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# Greener and efficient one-pot synthesis of novel multi-substituted 3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives by using recyclable catalyst under microwave irradiation

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**A B S T R A C T**

The novel class of multi-substituted indolylimidazole derivatives series substituted 3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole and substituted 5-bromo-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole was synthesized utilising a green and efficient one-pot four components condensation of indole-3-carbaldehyde, benzil, ammonium acetate and various amines under microwave irradiation using Amberlyst A-15 as a recyclable catalyst. The catalyst Amberlyst A-15 has recovered from the reaction mixture and reused repeatedly for the next reaction. The key advantage of this process involves eco-friendly, very short reaction time, cost-effectiveness with the reusability of catalyst, easy workup, and purification of the product with excellent yields. FTIR, $^1$HNMR and Mass spectrometric studies analyzed and established the structures of all newly synthesized compounds.



## 1. Introduction

Natural and synthesized indolylimidazole compounds that contain both indole and imidazole rings play an important role in medicinal science because of their wide spectrum of biological and pharmacological activities.[1] The 3-substituted indole alkaloids with additional imidazole ring and indole alkaloid with additional multi-substituted imidazole ring show most biological activities, and their applications are very advantageous in various fields of science.

Indolylimidazole structure resembling natural compounds such as Topsentin was first reported in 1987 and isolated from marine sponges.[2-5] These Topsentin and its derivatives showed different biological activities such as antibacterial,[6] antiviral,[7] antitumor,[7-9] and anti-inflammatory.[10-11] Nortopsentins A-C, topentin and bromotopsentin isolated from the deep-sea sponge *Spongosorites ruetzleri* and showed *in vitro* cytotoxicity against P388 cells and antifungal activity against *Candida*

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*Albicans.*[12] Nortopsentin-A exhibited antiplasmodial activity and inhibited parasite growth at the trophozoite stage at submicromolar 50% inhibitory concentrations (IC50).[13] Nortopsentins-D and *N*-methyl substituted Nortopsentin derivatives also showed cytotoxicity against P388 cells.[14] Discodermindole,[15] 6-Hydroxydiscodermindole[16] and 2-(Dimethylamino)-5-(1*H*-indol-3-yl)-4*H*-imidazol-4-one[17] have been isolated from the Bahama sponge *Discodermia polydiscus* and exhibited cytotoxicity against murine tumor cells. Trachycladindole A–G compounds are the product of southern Australian marine sponge *Trachycladuslae vispirulifer* and displayed promising selective cytotoxicity against a panel of human cancer cell lines.[18] Rhopaladins A-D compounds have been isolated from *Okinawan tunicate Rhopalaea sp.* in 1998. These compounds were reported as an antibacterial agent against *Sarcinalutea*, *Corynebacterium xerosis,* and showed inhibiting activity against cyclin-dependent kinase-4 and c-erb β-2 kinase.[19] Indolylimidazole skeleton containing some natural compounds have also been reported as anti-depressant agent,[20] protein kinase C inhibitor,[21,22] interleukin 6-production inhibitor,[23] Flt-1and topoisomerase inhibitor,[24] antibiotic and antitumor agent.[25]

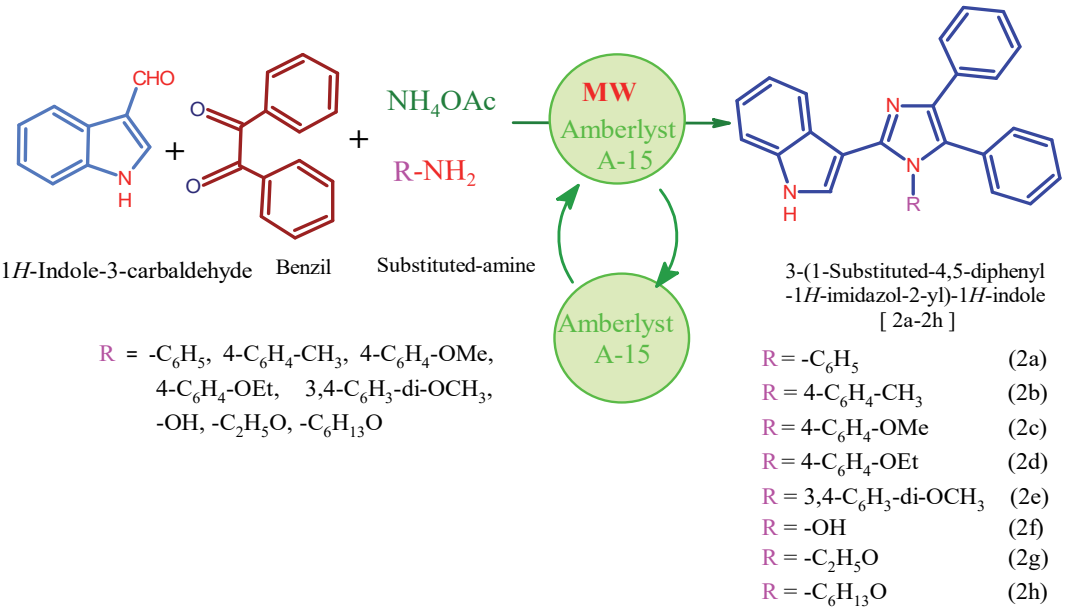
Due to most bioactivities of indolylimidazole, the field of indolylimidazole always attracted chemists for the synthesis. Indolylimidazole frame containing synthesized compounds also have shown various biological and pharmacological activities such as radio-sensitizer against HT-29 cell line,[26] cytotoxicity,[27] MRSA PK inhibitor,[28] antibiotic and antitumor agent,[29] antibacterial,[30,31] antimicrobial,[32,33] antifungal,[33] anti-urease,[33,34] antioxidant,[34,35] phosphodiesterase inhibitor,[36] anti-inflammatory, analgesic and antipyretic agents.[37,38] Therefore, there is a strong demand for a simple, highly efficient, environment-friendly and versatile method for the synthesis of substituted indolylimidazole derivatives for their great importance.

In recent years, the substituted indolylimidazole derivatives have been synthesized and reported, in the presence of a different catalyst such as $Zn^{2+}$ at KSF,[29] $SO_4^{2-}/Y_2O_3$,[32] acetic acid,[33,34,39-42] acetic acid in the presence of microwave,[43] strong protic acid $HNO_3$@nano $SiO_2$ at $100^OC$,[44] polymeric quaternary ammonium azide (QN3),[45] triphenyl (propyl-3-sulphonyl)phosphonium toluene sulfonate.[46] Multi-step reaction methods have also been reported for the synthesis of indolylimidazole derivatives in the presence of different conditions and catalysts such as selenium dioxide and ammonium acetate,[36] aluminium chloride and reflux in the presence of acetic acid,[37,38] trimethyl phosphine and microwave irradiation,[47] heat and acyl chloride.[48] Although some of these methods are efficient from the synthetic chemist's point of view. Many of the synthesis protocols for indolylimidazole derivatives that have been reported above sustain from one or more drawbacks, such as severe reactions, low yields, blend of products, spare of chemicals, extreme thermal conditions, elongated reaction time, multi-step reaction, use of solvents, use of fatal and usually classy and excessive acid catalysts.

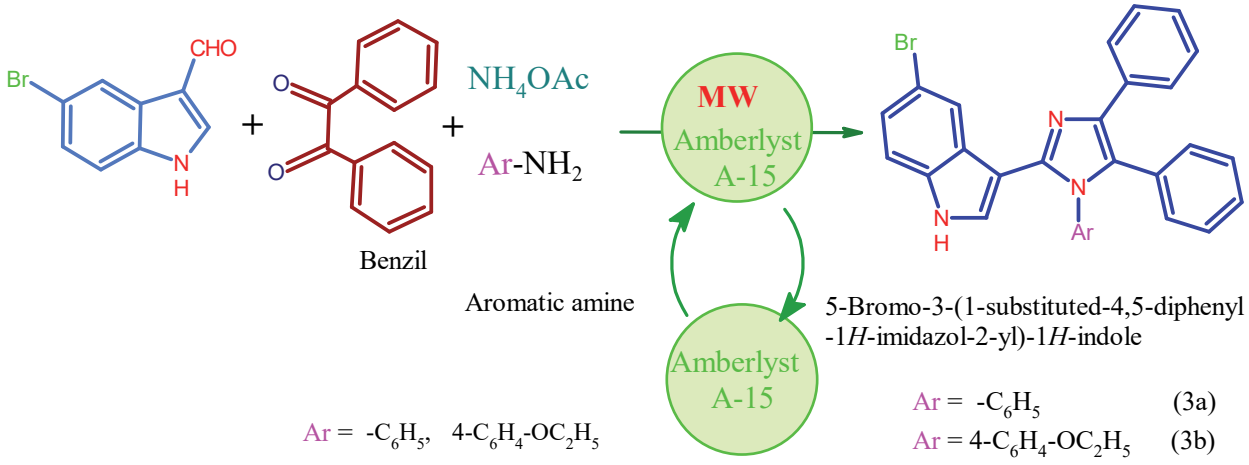
## 2. Result and Discussion

In this paper, an efficient, green, and eco-friendly one-pot multi-component condensation method has been developed for the synthesis of indolylimidazole derivatives **(2a-2h**) and (**3a–3b**) by using Amberlyst A-15 as an effective, reusable catalyst under microwave irradiation [**Scheme 1** and **Scheme 2**]. The 3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (**2a-2h**) were synthesized by one-pot four components condensation of 1*H*-indole-3-carbaldehyde, benzil, NH4OAc, substituted-amine under microwave irradiation using Amberlyst A-15 as a recyclable catalyst.

The 5-bromo-3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (**3a-3b**) were synthesized by one-pot four components condensation of 5-bromoindol-3-carbaldehyde, benzil, $NH_4OAc$ and substituted-amine under microwave irradiation using Amberlyst A-15 as a recyclable catalyst [**Scheme 2**].




**Scheme 1.** Synthesis of 3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives



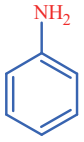
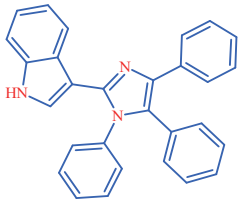
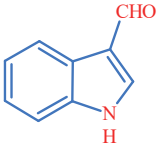
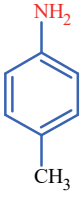
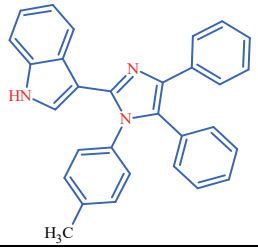
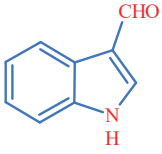
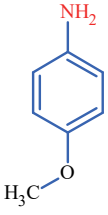
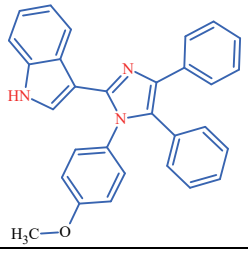
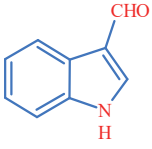
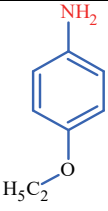
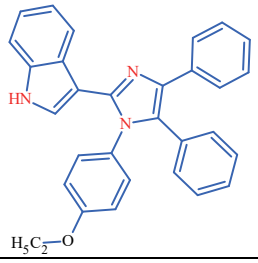
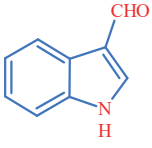
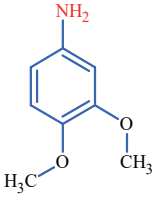
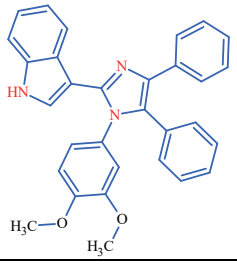
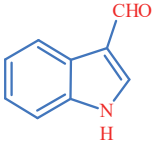
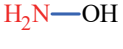
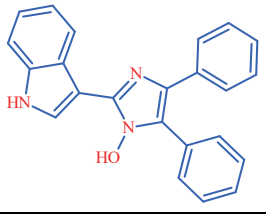

**Scheme 2.** Synthesis of 5-Bromo-3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives

The synthesized molecules (**2a-2h**) and (**3a–3b**) were identified by using FTIR, $^{1}$HNMR and Mass spectrometric studies. These indolylimidazole compounds have been obtained in excellent yields with shorter reaction times. **Table 1** and **Table 2** showed the structure of new molecules with yields percentage and reaction time. The products (**2a-2d**) were achieved in out-of-sight yield whereas those replaced by Bromine also produced in wonderful percentage. Data of Both **Table 1** and **Table 2** is under our presumption that the use of Amberlyst-A-15 provides better yield in a shorter period**.** The purity of synthesized compounds has been confirmed by elemental analysis and described in the experimental section.

All the compounds give an absorption in 3450-3386 $cm^{-1}$ due to N-H starching of indole in FT-IR spectra. The absorption of 1673-1611 $cm^{-1}$ due to aromatic C=N function. The absorption of 3688-3644 $cm^{-1}$ (str.) 1444-1414 $cm^{-1}$ (def.-ip) and 641-635 (def.-oop) due to O-H group (**2f-2h**). The compounds **3a** and **3b** give an absorption in 580 $cm^{-1}$ due to C-Br function. The absence of amine and carbonyl group in FT-IR range supported the condensation of the new compounds.

All the compounds exhibited a singlet in δ = 12.463 to 11.135 ppm region due to N-H proton of indole in the $^1$H NMR spectra. The multiplat was observed at δ = 7.627 to 7.159 ppm due to aromatic protons of benzene ring in all compounds. A singlet was observed at δ = 14.956 to 11.840 ppm due to hydroxy protons in **2f-2h**. The mass spectra showed molecular ion peak, which are concorded with molecular formula.

**Table. 1.** Synthesis of 3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (2a-2h)

| Entry | Carbaldehyde | Substituted-amine | Products | Reaction Time (Min.) | Yield (in %) | M.Pt. (°C) |
|---|---|---|---|---|---|---|
| 2a |  |  |  | 12 | 94 | 235-236 |
| 2b |  |  |  | 12 | 93 | 238-239 |
| 2c |  |  |  | 10 | 96 | 242-243 |
| 2d |  |  |  | 9 | 97 | 207-209 |
| 2e |  |  |  | 10 | 83 | 244–246 |
| 2f |  |  |  | 14 | 80 | 190-192 |

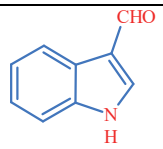
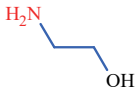
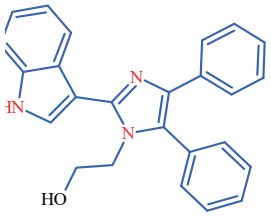
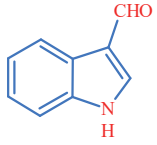
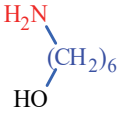
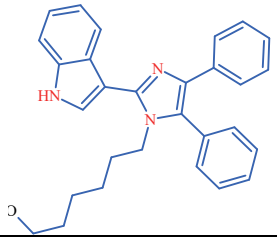
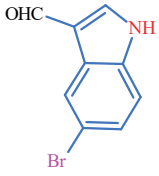
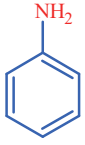
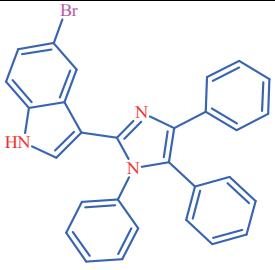
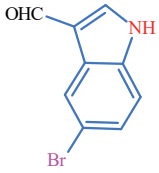
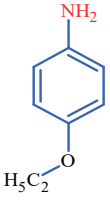
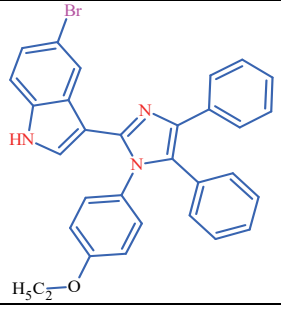
| | | | | | | |
|---|---|---|---|---|---|---|
| 2g |  |  |  | 13 | 81 | 130-132 |
| 2h |  |  |  | 10 | 83 | 170-172 |

**Table. 2.** Synthesis of 5-Bromo-3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (3a-3b)

| Entry | Carbaldehyde | substituted-amine | Products | Reaction Time (Min.) | Yield (in %) | M.Pt. (ºC) |
|---|---|---|---|---|---|---|
| 3a |  |  |  | 11 | 94 | 235-236 |
| 3b |  |  |  | 9 | 89 | 260-262 |

Some of these types of compounds have been synthesized and reported in the presence of different catalysts. However, reported methods suffer from several drawbacks such as drastic reaction conditions, wastes of catalyst and solvent, difficulty to handle, longer reaction time, tedious workup, and low yields. All such drawbacks are overcome in the present procedure by using recyclable Amberlyst A-15, which is easy to handle with shorter reaction time and uncomplicated workup procedure. Present work has been compared with the reported method shown in **Table 3**.

**Table. 3.** Comparison of Amberlyst A-15 with other catalysts

| S.No. | Catalyst | Condition | Time (min) | % Yield[a] | References |
|---|---|---|---|---|---|
| 1 | $Zn^{2+}$@KSF | EtOH | 35 | 78 | 29 |
| 2 | $HNO_3$@nano $SiO_3$ | 100ºC | 330 | 74 | 43 |
| 3 | Amberlyst A-15 | MW | 8 | 97 | Present work |

[a]Isolated yields, comparison for module reaction of compound 2c.

The data in **Table 3** depicts that using Amberlyst A-15 in combination with the microwave not only provides a greener and non-corrosive path but also a remarkable yield. We have achieved an excellent yield percentage with shorter reaction time in the present work as compared to reported methods. The catalyst Amberlyst A-15 was recycled for the same reaction repeatedly and found that Amberlyst A-15 could be reused for seven cycles with negligible loss of their activity [**Fig. 1**].

## 3. Conclusion

In summary, we have presented an efficient, mild, and rapid approach for the synthesis of novel multi-substituted indolylimidazole derivatives through one-pot condensation of a representative benzil with various substituted-amine, 1*H*-indole-3-carbaldehyde, ammonium acetate and using Amberlyst A-15 as a new and highly effective catalyst under solvent-free and microwave conditions. These indolylimidazole compounds have been obtained in excellent yields with shorter reaction times. The products (**2a-2d**) were achieved in out-of-sight yield whereas those replaced by Bromine also produced in wonderful percentage in **3a-3b**. Non-corrosiveness, secured with low waste, shorter reaction time with high yields, and environmentally friendly are some advantages of this method. Amberlyst A-15 was a recyclable catalyst and easy to handle. This catalyst could be reused in the next reactions with negligible loss of their activity.

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## 4. Experimental

### *4.1. Materials and methods*

A microwave oven (IFB, 23BC4, 1400 W) was used for synthesis. The melting point of products was measured by the use of an open capillary method. IR spectra were obtained in KBr by Jasco - FTIR-4100 spectrometer. $^{1}$HNMR spectra were recorded in DMSO with TMS as the internal reference on JEOL - 400 MHz NMR spectrometer with multiple probe facility (AL-400). The mass spectra were recorded on LCMS SQD-2 with H Class UPLC instrument. All the chemicals and reagents used were procured from MERCK and Ranbaxy.

### *4.2. General procedure*

Microwave irradiation (MW) was used for the synthesis of 2,4,5-triphenyl-1*H*-imidazole derivatives by condensation of substituted-benzaldehyde, benzil, ammonium acetate and substituted-amine in the presence of Amberlyst A-15 catalyst.[49-51]

The above techniques have been employed for preparing simple imidazoles without indole ring. After some modifications, this technique was utilized for the synthesis of indolylimidazoles that contain both indole and imidazole ring under MW treatment using Amberlyst A-15 as a recyclable catalyst.

#### *4.2.1. Synthesis of 3-(1-substituted-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives(**2a-2h**)*

A mixture of 1*H*-indole-3-carbaldehyde (1 mmol), benzil (1 mmol), $NH_4OAc$ (1 mmol), substituted-amine (1 mmol) and Amberlyst A-15 (0.12g) was taken into 50 mL borosil beaker and irradiated with microwave for 8-15 minutes at almost constant temperature 80°C. Thin-layer chromatography (ethyl acetate: petroleum ether 1:9) technique was used to monitor the headway of the reaction where Silica gel G-60 as a stationary phase. After completion, the reaction mixture was brought to room temperature and added dichloromethane. The solid Amberlyst A-15 was filtered and washed several times with dichloromethane. Pure Amberlyst A-15 was dried at 80°C and reused again for the

next reaction. The organic layer was extracted with water and dried by anhydrous $Na_2SO_4$ until the $Na_2SO_4$ swirls freely in the flask. The filtrate was then purposive by vacuum. The prepared products were washed first with dichloromethane then recrystallized with cold ethanol and dried. The purity of the obtained compound (**2a-2h**) was checked by TLC besides microanalysis.

*4.2.2. Synthesis of 5-Bromo-3-(1-substituted-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives (**3a-3b**)*

The 5-Bromo-3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (**3a-3b**) were prepared by a similar procedure using 5-bromoindol-3-carbaldehyde (1 mmol), benzil (1 mmol), $NH_4OAc$ (1 mmol) and substituted-amine (1 mmol).

*4.3. Recyclability of the catalyst*

To explore the recyclability of the catalyst, the Amberlyst A-15 was used repeatedly for the same reaction. The relation between the number of cycles of the reaction and recyclability in terms of yield of the catalyst is presented in **Fig. 1**. It is concluded that Amberlyst A-15 could be reused for seven cycles with negligible loss of their activity.

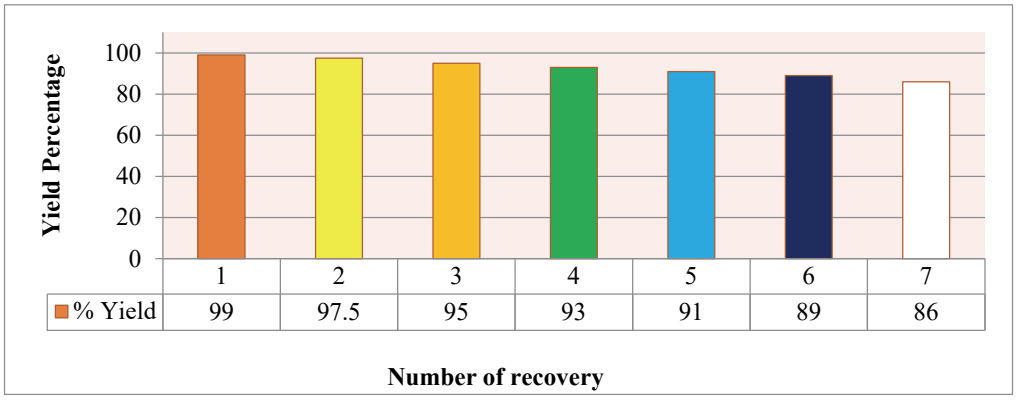


**Fig. 1.** Amberlyst A-15 recovery yield percentage for framework reaction

*4.4. Physical and spectral data*
**Key diagnostic signals in Bold text**

*3-(1-(4-Methylphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (**2b**)*

Colorless solid, Anal.: (Calcd): C (84.68%), H (5.45%), N (9.87%), (Found): C (84.70%), H (5.43%), N (9.85%). FTIR (KBr, cm−1): Vmax: **3418**, 3125, 3091, **2945**, 1625, 1600, 1595, 1570, 1495, 1440, 1420, **1394**, 1242, 1050, **815**, 774, 760, 692. $^1$HNMR (400 MHz, DMSO-d6): 11.754 (s, 1H, indole); 8.512 (s, 1H); 8.420 (d, 1H, J = 7.4 Hz); 7.807 (t, 1H. J = 7.4 Hz); 7.651 (d, 1H, J = 3.6 Hz); 7.579 (t, 1H, J = 3.7 Hz); 6.652 (d, 2H, J = 2.6 Hz); 6.199 (d, 2H, J = 2.6 Hz); 7.589–7.148 (m, 14H, Ar-H) 3.126 (s, 3H) ppm. HRMS ((+)-ESI): m/z = 425.515 (calculated: 425.524).

*3-(1-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (**2e**)*

Colourless solid, Anal.: (Calcd): C (81.61%), H (5.25%), N (9.52%), O (3.62%), (Found): C (81.59%), H (5.28%), N (9.49%), O (3.60%). FTIR (KBr, cm−1): Vmax: 3400, 3060, 3036, 2980, 2950, 2930, 1618, 1600, 1580, 1543, 1493, 1450, 1445, **1409**, 1390, **1250**, **1195**, 1032, **876**, **790**, 798, 768, 696. $^1$HNMR (400 MHz, DMSO-d6): 11.843 (s, 1H, indole), 8.661 (s, 1H, Ar-H, Indole), 8.383 (d, 1H, J=8.00 Hz), 7.553 (dd, 1H, J=2.4 Hz), 7.692 (dd, 1H, J=7.65 Hz, 2.5 Hz), 7.761 (d, 1H, J=7.51 Hz), 7.547-7.171 (m, 10H, Ar-H), 8.001 (s, 1H, Ar-H), 7.151 (d, 1H, Ar-H, J=6.95 Hz), 7.103 (d, 1H, Ar-H, J=6.92 Hz), 3.852 (s, 3H), 3.753 (s, 3H) ppm. HRMS ((+)-ESI): m/z = 473.50 (calculated: 473.56).

*2-(1H-Indol-3-yl)-4,5-diphenyl-1H-imidazol-1-ol (**2f**)*

Colourless solid, Anal.: (Calcd): C (78.61%), H (4.88%), N (11.96%), O (4.55%), (Found): C (78.63%), H (4.86%), N (11.99%), O (4.52%). FTIR (KBr, cm−1): *V*max: **3645**, 3386, 3157, 3050, 3015, 2891, 2837, 2010, 1675, 1641, 1619, 1596, 1580, 1521, 1448, **1414**, **1341**, **1227**, 1099, 867, 705, 747, 692, **635**. $^{1}$HNMR (400 MHz, DMSO-d6): 11.840 (s, O-H), 11.205 (s, 1H, indole), 8.225 (s, 1H, Ar-H, Indole), 7.865 (d, 1H, J=7.1 Hz), 7.105 (dd, 1H, J=7.1 Hz), 7.120 (dd, 1H, J=7.4 Hz), 7.613 (d, 1H, J=7.4 Hz), 7.535-7.165 (m, 10H, Ar-H) ppm. HRMS ((+)-ESI): m/z = 351.90 (calculated: 351.40).

*2-[2-(1H-Indol-3-yl)-4,5-diphenyl-1H-imidazol-1-yl]ethan-1-ol (**2g**)*

Colourless solid, Anal.: (Calcd): C (79.13%), H (5.58%), N (11.07%), O (4.22%), (Found): C (79.09%), H (5.62%), N (11.05%), O (4.18%). FTIR (KBr, $cm^{-1}$): *V*max: **3644**, 3386, 3157, 3050, 3014, 2893, **2839**, 1987, 1675, 1634, 1619, 1597, 1581, 1521, 1448, **1493**, **1414**, **1340**, **1026**, **1227**, 950, 931, 906, 869, 706, 747, 691, **635**. $^{1}$H NMR (400 MHz, DMSO-d6): 12.132 (s, O-H), 11.517 (s, 1H, indole), 8.272 (s, 1H, Ar-H, Indole), 8.099 (d, 1H, J=7.2 Hz), 7.351 (dd, 1H, J=7.1 Hz), 7.650 (dd, 1H, J=7.4 Hz), 7.896 (d, 1H, J=7.4 Hz), 7.557-7.449 (m, 10H, Ar-H), 4.034 (t, 2H, J=6.6 Hz) 3.393 (dd, 2H, $J_1$=12.3, $J_2$=6.5 Hz) ppm. HRMS ((+)-ESI): m/z = 379.90 (calculated: 379.45).

*2-[2-(1H-Indol-3-yl)-4,5-diphenyl-1H-imidazol-1-yl]hexan-1-ol (**2h**)*

Colourless solid, Anal.: (Calcd): C (79.97%), H (6.71%), N (9.65%), O 3.67%), (Found): C (79.99%), H (6.74%), N (9.62%), O (3.63%). FTIR (KBr, $cm^{-1}$): *V*max: **3688**, 3387, 3138, 3111, 3057, 2976, **2926**, **2855**, 1967, 1634, 1600, 1580, 1520, 1500, 1460, **1485**, **1440**, **1444**, **1340**, **1241**, **1073**, 951, 931, 877, 716, 749, 696, **641**. $^{1}$HNMR (400 MHz, DMSO-d6): 14.956 (s, brs, O-H), 12.463 (s, 1H, indole), 8.100 (s, 1H, Ar-H, Indole), 7.938 (d, 1H, J=7.2 Hz), 7.220 (dd, 1H, J=7.5 Hz), 7.292 (dd, 1H, J=7.5 Hz), 7.786 (d, 1H, J=7.5 Hz), 7.545-7.328 (m, 10H, Ar-H), 4.357 (t, 2H, J=7.1 Hz), 3.870 (t, 2H, J=6.5 Hz), 1.34 (m, 2H), 0.933(m, 2H), 0.404 (m, 2H) ppm. HRMS ((+)-ESI): m/z = 435.00 (calculated: 435.56).

*5-Bromo-3-(1,4,5-Triphenyl-1H-imidazol-2-yl)-1H-indole (**3a**)*

Colourless solid, Anal.: (Calcd): C (71.21%), H (4.31%), N (8.55%), Br (16.55%), (Found): C (71.031%), H (4.11%), N (8.57%), Br (16.29%). FTIR (KBr, $cm^{-1}$): *V*max: 3450, 3055, 3020, 1650, 1600, 1580, 1522, 1450, **1245**, 1130, 780, 732, **765**, **695**, **580**. $^{1}$HNMR (400 MHz, DMSO-d6): 11.952 (s, 1H, indole), 8.535 (s, 1H, Ar-H, Indole), 8.421 (s, 1H), 7.942 (d, 1H, J=7.71 Hz), 7.959 (d, 1H, J=7.56 Hz), 7.615-7.312 (m, 15H, Ar-H) ppm. HRMS ((+)-ESI): m/z = 490.40 (calculated: 490.39).

*5-Bromo-3-(1-(4-ethoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (**2b**)*

Colourless solid, Anal.: (Calcd): C (69.67%), H (4.53%), N (7.86%), Br (14.95%), O (2.99%), (Found): C (67.65%), H (4.50%), N (7.89%), Br (14.93%) O (2.97%). FTIR (KBr, $cm^{-1}$): 3420, 3105, 3092, 2950, 1630, 1602, 1590, 1540, 1490, **1465**, **1394**, **1407**, 1250, **1243**, **1195**, 1123, 815, 775, 760, 692, **580**. *V*max: $^{1}$HNMR (400 MHz, DMSO-d6):12.124 (s, 1H, indole), 8.492 (s, 1H, Ar-H, Indole), 8.451 (s, 1H), 7.937 (d, 1H, J=7.48 Hz), 7.961 (d, 1H, J=7.51 Hz), 7.627-7.216 (m, 10H, Ar-H), 7.832 (d, 2H, J=7.58 Hz), 7.080 (d, 2H, J=8.41 Hz), 3.95-2.90 (q, 2H, J=7.05 Hz), 1.391 (t, 2H, J=6.99 Hz) ppm. HRMS ((+)-ESI): m/z = 536.48 (calculated: 536.46).

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