An Efficient, Simple, and Scaleable Domino Reaction to Diverse *N*-(1-Oxo-1*H*-inden-2-yl)benzamides Catalyzed by HPW@nano-SiO_2 under Microwave Irradiation

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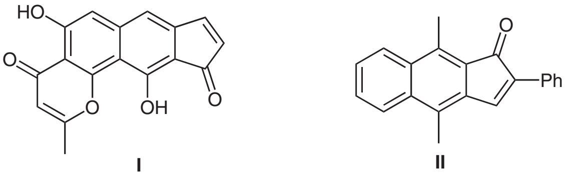
Abstract: A facile, efficient, and large-scale strategy for the synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamide derivatives via domino reaction between aryl aldehydes, hippuric acid, and acetic anhydride catalyzed by HPW@nano-SiO_2 was accomplished under microwave irradiation. The reaction conditions are very simple and offer easy isolation of the product. Moreover, the catalyst can be reused up to five times in 86% average yield after simple filtration.

Keywords: tandem reaction, indenones, heterogeneous catalyst, microwave irradiation, nanosilica, heteropoly acid

The presence of indenone skeleta in a number of naturally occurring compounds and synthetic materials, coupled with their role in biological systems, underpins the development of new methods for the preparation and functionalization of these compounds. For instance, euplectin (**I**, Figure 1), is a natural product with an indenone moiety, reported to exhibit cytotoxicity against the growth of murine P-815 mastocytoma cells.[1] Furthermore, indenone derivatives have been used as starting materials in the synthesis of kinamycin antibiotics, which show excellent activity against gram-positive bacteria.[2] On the other hand, growing efforts have been directed toward the development of new indenone-based structures as ligands in organometallic chemistry (**II**, Figure 1).[3]



I **II**

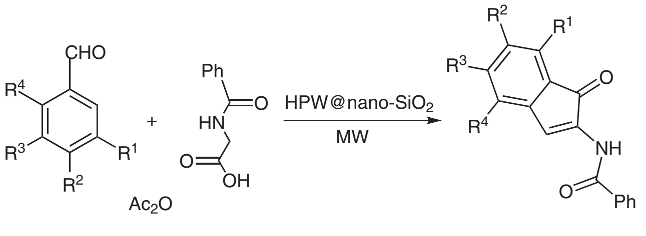
Figure 1 Structure of euplectin (**I**) and indenone-based ligand **II**

Recently, Murakami et al. reported that 2-alkynylbenzoyl cyanides can react with carboxylic acids via a cyclic allene intermediate to produce 2-acylamino-3-acylindenones after heating for 24 hours in *p*-xylene.[4] The intramolecular Friedel–Crafts (IFC) reaction is an attractive method for the formation of these types of compounds. This method was established for the synthesis of 2-benzamidoindenone by Awad et al.[5] Recently, this transformation was modified by Kangani et al. through IFC reaction of 2-benzylamino-3-phenylacrylic acid using cyanuric chloride, pyridine, and $AlCl_3$.[6] However, one of the challenging problems in such processes is the introduction of appropriate substituents during cyclization because, in some cases, the presence of functionality often hinders the desired IFC reaction.

Recently, applications of heteropoly acids (HPA) in synthesis have grown tremendously due to the potential for green benefits.[7] Among the HPA, $H_3PW_{12}O_{40}$ (HPW) is usually the catalyst of choice owing to its stronger Brønsted acidity and higher thermal stability compared to other HPA.[8] Furthermore, modifications to the activity of HPW have been performed by supporting on solids such as silica.[9]

Recent examination of functionalized silica nano particles (nano-SiO_2) and applications in organic synthesis have shown unusual behaviors.[10] To achieve an effective and new solid-acid catalytic system for organic synthesis, we decided to concentrate our attention on HPW supported on nanosilica as a powerful solid Brønsted acid which could be prepared easily by impregnating nano-SiO_2 with aqueous HPW solution.[11] This procedure yielded a white solid which could be stored at room temperature for months in a desiccator without loss of activity.

In continuation of our recent investigation on nano catalysts[12] and also fine chemicals,[13] we herein report a new, efficient, simple, and green domino reaction for the synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamide catalyzed by HPW@nano-SiO_2 (200 mg, 4 mol%) with aryl aldehydes, hippuric acid, and acetic anhydride as substrates under microwave irradiation (Scheme 1).[14]



Scheme 1 Synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides

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At the outset, 4-chlorobenzaldehyde (1 mmol), hippuric acid (1 mmol), and acetic anhydride (2 mmol) in the presence of HPW@nano-SiO_2 (200 mg, 4 mol%) was selected as a model system to investigate solvent and temperature effects under conventional heating (Table 1, entries 1–5).

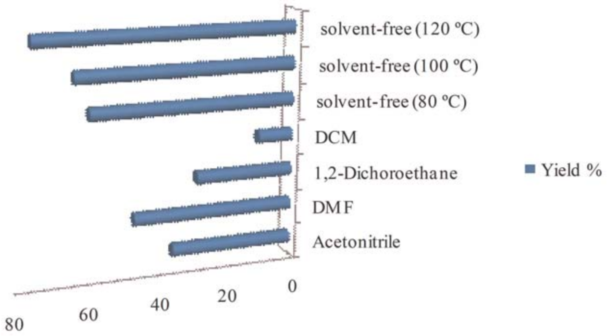


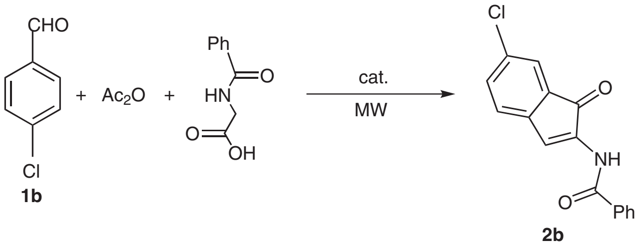
Figure 2 Solvent and temperature effects. *Reagents and conditions*: 4-chlorobenzaldehyde (1 mmol), hippuric acid (1 mmol), Ac_2O (2 mmol), HPW@nano-SiO_2 (200 mg, 4 mol%), solvent (2 mL), 1.5 h. The reaction was conducted under reflux conditions (in solvent).

As shown in Figure 2, the desired product was obtained in dichloromethane in very low yield (<10%), while the conversion of **2b** was 28% in 1,2-dichloroethane. The corresponding product in polar solvents such as acetonitrile or *N*,*N*-dimethylformamide was produced in unsatisfactory conversion (35% and 46%, respectively). A large improvement in the conversion (62%) was achieved for the reaction under solvent-free conditions at 100 °C. Higher reaction temperature (120 °C) makes an obvious difference in the yield of products (73%) but using lower reaction temperature (80 °C), sharply decreased the conversion to about 50% even with prolonged reaction times. Accordingly, performing the reaction under solvent-free microwave irradiation conditions at 120 °C was deemed to be optimal for the domino reaction.

In order to show the effect of microwave irradiation, we performed the reaction using conventional heating and compared it with the data obtained in the microwave-assisted procedure. With standard heating a 73% yield was obtained after 1.5 hours; however, prolonged reaction time did not give any improvement in the yield. We then investigated the reaction under microwave irradiation with a temperature-controlled program. During irradiation, the temperature was monitored by an IR sensor which controlled microwave power levels. At 80 °C only 74% of conversion was registered after 35 minutes (Table 1, entry 2). However, surprisingly, by increasing the temperature up to 120 °C, quantitative conversion was registered after 35 minutes, and 93% of the domino adduct **2b** was isolated (Table 1, entry 1). Notably, lower yields were obtained when the same reaction was carried out with a lesser amount of catalyst (Table 1, entry 4).

A comparison of catalytic activity between homogeneous Brønsted acids, Lewis acids, or other solid acids was examined in the model reaction under the optimal reaction conditions, showing the highest catalytic activity for HPW@nano-SiO_2 (Table 1, entries 1, 8–17). No reaction occurred in the absence of a catalyst (Table 1, entry 5) and no useful conversion was obtained in the presence of nano-SiO_2, SiO_2, or Al_2O_3 without HPW (Table 1, entries 6–8). In contrast, using HPW on solid supports such as Al_2O_3 or SiO_2 instead of nano-SiO_2 gave the product, but in lower yields (Table 1, entries 9 and 10). Homogeneous Brønsted acids such as H_2SO_4, ionic liquids such as 1-butyl-3-methyl-imidazolium hexafluorophosphate, and Lewis acids such as $BiCl_3$, $Bi(NO_3)_3{\cdot}5H_2O$, $AlCl_3$, $Zn(OTf)_2$, and even polyoxometalates such as $K_5CoW_{12}O_{40}$ gave **2b** in very poor yields (0–37%) with large amounts of side products (Table 1, entries 11–17).

Table 1 The Effect of Catalysts on the Yield of **2b** Using Microwave Energy[a]



Entry	Catalyst	Temp (°C)	Yield (%)[b]
1	HPW@nano-SiO_2 (200 mg, 4 mol%)	120	93
2	HPW@nano-SiO_2 (200 mg, 4 mol%)	80	74
3	HPW@nano-SiO_2 (200 mg, 4 mol%)	100	84
4	HPW@nano-SiO_2 (150 mg, 4 mol%)	120	75
5	–	120	n.r.
6	nano-SiO_2 (200 mg)	120	35
7	SiO_2 (200 mg)	120	30
8	alumina (200 mg)	120	20
9	HPW@SiO_2 (200 mg, 4 mol%)	120	87
10	HPW@Al_2O_3 (200 mg, 4 mol%)	120	83
11	H_2SO_4 (concd) (4 mol%)	120	37
12	[bmim]PF_6 (4 mol%)	120	10
13	$BiCl_3$ (4 mol%)	120	20
14	$Bi(NO_3)_3{\cdot}5H_2O$ (4 mol%)	120	18
15	$AlCl_3$ (4 mol%)	120	34
16	$Zn(OTf)_2$ (4 mol%)	120	5
17	$K_5CoW_{12}O_{40}$ (4mol%)	120	–

[a] Reaction conditions: 4-chlorobenzaldehyde (1 mmol), hippuric acid (1 mmol), Ac_2O (2 mmol), and catalyst after 35 min under microwave irradiation (650 W).

[b] Isolated yield.

The high catalytic performance of HPW@nano-SiO_2 was also confirmed for the scale-up reaction of **1b** (50 mmol) with hippuric acid (50 mmol), and acetic anhydride (75 mmol) in the presence of 400 mg of HPW@nano-SiO_2 in 50 minutes. After the reaction was completed, the used catalyst was easily separated by filtration from the reaction mixture, and **2b** was obtained in 91% yield after recrystallization from hot ethanol.

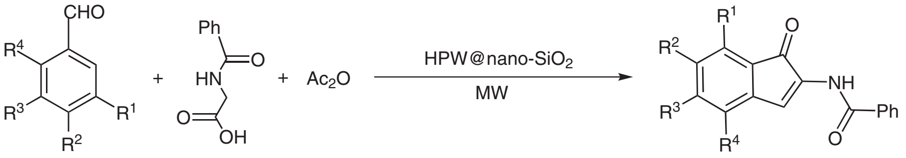
After successful generation of **2b**, we considered introduction of more diversity into the *N*-(1-oxo-1*H*-inden-2-yl)benzamide scaffold via this domino reaction. With the optimized reaction conditions in hand, we examined several aryl aldehydes and found that HPW@nano-SiO_2 is an efficient catalyst for the synthesis of a large spectrum of *N*-(1-oxo-1*H*-inden-2-yl)benzamides through this protocol (Table 2).

It was generally observed that high to excellent yields of the products were obtained in all cases, irrespective of the kind of substituent present in the aromatic ring of the aryl aldehyde, and the indene derivatives **2a**–**m** were obtained exclusively (Table 2). It was found that aryl aldehydes carrying electron-donating groups could be smoothly converted into the desired products (87–94% yields, Table 2, entries 7–9). The coupling of aryl aldehydes containing electron-withdrawing groups also afforded indenone derivatives in high to excellent isolated yields. With aryl dicarbaldehydes such as terephthalaldehyde the corresponding product was also obtained in high yield (Table 2, **2j**). Moreover, this reaction works well with heteroaromatic carbaldehydes such as 5-methylthiophene-2-carbaldehyde (Table 2, entry 11) or indole-3-carbaldehyde (Table 2, entry 12). indicating that the domino reaction is general for this transformation.

The recovered HPW@nano-SiO_2 could also be reused without any significant lessening of its catalytic performance. The catalyst was separated by filtration, washed with ethanol, and activated at 80 °C under reduced pressure. In this way, HPW@nano-SiO_2 retained its activity after five consecutive runs.

A plausible rationalization for the formation of *N*-(1-oxo-1*H*-inden-2-yl)benzamides is shown in Scheme 2. Initially, a HPW@nano-SiO_2-catalyzed azlactone **A** as an intermediate would be obtained. Subsequently, **A** undergoes IFC reaction and subsequent rearrangement to an amide, which is converted into the corresponding product.

Table 2 Synthesis of *N*-(1-Oxo-1*H*-inden-2-yl)benzamide Catalyzed by HPW@nano-SiO_2 via Domino Reaction of Aryl Aldehydes, Hippuric Acid, and Acetic Anhydride under Solvent-free Microwave Conditions



1 **2**

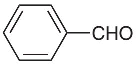
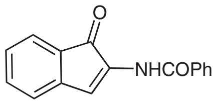
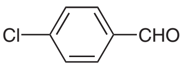
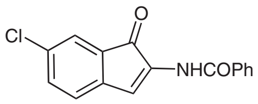
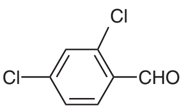
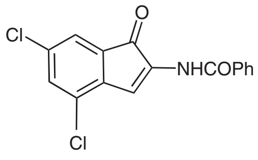
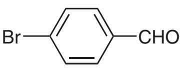
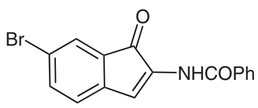
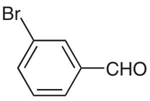
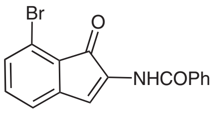
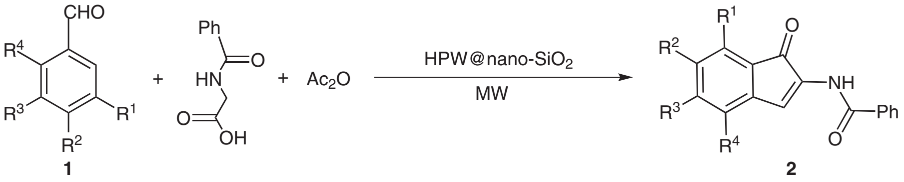
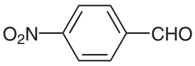
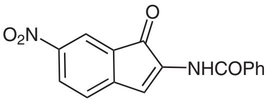
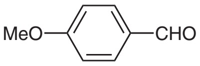
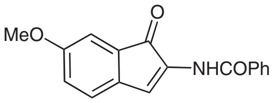
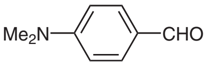
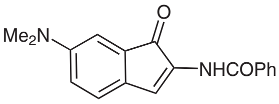
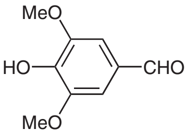
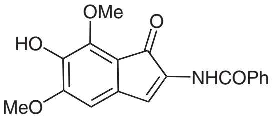
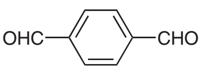
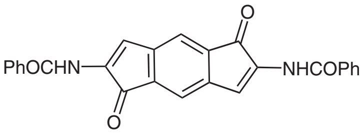
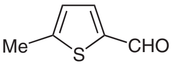
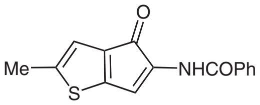
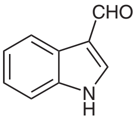
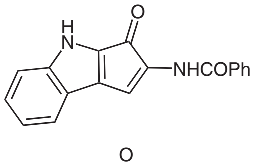
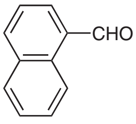
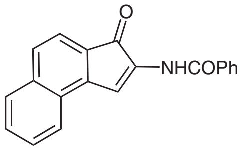
Entry	Substrate	Product		Time (min)	Yield (%)[a]
1			**2a**	40	85
2			**2b**	35	93
3			**2c**	38	82
4			**2d**	28	95
5			**2e**	35	85

Table 2 Synthesis of *N*-(1-Oxo-1*H*-inden-2-yl)benzamide Catalyzed by HPW@nano-SiO_2 via Domino Reaction of Aryl Aldehydes, Hippuric Acid, and Acetic Anhydride under Solvent-free Microwave Conditions (continued)



Entry	Substrate	Product		Time (min)	Yield (%)[a]
6			**2f**	45	90
7			**2g**	35	94
8			**2h**	32	90
9			**2i**	35	87
10			**2j**	45	83
11			**2k**	35	87
12			**2l**	43	85
13			**2m**	29	90

[a] Isolated Yield

To confirm this mechanism we also isolated the intermediate **A** and, after irradiation in the microwave oven in the presence of the catalyst, the corresponding product was afforded quantitatively.

In conclusion, we have demonstrated a practical and concise synthesis of structurally diverse *N*-(1-oxo-1*H*-inden-2-yl)benzamides via the domino microwave-assisted reaction. In this flexible and straightforward synthetic route, HPW@nano-SiO_2 was found to be a powerful catalyst which was capable of reuse without loss of efficiency for at least five runs. Notable features of our approach are the use of simple precursors, applicability of this procedure to a wide spectrum of these indenone derivatives, scalable synthesis of the indenone derivatives, and the recycling of the catalyst. We believe that the protocol described herein represents a new and efficient way for the large-scale synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides. Further research in this field is in progress.

Acknowledgment

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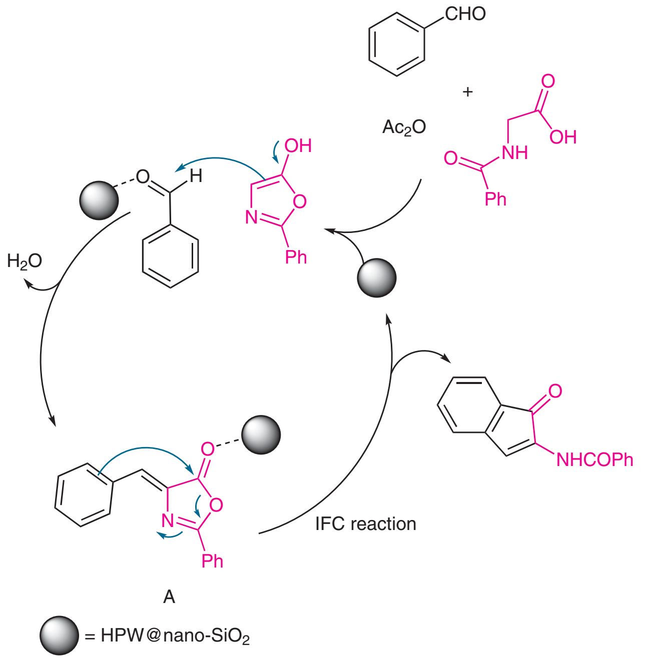

Scheme 2 Plausible mechanism

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(11) The supported $H_3PW_{12}O_{40}$ on nano-SiO$_2$ was prepared by the method of incipient wetness. In a typical process, $H_3PW_{12}O_{40}$ (400 mg) was dissolved in deionized water and impregnated dropwise onto nano-SiO$_2$ (1600 mg) with constant agitation. The resulting paste was dried for 8 h at 120 °C and calcined for 4 h at 250 °C.
(12) Khorsandi, Z.; Khosropour, A. R.; Mirkhani, V.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S. *Tetrahedron Lett.* **2011**, *52*, 1213.
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(14) **General Procedure for Synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides**

In a high-pressure Teflon reactor equipped with a magnetic stir bar and an IR sensor (for controlling of reaction temperature), a mixture of aryl aldehyde **1** (1 mmol), hippuric acid (0.179 g, 1 mmol), Ac$_2$O (0.204 g, 2 mmol), and PW@nano-SiO$_2$ (200 mg, 4 mol%) was submitted to microwave irradiation at 120 °C (650 W) using a Micro-SYNTH labstation reactor for 28–45 min. During this time, the power was modulated automatically to hold the reaction mixture at 120 °C. After the reaction was complete (monitoring by TLC), the reaction mixture was cooled to r.t., filtered, washed with a hot mixture of EtOAc–EtOH (10:1, 2 × 10 mL) and concentrated in vacuo to give crude **2**, which was purified as appropriate by recrystallization with EtOH (95%).

***N*-(6-Chloro-1-oxo-1*H*-inden-2-yl)benzamide (2b)**

FTIR (KBr, solid): 3235, 1698, 1644, 1470, 1423, 1311, 1277, 1088, 910, 699, 524 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 9.54 (s, 1 H), 7.88–7.89 (d, J = 7.55 Hz, 2 H), 7.54–7.56 (t, J = 7.80 Hz, 1 H), 7.47–7.50 (t, J = 7.80 Hz, 2 H), 7.34–7.35 (d, J = 8.10 Hz, 1 H), 7.28–7.29 (d, J = 8.10 Hz, 2 H), 7.16 (s, 1 H). ^{13}C NMR (125 MHz, DMSO): δ = 167.6, 163.5, 149.5, 137.1, 135.8, 134.7, 131.4, 130.9, 130.4, 128.4, 127.6, 127.3, 124.2, 122.9. MS (EI): *m/z* = 149.94 [M + 2], 104.87, 76.86, 50.9.

***N*-(6-Bromo-1-oxo-1*H*-inden-2-yl)benzamide (2d)**

FTIR (KBr, solid): 3235.97, 1696, 1644.98, 1477, 1438, 1314, 1279, 1072, 913, 693, 528 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 9.92 (s, 1 H), 7.94–7.95 (d, J = 7.35 Hz, 2 H), 7.58–7.60 (m, 4 H), 7.49–7.55 (m, 2 H), 7.37 (s, 1 H). ^{13}C NMR (125 MHz, DMSO): δ = 166.15, 165.83, 149.35, 133.48, 133.17, 131.76, 131.46, 130.98, 130.94, 128.41, 128.22, 127.62, 122.30. MS (EI): *m/z* = 195.96 [M + 2], 104.98, 76.97, 51. Anal. Calcd for $C_{16}H_{10}BrNO_2$: C, 58.56; H, 3.07; N, 4.27. Found: C, 58.02; H, 3.56; N, 4.07.

***N*-(6-Nitro-1-oxo-1*H*-inden-2-yl)benzamide (2f)**

FTIR (KBr, solid): 3216, 1699, 1651, 1518, 1478, 1432, 1343, 1272, 1109, 691, 326 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 9.66 (s, 1 H), 7.88–7.90 (d, J = 7.61 Hz, 1 H), 7.56–7.57 (d, J = 6.40 Hz, 1 H), 7.49–7.52 (t, J = 7.20 Hz, 2 H), 7.36–7.38 (d, J = 8.00 Hz, 2 H), 7.29–7.31 (d, J = 7.22 Hz, 2 H), 7.10 (s, 1 H). ^{13}C NMR (125 MHz, DMSO): δ = 166.14, 165.83, 149.35, 133.48, 133.18, 131.76, 131.48, 131.47, 130.98, 130.94, 128.41, 128.22, 127.62, 122.29. MS (EI): *m/z* = 294.01, 104.98, 77.03, 55.66.

***N*-(6-Methoxy-1-oxo-1*H*-inden-2-yl)benzamide (2g)**

FTIR (KBr, solid): 3386, 2929, 2839, 1690, 1653, 1439, 1079, 980, 896, 811, 516 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 9.42 (s, 1 H), 7.48–7.57 (m, 5 H), 7.36–7.38 (d, J = 8.20 Hz, 2 H), 6.83–6.85 (d, J = 8.41 Hz, 1 H), 6.78–6.80 (d, J = 8.00 Hz, 1 H), 3.73 (s, 3 H). ^{13}C NMR (125 MHz, DMSO): δ = 166.54, 165.82, 158.85, 145.98, 133.47, 133.17, 131.76, 131.5, 131.45, 130.98, 130.94, 128.4, 128.22, 122.3, 55.98. MS (EI): *m/z* = 264.08 [M – 15], 105.06, 77.03, 55.12. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.99; H, 5.00; N, 4.89.

***N,N′*-(1,5-Dioxo-1,5-dihydros-indacene-2,6-diyl)dibenzamide (2j)**

FTIR (KBr, solid): 3374, 1703, 1610, 1569, 1437, 1266, 1026, 675, 589 cm^{-1}.^{1}H NMR (400 MHz, DMSO): δ = 9.7 (s, 2 H), 7.94–7.95 (d, J = 7.10 Hz, 2 H), 7.84–7.85 (d, J = 7.10 Hz, 2 H), 7.66 (br s, 2 H), 7.49–7.51 (t, J = 8.40 Hz, 4 H), 7.41–7.44 (t, J = 8.35 Hz, 4 H). ^{13}C NMR (300 MHz, DMSO): δ = 167, 165.93, 152.17, 142.38, 133.22, 131.76, 131.48, 128.41, 127.63, 126.40, 121.48. MS (EI): *m/z* = 420.19, 105.01, 77.02, 55.04.

***N*-(2-Methyl-4-oxo-4*H*-cyclopenta[*b*]thiophen-5-yl)benzamide (2k)**

FTIR (KBr, solid): 3395, 1695, 1610, 1539, 1448, 1028, 670, 469 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 9.3 (s, 1 H), 7.99 (s, 2 H), 7.33–7.68 (m, 3 H), 7.01 (s, 1 H), 6.71 (s, 1 H), 2.35

(s, 3 H). ^{13}C NMR (125 MHz, DMSO): δ = 166.09, 163.80, 149.89, 144.12, 141.57, 135.82, 130.91, 130.4, 128.46, 127.65, 127.32, 121.99, 17.21. MS (EI): *m/z* = 148.96 (M-120), 104.94, 76.95, 57.04. Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20. Found: C, 66.45; H, 4.40; N, 5.09.

***N*-(3,4-Dihydro-3-oxocyclopenta[*b*]indol-2-yl)benzamide (2l)**

FTIR (KBr, solid): 3364, 3343, 1698, 1644, 1539, 1079, 962, 889, 792, 437 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ = 10.31 (s, 1 H), 9.98 (s, 1 H), 7.83–7.85 (d, *J* = 5.58 Hz, 2 H), 7.65 (br s, 3 H), 7.48–7.49 (d, *J* = 4.40 Hz, 2 H), 7.40–7.43 (t, *J* = 4.70 Hz, 2 H), 7.30 (s, 1 H). ^{13}C NMR (125 MHz, DMSO): δ = 166.15, 163.73, 149.35, 137.98, 133.48, 133.18, 131.76, 131.47, 131.46, 130.97, 130.84, 128.41, 128.22, 127.63, 122.29, 117.99. MS (EI): *m/z* = 167.07 [M – 120], 149, 71, 57. Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.85; H, 4.68; N, 9.01.