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Full Paper

# Direct One-Pot Cobalt(II) Phthalocyanine Catalyzed Synthesis of *N*-Substituted Isoindolinones

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A direct one-pot synthetic approach is described wherein cobalt(II) phthalocyanine (CoPc) catalyzed reductive amination of 2-carboxybenzaldehyde, followed by intramolecular amidation afforded *N*-substituted isoindolinones. The method used diphenylsilane as reducing agent in ethanol. High chemoselectivity with excellent yield was obtained in most of the studied substrates.

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## Introduction

The isoindolinone skeleton is widespread among many drugs of natural and synthetic origin.[1] *N*-substituted isoindolinones are known to possess important biological activities such as anti-inflammation, anticancer, and immunomodulation. (Fig. 1).[2] Lenalidomide is a United States Food and Drug Administration (FDA) approved drug for the treatment of multiple myeloma.[3] It has also been approved for the treatment of hematological disorders known as myelodysplastic syndromes in 2006.[3] Another analogue, CC3052, is a potent inhibitor of TNF-α production.[4] Indoprofen is a non-steroidal antiinflammatory drug and has been found to increase production of the survival of the motor neuron protein.[5] Recently, Uno et al. have described these compounds as potent hypoxia-inducible factor-1α inhibitors.[6]

Several synthetic strategies have been developed for the synthesis of *N*-substituted isoindolinones such as condensation of amines with phthalide or 2-(bromomethyl)benzoate,[7] mono-reduction of phthalimide,[7,8] and Pd catalyzed cycloaminocarbonylation of 2-iodobenzylbromide, 2-iodobenzylamine,[9] and 2-bromobenzaldehyde (Fig. 2).[10] Cao et al. described Pd catalyzed carbonylation-hydroamination reactions of 1-halo-2-alkynylbenzene and amines for the synthesis of isoindolinone derivatives in ionic liquid.[11] Rousseaux et al. described a Pd catalyzed intramolecular alkylation of amides to obtain this skeleton.[12] Marion et al. have developed a Pt catalyzed approach involving cycloisomerization of *o*-halobenzyl- or *o*-halobenzoylynamides.[13] However, methods involving environmentally benign reaction conditions, a cheap catalytic system, and easily available starting material avoiding the use of highly toxic CO are always in demand.

In continuation of our work on metal phthalocyanines as catalysts,[14] we have recently reported the cobalt(II) phthalocyanine (CoPc)/$Ph_2SiH_2$/EtOH catalyzed highly chemoselective reductive amination of carbonyl compounds, and got *N*-phenyl isoindolinone as the only product in the reaction of 2-carboxybenzaldehyde and aniline.[15] Inspired by this result and the importance of these compounds, we explored the CoPc/$Ph_2SiH_2$/EtOH system for the synthesis of different *N*-substituted isoindolinone derivatives. More recently, Shi et al. have reported on a Pt nanowires catalyzed method for the synthesis of these compounds from 2-carboxybenzaldehyde in dioxane (Fig. 2).[16] The use of a costly Pt metal catalyst, which is at high risk of depletion, and a toxic solvent[17] were the limitations. Also, Capello et al. have found that solvents like dioxane and DMF are among the worst concerning health, safety, environmental factors, energy requirements, and environmental impact of the synthesis. In contrast, small alcohols such as ethanol and methanol are among the green solvents.[18]

In this context, we report here on the first CoPc catalyzed highly chemoselective synthesis of *N*-substituted isoindolinones in ethanol as an inexpensive and safe solvent.

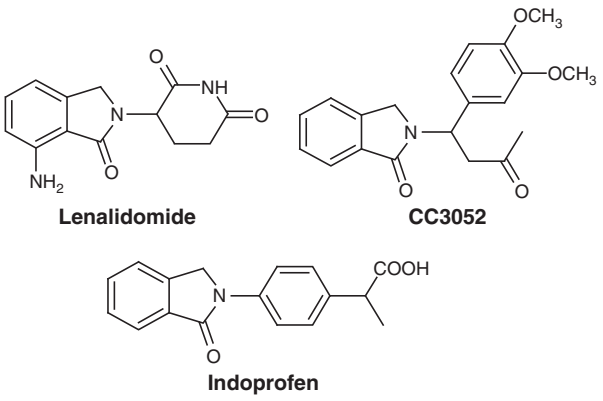



**Fig. 1.** Examples of clinically used *N*-substituted isoindolinones.

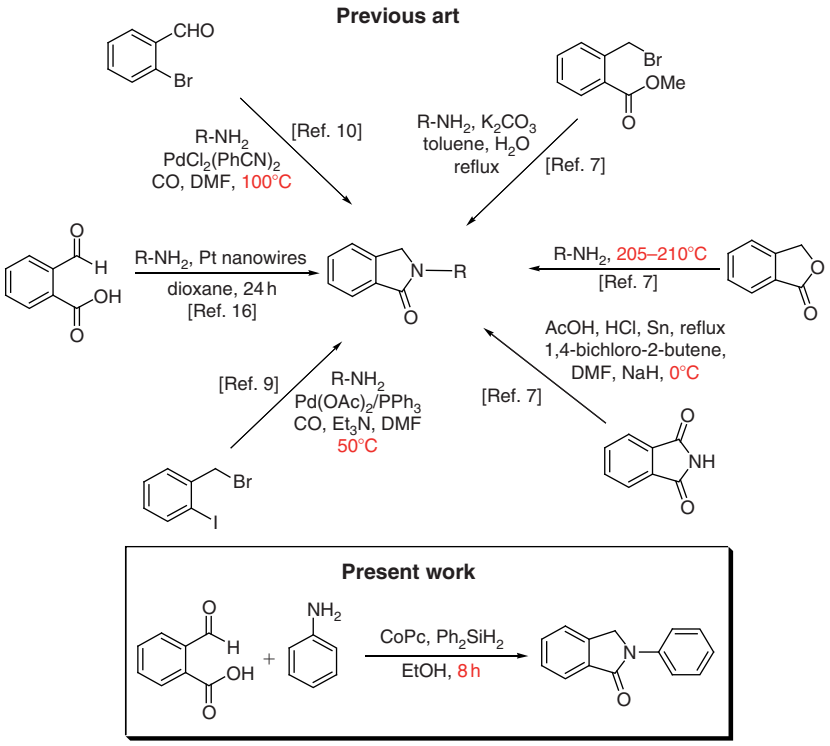
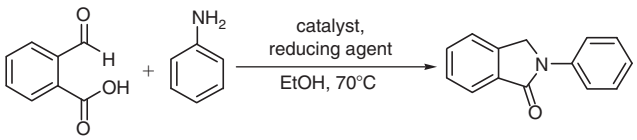



**Fig. 2.** Comparison of previous art and present work for the synthesis of *N*-substituted isoindolinones.

**Table 1. Optimization of reaction conditions**[A]




| Entry | Catalyst | Reducing agent | Yield [%][B] |
|---|---|---|---|
| 1 | – | – | ND |
| 2 | – | $Ph_2SiH_2$ | ND |
| 3 | CoPc | – | ND |
| 4[C] | CoPc | $Ph_2SiH_2$ | ND |
| 5 | CoPc | $Ph_2SiH_2$ | 92[D] |
| 6 | $CoSO_4{\cdot}6H_2O$ | $Ph_2SiH_2$ | Traces |
| 7 | $CoCl_2{\cdot}6H_2O$ | $Ph_2SiH_2$ | Traces |

[A]Reaction conditions: 2-carboxybenzaldehyde (1 mmol), aniline (1 mmol), catalyst (1 mol-%), reducing agent (1.5 equiv.) at 70°C for 8 h.
[B]Yield based on GC-MS analysis. ND, not detected.
[C]Reaction carried out at room temperature for 12 h.
[D]Isolated yield.

## Results and Discussion

Reaction between 2-carboxybenzaldehyde and aniline was used as a model reaction to determine the effect of the catalyst and the reducing agent. While no desired product was obtained at room temperature using the CoPc/$Ph_2SiH_2$ system (Table 1, entry 4), an excellent yield (92 %) of *N*-phenyl isoindolinone was obtained at 70°C (Table 1, entry 5). Also, in the absence of catalyst or reducing agent, the desired product was not detected and most of the substrate was converted to imine, 2-(phenylimino)benzoic acid (Table 1, entries 1–3). Using cobalt salts such as $CoSO_4.6H_2O$ and $CoCl_2{\cdot}6H_2O$ afforded the desired product in traces (Table 1, entries 6 and 7).

Further, to check the substrate scope, a wide range of aromatic amines (Fig. 3) was investigated and the results are summarized in Table 2. The reaction with aniline (**2a**) afforded the desired isoindolinone in excellent yield (Table 2, entry 1). No significant effect of the electron-withdrawing or releasing nature of the substituent was observed. Aromatic amines having electron-donating substituents, such as 4-$OCH_3$, 4-$CH_3$, and 4-I **2b**–**2d**, gave the desired products in excellent yields with high chemo-selectivity (Table 2, entries 2–4). The effect of steric hindrance was seen in the reaction of *o*-substituted anilines **2g**–**2h** giving the desired product in comparatively lower yields (Table 2, entries 7 and 8). The $NO_2$ group is highly susceptible to reduction;[16] however, in the present case, this group remained unaffected and the desired product was obtained in good yield (Table 2, entry 5). An aniline with a strong electron-withdrawing substituent such as 4-$COCH_3$ generally affords a low yield of product in the reductive amination step.[14] In the presence of the CoPc/$Ph_2SiH_2$ system, the reaction of 4-acetylaniline (**2f**) proceeded smoothly and the desired product was obtained in an excellent yield of 93 % (Table 2, entry 6). The reaction was also successful with a heteroaromatic amine, 6-aminobenzothiazole (**2i**) and the product was obtained in good yield (Table 2, entry 9).

A wide range of aliphatic amines (Fig. 3) were also tried and gave excellent yields of products (Table 3). In a Pd catalyzed approach by Cho and Ren involving cycloaminocarbonylation of 2-bromobenzaldehyde for the synthesis of the isoindolinone skeleton,[10] a very low yield of the product was obtained for aliphatic amines such as benzylamine. However, under our present reaction conditions, good to excellent yields were

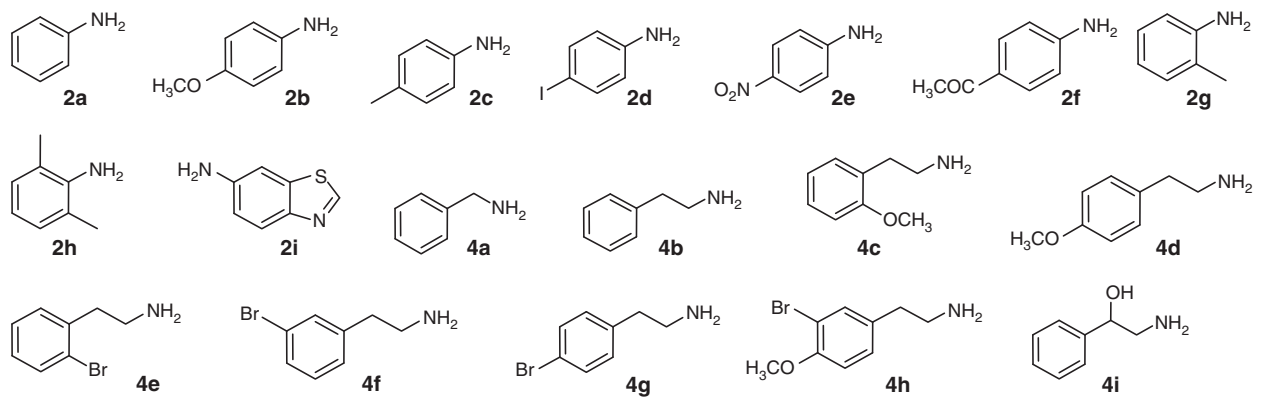
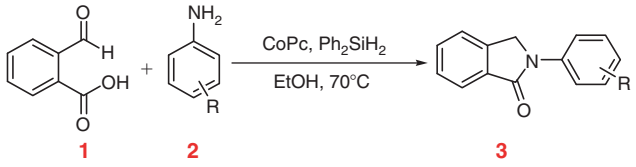



**Fig. 3.** Amines employed in the reaction.

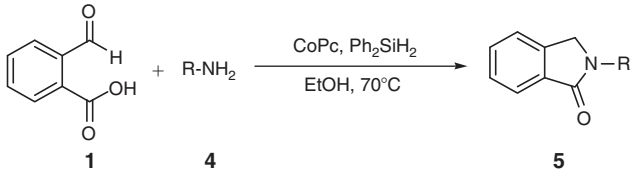
**Table 2. CoPc catalyzed synthesis of *N*-substituted isoindolinones using aromatic amines[A]**




| Entry | Amine | Product | Time [h] | Yield [%][B] |
|---|---|---|---|---|
| 1 | **2a** | **3a** | 6 | 92 |
| 2 | **2b** | **3b** | 5 | 94 |
| 3 | **2c** | **3c** | 5 | 92 |
| 4 | **2d** | **3d** | 7 | 94 |
| 5 | **2e** | **3e** | 8 | 75[C] |
| 6 | **2f** | **3f** | 8 | 93[C] |
| 7 | **2g** | **3g** | 7 | 70[C] |
| 8 | **2h** | **3h** | 8 | 58 |
| 9 | **2i** | **3i** | 8 | 71 |

[A]Reaction conditions: 2-carboxybenzaldehyde (1 mmol), amine (1 mmol), diphenylsilane (1.5 mmol), CoPc (1 mol-%) in EtOH (5 mL) at 70°C.
[B]Isolated yield.
[C]Yield based on GC-MS analysis of reaction mixture.

**Table 3. CoPc catalyzed synthesis of *N*-substituted isoindolinones using aliphatic amines[A]**



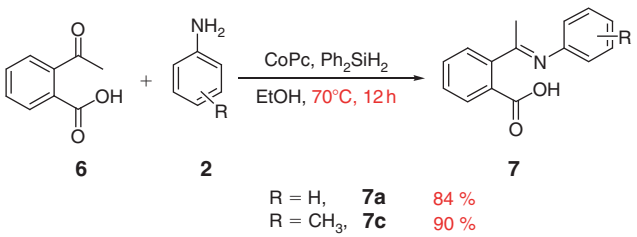

| Entry | Amine | Product | Time [h] | Yield [%][B] |
|---|---|---|---|---|
| 1 | **4a** | **5a** | 8 | 91[C] |
| 2 | **4b** | **5b** | 8 | 92 |
| 3 | **4c** | **5c** | 8 | 89 |
| 4 | **4d** | **5d** | 8 | 93 |
| 5 | **4e** | **5e** | 8 | 90 |
| 6 | **4f** | **5f** | 8 | 96 |
| 7 | **4g** | **5g** | 8 | 93 |
| 8 | **4h** | **5h** | 8 | 94 |
| 9 | **4i** | **5i** | 8 | 85 |

[A]Reaction conditions: 2-carboxybenzaldehyde (1 mmol), amine (1 mmol), diphenylsilane (1.5 mmol), CoPc (1 mol-%) in EtOH (5 mL) at 70°C.
[B]Isolated yield.
[C]Yield based on GC-MS analysis of reaction mixture.

obtained (Table 3, entries 1–9). 2-Acetylbenzoic acid was also tested in the reaction with different amines, however, the reaction stopped at the imine stage and the desired isoindolinone was not observed (Scheme 1), which may be due to steric hindrance of hydride.

## Conclusions

A series of *N*-substituted isoindolinones has been synthesized by reductive amination-intramolecular amidation of 2-carboxybenzaldehyde in one pot using $Ph_2SiH_2$ as reducing agent in ethanol. Use of a green solvent and easily available starting material with low loading of catalyst under ambient reaction conditions makes the present method superior to earlier reported methods. Other remarkable advantages of this methodology include high isolated yields, clean reactions, and an easy work-up procedure.




**Scheme 1.**

## Experimental

### *General*

Cobalt phthalocyanine was synthesized by a reported procedure[19] with some modification and characterized by infrared spectroscopy and UV-VIS spectroscopy. Silica gel (60–120 mesh) was used for column chromatography and was purchased

from Sisco Research Laboratories Pvt. Ltd India. Other chemicals were purchased from Spectrochem (India), Merck (Germany), and Sigma–Aldrich (USA) and were used without further purification. NMR spectra were recorded on a Bruker Avance-300 spectrometer. Mass spectra were recorded on a QTOF-Micro instrument from Waters Micromass and Maxis-Bruker. The GC-MS analysis was carried out on a Shimadzu (QP 2010) series Gas Chromatogram-Mass Spectrometer (Tokyo, Japan), AOC-20i auto-sampler coupled, and a DB-5MS capillary column, (30 m × 0.25 mm i.d., 0.25 μm). The initial temperature of the column was 70°C held for 4 min and was programmed to 230°C at 4°C $min^{-1}$, then held for 15 min at 230°C; the sample injection volume was 2 μL in GC grade dichloromethane. Helium was used as carrier gas at a flow rate of 1.1 mL $min^{-1}$ on split mode (1 : 50).

### *General Procedure for the Synthesis of* N*-Substituted Isoindolinones*

To a stirred suspension of CoPc (0.01 mmol) in ethanol were added 2-carboxybenzaldehyde (1.0 mmol), amine (1.0 mmol), and diphenylsilane (1.5 mmol) at room temperature. The temperature was then raised to 70°C. After, completion of the reaction (as monitored by TLC), the reaction mixture was filtered and passed through anhydrous $Na_2SO_4$. The crude product was purified by column chromatography over silica-gel (60–120) mesh.

### *Characterization Data of Products*

#### N*-Phenylisoindolone* ***3a***

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.47, white solid, mp 133–135°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.88–7.96 (m, 2H), 7.78 (m, 1H), 7.59–7.61 (m, 1H), 7.52–7.55 (m, 1H), 7.42–7.50 (m, 3H), 7.17–7.22 (m, 1H), 4.76–4.88 (m, 2H); $\delta_C$ (75 MHz, $CDCl_3$) 168.0, 140.5, 139.9, 133.6, 132.4, 129.5, 128.7, 124.8, 124.5, 123.0, 119.8, 51.1; HRESIMS calcd for $C_{14}H_{11}NNaO$ $[M+Na]^+$ 232.0738, found 232.0739.

#### N*-(4-Methoxyphenyl)isoindolinone* ***3b***

Eluent – ethyl acetate : *n*-hexane (3 : 7), $R_F$ 0.50, yellow solid, mp 193–195°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.92 (d, *J* 7.9, 1H), 7.75 (d, *J* 8.8, 2H), 7.48–7.60 (m, 3H), 6.97 (d, *J* 8.8, 2H), 4.79 (s, 2H), 3.82 (s, 3H); $\delta_C$ (75 MHz, $CDCl_3$) 167.6, 157.0, 140.5, 133.6, 132.2, 128.8, 128.0, 124.3, 122.9, 121.8, 114.7, 55.8, 51.5.

#### N*-(4-Methylphenyl)isoindolinone* ***3c***

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.54, brown solid, mp 134–135°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.93 (d, *J* 7.6, 1H), 7.75 (d, *J* 8.0, 2H), 7.57–7.62 (m, 1H), 7.50–7.52 (m, 2H), 7.24 (d, *J* 8.0, 2H), 4.82 (s, 2H), 2.36 (s, 3H); $\delta_C$ (75 MHz, $CDCl_3$) 167.7, 140.5, 137.3, 134.5, 133.7, 132.3, 130.0, 128.7, 124.4, 122.9, 119.9, 51.2, 21.2.

#### N*-(4-Iodophenyl)isoindolinone* ***3d***

Eluent – ethyl acetate : *n*-hexane (1 : 9), $R_F$ 0.43, yellow solid, mp 140–142°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.90 (d, *J* 7.5, 1H), 7.64–7.72 (m, 4H), 7.59–7.61 (m, 1H), 7.50–7.52 (m, 2H), 4.80 (s, 2H); $\delta_C$ (75 MHz, $CDCl_3$) 167.9, 140.2, 139.6, 138.4, 133.2, 132.7, 128.9, 124.5, 123.0, 121.3, 88.2, 50.8.

#### N*-(2,6-Dimethylphenyl)isoindolinone* ***3h***

Eluent –ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.45, brown oil. $\delta_H$ (300 MHz, $CDCl_3$) 7.99 (d, *J* 7.8, 1H), 7.61–7.63 (m, 1H), 7.52–7.56 (m, 2H), 7.16–7.21 (m, 3H), 4.62 (s, 2H), 2.20 (s, 6H); $\delta_C$ (75 MHz, $CDCl_3$) 168.3, 142.1, 137.2, 134.8, 132.7, 132.1, 128.98, 128.91, 128.6, 124.7, 123.3, 51.6, 18.3.

#### N*-Phenethylisoindolinone* ***5b***

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.50, brown solid, mp 88–90°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.86 (d, *J* 7.2, 1H), 7.43–7.54 (m, 2H), 7.39 (d, *J* 7.2, 1H), 7.21–7.33 (m, 5H), 4.22 (s, 2H), 3.89 (t, *J* 7.3, 2H), 3.01 (t, *J* 7.3, 2H); $\delta_C$ (75 MHz, $CDCl_3$) 168.8, 141.5, 139.2, 133.2, 131.5, 129.1, 129.0, 128.3, 126.9, 124.0, 123.0, 51.0, 44.5, 35.3; HRESIMS calcd for $C_{16}H_{15}NNaO$ $[M+Na]^+$ 260.1051, found 260.1042.

#### N*-(2′-Methoxyphenethyl)isoindolinone* ***5c***

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.55, brown oil. $\delta_H$ (300 MHz, $CDCl_3$) 7.85 (d, *J* 7.3, 1H), 7.42–7.51 (m, 2H), 7.38 (d, *J* 7.3, 1H), 7.14–7.24 (m, 2H), 6.83–6.89 (m, 2H), 4.25 (s, 2H), 3.84–3.89 (m, 2H), 3.81 (s, 3H), 2.99–3.04 (m, 2H); $\delta_C$ (75 MHz, $CDCl_3$) 168.8, 158.0, 141.7, 133.4, 131.4, 130.9, 128.2, 127.5, 123.9, 122.9, 121.0, 110.6, 55.6, 50.9, 42.9, 30.0; HRESIMS calcd for $C_{17}H_{17}NNaO_2$ $[M+Na]^+$ 290.1157, found 290.1156.

#### N*-(4′-Methoxyphenethyl)isoindolinone* ***5d***

Eluent – ethyl acetate : *n*-hexane (3 : 7), $R_F$ 0.60, yellow solid, mp 95–97°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.85 (d, *J* 7.3, 1H), 7.42–7.53 (m, 2H), 7.38 (d, *J* 7.3, 1H), 7.16 (d *J* 8.3, 2H), 6.83 (d, *J* 8.3, 2H), 4.20 (s, 2H), 3.81–3.86 (m, 2H), 3.78 (s, 3H), 2.92–2.97 (m, 2H); $\delta_C$ (75 MHz, $CDCl_3$) 168.8, 158.6, 141.5, 133.2, 131.5, 131.2, 130.0, 128.3, 123.9, 123.0, 114.4, 55.6, 51.0, 44.6, 34.3; HRESIMS calcd for $C_{17}H_{17}NNaO_2$ $[M+Na]^+$ 290.1157, found 290.1162.

#### N*-(2′-Bromophenethyl)isoindolinone* ***5e***

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.55, yellow solid, mp 86–88°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.84 (d, *J* 7.4, 1H), 7.51–7.55 (m, 2H), 7.45 (d, *J* 7.4, 1H), 7.37–7.40 (m, 1H), 7.27–7.31 (m, 1H), 7.17–7.22 (m, 1H), 7.06–7.11 (m, 1H), 4.26 (s, 2H), 3.84–3.89 (m, 2H), 3.10–3.15 (m, 2H); $\delta_C$ (75 MHz, $CDCl_3$) 168.9, 141.6, 138.4, 133.3, 133.1, 131.6, 131.3, 128.8, 128.3, 128.1, 124.8, 124.0, 123.0, 50.9, 42.7, 35.4; HRESIMS calcd for $C_{16}H_{14}BrNNaO$ $[M+Na]^+$ 338.0156, found 338.0141.

#### N*-(3′-Bromophenethyl)isoindolinone* ***5f***

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.50, light brown solid, mp 118–120°C. $\delta_H$ (300 MHz, [D4]methanol) 7.68 (d, *J* 7.4, 1H), 7.49–7.51 (m, 1H), 7.39–7.45 (m, 3H), 7.27–7.29 (m, 1H), 7.13–7.20 (m, 2H), 4.32 (s, 2H), 3.75–3.80 (m, 2H), 2.89–2.96 (m, 2H); $\delta_C$ (75 MHz, [D4]methanol) 170.2, 142.8, 142.3, 132.8, 132.4, 130.9, 130.2, 128.7, 128.2, 123.7, 123.6, 123.1, 51.3, 44.4, 34.6.

#### N*-(4′-Bromophenethyl)isoindolinone* ***5g***

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.55, off white solid, mp 120–122°C. $\delta_H$ (300 MHz, [D4]methanol) 7.75 (d, *J* 7.5, 1H), 7.46–7.59 (m, 3H), 7.41–7.43 (m, 2H), 7.17–7.20 (m, 2H), 4.40 (s, 2H), 3.84–3.89 (m, 2H), 2.96–3.01 (m, 2H); $\delta_C$

(75 MHz, [D4]methanol) 169.6, 142.2, 138.4, 132.3, 131.8, 131.6, 130.7, 128.1, 123.1, 123.0, 120.2, 50.7, 43.8, 33.8.

### *N-(3′-Bromo-4′-methoxyphenethyl)isoindolinone* **5h**

Eluent – ethyl acetate : *n*-hexane (3 : 7), $R_F$ 0.45, yellow solid, mp 114–116°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.84 (d, *J* 7.4, 1H), 7.43–7.52 (m, 3H), 7.40 (d, *J* 7.4, 1H), 7.12–7.16 (m, 1H), 6.80–6.83 (m, 1H), 4.24 (s, 2H), 3.86 (s, 3H), 3.80–3.82 (m, 2H), 2.89–2.94 (m, 2H); $\delta_C$ (75 MHz, $CDCl_3$) 168.9, 154.9, 141.4, 133.8, 133.1, 132.7, 131.6, 129.0, 128.4, 124.0, 123.0, 112.4, 112.0, 56.6, 50.9, 44.4, 34.0.

### *N-(1-Hydroxyphenethyl)isoindolinone* **5i**

Eluent – ethyl acetate : *n*-hexane (4 : 6), $R_F$ 0.60, brown solid, mp 153–155°C. $\delta_H$ (300 MHz, [D6]DMSO) 7.67 (d, *J* 7.4, 1H), 7.55–7.61 (m, 2H), 7.44–7.51 (m, 1H), 7.25–7.40 (m, 5H), 5.61–5.63 (m, 1H), 4.84–4.90 (m, 1H), 4.57–4.63 (m, 1H), 4.33–4.39 (m, 1H), 3.66–3.68 (m, 2H); $\delta_C$ (75 MHz, [D6]DMSO) 167.7, 143.5, 142.3, 132.5, 131.4, 128.3, 127.9, 127.4, 126.2, 123.4, 122.8, 71.4, 51.2, 50.1.

### *2-(1′-Methyl-N-phenylimino)benzoic acid* **7a**

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.45, off white solid, $\delta_H$ (300 MHz, $CDCl_3$) 7.89–7.92 (m, 1H), 7.66–7.71 (m, 1H), 7.55–7.59 (m, 2H), 7.02–7.08 (m, 2H), 6.82–6.87 (m, 1H), 6.54–6.57 (m, 2H), 1.96 (s, 3H); $\delta_C$ (75 MHz, $CDCl_3$) 169.1, 150.6, 142.4, 134.8, 130.5, 129.3, 128.0, 126.1, 122.7, 122.2, 119.6, 97.8, 29.0.

### *2-(1′-Methyl-N-tolylimino)benzoic acid* **7c**

Eluent – ethyl acetate : *n*-hexane (2 : 8), $R_F$ 0.50, off white solid, $\delta_H$ (300 MHz, $CDCl_3$) 7.86–7.88 (m, 1H), 7.66–7.69 (m, 1H), 7.55–7.59 (m, 2H), 6.87 (d, *J* 8.2, 2H), 6.53 (d, *J* 8.2, 2H), 2.19 (s, 3H), 1.95 (s, 3H); $\delta_C$ (75 MHz, $CDCl_3$) 169.2, 150.5, 139.5, 134.6, 132.5, 130.4, 129.8, 128.1, 126.0, 122.8, 121.5, 98.6, 28.6, 20.9.

## Supplementary Material

General experimental, procedure for synthesis of cobalt phthalocyanines, general procedure for the synthesis of *N*-substituted isoindolinones, and $^1H$ and $^{13}C$ NMR spectra of synthesized compounds are available on the Journal's website.

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## References

[1] (a) C. Riedinger, J. A. Endicott, S. J. Kemp, L. A. Smyth, A. Watson, E. Valeur, B. T. Golding, R. J. Griffin, I. R. Hardcastle, M. E. Noble, J. M. McDonnell, *J. Am. Chem. Soc.* **2008**, *130*, 16038. doi:10.1021/JA8062088
(b) J. T. Link, S. Raghavan, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 552. doi:10.1021/JA00106A072
(c) D. L. Comins, S. Schilling, Y. Zhang, *Org. Lett.* **2005**, *7*, 95. doi:10.1021/OL047824W
(d) F. A. Luzzio, A. V. Mayorov, S. S. W. Ng, E. A. Kruger, W. D. Figg, *J. Med. Chem.* **2003**, *46*, 3793. doi:10.1021/JM020079D
(e) W. T. Jiaang, Y. S. Chen, T. Hsu, T. H. Wu, C. H. Chien, C. N. Chang, S. P. Chang, S. J. Lee, X. Chen, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 687. doi:10.1016/J.BMCL.2004.11.023

[2] (a) G. W. Muller, R. Chen, S. Y. Huang, L. G. Corral, L. M. Wong, R. T. Patterson, Y. Chen, G. Kaplan, D. I. Stirling, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1625. doi:10.1016/S0960-894X(99)00250-4
(b) U. Ghosh, R. Bhattacharyya, A. Keche, *Tetrahedron* **2010**, *66*, 2148. doi:10.1016/J.TET.2010.01.070
(c) I. Takahashi, E. Hirano, T. Kawakami, H. Kitajima, *Heterocycles* **1996**, *43*, 2343. doi:10.3987/COM-96-7596

[3] P. L. McCarthy, K. Owzar, C. C. Hofmeister, *N. Engl. J. Med.* **2012**, *366*, 1770. doi:10.1056/NEJMOA1114083

[4] J. B. Marriott, M. Westby, S. Cookson, M. Guckian, S. Goodbourn, G. Muller, M. G. Shire, D. Stirling, A. G. Dalgleish, *J. Immunol.* **1998**, *161*, 4236.

[5] M. R. Lunn, D. E. Root, A. M. Martino, *Chem. Biol.* **2004**, *11*, 1489. doi:10.1016/J.CHEMBIOL.2004.08.024

[6] M. Uno, H. S. Ban, H. Nakamura, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3166. doi:10.1016/J.BMCL.2009.04.122

[7] M. H. Norman, D. J. Minick, G. C. Rigdon, *J. Med. Chem.* **1996**, *39*, 149. doi:10.1021/JM9502201

[8] S. Das, D. Addis, L. R. Knopke, U. Bentrup, K. Junge, A. Brukner, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 9180. doi:10.1002/ANIE.201104226

[9] D. Marosvölgyi-Haskó, A. Takacs, Z. Riedl, L. Kollar, *Tetrahedron* **2011**, *67*, 1036. doi:10.1016/J.TET.2010.11.099

[10] C. S. Cho, W. X. Ren, *Tetrahedron Lett.* **2009**, *50*, 2097. doi:10.1016/J.TETLET.2009.02.109

[11] H. Cao, L. McNamee, H. Alper, *Org. Lett.* **2008**, *10*, 5281. doi:10.1021/OL8021403

[12] S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692. doi:10.1021/JA103081N

[13] F. Marion, J. Coulomb, A. Servais, C. Courillon, L. Fensterbank, M. Malacria, *Tetrahedron* **2006**, *62*, 3856. doi:10.1016/J.TET.2005.11.092

[14] (a) U. Sharma, P. Kumar, N. Kumar, V. Kumar, B. Singh, *Adv. Synth. Catal.* **2010**, *352*, 1834. doi:10.1002/ADSC.201000191
(b) U. Sharma, P. K. Verma, N. Kumar, V. Kumar, M. Bala, B. Singh, *Chemistry* **2011**, *17*, 5903. doi:10.1002/CHEM.201003621
(c) P. K. Verma, U. Sharma, N. Kumar, M. Bala, V. Kumar, B. Singh, *Catal. Lett.* **2012**, *142*, 907. doi:10.1007/S10562-012-0832-2
(d) U. Sharma, N. Kumar, P. K. Verma, V. Kumar, B. Singh, *Green Chem.* **2012**, *14*, 2289. doi:10.1039/C2GC35452G

[15] V. Kumar, U. Sharma, P. K. Verma, N. Kumar, B. Singh, *Adv. Synth. Catal.* **2012**, *354*, 870. doi:10.1002/ADSC.201100645

[16] L. Shi, L. Hu, J. Wang, X. Cao, H. Gu, *Org. Lett.* **2012**, *14*, 1876. doi:10.1021/OL300471A

[17] P. G. Jessop, *Green Chem.* **2011**, *13*, 1391. doi:10.1039/C0GC00797H

[18] C. Capello, U. Fischer, K. Hungerbuhler, *Green Chem.* **2007**, *9*, 927. doi:10.1039/B617536H

[19] K. S. Jung, J. H. Kwon, S. M. Shon, J. P. Ko, J. S. Shin, S. S. Park, *J. Mater. Sci.* **2004**, *39*, 723. doi:10.1023/B:JMSC.0000011541.91490.88