benzamide arene rings at C2 and C5. Also, while one of the 2-phenylindole substituents remains intact, the other indole ring has been opened to give an aryl amide.

A feasible mechanism of the reaction could involve an intermolecular coupling of two imino chlorides. The reaction of 3-amidoindoles with phosphoryl chloride would be expected to give imino chlorides, which could undergo dimerisation to form the imidazole ring (Scheme 3). Formation of the aromatic imidazole ring would be favoured and would result in the formation of a 2-benzamido substituent at the imidazole C4 position.



Scheme 3: Possible mechanism for the formation of imidazoles **5a-f**.

This simply-performed reaction represents a completely new synthetic approach to imidazoles. Although it does not allow wide scope, it should be adaptable to include amides derived from indoles with 2-substituents other than phenyl, and also with substituents in positions C4 to C7. It inevitably leads to tetrasubstituted imidazoles and is probably limited to amidoindoles.

Preliminary biological testing for the new indole-imidazoles **5a-f** indicates that they show antibacterial activity against *Staphylococcus aureus* and weak activity against *Escherichia coli*.

3. Conclusions

Treatment of 3-amidoindoles with phosphoryl chloride leads to a dimerization of the resulting iminochlorides to form tetrasubstituted imidazoles in moderate yield. One indole ring undergoes ring-opening to allow the formation of the imidazole ring. This strategically simple synthesis considerably expands the scope of delivering *N*-indolylimidazoles.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. 1H and 13C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet-visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. Column chromatography was carried out using Merck 230-400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 60GF254.

Crystallographic data for the structure of compound **5b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 769425.

4.2. Synthesis of 3-amidoindoles

The 3-amidoindoles **5a-f** have been reported in our previous work.[1]

4.3.1. Synthesis of N-(3-indolyl)-imidazoles

4.3.2. General preparative method

The 3-amidoindole was dissolved in phosphoryl chloride and heated at 110-120 ^{o}C for 3-5 h. The resulting red solution was poured into ice water, and neutralized with 2M sodium hydroxide solution. The mixture was allowed to cool to room temperature with thorough stirring, then extracted with ethyl acetate and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by column chromatography and eluted with dichloromethane/light petroleum (70:30) to give the indolylimidazole. Recrystallization from ethanol resulted in yellow needles.

4.3.3. *N*-(2-(2,5-Dimethyl-1-(2-phenyl-1*H*-indol-3-yl)-1*H*-imidazol-4-yl)phenyl) benzamide (5a)

This was prepared from indole-3-amide **3a** (0.1 g, 0.4 mmol) in phosphoryl chloride (3 mL) during 3 h to yield indolylimidazole **5a** (0.04 g, 40%) as a brown solid. mp 268-270 °C. (found: C, 78.9; H, 5.5; N, 11.2. $C_{32}H_{26}N_4O$ 0.25 H_2O requires C, 78.9; H, 5.6; N, 11.5 %.) ν_{max} (KBr): 3185, 3059, 1649, 1618, 1584, 1545, 1521, 1455, 1399, 1327, 1262, 744, 693 cm^{-1}. λ_{max} (MeOH): 202 nm (ε 161,300 cm^{-1}M^{-1}), 204 (160,700), 302 (44,000). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 2.07 (3H, s, Me), 2.48 (3H, s, Me), 7.11-7.19 (2H, m, ArH), 7.24-7.34 (8H, m, ArH), 7.47-7.56 (5H, m, ArH), 8.01 (2H, d, *J* 7.8 Hz, ArH), 8.62 (1H, d, *J* 7.8 Hz, ArH), 12.09 (1H, s, NHCO), 12.79 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 10.7 (Me), 13.1 (Me), 111.6 (Ar-CH), 117.6 (Ar-CH), 121.5 (Ar-CH), 123.2 (Ar-C), 123.7 (Ar-CH), 125.5 (3 x Ar-CH), 125.6 (Ar-C), 127.0 (Ar-C), 127.5 (3 x Ar-CH), 128.1 (Ar-C), 128.3 (4 x Ar-CH), 128.7 (Ar-C), 129.4 (3 x Ar-CH), 129.7 (Ar-C), 131.2 (Ar-CH), 133.1 (Ar-C), 134.4 (Ar-C), 135.7 (Ar-C), 136.9 (Ar-C), 144.4 (C=N), 165.4 (CO). HRMS (ESI$^+$): found m/z 483.2179, [M+H$^+$], $C_{32}H_{27}N_4O$ requires 483.2185).

4.3.4. *N*-(2-(2,5-Diphenyl-1-(2-phenyl-1*H*-indol-3-yl)-1*H*-imidazol-4-yl)phenyl) benzamide (5b)

This was prepared from 3-benzamido indole **3b** (0.1 g, 0.6 mmol) in phosphoryl chloride (3mL) during 3 h to yield indolylimidazole **5b** (0.09 g, 46%) as a white solid. mp 287-289 °C. (found: C, 81.8; H, 5.2; N, 9.0. $C_{42}H_{30}N_4$ O 0.5 H_2O requires C, 81.9; H, 5.1; N, 9.0 %.) ν_{max} (KBr): 3225, 1647, 1585, 1538, 1491, 1471, 1451, 1326, 1260, 744, 696 cm^{-1}. λ_{max} (MeOH): 226 nm (ε 82,700 cm^{-1}M^{-1}), 300 (33,800). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 6.78 (1H, t, *J* 7.4 Hz, ArH), 6.83-7.33 (20H, m, ArH), 7.34-7.38 (4H, m, ArH), 7.49 (1H, t, *J* 7.4 Hz, ArH), 7.98 (2H, d, *J* 7.4 Hz, ArH), 8.59 (1H, d, *J* 7.4 Hz, ArH), 11.76 (1H, s, NHCO), 12.89 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 109.2 (Ar-C), 112.3 (Ar-CH), 117.5 (Ar-CH), 121.2 (Ar-CH), 121.3 (Ar-CH), 122.0 (Ar-C), 123.2 (Ar-CH), 125.9 (2 x Ar-CH), 126.1 (Ar-C), 127.5 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.9 (Ar-CH), 128.7 (8 x Ar-CH), 128.8 (Ar-CH), 129.0 (2 x Ar-CH), 129.3 (2 x Ar-CH), 129.8 (Ar-C), 130.1 (2 x Ar-C), 130.4 (2 x Ar-CH), 132.1 (Ar-CH), 133.6 (2 x Ar-C), 134.5 (Ar-C), 135.4 (Ar-C), 136.5 (Ar-C), 137.2 (Ar-C), 146.7 (C=N), 164.7 (CO). HRMS (ESI$^+$): found m/z 607.2493, [M+H$^+$], $C_{42}H_{31}N_4O$ requires 607.2498).

4.3.5. *N*-(2-(2,5-bis(4-Bromophenyl)-1-(2-phenyl-1*H*-indol-3-yl)-1*H*-imidazol-4-yl) phenyl)benzamide (5c)

This was prepared from 3-benzamidoindole **3c** (0.1 g, 0.25 mmol) in phosphoryl chloride (3 mL) during 3.5 h to yield indolylimidazole **5c** (0.03 g, 31%) as a yellow solid. mp 165-168 °C. (found: C, 65.4; H, 4.2; N, 7.0. $C_{42}H_{28}Br_2N_4O$ 0.5 H_2O requires C, 65.2; H, 3.8; N, 7.2 %.) ν_{max} (KBr): 3413, 3255, 1656, 1614, 1585, 1537, 1487, 1455, 1314, 1260, 1071, 1010, 966, 826, 745, 705, 693 cm^{-1}. λ_{max} (MeOH): 229 nm (ε 92,400 cm^{-1}M^{-1}), 301 (48,300). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 6.88-6.93 (2H, m, ArH), 6.98-7.09 (5H, m, ArH), 7.10-7.33 (10H, m, ArH), 7.40 (4H, d, *J* 8.4 Hz, ArH), 7.51 (1H, t, *J* 7.6 Hz, ArH), 7.95 (2H, d, *J* 7.6 Hz, ArH), 8.50 (1H, d, *J* 7.6 Hz, ArH), 11.87 (1H, s, NHCO), 12.40 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 108.8 (Ar-C), 112.5 (Ar-CH),

117.4 (Ar-CH), 121.3 (Ar-CH), 121.8 (Ar-CH), 122.4 (Ar-C), 123.5 (Ar-CH), 123.6 (Ar-CH), 125.8 (Ar-C), 125.9 (2 x Ar-CH), 127.5 (2 x Ar-CH), 128.2 (Ar-CH), 128.5 (Ar-C), 128.7 (Ar-CH), 128.8 (Ar-C), 128.9 (2 x Ar-CH), 129.0 (Ar-C), 129.1 (Ar-C), 129.2 (Ar-CH), 129.3 (2 x Ar-CH), 129.4 (2 x Ar-CH), 131.6 (2 x Ar-CH), 131.7 (2 x Ar-CH), 132.2 (Ar-CH), 132.3 (2 x Ar-CH), 133.5 (Ar-C), 133.7 (Ar-C), 134.2 (Ar-C), 134.5 (Ar-C), 135.4 (Ar-C), 137.1 (Ar-C), 137.3 (Ar-C), 145.9 (C=N), 165.1 (CO). HRMS (ESI^+): found m/z 763.0703, $[M+H^+]$, $C_{42}H_{29}Br_2N_4O$ requires 763.0708).

4.3.6. *N*-(2-(2,5-bis(4-Chlorophenyl)-1-(2-phenyl-1*H*-indol-3-yl)-1*H*-imidazol-4-yl) phenyl)benzamide (5d)

This was prepared from 3-benzamidoindole **3d** (0.1 g, 0.29 mmol) in phosphoryl chloride (3 mL) during 3.5 h to yield indolylimidazole **5d** (0.05 g, 52%) as a yellow solid. mp 166-169 °C. (found: C, 74.9; H, 4.4; N, 8.2. $C_{42}H_{28}Cl_2N_4O$ requires C, 74.7; H, 4.2; N, 8.3 %.) ν_{max} (KBr): 3260, 3060, 1655, 1617, 1586, 1537, 1489, 1451, 1410, 1313, 1259, 1091, 1014, 965, 830, 764, 745, 705, 693 cm^{-1}. λ_{max} (MeOH): 229 nm (ε 100,600 $cm^{-1}M^{-1}$), 300 (63,700). ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 6.89-7.03 (5H, m, ArH), 7.09-7.19 (5H, m, ArH), 7.21-7.33 (11H, m, ArH), 7.40 (1H, d, *J* 8.1 Hz, ArH), 7.52 (1H, t, *J* 7.3 Hz, ArH), 7.95 (2H, d, *J* 8.1 Hz, ArH), 8.51 (1H, d, *J* 8.1 Hz, ArH), 11.84 (1H, s, NHCO), 12.42 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 108.7 (Ar-C), 112.5 (Ar-CH), 117.4 (Ar-CH), 121.3 (Ar-CH), 121.7 (Ar-CH), 122.3 (Ar-C), 123.5 (Ar-CH), 123.6 (Ar-CH), 125.7 (Ar-C), 126.0 (2 x Ar-CH), 127.5 (3 x Ar-CH), 128.2 (Ar-CH), 128.6 (Ar-C), 128.7 (Ar-CH), 128.8 (4 x Ar-C), 128.9 (3 x Ar-CH), 129.2 (3 x Ar-CH), 129.4 (2 x Ar-CH), 129.9 (Ar-C), 132.2 (2 x Ar-CH), 132.4 (Ar-C), 133.7 (Ar-C), 134.1 (Ar-C), 134.6 (Ar-C), 135.3 (Ar-C), 137.2 (Ar-C), 137.2 (Ar-C), 145.9 (C=N), 164.7 (CO). HRMS (ESI^+): found m/z 675.1713, $[M+H^+]$, $C_{42}H_{29}Cl_2N_4O$ requires 675.1718).

4.3.7. *N*-(2-(2,5-bis(4-Fluorophenyl)-1-(2-phenyl-1*H*-indol-3-yl)-1*H*-imidazol-4-yl) phenyl)benzamide (5e)

This was prepared from 3-benzamidoindole **3e** (0.07 g, 0.2 mmol) in phosphoryl chloride (3 mL) during 5 h to yield indolylimidazole **5e** (0.03 g, 44%) as a yellow solid. mp 267-269 °C. (found: C, 75.6; H, 4.3; N, 8.4. $C_{42}H_{28}F_2N_4O$ 1.25 H_2O requires C, 75.8; H, 4.6; N, 8.4 %.) ν_{max} (KBr): 3416, 3278, 1661, 1586, 1523, 1506, 1493, 1451, 1384, 1322, 1232, 1158, 837, 746, 693 cm^{-1}. λ_{max} (MeOH): 229 nm (ε 100,000 $cm^{-1}M^{-1}$), 298 (54,100). ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 6.84-6.95 (3H, m, ArH), 6.98-7.05 (6H, m, ArH), 7.07-7.17 (3H, m, ArH), 7.22-7.40 (10H, m, ArH), 7.51 (1H, t, *J* 7.1 Hz, ArH), 7.96 (2H, d, *J* 8.0 Hz, ArH), 8.56 (1H, d, *J* 8.0 Hz, ArH), 11.81 (1H, s, NHCO), 12.49 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 109.0 (Ar-C), 112.6 (Ar-CH), 115.8 (2 x Ar-CH), 116.1 (2 x Ar-CH), 117.6 (Ar-CH), 121.4 (Ar-CH), 121.7 (Ar-CH), 122.2 (Ar-C), 123.6 (2 x Ar-CH), 125.8 (Ar-C), 126.0 (Ar-C), 126.1 (2 x Ar-CH), 126.5 (Ar-C), 126.6 (Ar-C), 126.7 (Ar-C), 127.6 (2 x Ar-CH), 128.2 (Ar-CH), 128.9 (Ar-CH), 129.1 (3 x Ar-CH), 129.5 (2 x Ar-CH), 129.9 (Ar-C), 130.1 (Ar-CH), 130.2 (Ar-CH), 132.4 (Ar-CH), 132.5 (Ar-C), 132.8 (Ar-CH), 132.9 (Ar-CH), 133.8 (Ar-C), 134.7 (Ar-C), 135.5 (Ar-C), 136.9 (Ar-C), 137.4 (Ar-C), 146.1 (C=N), 164.9 (CO). HRMS (ESI^+): found m/z 643.2304, $[M+H^+]$, $C_{42}H_{29}F_2N_4O$ requires 643.2309).

4.3.8. *N*-(2-(2,5-bis(4-Methoxyphenyl)-1-(2-phenyl-1*H*-indol-3-yl)-1*H*-imidazol-4-yl)phenyl)benzamide (5f)

This was prepared from 3-benzamido indole **3f** (0.1 g, 0.3 mmol) in phosphoryl chloride (3 mL) during 5 h to yield indolylimidazole **5f** (0.05 g, 52%) as a yellow solid. mp 175-178 °C. (found: C, 79.0; H, 5.4; N, 8.2. $C_{44}H_{34}N_4O_3$ 0.25 H_2O requires C, 78.7; H, 5.2; N, 8.3 %.) ν_{max} (KBr): 3255, 3059, 1654, 1613, 1585, 1526, 1507, 1494, 1452, 1386, 1313, 1293, 1250, 1175, 833, 746, 706 cm^{-1}. λ_{max} (MeOH): 229 nm (ε 61,000 $cm^{-1}M^{-1}$), 284 (21,900). ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 3.59 (3H, s, OMe), 3.66 (3H, s, OMe), 6.20 (2H, d, *J* 8.4 Hz, ArH), 6.73 (2H, d, *J* 8.4 Hz, ArH), 6.79-6.90 (3H, m, ArH), 6.99-7.04 (2H, m, ArH), 7.12-7.34 (12H, m, ArH), 7.39 (1H, d, *J* 8.4 Hz, ArH), 7.52 (1H, t, *J* 8.4 Hz, ArH), 7.99 (2H, d, *J* 8.4 Hz, ArH), 8.59 (1H, d, *J* 8.4 Hz, ArH), 11.72 (1H, s, NHCO), 12.92 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 55.3 (OCH_3), 55.5 (OCH_3), 109.5, 112.4 (Ar-CH), 114.1 (4 x Ar-CH), 117.5 (Ar-CH), 121.2 (2 x Ar-CH), 122.1 (Ar-C), 122.2 (Ar-C), 122.3 (Ar-C), 123.2 (Ar-CH), 123.3 (Ar-CH), 125.9 (2 x Ar-CH), 126.4 (Ar-C), 127.5 (2 x Ar-CH), 127.7 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 129.0 (2 x Ar-CH), 129.1 (2 x Ar-CH), 129.3 (2 x Ar-CH), 130.0 (Ar-C), 130.2 (Ar-CH), 131.8 (2 x Ar-CH), 132.2 (Ar-CH), 133.1 (Ar-C), 133.5 (Ar-C), 134.5 (Ar-C), 135.4 (Ar-C), 136.1 (Ar-C), 137.2 (Ar-C), 146.5 ($PhOCH_3$), 159.4 ($PhOCH_3$), 159.9 (C=N), 164.8(CO). HRMS (ESI^+): found m/z 667.2704, $[M+H^+]$, $C_{44}H_{35}N_4O_3$ requires 667.2709).

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