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AN EFFICIENT SYNTHESIS OF *N*-ARYL-2-(INDOL-3-YL)-ACETAMIDES VIA MULTI-COMPONENT REACTIONS

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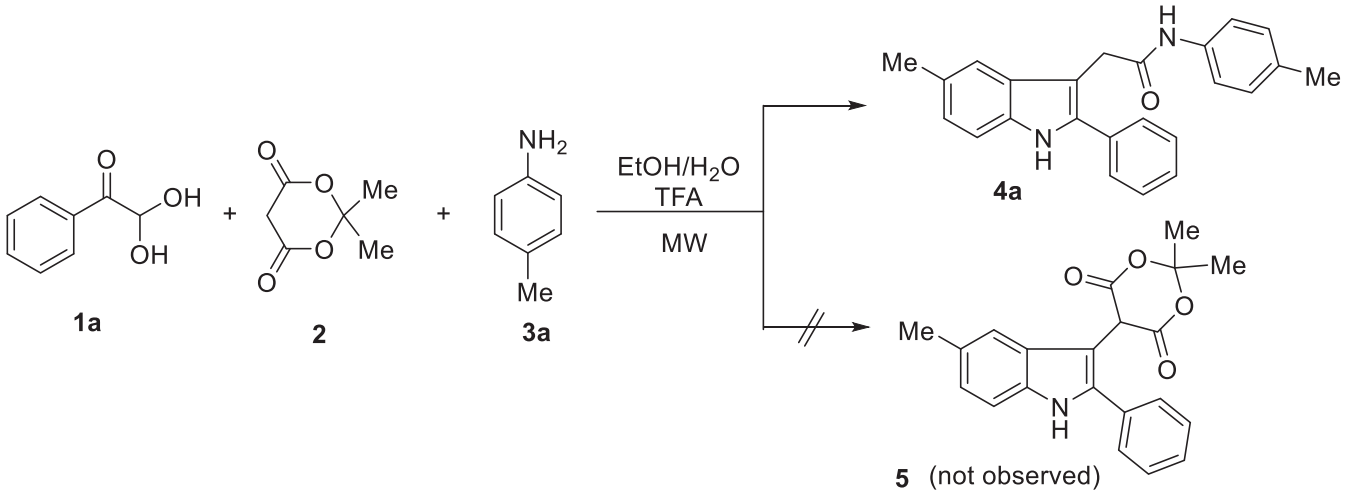
Abstract – An efficient synthesis of *N*-aryl-2-(indol-3-yl)acetamide derivatives via a four-component reaction of arylglyoxal monohydrate, Meldrum's acid and anilines under microwave irradiations is described. This protocol has the advantages of high efficiency, mild reaction conditions, a one-pot procedure, and materials available.

Indole scaffolds are interesting natural products and synthetic targets because these compounds have important biological activities, including anticancer,[1] anti-HIV,[2] antioxidant,[3] antiproliferative,[4] antirheumatoidal,[5] antineoplastic and antiestrogenic activities.[6] In addition, some 2-(indol-3-yl)acetamide moiety have been attracted great attention from synthetic as well as medicinal chemists because of their wide applications as drugs and pharmaceuticals, such as antiallergic agents,[7] selective CB2 cannabinoid receptor,[8] antianxiety agents,[9] and α_1-adrenoceptor antagonists.[10] Although several methods have been reported in the literature for construction of 2-(indol-3-yl)acetamide derivatives, these methods invariably require long multistep process and provide low yields of the desired products. Thus, the development of an efficient method for their synthesis still attracts much interest using readily available starting materials.

The development of environmentally friendly synthetic methods is a challenge in modern organic synthesis. Multi-component reactions (MCRs) in which multiple reactions are combined into one synthetic operation are promising powerful tools in organic, combinatorial, and medicinal chemistry.[11]

MCRs offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents.[12] In the past decade, MCRs have been widely used in the construction of complex natural products and heterocycles.[13] Recently, our group has developed a convenient and efficient synthesis of some new heterocycles using MCRs.[14] In this paper, we developed efficient access to the synthesis of 2-(indol-3-yl)acetamide derivatives via four-component reactions of arylglyoxal monohydrate, Meldrum's acid and anilines under microwave irradiations.

According to our previously reported synthetic procedure,[15] the desired product **5** could not be obtained when arylglyoxal monohydrate (**1a**), Meldrum's acid (**2**) and *p*-toluidine (**3a**) were used as starting materials, catalyzed by CF_3CO_2H (TFA) in the mixture of ethanol and water under microwave irradiation conditions, while the unexpected four-component reaction product **4a** was obtained in 30% yield (Scheme 1). In terms of the low yield of **4a**, some reaction conditions were optimized using a four-component reaction of arylglyoxal monohydrate (**1a**), Meldrum's acid (**2**) and *p*-toluidine (**3a**) as the model reaction.

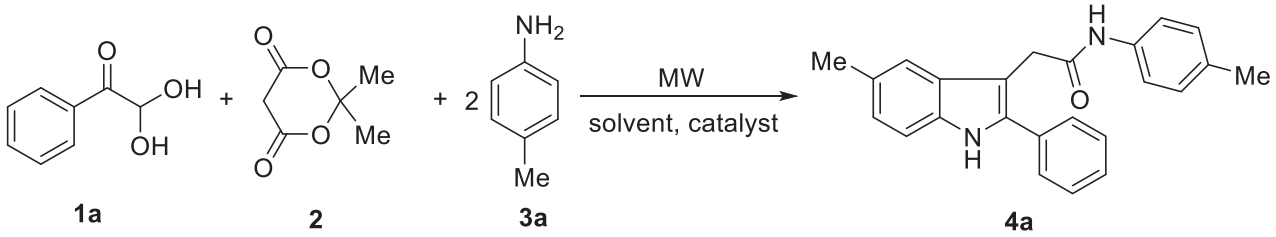


Scheme 1. The selectivity of the multi-component reaction

The effects of solvents and catalysts were evaluated for this reaction, and the results are summarized in Table 1. Firstly, different solvents were evaluated. The results revealed that MeCN provided much better results than EtOH-water (1:1), toluene, DMF, EtOH, and AcOH (entries 1-6, Table 1) under catalyst-free conditions. To improve the yield, several catalysts were evaluated: *p*-toluenesulfonic acid (*p*-TSA), CF_3CO_2H (TFA), L-proline, Et_3N, piperidine and K_2CO_3 (entries 7−12, Table 1). The results revealed that the catalytic efficiency of K_2CO_3 was the highest. Then we evaluated the amount of K_2CO_3 required for this reaction. The results from Table 1 (entries 12-15) show that 20 mol% K_2CO_3 is sufficient to initiate the reaction. Higher loading of the catalyst had no significant influence on the reaction yield. On the basis

of all of these experiments, the optimum reaction conditions were identified as ethanol at 80 °C for 40 min under microwave irradiation catalyzed by 20 mol% K_2CO_3. It is noted that when this reaction is performed at refluxing temperature for 40 min in MeCN the target product was afforded only in trace and thus the reaction time was prolonged. After refluxing for 8 h, the product was obtained in 54% yield.

Table 1. Optimization of the reaction conditions for the synthesis of compound **4a**



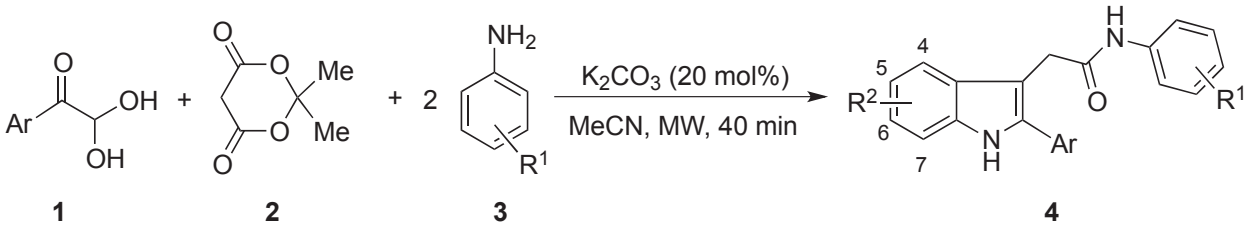
1a **2** **3a** **4a**

Entry	Solvent	Catalyst (mol%)	*T* (°C)	Time (min)	Yield [b] (%)
1	EtOH/H_2O (1:1)	no	100	40	10
2	toluene	no	100	40	18
3	DMF	no	100	40	23
4	EtOH	no	80	40	trace
5	MeCN	no	80	40	28
6	AcOH	no	100	40	25
7	MeCN	*p*-TSA (20)	80	40	30
8	MeCN	TfOH (20)	80	40	35
9	MeCN	L-proline (20)	80	40	32
10	MeCN	Et_3N (20)	80	40	55
11	MeCN	piperidine (20)	80	40	43
12	MeCN	K_2CO_3 (20)	80	40	71
13	MeCN	K_2CO_3 (10)	80	40	60
14	MeCN	K_2CO_3 (15)	80	40	67
15	MeCN	K_2CO_3 (25)	80	40	65
16	MeCN	K_2CO_3 (20)	reflux, no MW	40	trace
17	MeCN	K_2CO_3 (20)	reflux, no MW	480	54

[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), **3a** (2 mmol), solvent (4 mL). [b]Isolated Yields.

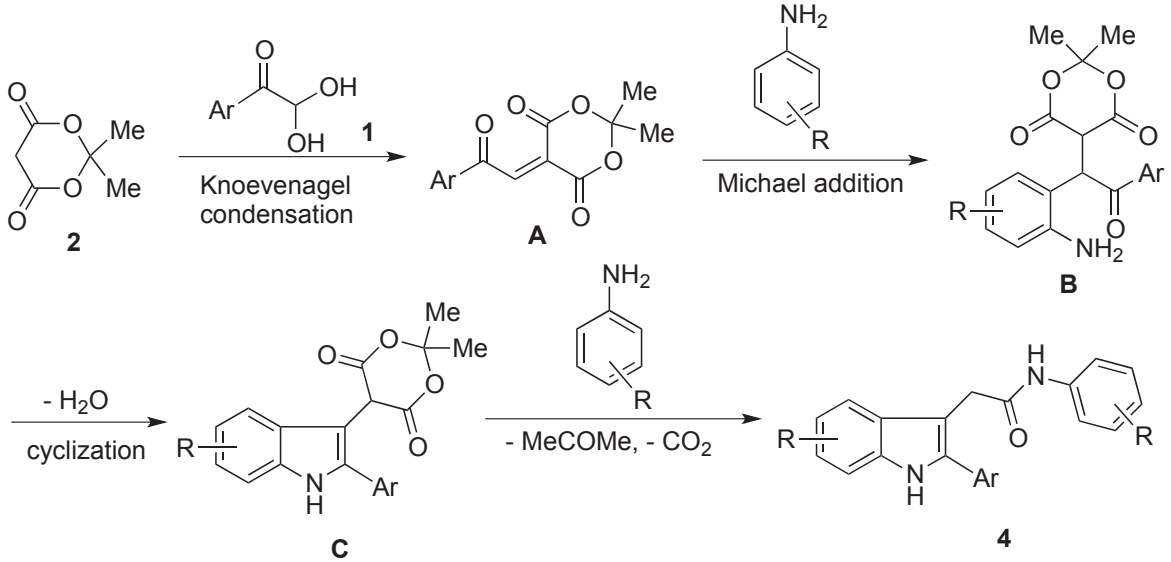
With the optimal reaction conditions in hand, the substrate scope of the transformation was then evaluated using four arylglyoxal monohydrates **1**, and four anilines **3**. The corresponding *N*-aryl-2-(indol-3-yl)-acetamides were obtained, and the results are summarized in Table 2. As shown in Table 2, the anilines bearing electron-donating groups were tolerated under this reaction conditions, leading to the final products in satisfactory yields. The structures of the products synthesized in the current study were identified using IR, ^{1}H NMR, and ^{13}C NMR spectroscopies, as well as HRMS analysis.

Table 2. The synthesis of *N*-aryl-2-(indol-3-yl)acetamides **4**



Entry	Compound	Ar	R^1	R^2	Isolated Yield (%)
1	**4a**	C_6H_5	4-Me	5-Me	71
2	**4b**	C_6H_5	3-Me	6-Me	60
3	**4c**	C_6H_5	4-EtO	5-EtO	76
4	**4d**	4-BrC_6H_4	4-Me	5-Me	64
5	**4e**	4-BrC_6H_4	3-Me	6-Me	52
6	**4f**	4-BrC_6H_4	2-Me	7-Me	57
7	**4g**	3-ClC_6H_4	4-Me	5-Me	48
8	**4h**	3-ClC_6H_4	4-EtO	5-EtO	56
9	**4i**	4-ClC_6H_4	4-Me	5-Me	42
10	**4j**	4-ClC_6H_4	3-Me	6-Me	50

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of compound **4** could be explained by the reaction sequence in Scheme 2. Intermediate A is formed through Knoevenagel condensation of arylglyoxal monohydrate (**1**) with Meldrum's acid (**2**). The subsequent Michael addition of anilines (**3**) to intermediate **A** gives intermediate **B**, which undergoes an intramolecular nucleophilic addition reaction followed by loss of water to form the intermediate **C**.



Scheme 2. Proposed mechanism for the synthesis of compound **4**

The product **4** was obtained by the nucleophilic addition reaction of intermediate **C** with anilines (**3**) and followed by loss of acetone and CO_2. The similar ring-opening reaction of Meldrum's acid with amines has been reported in our previous works.[16]

In summary, we have developed an efficient method for the synthesis of pharmacologically important *N*-aryl-2-(indol-3-yl)acetamide derivatives by a four-component reaction arylglyoxal monohydrate, Meldrum's acid and anilines catalyzed by 20 mol% K_2CO_3 under microwave irradiations. This method has the advantages of high efficiency, mild reaction conditions, a one-pot procedure, and convenient operation.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Bruker Vertex 70 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR and ^{13}C NMR were determined on Bruker-400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ solutions. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS analyses were carried out using a Bruker micrOTOF-Q II mass spectrometer with an ESI resource. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured using an infrared detector during microwave heating.

Starting Materials. All chemicals used in this study were commercially available.

Typical experimental procedure for the synthesis of *N*-aryl(indol-3-yl)acetamides 4. Arylglyoxal monohydrate (**1**) (1 mmol), Meldrum's acid (**2**) (1 mmol), and anilines (**3**) (1 mmol) were introduced into a 10 mL initiator microwave reaction vial, and 20 mol% K_2CO_3 as well as MeCN (4 mL) were then successively added. Subsequently, the reaction vial was closed and then stirred for 10 sec. The reaction mixture was irradiation at 80 ºC for 40 min with Initiator 2.5 Microwave Synthesizer. The reaction was monitored by TLC (3:1 mixture of petroleum ether and EtOAc). After the completion, the reaction mixture was then cooled to room temperature. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography using petroleum ether and EtOAc as the eluent, giving pure compound **4**.

***N*-(*p*-Tolyl)-2-(5-methyl-2-phenyl-1*H*-indol-3-yl)acetamide (4a):** White solid; mp 200-201 ºC; IR (KBr) 3402, 3287, 2915, 1659, 1523, 1449, 1405, 1251, 1183, 814, 799, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H, NH), 10.13 (s, 1H, NH) 7.81-7.73 (m, 2H, ArH), 7.47 (dd, *J* = 15.4, 8.1 Hz, 5H, ArH) 7.39-7.31 (m, 2H , ArH), 7.23 (d, *J* = 8.2 Hz, 1H, ArH), 7.07 (d, *J* = 8.3 Hz, 2H, ArH), 6.90 (dd, *J* = 8.3, 1.3 Hz, 1H, ArH), 3.77 (s, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.21 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 137.3, 136.6, 134.7, 133.1, 132.5, 129.7, 129.6, 129.5, 129.1, 128.4, 127.9, 127.7, 123.63, 119.7, 118.8, 114.5, 111.3, 105.9, 33.2, 21.8, 20.9; HRMS calcd for $C_{24}H_{22}N_2NaO$ $[M+Na]^+$

377.1622, found 377.1627.

***N*-(*m*-Tolyl)-2-(6-methyl-2-phenyl-1*H*-indol-3-yl)acetamide (4b):** White solid; mp 171-173 ºC; IR (KBr) 3385, 3279, 2975, 1656, 1513, 1454, 1409, 1247, 1058, 828, 771, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H, NH), 10.18 (s, 1H, NH), 7.81 (d, J = 7.3 Hz, 3H), 7.52 (d, J = 1.9 Hz, 1H), 7.49 (d, J = 7.8 Hz, 3H, ArH), 7.39 (m, 2H, ArH), 7.17 (dd, J = 9.4, 6.1 Hz, 2H, ArH), 6.85 (t, J = 7.2 Hz, 2H, ArH), 3.81 (s, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR (100MHz, DMSO-d_6) δ 169.9, 139.2, 137.8, 136.3, 135.4, 132.7, 130.6, 128.6, 128.5, 127.9, 127.4, 126.9, 123.9, 120.6, 119.8, 118.5, 116.4, 110.9, 105.8, 32.9, 21.5, 21.2; HRMS calcd for $C_{24}H_{23}N_2O$ $[M+H]^+$ 355.1810, found 355.1805.

***N*-(4-Ethoxyphenyl)-2-(5-ethoxy-2-phenyl-1*H*-indol-3-yl)acetamide (4c):** White solid; mp 217-218 ºC; IR (KBr) 3413, 3300, 2918, 1662, 1551, 1489, 1193, 1246, 845, 789, 765, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, NH), 7.53 (d, J = 7.2 Hz, 2H, ArH), 7.48 (t, J = 7.6 Hz, 2H, ArH), 7.39 (t, J = 7.2 Hz, 2H, ArH, NH), 7.33 (d, J = 8.8 Hz, 1H, ArH), 7.20 (d, J = 9.0 Hz, 2H, ArH), 7.03 (d, J = 2.2 Hz, 1H, ArH), 6.93 (dd, J = 8.7, 2.3 Hz, 1H, ArH), 6.76 (d, J = 9.0 Hz, 2H, ArH), 4.05 (q, J = 7.0 Hz, 2H, CH_2O), 3.98-3.93 (m, 4H, 2×CH_2), 1.42 (t, J = 7.0 Hz, 3H, CH_3), 1.36 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.01, 155.41, 153.75, 136.98, 131.43, 130.50, 130.06, 128.80, 127.92, 127.22, 121.57, 114.17, 113.62, 111.57, 104.59, 100.62, 63.73, 63.19, 33.45, 14.49, 14.32; HRMS calcd for $C_{26}H_{26}N_2NaO_3$ $[M+Na]^+$ 437.1841, found 437.1833.

***N*-(*p*-Tolyl)-2-(2-(4-bromophenyl)-5-methyl-1*H*-indol-3-yl)acetamide (4d):** White solid; mp 198-199 ºC; IR (KBr) 3450, 3285, 3265, 1657, 1604, 1540, 1404, 1244, 1073, 830, 798, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, NH), 7.61 (d, J = 8.5 Hz, 2H, ArH), 7.43 (s, 1H, ArH), 7.41 (d, J = 2.5 Hz, 2H, ArH), 7.39 (s, 1H, NH), 7.34 (d, J = 8.3 Hz, 1H, ArH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 7.12 (d, J = 8.2 Hz, 1H, ArH), 7.05 (d, J = 8.3 Hz, 2H, ArH), 3.91 (s, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 137.2, 135.4, 134.8, 132.6, 132.3, 132.0, 130.3, 129.5, 127.8, 124.0, 121.3, 119.7, 118.8, 111.4, 106.5, 33.1, 21.8, 20.9; HRMS calcd for $C_{24}H_{21}BrN_2NaO$ $[M+Na]^+$ 455.0735, found 455.0717.

***N*-(*m*-Tolyl)-2-(2-(4-bromophenyl)-6-methyl-1*H*-indol-3-yl)acetamide (4e):** White solid; mp 198-199 ºC; IR (KBr) 3429, 3194, 2915, 1654, 1612, 1542, 1488, 1217, 1075, 808, 781, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, NH), 7.64-7.58 (m, 2H, ArH), 7.51 (d, J = 8.1 Hz, 1H, ArH), 7.45-7.39 (m, 3H, ArH), 7.25 (s, 1H, NH), 7.17 (s, 1H, ArH), 7.15-7.08 (m, 2H, ArH), 7.05 (d, J = 8.1 Hz, 1H, ArH), 6.88 (d, J = 6.8 Hz, 1H, ArH), 3.92 (s, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100

MHz, $CDCl_3$) δ 169.42, 138.84, 137.38, 136.52, 134.88, 133.61, 132.42, 130.83, 129.13, 128.69, 126.54, 125.30, 122.79, 122.46, 120.71, 118.38, 117.17, 111.23, 105.56, 34.13, 21.84, 21.40; HRMS calcd for $C_{24}H_{22}BrN_2O$ $[M+H]^+$ 433.0916, found 433.0895.

***N*-(*o*-Tolyl)-2-(2-(4-bromophenyl)-7-methyl-1*H*-indol-3-yl)acetamide (4f):** White solid; mp 189-190 ºC; IR (KBr) 3429, 3245, 2916, 1654, 1612, 1542, 1612, 1542, 1488, 1422, 1301, 808, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H, NH), 7.61 (d, J = 8.4 Hz, 2H, ArH), 7.51 (d, J = 8.2 Hz, 1H, ArH), 7.44-7.38 (m, 3H, ArH), 7.25 (s, 1H, NH), 7.17 (s, 1H, ArH), 7.15-7.03 (m, 3H, ArH), 6.88 (d, J = 6.9 Hz, 1H, ArH), 3.92 (s, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 169.4, 138.8, 137.4, 136.5, 134.9, 133.6, 132.4, 130.8, 129.1, 128.7, 126.5, 125.3, 122.8, 122.4, 120.7, 118.4, 117.2, 111.2, 105.6, 34.1, 30.9, 21.8, 21.4; HRMS calcd for $C_{24}H_{21}BrN_2NaO$ $[M+Na]^+$ 455.0735, found 455.0752.

***N*-(*p*-Tolyl)-2-(2-(3-chlorophenyl)-5-methyl-1*H*-indol-3-yl)acetamide (4g):** White solid; mp 177-178 ºC; IR (KBr) 3392, 3281, 2911, 1655, 1600, 1524, 1406, 1308, 1184, 801, 785, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, NH), 7.55 (s, 1H, ArH), 7.46-7.32 (m, 5H, ArH, NH), 7.22 (d, J = 8.4 Hz, 2H, ArH), 7.13 (d, J = 7.3 Hz, 1H, ArH), 7.05 (d, J = 8.2 Hz, 2H, ArH), 3.94 (s, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 135.3, 134.9, 134.4, 134.2, 133.7, 130.5, 129.4, 128.4, 127.6, 126.0, 125.3, 120.2, 118.4, 111.0, 105.7, 99.9, 33.9, 30.9, 21.6, 20.8; HRMS calcd for $C_{22}H_{12}ClN_2NaO$ $[M+Na]^+$ 411.1240, found 411.1250.

***N*-(4-Ethoxyphenyl)-2-(2-(3-chlorophenyl)-5-ethoxy-1*H*-indol-3-yl)acetamide (4h):** White solid; mp 188-190 ºC; IR (KBr) 3392, 3279, 2977, 1654, 1597, 1515, 1453, 1216, 1043, 838, 792, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H, NH), 7.56 (s, 1H, ArH), 7.47-7.43 (m, 2H, ArH), 7.42-7.35 (m, 3H, ArH, NH), 7.24 (d, J = 9.0 Hz, 2H, ArH), 7.06 (d, J = 2.2 Hz, 1H, ArH), 6.98 (dd, J = 8.8, 2.3 Hz, 1H, ArH), 6.81 (d, J = 9.0 Hz, 2H, ArH), 4.09 (q, J = 7.0 Hz, 2H, CH_2), 3.99 (q, J = 7.0 Hz, 2H, CH_2), 3.95 (s, 2H, CH_2), 1.45 (t, J = 7.0 Hz, 3H, CH_3), 1.39 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100MHz, DMSO-d_6) δ 169.8, 155.0, 153.03, 135.5, 135.2, 133.8, 132.7, 131.6, 130.9, 129.6, 127.9, 127.7, 126.9, 121.4, 114.8, 113.1, 112.4, 107.3, 102.4, 63.9, 63.5, 33.1, 15.3, 15.2; HRMS calcd for $C_{26}H_{25}ClN_2NaO_3$ $[M+Na]^+$ 471.1451, found 471.1460.

***N*-(*p*-Tolyl)-2-(2-(4-chlorophenyl)-5-methyl-1*H*-indol-3-yl)acetamide (4i):** Yellow solid; mp 197-198 ºC; IR (KBr) 3447, 3285, 2921, 1656, 1603, 1538, 1509, 1243, 1092, 816, 797, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, NH), 7.51-7.43 (m, 4H, ArH), 7.41 (s, 2H, ArH, NH), 7.34 (d, J = 8.3 Hz, 1H, ArH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 7.12 (d, J = 8.3 Hz, 1H, ArH), 7.05 (d, J = 8.3 Hz, 2H, ArH), 3.92 (s,

2H, CH_2), 2.46 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 169.4, 135.6, 134.9, 134.4, 134.2, 130.4, 129.5, 129.4, 128.9, 125.1, 120.2, 118.3, 111.0, 105.2, 33.9, 30.9, 21.6, 20.8; HRMS calcd for $C_{24}H_{21}ClN_2NaO$ $[M+Na]^+$ 411.1240, found 411.1252.

***N*-(*m*-Tolyl)-2-(2-(4-chlorophenyl)-6-methyl-1*H*-indol-3-yl)acetamide (4j):** Yellow solid; mp 178-179 ºC; IR (KBr) 3300, 3061, 1630, 1608, 1550, 1455, 1350, 1187, 1092, 829, 771, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, NH), 7.52-7.43 (m, 6H, ArH), 7.25 (s, 1H, NH), 7.17 (s, 1H, ArH), 7.16-7.07 (m, 2H, ArH), 7.05 (d, J = 8.1 Hz, 1H, ArH), 6.88 (d, J = 6.7 Hz, 1H, ArH), 3.92 (s, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.8, 137.4, 136.5, 134.9, 134.3, 133.6, 130.4, 129.5, 128.9, 128.7, 126.5, 125.3, 122.8, 120.7, 118.4, 117.2, 111.2, 105.5, 34.1, 21.8, 21.4; HRMS calcd for $C_{24}H_{21}ClN_2NaO$ $[M+Na]^+$ 411.1240, found 411.1254.

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