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Synthesis of (*E*)-3-Alkylideneindolin-2-ones by an Iron-Catalyzed Aerobic Oxidative Condensation of Csp^3–H Bonds of Oxindoles and Benzylamines

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Dedicated to Prof. Sambasivarao Kotha for his outstanding contribution to the transition metal mediated organic synthesis.

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http://www.du.ac.in/du/uploads/Faculty%20Profiles/Chemistry/Chem_Gopalaiah_Kovuru.pdf

Abstract

A novel synthetic route for the construction of (*E*)-3-alkylideneindolin-2-ones via iron-catalyzed aerobic oxidative condensation of oxindoles with benzylamines has been developed. This oxidative reaction involves a sequence of C-H activation, amine self-condensation, nucleophilic addition, and C-C double bond formation. The synthetic importance of this protocol has been demonstrated by preparing tyrosine kinase inhibitors, anticonvulsant and antitumor agents, and other valuable 3-alkylideneindolin-2-one derivatives. Key intermediates are isolated and a plausible mechanistic pathway for the reaction has been discussed.

Keywords*: oxidative condensation, 3-alkylideneindolin-2-ones, iron catalyst, C-H activation, oxindoles*

Introduction

The 3-alkylideneindolin-2-one scaffold is a prevalent motif found in many biologically active compounds (Figure 1).[1] In addition, 3-alkylideneindolin-2-ones serve as useful precursors for the synthesis of naturally occurring alkaloids[2] and drug candidates.[3] The traditional method for preparing these compounds is the Knoevenagel reaction between oxindole and carbonyl compounds, but it is limited due to its low stereoselectivity (eq. 1 in Scheme 1).[4] In the past few years, tremendous efforts have been made toward the stereoselective synthesis of these important molecules via the transition-metal-catalyzed intramolecular hydroarylation and sequential reactions. For instance, Taylor and co-workers reported a tandem Horner-Wadsworth-Emmons olefination/Pd-catalyzed intramolecular Heck reaction of *ortho*-halo-anilides with aldehydes (eq. 2 in Scheme 1).[5] Yamamoto et al. and Murakami et al. independently demonstrated the palladium or rhodium-catalyzed cyclization reactions of 2-(alkynyl)aryl isocyanates with terminal alkynes and organoboronic acids, respectively to construct 3-alkylideneindolin-2-one derivatives (eq. 3 in Scheme 1).[6] Ma and other research groups reported the formation of 3-alkylideneindolin-2-ones through the cyclization of 2-alkynylanilines in the presence of carbon dioxide/carbon monoxide using palladium, rhodium and nickel catalysts (eq. 4 in Scheme 1).[7] Zhu et al.[8] and Li et al.[9] independently developed palladium-catalyzed domino carbopalladation/C-H activation/C-C bond-forming reactions that employs an anilide sp^2 C-H bond and either an electrophilic reagent (Ar-I) or a nucleophilic reagent (Ar-H, R-OH, R-CO_2H, Ar$I(OAc)_2$, and phthalimide) as the coupling partners to give 3-alkylideneindolin-2-ones (eq. 5 in Scheme 1). Nagasawa's group demonstrated the formation of 3-alkylideneindolin-2-ones from *N*-cinnamoylanilines via palladium-catalyzed aromatic C-H activation and intramolecular alkenylation (eq. 6 in Scheme 1).[10] Despite their usefulness, many of these precious metal

catalyzed processes are not applicable in biotechnological or pharmaceutical applications due to the toxicity concerns, and the requirement of specially functionalized starting materials, expensive catalysts, and large amount of oxidants and bases. Therefore, the more straightforward, stereospecific, cost-effective, and environmentally benign routes to construct 3-alkylideneindolin-2-ones are highly needed.

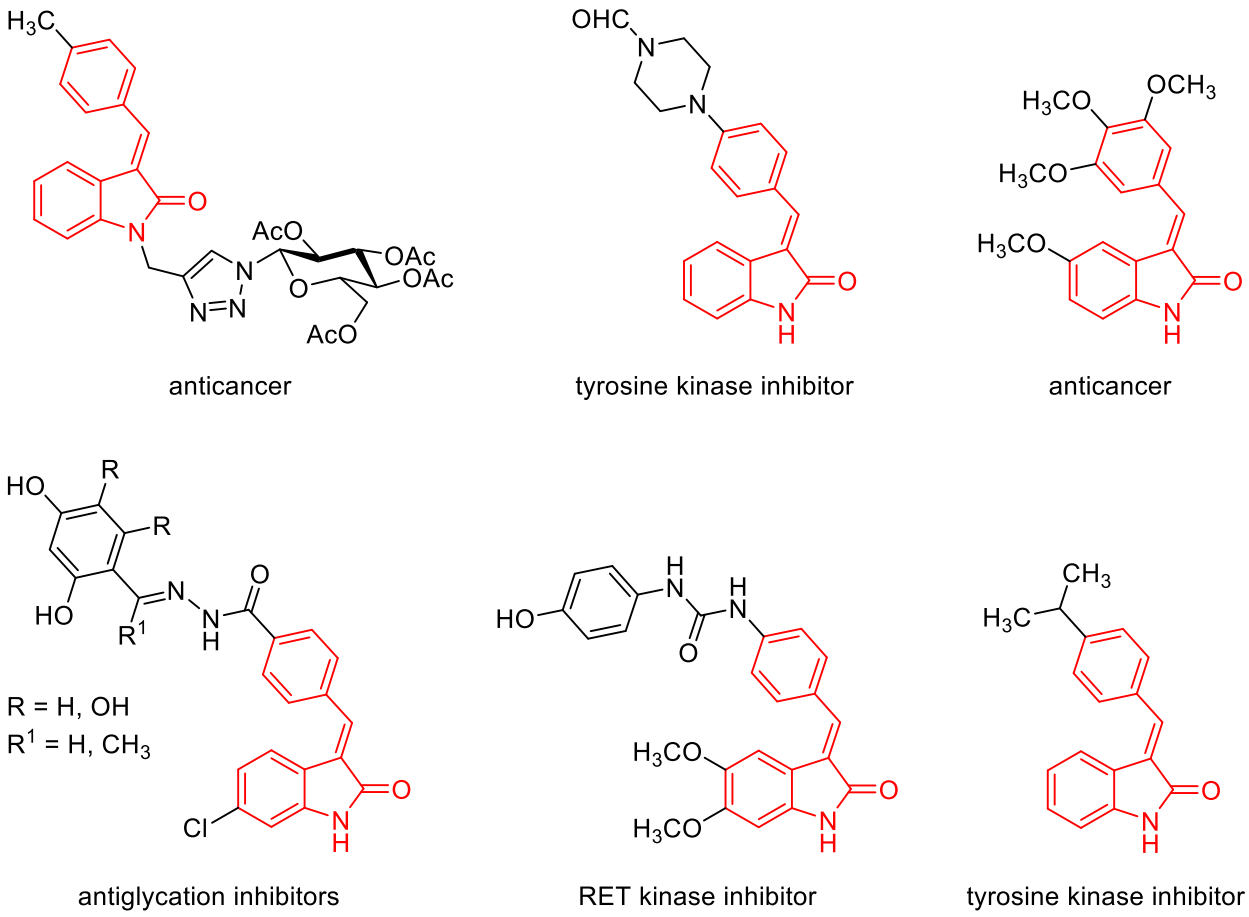

Figure 1. Representative 3-Alkylideneindolin-2-one Based Biologically Active Compounds

In recent years, researchers have made impressive developments in the iron-catalyzed C-H bond oxidative transformations owing to their low-cost, availability, and environmentally friendly features.[11] For these oxidative reactions, oxygen or air are ideal oxidants because they are cheap, renewable, and generates at best water as the by-product. Our group and others successfully employed the Fe(II or III)/O_2 (air) catalytic system for oxidative transformation of C-H bonds and X-H (X is a heteroatom) bonds to construct carbon-carbon and carbon-heteroatom bonds.[12,13] Inspired by these studies, we expected that 3-alkylideneindolin-2-ones could be furnished from oxindoles and benzylamines when iron salts are employed as catalysts. Herein we describe an iron(II)-catalyzed oxidative condensation of Csp^3–H bonds of oxindoles and benzylamines for the synthesis of (*E*)-3-alkylideneindolin-2-one scaffolds under aerobic conditions (eq. 7 in Scheme 1).

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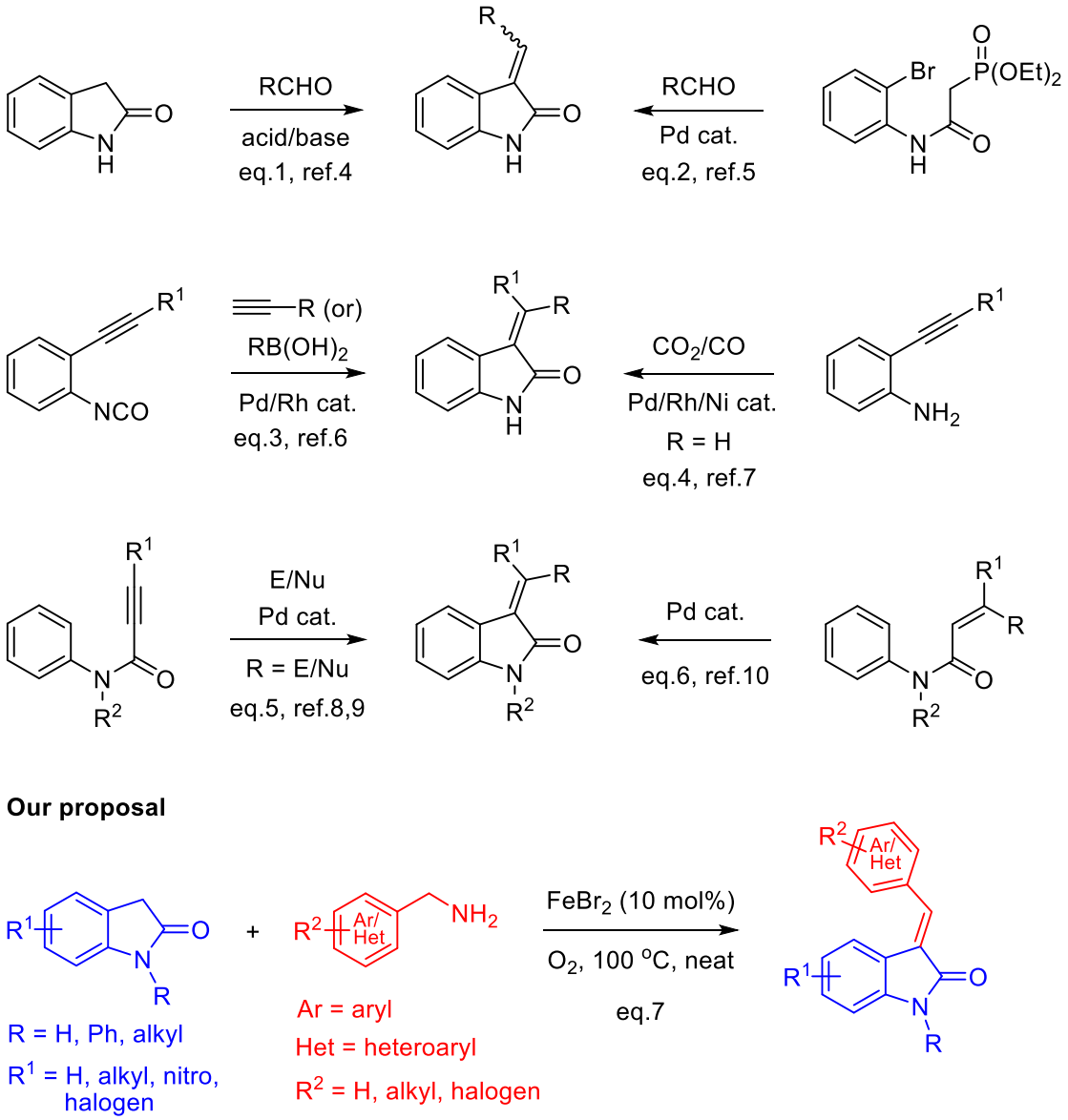
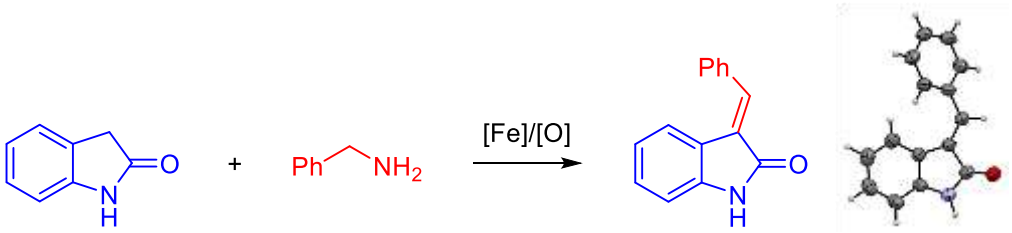


Scheme 1. Strategies for the Synthesis of 3-Alkylideneindolin-2-ones

Results and Discussion

The reaction of oxindole (**1a**) and benzylamine (**2a**) was chosen as a model system to investigate the optimal reaction conditions (Table 1). After screening of several iron(II) and iron(III) catalysts in toluene at 100 ^{o}C for 8 h under the atmosphere of molecular oxygen (entries 1-8), $FeBr_2$ turned out to be the most effective catalyst, and afforded ((*E*)-3-benzylideneindolin-2-one (**3a**) in 68% yield as a single stereoisomer (*E*/*Z* = >25:1 by ^{1}H NMR) (entry 6). The *E*-configuration of the trisubstituted double bond was unambiguously assigned by X-ray analysis.[14] We next surveyed the effect of various solvents. The reactions proceeded with low yields in DME (1,2-dimethoxyethane), 1,4-dioxane, and DMSO (entries 9-11). To our delight, in the absence of solvent, the reaction efficiency was enhanced and yield of the product **3a** was increased to 81% (entry 12). The effect of air or molecular oxygen as oxidant in the reaction was also examined. A lower yield of **3a** was observed when the reaction carried out under air atmosphere, and only trace amount of product was formed in the absence of oxygen (entries 13 and 14). Subsequently, other conditions, such as temperature and reaction time, were evaluated using $FeBr_2/O_2$ system. No substantial improvement in the yield was observed when elevating the reaction temperature to 120 ^{o}C, while low yield of the product was noticed at 80 ^{o}C (entries 15 and 16). Interestingly, when the reaction time was extended from 8 to 16 h, the yield of **3a** was further improved to 90% (entry 17). Furthermore, we carried out the reaction with iron(III) bromide under solvent-free conditions, which gave the product **3a** in 65% yield (entry 18). This oxidative reaction did not proceed in the absence of iron catalyst (entry 19).

Table 1. Screening of Reaction Parameters[a]



1a **2a** **3a** CCDC 2026460

entry	catalyst	solvent	yield (%)[b]
1	Fe_2O_3	toluene	14
2	$FeCl_3$	toluene	26
3	$FeBr_3$	toluene	34
4	$Fe(acac)_3$	toluene	11
5	$FeCl_2$	toluene	53
6	$FeBr_2$	toluene	68
7	$Fe(OAc)_2$	toluene	37
8	$Fe(ClO_4)_2.xH_2O$	toluene	49
9	$FeBr_2$	DME	40
10	$FeBr_2$	1,4-dioxane	53
11	$FeBr_2$	DMSO	12
12	$FeBr_2$	--	81
13[c]	$FeBr_2$	--	52
14[d]	$FeBr_2$	--	trace
15[e]	$FeBr_2$	--	83
16[f]	$FeBr_2$	--	56
17[g]	$FeBr_2$	--	90
18[g]	$FeBr_3$	--	65
19	--	--	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), [Fe] (5 mol %) in solvent (2 mL) at 100 °C for 8 h under oxygen atmosphere, unless otherwise specified. [b] Isolated yields. [c] Performed under air atmosphere. [d] Performed in sealed tube. [e] Performed at 120 °C. [f] Performed at 80 °C. [g] Reaction time is 16 h.

With the established reaction conditions in hand (Table 1, entry 17), we first studied the scope of oxindoles bearing different substituents on the arene periphery (Scheme 2). As illustrated, the oxindoles possessing electron-donating groups such as methyl, *iso*-propyl, or methoxy at the 5 position of the aryl ring were efficiently reacted with benzylamine, producing the desired products with high yields (**3b**, **3c**, **3d**). Electron-releasing disubstituted oxindole also furnished excellent yield of the product (**3e**). Oxindoles bearing electron-withdrawing substituents such as fluoro, chloro, bromo, or iodo groups at the 5 position also smoothly underwent the reaction to furnish the corresponding alkenylated products in good to high yields (**3f**, **3h**, **3k**, **3l**). In addition, oxindole derivatives with chloro substituent in the 4, 6, or 7 position performed well, giving the desired products in high yields (**3g**, **3i**, **3j**). Notably, even when a strong electron-withdrawing group such as NO_2 substituted oxindole was employed as substrate, the reaction proceeded to give the desired alkenylated product **3m** in synthetically useful yield.

Next, we examined the reactions of oxindoles bearing different substituents on the nitrogen with benzylamine. The *N*-alkyl oxindoles viz., *N*-methyloxindole, *N*-benzyloxindole, and *N*-hexyloxindole were compatible under the reaction conditions, affording the desired products in high yields (**3n**, **3o**, **3p**). *N*-Phenyloxindole also smoothly participated in the reaction to obtain the alkenylated product in 87 % yield (**3q**). Unfortunately, *N*-acyl substrates such as *N*-acetyloxindole and *N*-benzoyloxindole failed to give the desired products.

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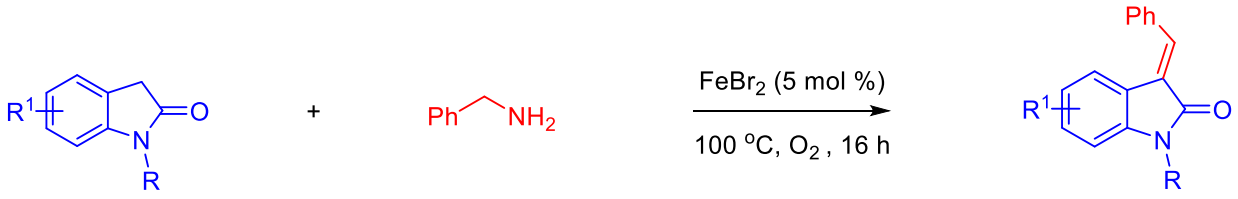
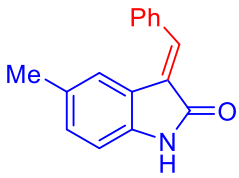
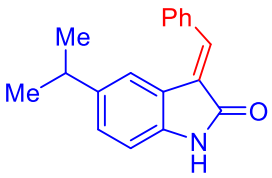


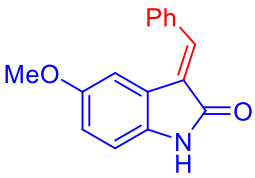
1 **2a** **3**



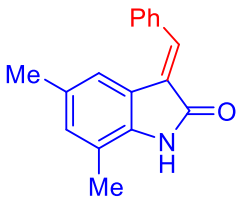
3b, 92%



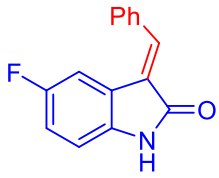
3c, 90%



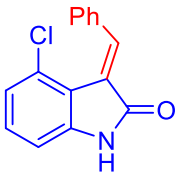
3d, 89%



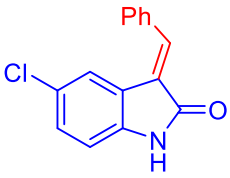
3e, 94%



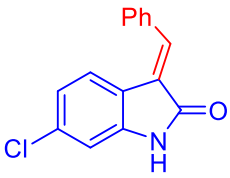
3f, 85%



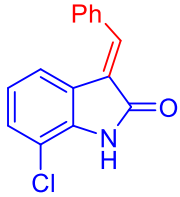
3g, 86%



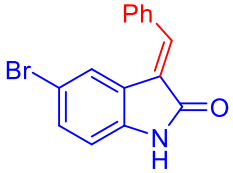
3h, 90%



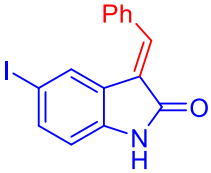
3i, 87%



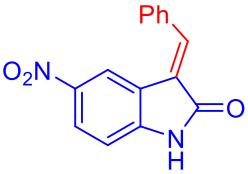
3j, 88%



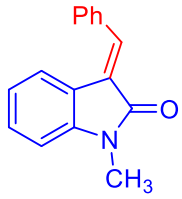
3k, 83%



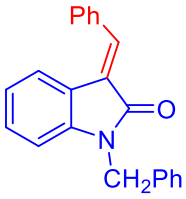
3l, 81%



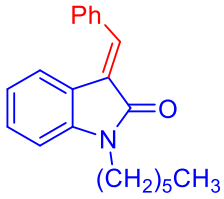
3m, 76%



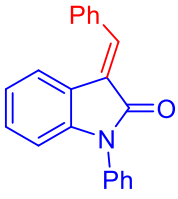
3n, 89%



3o, 91%



3p, 90%



3q, 87%

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.2 mmol), $FeBr_2$ (5 mol %), 100 °C, O_2 balloon, 16 h. [b] Isolated yields.

Scheme 2. Substrate Scope of Oxindoles in Fe-Catalyzed Oxidative Condensation Reaction[a,b]

To further test the generality of the oxidative condensation, a series of benzylamines were investigated under the optimized catalytic conditions (Scheme 3). Electron-donating benzylamines underwent the oxidative condensation with oxindole to give the corresponding products in good to excellent yields (**4a**-**4g**). The structure of compound **4a** was confirmed by its single-crystal X-ray diffraction analysis.[15] Piperonylamine and 1-(1-naphthyl)methanamine were tolerated well in this transformation, thus providing **4h** and **4i** in 83% and 86% yields, respectively. It is noteworthy that the halo-substituted benzylamines reacted smoothly with oxindole, leading to halo-substituted 3-alkylideneindolin-2-ones (**4j**-**4m**), which could be further utilized in conventional Pd-catalyzed cross-coupling transformations. In addition, trifluoromethyl groups containing benzylamine, 3,5-bis(trifluoromethyl)benzylamine was also tolerated under the reaction conditions, affording **4n** in 80% yield. Heteroarylmethanamines such as furfurylamine and 2-thiophenemethylamine were also served as suitable substrates in this oxidative condensation reaction (**4o**, **4p**). 2-Thiophenemethylamine was observed to produce a mixture of *E* and *Z* alkenylated products ((*E*)-**4p**:(*Z*)-**4p** = 1:1.2 ratio by ^{1}H NMR). It is known that the 3-[(substituted furanyl)methylidenyl]indolin-2-ones favors the *E* isomer form due to the electrostatic repulsion between the C-2 carbonyl oxygen atom of the indolin-2-one and the O-1′ of furan in their *Z* isomer form.[1b] On the other hand, the 3-[(substituted thienyl)methylidenyl]-indolin-2-ones favors the *Z* isomer form due to the electrostatic interaction between the C-2 carbonyl oxygen and partial positively charged S-1′ of thiophene in their *Z* isomeric form.[1b] However, an alkyl amine namely *n*-octylamine did not afford the desired product.

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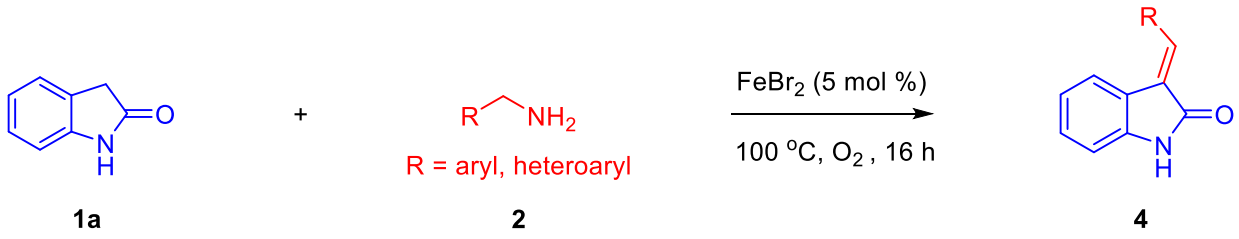
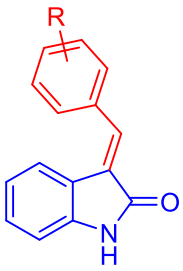




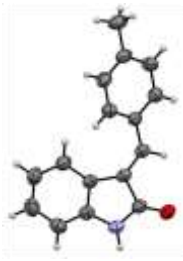
4a: R = 4-Me, 93%

4b: R = 4-*i*-Pr, 92%

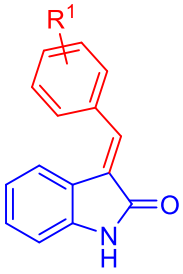
4c: R = 2-OMe, 89%

4d: R = 3-OMe, 93%

4e: R = 4-OMe, 88%



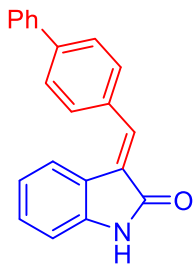
4a: CCDC 2026460



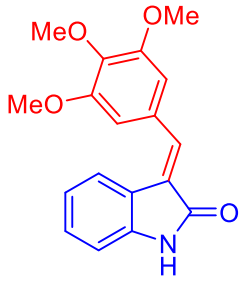
4j: R^1 = 4-Br, 93%

4k: R^1 = 4-Cl, 95%

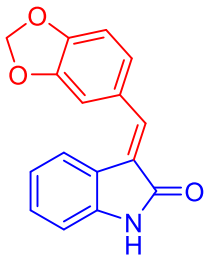
4l: R^1 = 2-Cl, 87%



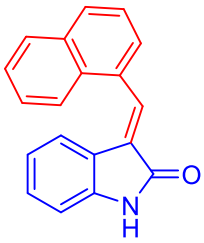
4f, 91%



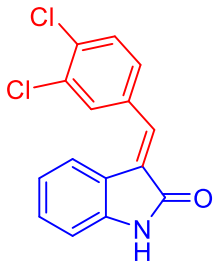
4g, 85%



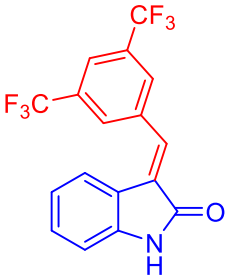
4h, 83%



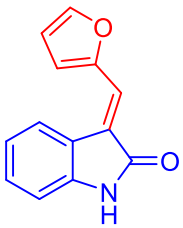
4i, 86%



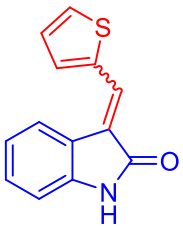
4m, 88%



4n, 80%



4o, 79%



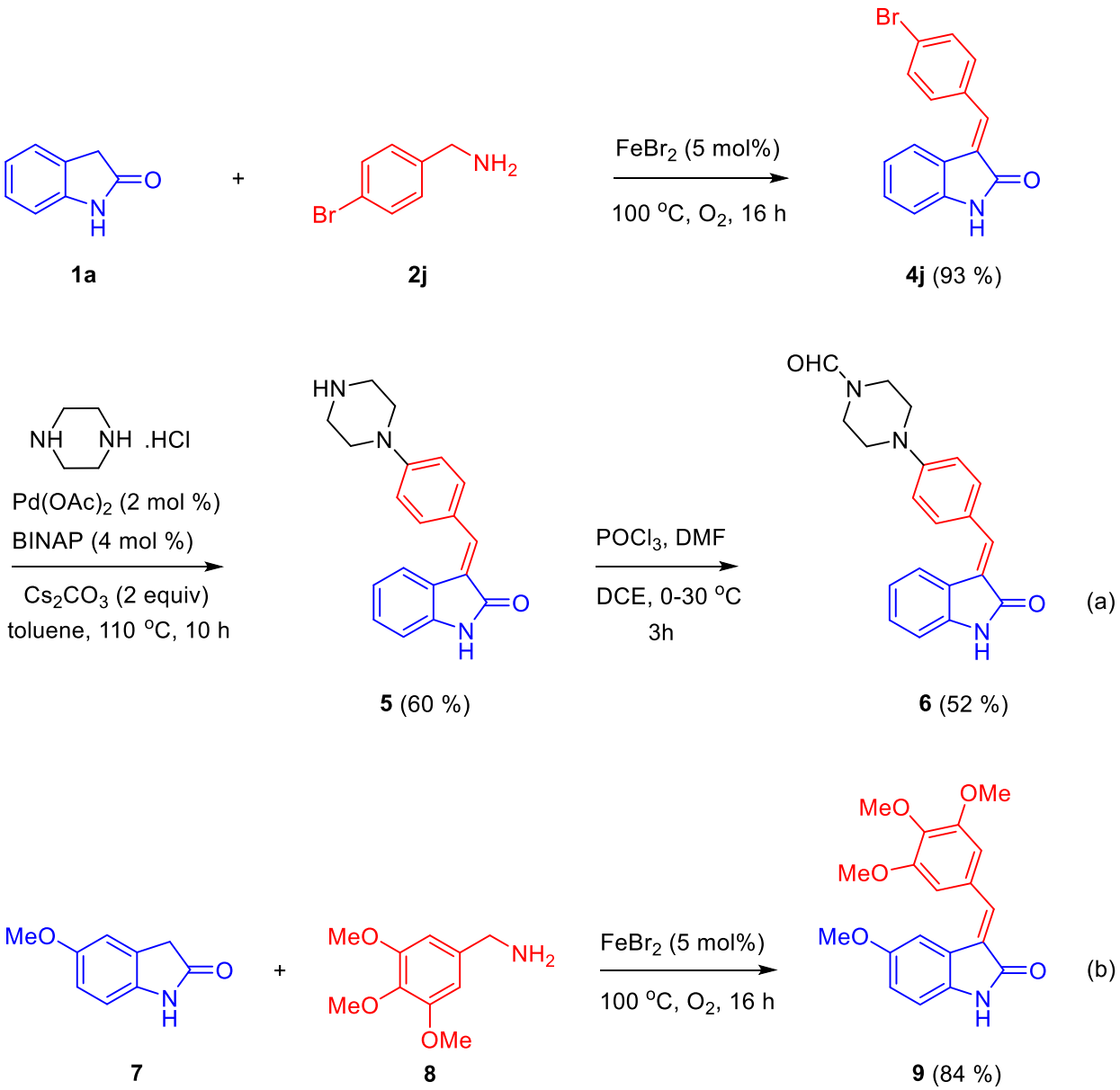
(*E*)-**4p**, 36%

(*Z*)-**4p**, 45%

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.2 mmol), $FeBr_2$ (5 mol %), 100 °C, O_2 balloon, 16 h.
[b] Isolated yields.

Scheme 3. Substrate Scope of Benzylamines in Fe-Catalyzed Oxidative Condensation Reaction[a,b]

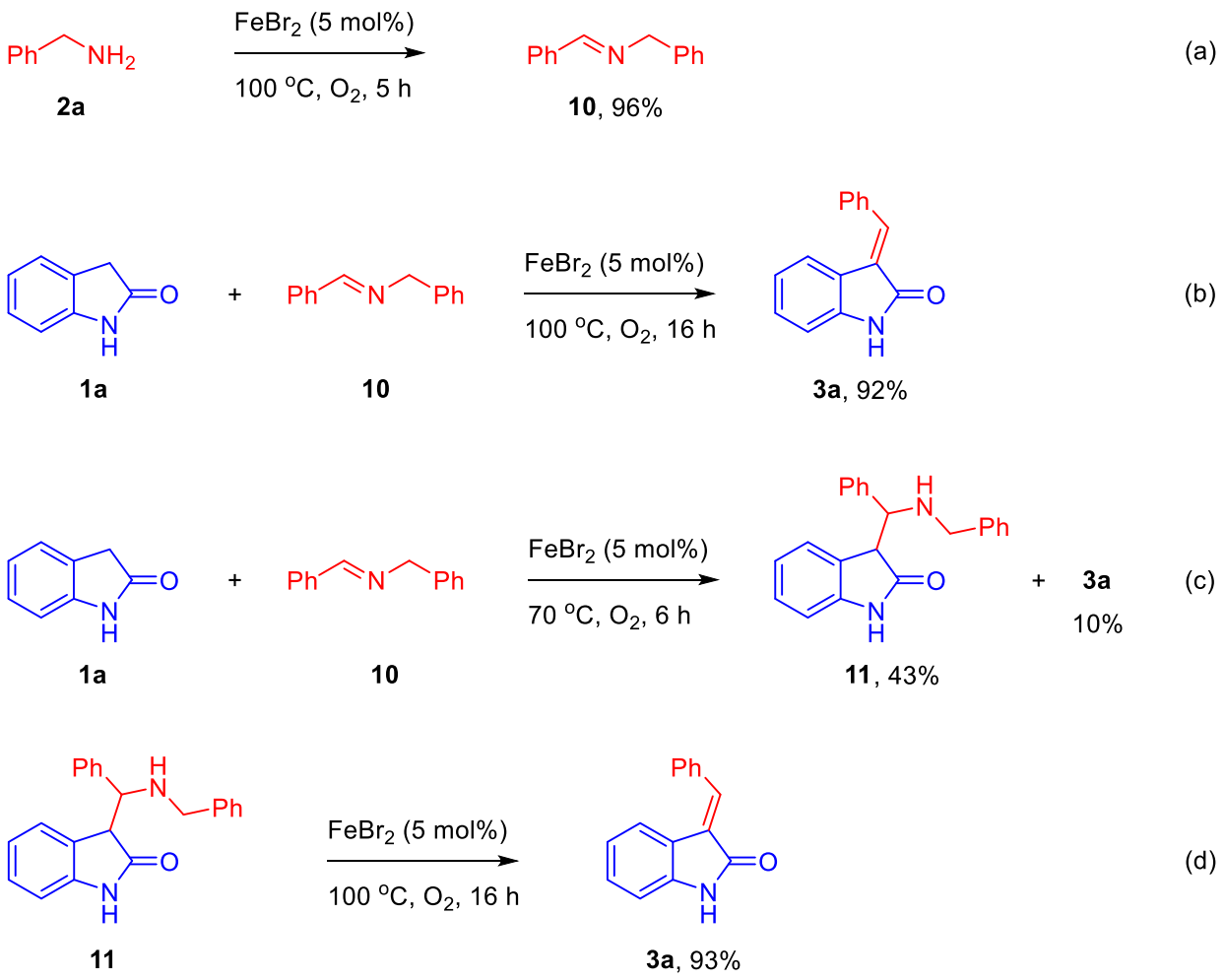
To demonstrate the utility of this synthetic approach, several pharmaceutically relevant (*E*)-3-alkylideneindolin-2-one molecules have been prepared. For example, (*E*)-3-benzylidene-6-chloroindolin-2-one (**3i**), (*E*)-3-(4-isopropylbenzylidene)indolin-2-one (**4b**) and (*E*)-3-[4-(1-formylpiperazin-4-yl)benzylidenyl]indolin-2-one (**6**) are reported as excellent inhibitors of tyrosine kinase activities.[1b,1f,16] Compound **6** could be prepared by a three-step procedure involving the oxidative condensation of oxindole (**1a**) with 4-bromobenzylamine (**2j**) to give (*E*)-3-(4-bromobenzylidene)indolin-2-one (**4j**) in 93% yield under the optimized reaction conditions, followed by Buchwald–Hartwig amination, and *N*-formylation reaction as shown in Scheme 4a. In addition, (*E*)-3-(benzo[*d*][1,3]dioxol-5-ylmethylene)indolin-2-one (**4h**) and (*E*)-3-(3,4,5-trimethoxybenzylidene)-5-methoxyindolin-2-one (**9**) are identified as potent anticonvulsant agent and antitumor agent, respectively.[1c,17] Compound **9** could be synthesized by oxidative reaction of 5-methoxyoxindole (**7**) with 3,4,5-trimethoxybenzylamine (**8**) under the standard conditions (Scheme 4b). Besides, many of the synthesized 3-alkylideneindolin-2-one compounds, namely (*E*)-3-benzylidene-7-chloroindolin-2-one (**3j**), (*E*)-3-benzylidene-5-bromoindolin-2-one (**3k**) and (*E*)-3-(4-methylbenzylidene)indolin-2-one (**4a**) are used as key precursors for the synthesis of bioactive molecules;[1a,18] and (*E*)-3-(3,4,5-trimethoxybenzylidene)indolin-2-one (**4g**) is employed as precursor for the preparation of cyanide-scavenging material.[19]



Scheme 4. Synthesis of Pharmaceutically Relevant (*E*)-3-Alkylideneindolin-2-one Products

10.1002/ejoc.202001300

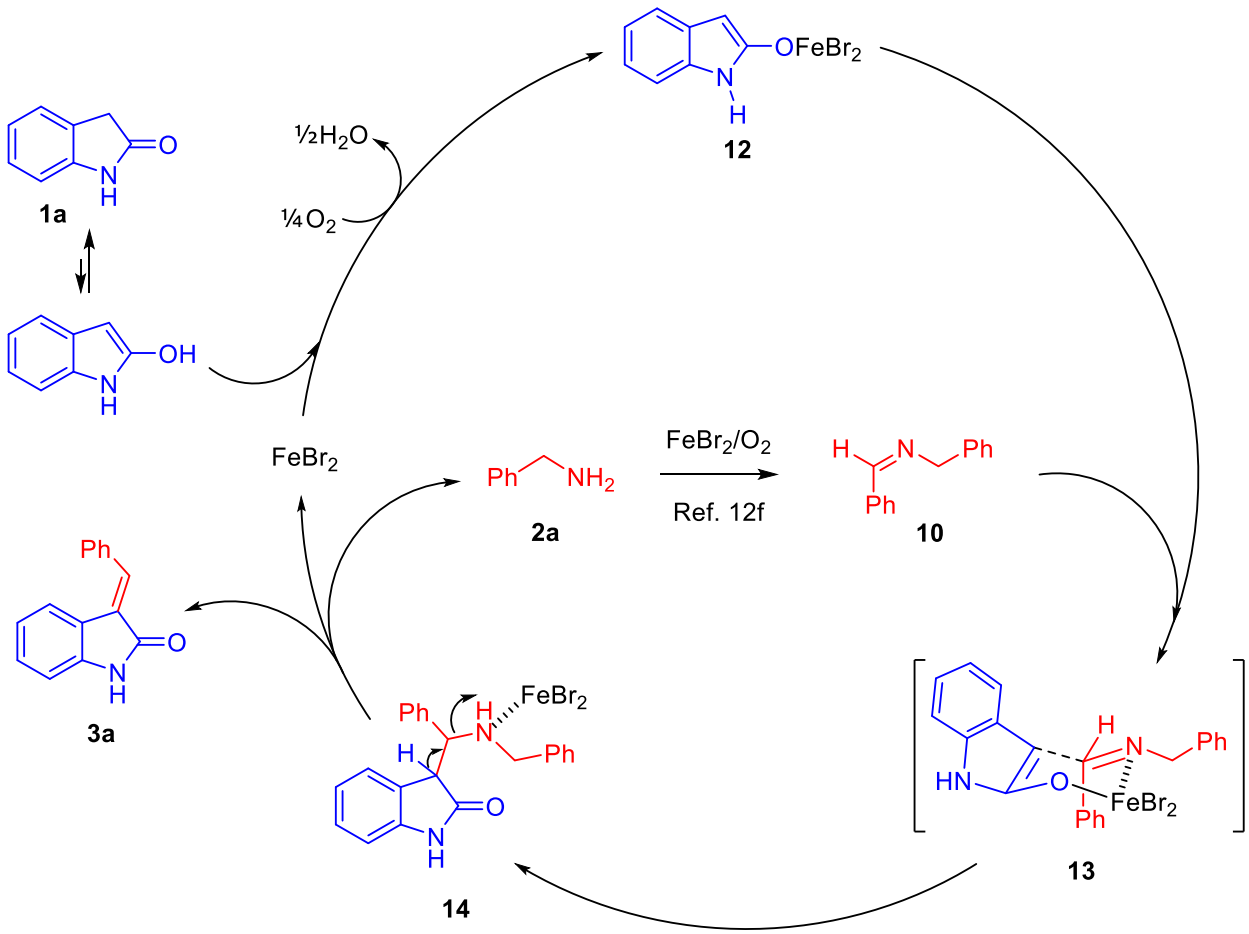
In order to understand the reaction mechanism, we carried out some control experiments (Scheme 5). Initially, benzylamine (**2a**) was treated with $FeBr_2$ and molecular oxygen at 100 °C for 5 h, which resulted the formation of self-condensation product *N*-benzylidenebenzylamine (**10**) in 96% isolated yield (Scheme 5a). Subsequently, the isolated imine **10** was allowed to react with oxindole (**1a**) under the standard reaction conditions, leading to the desired product (*E*)-3-benzylideneindolin-2-one (**3a**) in 92% yield (Scheme 5b). In another experiment, the imine **10** was treated with oxindole (**1a**) in the presence of $FeBr_2$ and molecular oxygen at 70 ºC for 6 h, fortunately, an intermediate, 3-[(benzylamino)(phenyl)methyl]indolin-2-one (**11**) was isolated along with the desired product **3a** in 43% and 10% yields, respectively (Scheme 5c), and the unreacted starting materials were also recovered. Although there is a possibility of the formation of a mixture of diastereomers, we able to isolate one of the diastereomers, because the diastereomeric intermediates are unstable under the reaction conditions as they undergo dehydrogenation to form the thermodynamically stable product *E*-**3a**. The intermediate **11** successfully produced the desired product **3a** in 93% yield under the standard conditions (Scheme 5d).



Scheme 5. Control Experiments

On the basis of above experimental results and earlier reports,[4a,12f] a plausible mechanism is outlined in Scheme 6. Initially, the enol form of oxindole reacts with iron(II) bromide in the presence of oxygen to give an iron(III) enolate **12**. Concomitantly, benzylamine is participated in the oxidative self-condensation to form *N*-benzylidenebenzylamine (**10**) in the presence of iron(II) bromide and molecular oxygen. Subsequently, the nucleophilic attack of **12** takes place on the imine **10** to generate 3-alkylated oxindole **14** via a six-membered transition state **13**. Finally, the intermediate **14** breaks down to the thermodynamically driven stable product (*E*)-3-

benzylideneindolin-2-one (**3a**), and generating the benzylamine (**2a**) and iron(II) bromide in the process.



Scheme 6. Plausible Reaction Mechanism

Conclusions

In summary, we have developed a novel reaction protocol for the synthesis of (*E*)-3-alkylideneindolin-2-ones via iron-catalyzed aerobic oxidative condensation of oxindoles with benzylamines. This approach exhibited a broad substrate scope relating to both the reaction partners and allowed the synthesis of many biologically active molecules. The mechanistic investigations disclosed that this oxidative reaction proceeded through C-H activation, amine self-condensation, nucleophilic addition, and C-C double bond formation. Cheap iron salt as the catalyst and molecular oxygen as the oxidant were used in this one-pot procedure, which makes the transformation very economical and practical.

Experimental Section

General Information. All chemicals were purchased from commercial suppliers and used as received. The reactions were performed in oven-dried glassware under appropriate atmosphere. The reactions were monitored by Thin-layer chromatography (TLC) on 0.25 mm Merck Silica gel 60 F_{254} plates using UV light for visualization. The column chromatography was performed with 100−200 mesh silica gel using hexane and ethylacetate as eluents. NMR spectra were recorded on a Jeol ECZ-400S spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz), using DMSO-*d*6 or $CDCl_3$ or acetone-*d*6 as the solvent with TMS as the internal standard. The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, dd = doublet of doublet, td = triplet of doublet, br s = broad singlet. Chemical shifts (δ) are reported relative to residual solvent signals (Chloroform-*d*, 7.26 ppm for ^{1}H NMR and triplet centered at 77.00 ppm for ^{13}C NMR; DMSO-d_6, 2.50 ppm for ^{1}H NMR and septet centered at 39.50 ppm for ^{13}C NMR; Acetone-d_6, 2.05 ppm for ^{1}H NMR and septet centered at 29.84 ppm for ^{13}C NMR). Melting points were determined using Büchi melting point apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded using an electrospray quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer. The X-ray data for compounds **3a** and **4a** were collected at 298

K with an Oxford XCalibur CCD diffractometer equipped with graphite monochromatic Mo Kα radiation (λ = 0.71073 Å).

General procedure for the synthesis of skeletons 3 and 4: Oxindole **1** (1 mmol), benzylamine **2** (1.2 mmol) and iron(II) bromide (5 mol %) were added into an oven-dried 10 mL Schlenk tube equipped with oxygen balloon. The tube was immersed in silicon oil bath placed over magnetic stirrer and heated at 100 °C with constant stirring for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with water (2 x 20 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using hexane and ethyl acetate as eluents to afford the compounds **3a-q** and **4a-p**.

(*E*)-3-Benzylideneindolin-2-one (3a). Yellow solid; yield: 90%; mp 178-180 °C (lit.[10] mp 178-179 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (br s, 1H), 7.86 (s, 1H), 7.69-7.63 (m, 3H), 7.50-7.42 (m, 3H), 7.24-7.19 (m, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.89-6.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 141.8, 137.5, 134.8, 129.9, 129.6, 129.3, 128.6, 127.7, 122.9, 121.8, 121.6, 110.4; HRMS (ESI) m/z calcd for $C_{15}H_{11}NO$ $[M + H]^+$: 222.0913, found 222.0916.

(*E*)-3-Benzylidene-5-methylindolin-2-one (3b). Red solid; yield: 92%; mp 178-180 °C (lit.[10] mp 178-180 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (br s, 1H), 7.82 (s, 1H), 7.67 (d, *J* = 6.4 Hz, 2H), 7.50-7.44 (m, 4H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 139.5, 137.1, 134.9, 131.1, 130.4, 129.6, 129.3, 128.6, 127.8, 123.6, 121.7, 110.0, 21.2; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO$ $[M + H]^+$: 236.1070, found 236.1073.

(*E*)-3-Benzylidene-5-isopropylindolin-2-one (3c). Brown solid; yield: 90%; mp 191-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (br s, 1H), 7.83 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.54 (s, 1H), 7.51-7.44 (m, 3H), 7.09 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 2.82-2.72 (m, 1H), 1.16 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 142.3, 139.8, 136.9, 134.9, 129.6, 129.3, 128.5, 128.1, 127.9, 121.6, 120.9, 110.1, 33.7, 24.1; HRMS (ESI) m/z calcd for $C_{18}H_{17}NO$ $[M + H]^+$: 264.1383, found 264.1388.

(*E*)-3-Benzylidene-5-methoxyindolin-2-one (3d). Orange solid; yield: 89%; mp 180-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (br s, 1H), 7.84 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.49-7.42 (m, 3H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.76 (m, 1H), 3.65 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 170.9, 154.8, 137.6, 135.7, 134.6, 129.7, 129.2, 128.6, 128.2, 122.4, 114.9, 110.7, 109.6, 55.6; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ $[M + H]^+$: 252.1019, found 252.1025.

(*E*)-3-Benzylidene-5,7-dimethylindolin-2-one (3e). Orange-yellow solid; yield: 94%; mp 216-217 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 7.81 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.49-7.41 (m, 3H), 7.31 (s, 1H), 6.88 (s, 1H), 2.29 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 138.3, 137.1, 134.9, 131.9, 130.9, 129.5, 129.4, 128.6, 128.3, 121.3, 121.1, 119.1, 21.1, 16.3; HRMS (ESI) m/z calcd for $C_{17}H_{15}NO$ $[M + H]^+$: 250.1226, found 250.1236.

(*E*)-3-Benzylidene-5-fluoroindolin-2-one (3f). Brown solid; yield: 85%; mp 196-197 °C (lit.[10] mp 196-197 °C); ^1H NMR (400 MHz, $CDCl_3$): δ 9.13 (br s, 1H), 7.89 (s, 1H), 7.65-7.62 (m, 2H), 7.52-7.44 (m, 3H), 7.35 (dd, J = 9.2, 2.4 Hz, 1H), 6.93 (td, J = 8.8, 2.4 Hz, 1H), 6.87-6.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 158.3 (d, $^1J_{CF}$ = 237.7 Hz), 139.1, 137.7, 134.3, 130.1, 129.2, 128.8, 127.4, 122.6 (d, $^3J_{CF}$ = 8.6 Hz), 116.2 (d, $^2J_{CF}$ = 24.0 Hz), 110.7 (d, $^3J_{CF}$ = 7.7 Hz), 110.4 (d, $^2J_{CF}$ = 26.8 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{10}FNO$ $[M + H]^+$: 240.0819, found 240.0792.

(*E*)-3-Benzylidene-4-chloroindolin-2-one (3g). Yellow solid; yield: 86%; mp 187-188 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.71 (br s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 6.4 Hz, 1H), 7.58 (s, 1H), 7.52-7.46 (m, 2H), 7.25-7.21 (m, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.79 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3, 143.2, 133.0, 131.7, 131.5, 130.8, 130.5, 129.9, 129.7, 127.6, 122.7, 121.5, 120.6, 110.5; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClNO$ $[M + H]^+$: 256.0524, found 256.0528.

(*E*)-3-Benzylidene-5-chloroindolin-2-one (3h). Yellow solid; yield: 90%; mp 219-220 °C (lit.[10] mp 219-220 °C); ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (br s, 1H), 7.89 (s, 1H), 7.66-7.61 (m, 3H), 7.54-7.46 (m, 3H), 7.19 (dd, J = 8.4, 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 139.9, 139.3, 135.3, 134.2, 130.2, 129.6, 129.3, 128.9, 127.1, 126.7, 123.0, 111.1; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClNO$ $[M + H]^+$: 256.0524, found 256.0533.

(*E*)-3-Benzylidene-6-chloroindolin-2-one (3i). Orange solid; yield: 87%; mp 176-177 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (br s, 1H), 7.84 (s, 1H), 7.65-7.63 (m, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.51-7.45 (m, 3H), 6.91 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.0, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 142.6, 138.1, 135.4, 134.5, 129.9, 129.3, 128.8, 126.5, 123.8, 121.9, 120.1, 110.8; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClNO$ $[M + H]^+$: 256.0524, found 256.0529.

(*E*)-3-Benzylidene-7-chloroindolin-2-one (3j). Yellow solid; yield: 88%; mp 202-203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br s, 1H), 7.90 (s, 1H), 7.66-7.63 (m, 2H), 7.54-7.43 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.84-6.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 139.4, 139.0, 134.4, 130.0, 129.4, 129.3, 128.8, 127.3, 123.1, 122.6, 121.2, 115.4; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClNO$ $[M + H]^+$: 256.0524, found 256.0531.

(*E*)-3-Benzylidene-5-bromoindolin-2-one (3k). Yellow solid; yield: 83%; mp 200-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (br s, 1H), 7.87 (s, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.65-7.63 (m, 2H), 7.54-7.44 (m, 3H), 7.35-7.32 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 140.4, 139.3, 139.2, 134.2, 132.4, 132.2, 130.3, 129.3, 128.9, 125.8, 123.5, 111.6; HRMS (ESI) m/z calcd for $C_{15}H_{10}BrNO$ $[M + H]^+$: 300.0019, found 300.0018.

(*E*)-3-Benzylidene-5-iodoindolin-2-one (3l). Yellow solid; yield: 81%; mp 184-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (br s, 1H), 7.94 (d, *J* = 1.2 Hz, 1H), 7.86 (s, 1H), 7.65-7.63 (m, 2H), 7.54-7.45 (m, 4H), 6.70 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 140.9, 139.3, 138.3, 134.2, 132.2, 131.5, 130.3, 129.3, 128.8, 126.2, 124.0, 112.1; HRMS (ESI) m/z calcd for $C_{15}H_{10}INO$ $[M + H]^+$: 347.9880, found 347.9881.

(*E*)-3-Benzylidene-5-nitroindolin-2-one (3m). Pale yellow solid; yield: 76%; mp 184-185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (br s, 1H), 7.73-7.67 (m, 3H), 7.54-7.45 (m, 4H), 6.91-6.88 (m, 2H);^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7, 144.4, 136.9, 134.3, 132.1, 130.1, 129.5, 129.0, 128.4, 126.6, 123.7, 121.1, 110.3; HRMS (ESI) m/z calcd for $C_{15}H_{10}N_2O_3$ $[M + H]^+$: 267.0764, found 267.0769.

(*E*)-3-Benzylidene-1-methylindolin-2-one (3n). Orange oil; yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.63-7.60 (m, 3H), 7.49-7.39 (m, 3H), 7.25-7.22 (m, 1H), 6.87-6.83 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 144.1, 136.9, 134.8, 129.7, 129.4, 129.2, 128.5, 127.1, 122.6, 121.6, 120.9, 108.0, 26.0; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO$ $[M + H]^+$: 236.1070, found 236.1078.

(*E*)-1-Benzyl-3-benzylideneindolin-2-one (3o). Orange viscous oil; yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.66-7.62 (m, 3H), 7.48-7.41 (m, 3H), 7.35-7.29 (m, 4H), 7.27-7.23 (m, 1H), 7.16-7.11 (m, 1H), 6.85-6.81 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 143.3, 137.5, 135.9, 134.9, 131.9, 129.7, 129.5, 129.2, 128.7,

128.6, 127.5, 127.2, 126.9, 122.7, 121.8, 121.2, 109.1, 43.7; HRMS (ESI) m/z calcd for $C_{22}H_{17}NO$ $[M + H]^+$: 312.1383, found 312.1387.

(*E*)-3-Benzylidene-1-hexylindolin-2-one (3p). Red viscous oil; yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 3H), 7.46-7.37 (m, 3H), 7.24-7.20 (m, 1H), 6.86-6.81 (m, 2H), 3.77-3.74 (m, 2H), 1.73-1.66 (m, 2H), 1.39-1.31 (m, 6H), 0.91-0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 143.5, 136.8, 134.8, 129.5, 129.3, 129.0, 128.4, 127.0, 122.6, 121.3, 121.0, 108.2, 39.8, 31.3, 27.4, 26.5, 22.4, 13.9; HRMS (ESI) m/z calcd for $C_{21}H_{23}NO$ $[M + H]^+$: 306.1852, found 306.1857.

(*E*)-3-Benzylidene-1-phenylindolin-2-one (3q). Orange solid; yield: 87%; mp 50-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.68-7.65 (m, 3H), 7.49-7.43 (m, 3H), 7.37-7.25 (m, 5H), 7.17-7.13 (m, 1H), 6.87-6.83 (m, 1H), 6.73 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 143.4, 137.5, 135.9, 134.9, 129.7, 129.5, 129.2, 128.7, 128.6, 127.5, 127.2, 126.9, 122.7, 121.8, 121.2, 109.2; HRMS (ESI) m/z calcd for $C_{21}H_{15}NO$ $[M + H]^+$: 298.1226, found 298.1234.

(*E*)-3-(4-Methylbenzylidene)indolin-2-one (4a). Orange solid; yield: 93%; mp 197-198 °C (lit.[20] mp 199-200 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (br s, 1H), 7.82 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.21-7.17 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.88-6.84 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 141.5, 140.1, 137.9, 131.9, 129.6, 129.5, 129.3, 126.8, 122.9, 121.8, 121.7, 110.2, 21.6; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO$ $[M + H]^+$: 236.1070, found 236.1072.

(*E*)-3-(4-Isopropylbenzylidene)indolin-2-one (4b). Yellow solid; yield: 92%; mp 144-145 °C (lit.[10] mp 144-146 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (br s, 1H), 7.83 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.24-7.19 (m, 1H), 6.95-6.91 (m, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 3.04-2.93 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 151.1, 141.6, 137.9, 132.2, 129.7, 126.7, 122.9, 121.8, 121.7, 110.2, 34.2, 23.8; HRMS (ESI) m/z calcd for $C_{18}H_{17}NO$ $[M + H]^+$: 264.1383, found 264.1388.

(*E*)-3-(2-Methoxybenzylidene)indolin-2-one (4c). Mustard yellow solid; yield: 89%; mp 221-224 °C (lit.[21] mp 221-222 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 7.98 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.45-7.41 (m, 1H), 7.21-7.17 (m, 1H), 7.05-6.98 (m, 2H), 6.90-6.83 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 158.2, 141.3,

134.1, 131.5, 129.9, 129.5, 127.1, 123.7, 122.9, 122.0, 121.7, 120.1, 110.9, 109.9, 55.5; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ $[M + H]^+$: 252.1019, found 252.1023.

(*E*)-3-(3-Methoxybenzylidene)indolin-2-one (4d). Pale-yellow solid; yield: 93%; mp 151-152 °C (lit.[21] mp 150-152 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 7.82 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.41-7.37 (m, 1H), 7.27-7.19 (m, 3H), 6.98 (dd, *J* = 8.4, 2.4Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.89-6.86 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 159.6, 141.8, 137.3, 136.1, 129.9, 129.7, 127.8, 123.2, 121.8, 121.7, 121.6, 115.6, 114.2, 110.4, 55.3; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ $[M + H]^+$: 252.1019, found 252.1019.

(*E*)-3-(4-Methoxybenzylidene)indolin-2-one (4e). Reddish yellow solid; yield: 88%; mp 203-204 °C (lit.[10] mp 203-204 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (br s, 1H), 7.79 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.23-7.19 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.93-6.88 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 170.6, 160.9, 141.3, 137.8, 131.5, 129.4, 127.1, 125.6, 122.7, 121.9, 121.7, 114.1, 110.1, 55.4; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ $[M + H]^+$: 252.1019, found 252.1025.

(*E*)-3-([1,1'-Biphenyl]-4-ylmethylene)indolin-2-one (4f). Orange solid; yield: 91%; mp 144-145 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (br s, 1H), 8.36 (d, *J* = 8.0 Hz, 2H), 7.69-7.58 (m, 6H), 7.37-7.24 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 141.8, 140.8, 139.3, 136.3, 133.3, 132.8, 130.3, 129.2, 128.1, 126.9, 126.8, 126.4, 125.1, 121.2, 119.9, 109.5; HRMS (ESI) m/z calcd for $C_{21}H_{15}NO$ $[M + H]^+$: 298.1226, found 298.1229.

(*E*)-3-(3,4,5-Trimethoxybenzylidene)indolin-2-one (4g). Yellow solid; yield: 85%; mp 204-205 °C (lit.[20] mp 205-207 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (br s, 1H), 7.82 (s, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.48 (s, 1H), 7.25-7.21 (m, 1H), 7.07-7.03 (m, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 3.97 (s, 6H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 152.6, 140.4, 139.3, 138.0, 129.3, 128.6, 125.5, 125.2, 121.8, 119.0, 109.8, 109.4, 60.9, 56.2; HRMS (ESI) m/z calcd for $C_{18}H_{17}NO_4$ $[M + H]^+$: 312.1230, found 312.1034.

(*E*)-3-(Benzo[*d*][1,3]dioxol-5-ylmethylene)indolin-2-one (4h). Yellow solid; yield: 83%; mp 208-209 °C (lit.[22] mp 210 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (br s, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.53 (s, 1H), 7.29-7.19 (m, 3H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 6.8 Hz, 2H), 6.12 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9, 148.7, 147.7, 142.8, 136.1, 129.9, 128.3,

126.2, 124.7, 122.3, 121.2, 121.1, 110.2, 109.4, 108.7, 101.7; HRMS (ESI) m/z calcd for $C_{16}H_{11}NO_3$ $[M + H]^+$: 266.0812, found 266.0817.

(*E*)-3-(Naphthalen-1-ylmethylene)indolin-2-one (4i). Yellow solid; yield: 86%; mp 190-191 °C (lit.[20] mp 198-199 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 8.37 (s, 1H), 8.06-8.03 (m, 1H), 7.98-7.93 (m, 2H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.59-7.53 (m, 3H), 7.20-7.17 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 141.7, 135.5, 133.6, 132.1, 131.3, 130.0, 129.9, 129.4, 128.6, 126.9, 126.7, 126.5, 125.1, 124.8, 123.3, 121.8, 110.2; HRMS (ESI) m/z calcd for $C_{19}H_{13}NO$ $[M + H]^+$: 272.1070, found 272.1081.

(*E*)-3-(4-Bromobenzylidene)indolin-2-one (4j). Orange solid; yield: 93%; mp 162-163 °C (lit.[23] mp 191-192 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (br s, 1H), 7.78 (s, 1H), 7.69-7.65 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.17 (t, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.91-6.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 140.4, 139.3, 134.2, 132.4, 132.2, 130.3, 129.3, 128.9, 125.8, 123.5, 114.5, 111.6; HRMS (ESI) m/z calcd for $C_{15}H_{10}BrNO$ $[M + H]^+$: 300.0019, found 300.0022.

(*E*)-3-(4-Chlorobenzylidene)indolin-2-one (4k). Yellow solid; yield: 95%; mp 178-181 °C (lit.[21] mp 178-181 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 7.75 (s, 1H), 7.62-7.57 (m, 3H), 7.46-7.44 (m, 2H), 7.25-7.21 (m, 1H), 6.92-6.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 141.9, 135.8, 135.5, 133.2, 130.6, 130.2, 128.9, 128.1, 122.9, 121.9, 121.3, 110.5; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClNO$ $[M + H]^+$: 256.0524, found 256.0526.

(*E*)-3-(2-Chlorobenzylidene)indolin-2-one (4l). Yellow solid; yield: 87%; mp 176-177 °C (lit.[22] mp 178 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (br s, 1H), 7.88 (s, 1H), 7.74-7.72 (m, 1H), 7.53-7.50 (m, 1H), 7.41-7.32 (m, 3H), 7.24-7.19 (m, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.85-6.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 141.9, 134.4, 133.8, 133.5, 130.7, 130.3, 130.2, 129.9, 129.2, 126.6, 123.1, 121.8, 121.3, 110.4; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClNO$ $[M + H]^+$: 256.0524, found 256.0532.

(*E*)-3-(3,4-Dichlorobenzylidene)indolin-2-one (4m). Orange solid; yield: 88%; mp 195-197 °C (lit.[23] mp 195-197 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (br s, 1H), 7.93 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.73-7.67 (m, 1H), 7.54 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.26-7.23 (m, 1H), 6.89-6.82 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4, 143.3, 135.4, 132.9, 132.0, 131.7,

131.2, 131.1, 130.9, 129.3, 129.2, 122.7, 121.5, 120.5, 110.5; HRMS (ESI) m/z calcd for $C_{15}H_9Cl_2NO$ $[M + H]^+$: 290.0134, found 290.0138.

(*E*)-3-(3,5-Bis(trifluoromethyl)benzylidene)indolin-2-one (4n). Yellow solid; yield: 80%; mp 180-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (br s, 1H), 7.78 (s, 1H), 7.68-7.65 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.25-7.14 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.90-6.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 141.7, 136.3, 131.4 (d, $^1J_{CF}$ = 8.6 Hz), 130.8 ($^2J_{CF}$ = 3.8 Hz), 130.0, 127.5, 122.8, 121.9, 121.5, 115.9, 115.8, 110.4; HRMS (ESI) m/z calcd for $C_{17}H_9F_6NO$ $[M + H]^+$: 358.0661, found 358.0678.

(*E*)-3-(Furan-2-ylmethylene)indolin-2-one (4o). Brown-yellow solid; yield: 79%; mp 181-182 °C (lit.[22] mp 183 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (br s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.49-7.45 (m, 1H), 7.27-7.19 (m, 1H), 7.09-7.01 (m, 1H), 6.93-6.90 (m, 2H), 6.64-6.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 151.3, 127.8, 125.3, 125.1, 124.9, 124.6, 122.3, 122.1, 121.9, 120.8, 109.8, 109.7; HRMS (ESI) m/z calcd for $C_{13}H_9NO_2$ $[M + H]^+$: 212.0706, found 212.0739.

(*E*)-3-(Thiophen-2-ylmethylene)indolin-2-one ((*E*)-4p). Yellow solid; yield: 36%; mp 210-211 °C (lit.[22] mp 210 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (br s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.65-7.61 (m, 1H), 7.27-7.16 (m, 3H), 7.06-7.01 (m, 1H), 6.97-6.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 141.4, 137.8, 137.1, 134.7, 130.7, 129.6, 128.7, 128.5, 128.1, 123.6, 121.9, 110.3; HRMS (ESI) m/z calcd for $C_{13}H_9NOS$ $[M + H]^+$: 228.0478, found 228.0471.

(*Z*)-3-(Thiophen-2-ylmethylene)indolin-2-one ((*Z*)-4p). Yellow solid; yield: 45%; mp 221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (br s, 1H), 8.06 (s, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 5.2 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.19-7.14 (m, 2H), 6.97-6.93 (m, 1H), 6.82 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 140.5, 137.6, 137.4, 134.3, 128.5, 128.2, 127.5, 124.4, 121.7, 121.1, 119.5, 109.5; HRMS (ESI) m/z calcd for $C_{13}H_9NOS$ $[M + H]^+$: 228.0478, found 228.0485.

Preparation of (*E*)-3-(4-(piperazin-1-yl)benzylidene)indolin-2-one (5). To an oven-dried 10 mL Schlenk tube, (*E*)-3-(4-bromobenzylidene)indolin-2-one (**4j**, 1.0 mmol), palladium(II) acetate (2 mol %), BINAP (4 mol %), cesium carbonate (2 mmol), and toluene (1 mL) were added under N_2 atmosphere. Afterwards, piperazine hydrochloride (1.2 mmol) was added to the

reaction mixture in small portions over a period of 30 minutes with constant stirring. The tube was immersed in silicon oil bath placed over magnetic stirrer and heated at 110 °C for 10 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified on silica gel column using dichloromethane and methanol (CH_2Cl_2:MeOH = 8:2) as eluents to afford the compound **5** as yellow solid. Yield: 60%; mp 188-189 °C; ^{1}H NMR (400 MHz, Acetone-d_6): δ 7.63-7.57 (m, 1H), 7.54-7.47 (m, 1H), 7.21-7.12 (m, 2H), 7.06-6.93 (m, 2H), 6.86-6.74 (m, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 2.67-2.64 (m, 4H), 2.16 (br s, 2H), 1.99-1.94 (m, 4H); ^{13}C NMR (100 MHz, Acetone-d_6): δ 178.3, 140.6, 131.5, 131.2, 128.9, 128.5, 125.2, 122.2, 122.0, 120.9, 120.8, 110.1, 109.9, 46.8, 46.1; HRMS (ESI) m/z calcd for $C_{19}H_{19}N_3O$ $[M + H]^+$: 306.1601, found 306.1605.

Preparation of (*E*)-3-[4-(1-formylpiperazin-4-yl)benzylidenyl]indolin-2-one (6).

To a solution of 15 mL dimethylformamide in 10 mL of anhydrous 1,2-dichloroethane was added dropwise 15 mL of phosphorusoxychloride at 0 °C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 30 minutes and then cooled in an ice bath. (*E*)-3-(4-(Piperazin-1-yl)benzylidene)indolin-2-one (**5**, 1 mmol) was added to the above solution portionwise over a period of 15 minutes, and the reaction mixture was stirred at 30 °C for 3h. The reaction mixture was poured into ice-cold 1N NaOH solution and stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine until pH = 7, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was purified on a silica gel column eluting with a mixture of hexane and ethyl acetate (hexane:EtOAc = 8:2) to afford the product **6** as yellow solid. Yield: 52%; mp 176-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.80 (s, 1H), 7.64-7.59 (m, 2H), 7.46-7.39 (m, 3H), 7.18-7.14 (m, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 2.98-2.89 (m, 4H), 2.45 (br s, 1H), 2.27-2.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 162.6, 142.0, 137.2, 134.7, 129.8, 129.5, 129.3, 129.2, 128.5, 127.8, 122.8, 121.6, 110.4, 46.2, 44.8; HRMS (ESI) m/z calcd for $C_{20}H_{19}N_3O_2$ $[M + H]^+$: 334.1550, found 334.1556.

(*E*)-3-(3,4,5-Trimethoxybenzylidene)-5-methoxyindolin-2-one (9). Following the general procedure reported above for the synthesis of compounds **3** and **4**, 5-methoxyindolin-2-one (**7**, 1

mmol), 3,4,5-trimethoxybenzylamine (**8**, 1.2 mmol) and iron(II) bromide (5 mol %) were employed in the reaction to furnish the title compound **9** as orangish-red solid. Yield: 84%; mp 210-211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 10.43 (br s, 1H), 7.57 (s, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.05 (s, 2H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H) 6.80 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 6H), 3.74 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9, 154.2, 152.9, 138.8, 136.8, 136.6, 129.8, 127.4, 121.9, 115.2, 110.6, 109.3, 107.0, 60.3, 56.1, 55.5; HRMS (ESI) m/z calcd for $C_{19}H_{19}NO_5$ $[M + H]^+$: 342.1336, found 342.1339.

Preparation of *N*-benzylidenebenzylamine (10). Benzylamine (**2a**, 1.2 mmol) and iron(II) bromide (5 mol %) were added into an oven-dried 10 mL Schlenk tube equipped with oxygen balloon. The tube was immersed in silicon oil bath placed over magnetic stirrer and heated at 100 °C with constant stirring for 5h. The reaction mixture cooled to room temperature, adsorbed on basic alumina and purified by column chromatography (basic alumina, hexane–EtOAc) to afford the compound **10** (96% yield) as pale yellow oil. Yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.83-7.81 (m, 2H), 7.45-7.44 (m, 3H), 7.39-7.37 (m, 4H), 7.32-7.28 (m, 1H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 139.2, 136.1, 130.7, 128.5, 128.4, 128.2, 127.9, 126.9, 64.9; HRMS (ESI) m/z calcd for $C_{14}H_{13}N$ $[M + H]^+$: 196.1126, found 196.1123.

Preparation of 3-[(benzylamino)(phenyl)methyl]indolin-2-one (11). Oxindole (**1a**, 1 mmol), *N*-benzylidenebenzylamine (**10**, 1.2 mmol) and iron(II) bromide (5 mol %) were added into an oven-dried 10 mL Schlenk tube equipped with oxygen balloon. The tube was immersed in silicon oil bath placed over magnetic stirrer and heated at 70 °C with constant stirring for 6 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using hexane and ethyl acetate (hexane:EtOAc = 3:1) eluents to afford the compound **11** as creamy colour solid. Yield: 43%; mp 211-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (br s, 1H), 6.96-6.77 (m, 8H), 6.64 (d, *J* = 7.6 Hz, 2H), 6.55 (dd, *J* = 7.6, 2.8 Hz, 2H), 6.46-6.38 (m, 2H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J*= 8.4 Hz, 2H), 3.42-3.38 (m, 1H), 3.13 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.8, 142.9, 129.5, 129.4, 128.6, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 125.6, 121.2, 109.5, 55.0, 48.0, 46.7; HRMS (ESI) m/z calcd for $C_{22}H_{20}N_2O$ $[M + H]^+$: 329.1648, found 329.1650.

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