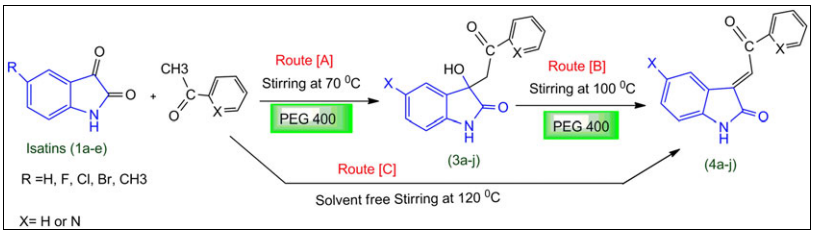
Eco-friendly Polyethylene Glycol-400 as a Rapid and Efficient Recyclable Reaction Medium for the Synthesis of Anticancer Isatin-linked Chalcones and Their 3-Hydroxy Precursor

Alpana K. Gupta,[a] Mausumi Bharadwaj,[b] and Ravi Mehrotra[a]*

[a]Division of Preventive Oncology, National Institute of Cancer Prevention and Research (ICMR-NICPR), Department of Health Research (Govt. of India), Noida, India
[b]Division of Molecular Genetics and Biochemistry, National Institute of Cancer Prevention and Research, Noida, India
*E-mail: rm8509@gmail.com; ravi.mehrota@gov.in

Received July 25, 2018
DOI 10.1002/jhet.3424
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



Isatin chalcones and their 3-hydroxy precursors are shown to possess potential anticancer activity and are also versatile substrates and key intermediates for the synthesis of a large variety of bioactive spiro-oxindoles. An environmental friendly tandem synthesis, using PEG 400 as green solvent cum phase transfer catalyst, for a series of 3-hydroxy-2-oxindoles and 3-methylene-2-oxindoles has been developed. Reported one-pot sustainable synthetic strategy was compared with the conventional method and was found to be superior to existing two-step syntheses in terms of simplicity, product yield, and reaction time and have a large substrate scope.

INTRODUCTION

2-Oxindoles have been recognized as privileged substructures in new drug discovery as many 2-oxindole derivatives have advanced into clinical trials for the treatment of cancer [1–3]. Various isatin derivatives exhibit diverse biological activities such as inhibition of the proteasome, antagonizing GHSR, and inhibiting the growth of human cancer cells [4–6]. 3-Substituted-3-hydroxy-2-oxindoles are the new scaffold for drug discovery [7], which are also versatile intermediates for the synthesis of potential bioactive chalcones [8,9], Isatin chalcones serve as the perfect electron-deficient olefins because of their high reactivity as Michael acceptors [10] and thus are suitable substrates for cycloaddition reactions to generate biologically privileged diverse spiro-oxindole scaffolds [11,12] (Fig. 1).

Isatins have been utilized in diverse organic reactions including the construction of diverse heterocycles [13–16]. Numerous methodologies have been developed to synthesize these bioactive motifs by reaction of isatin with ketone that includes catalysts like a base [17–19], organic molecules, or a metal complex [20–26]. In recent years, owing to a growing need for more environmentally acceptable processes, the direction of chemical research has shifted more towards the use of eco-friendly solvents and reusable catalysts [27,28]. Water has been used as the green medium for synthesis of 3-hydroxy-2-oxindoles [29–31] but has limitations of the low solubility of the substrates, compatibility with reagents, and mostly associated with long reaction time. Further, the nature of catalyst and solvent also affects the adduct of the aldol condensation reaction as in some cases conjugated enone (chalcones) are obtained directly instead of β-hydroxyl ketone [32–34].

Owing to the growing need for more environmentally acceptable yet efficient reusable solvents, liquid polyethylene glycols (PEGs) with low molecular weight are gaining interest because of their unique properties like nonvolatility, stability at high temperatures, low cost, reduced toxicity, recyclability, low inflammability, easy degradability, and high miscibility with organic compounds [35]. PEGs are the novel mild and efficient reaction medium cum phase transfer catalyst that are fast replacing expensive and environmentally harmful catalysts for chemical synthesis [36,37]. Various condensation reactions using PEG 400 are widely reported [38,39], but to the best of our knowledge, there is the first report exploiting PEG 400 as the green solvent for one-pot two-step Knoevenagel condensation of isatin with aromatic/heteroaromatic ketone for the synthesis of a series of new biological potential 3-methylene oxindoles *via* 3-hydroxy precursor without using any catalyst (Scheme 1).

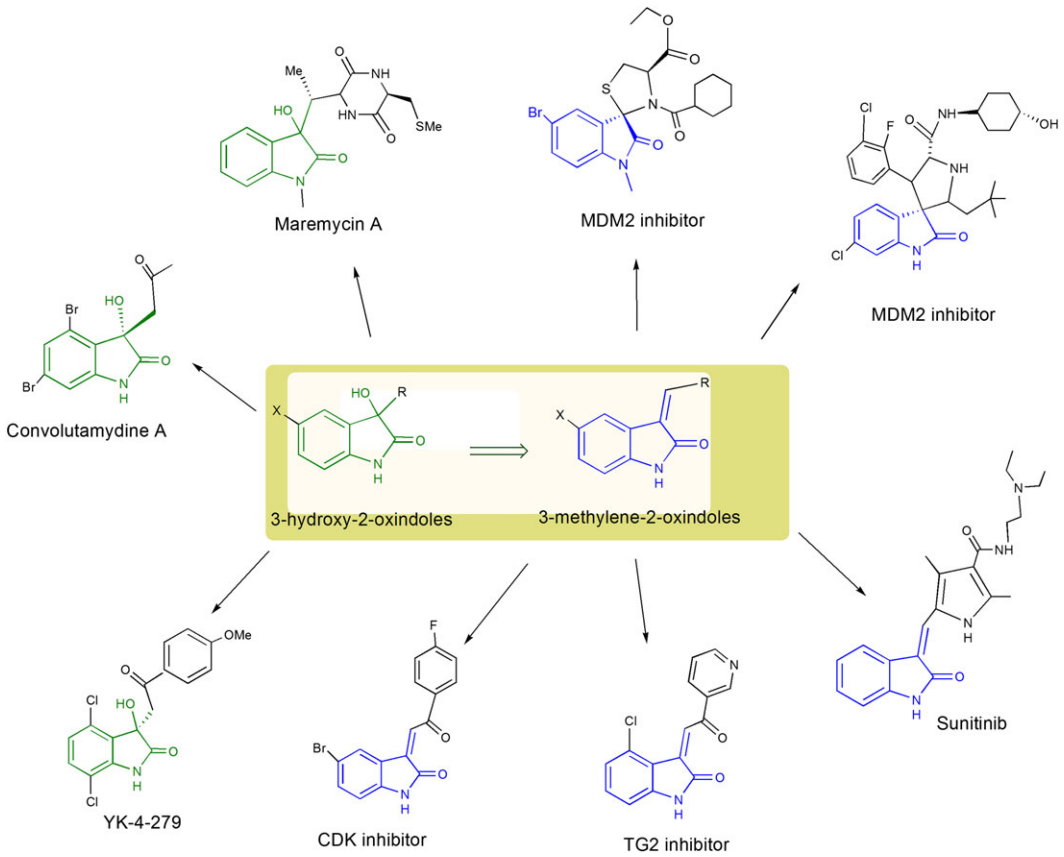
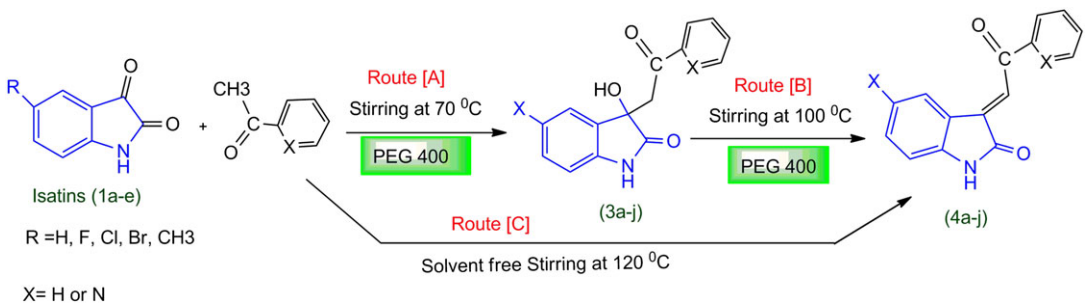


Figure 1. Representative 3-hydroxy-2-oxindoles and 3-methylene-2-oxindoles with potential anticancer activity. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. General procedure for the synthesis of 3-hydroxy-2-oxindoles and 3-methylene-2-oxindoles (**3a**–**j** and **4a**–**j**). [Color figure can be viewed at wileyonlinelibrary.com]



RESULTS AND DISCUSSION

Conventional thermal synthesis of isatin-linked chalcones occurs in two steps: In the first step, substituted indole-2,3-dione (isatin) and ketone and diethylamine as catalyst were refluxed in absolute ethanol to afford 3-hydroxy-2-oxindoles, which in second step, were dehydrated in the presence of acetic acid/HCl to furnish the desired 3-methylene-2-oxindoles [40]. Thus, overall thermal method is cumbersome especially because of long reaction time and environmental concerns.

Keeping the focus on the green protocol to avoid harmful solvents/catalyst, the efficacy of PEG 400 has been examined for the model reaction of acetophenone with isatin. For the first stage in chalcone precursor synthesis, solvent suitability, reaction temperature, and time were examined with respect to the yield and purity of the desired product (Table 1). It was observed that the reaction without solvent or catalyst support did not proceed at all (Table 1, entry 1). However, to our pleasant surprise, stirring of an equimolar mixture of isatin and acetophenone in PEG 400 without using any

Table 1

Optimization of solvent for synthesis of 3-hydroxy-2-oxindoles, **3a**, in PEG 400.[a]

Entry	Solvent	Temperature (°C)	Time (min)	Yield[b] (%)
1	—	60	10	—
2	PEG 400	25 (r.t.)	10	40
3	PEG 400	25 (r.t.)	20	44
4	PEG 400	30	20	46
5	PEG 400	40	20	68
6	PEG 400	50	16	90
7	**PEG 400**	**70**	**16**	**96**
8	PEG 400	90	16	92
9	PEG 400	100	16	78
10	Ethanol	50	16	—
11	Methanol	50	16	—
12	Dichloromethane	50	16	—
13	Acetonitrile	50	16	8
14	DMF	50	16	14
14	Benzene	80	16	—

[a]Reaction conditions: isatin (1 mmol) and acetophenone (1 mmol).
[b]Isolated yield.
Bold showed the best optimized reaction conditions.

catalyst at room temperature (25°C) for 20 min generated 3-hydroxy-2-oxindole, **3a**, in 40% yield (Table 1, entry 2). However, increasing reaction time did not show much improvement in yield (Table 1, entry 3), but increasing reaction temperature from 25 to 70°C showed a steady increase in yield (Table 1, entries 4–7), with maximum 96% at 70°C. It is found that further increasing the temperature has detrimental effect on the yield by raising the possibility of side reactions to occur (Table 1, entries 8 and 9). The reaction time was optimized at 16 min (Table 1, entry 7) by monitoring the progress of the reaction using thin-layer chromatography (TLC). The reaction can be quenched at this stage by pouring the reaction mixture in ice-cold water to obtain the 3-hydroxyl precursor, **3a**, in high yield and purity (Scheme 1, route A). After filtration, the obtained solid product was further purified by crystallization. The aqueous filtrate was distilled at 100°C to remove water, and thus, separated PEG 400 was recycled and reused.

In order to find the suitability of another solvent for the synthesis of title compounds without using any catalyst, the reaction of isatin with acetophenone was examined in different solvents such as ethanol, methanol, dichloroethane, acetonitrile, dimethylformamide, and water (Table 1, entries 9–14). It was found that a base was needed inevitably in all these cases even with polar solvents like ethanol and methanol. Being a hydrophilic protic solvent, PEG 400 has aprotic ethereal sites that might be responsible for its catalytical behavior as a general base and may facilitate the initial formation of carbanion/enolate from isatin, thereby helping to expedite the overall rate of the condensation. In addition, the recyclability of the solvent, PEG 400, was investigated and revealed the important observation that the PEG 400 was recovered and reused for five runs without loss of its activity but a weight loss of about 10% of PEG was observed for every run because of handling loss.

In the second step of one-pot tandem process, compound **3a** generated *in situ*, when further stirred at about 100°C for 6 min, undergoes dehydration. Reaction was monitored using TLC, and on completion, the reaction mixture was cooled, poured in ice-cold water, and stirred well when corresponding chalcone, **4a** (Scheme 1, route B), separated out in quantitative yield. The *E*-geometry of the chalcone was confirmed by ^{1}H NMR spectroscopy. The experimental procedure was remarkably simple and required no toxic catalyst, inert atmosphere, or corrosive substances, and no side reaction was observed.

Table 2

Comparative data of conventional and PEG 400 method for the synthesis of 3-hydroxy-2-oxindoles (**3a–j**).

Product no.	X	Ar	Reaction time (min)		Yield[c] (%)	
			PEG 400[a]	Conventional[b]	PEG 400	Conventional
			Route A			
3a	H	Phenyl	8	40	95	90
3b	F	Phenyl	9	60	96	78
3c	Cl	Phenyl	8	60	92	83
3d	Br	Phenyl	11	50	93	86
3e	CH_3	Phenyl	9	55	96	92
3f	H	2-Pyridyl	8	45	95	81
3g	F	2-Pyridyl	10	60	94	74
3h	Cl	2-Pyridyl	8	70	95	78
3i	Br	2-Pyridyl	7	80	95	80
3j	CH_3	2-Pyridyl	9	50	94	77

[a]Isatin **1** (1 mmol) and ketone **2** (1 mmol) in PEG 400 (5 mL) stirred at 70°C for the specified time.
[b]**1** (1 mmol), **2** (1.1 mmol), and diethylamine (0.5 mL) in ab. ethanol refluxed on water bath for the specified time and kept at room temperature for 2–3 days.
[c]Isolated yield.

Table 3

Comparative data of conventional and PEG 400 method for the synthesis of 3-methylene-2-oxindoles (**4a–j**).

			Reaction time (min)		Yield[c] (%)	
Product no.	X	Ar	PEG 400[a]	Conventional[b]	PEG 400	Conventional
4a	H	Phenyl	6	20	96	83
4b	F	Phenyl	8	25	93	81
4c	Cl	Phenyl	8	25	94	87
4d	Br	Phenyl	9	30	95	86
4e	CH_3	Phenyl	11	25	96	90
4f	H	2-Pyridyl	8	27	94	89
4g	F	2-Pyridyl	7	30	92	84
4h	Cl	2-Pyridyl	7	27	93	81
4i	Br	2-Pyridyl	8	30	92	79
4j	CH_3	2-Pyridyl	9	30	96	82

[a]Compound **3** (1 mmol) in PEG 400 is stirred at 100°C for the specified time.
[b]Compound **3** (1 mmol) in gl. acetic acid (10 mL) and conc. HCl (0.5 mL) is heated on a steam bath at 95°C for the specified time.
[c]Isolated yield.

However, the reaction of the corresponding isatin with acetophenone in the absence of any solvent or catalyst on stirring at 120°C for 7 min directly afforded the product, 3-methylene-2-oxindoles (chalcones), in high yield and purity without isolation of intermediate aldol product (Scheme 1, route C). But by using 1:1 equivalent of isatin and ketone, **4a** was obtained in 65% yield. We noticed also that increasing the quantity of ketone enhanced the efficiency of the reaction. Increasing the quantity of ketone to two equivalent makes the reaction to go to completion with almost 100% conversions without formation of any side product and reduces the reaction time drastically. This could be because excess of acetophenone acts as catalyst, thus facilitating the reaction. Although route C is shorter, the use of the twofold excess of ketone somewhat lowers the sustainability character of the procedure generating additional waste. Thus, for the synthesis of isatin-linked chalcone, route (A + B) using PEG 400 is more sustainable than the direct route C.

With a set of optimized reaction conditions at hand, the scope of this reaction was investigated using various 5-substituted isatins as the presence of small withdrawing group at 5-position of the 2-oxindole derivatives is associated with enhanced potency and drug-like properties [7]. This simple facile one-pot synthesis strategy with high atomic economy could be applied to gram scale synthesis. It represents a substantial improvement upon conventional synthesis of biological potential isatin-derived 2-oxindoles and has been extended to other aromatic ketones like acetylpyridine, acetylpyrrole, and acetyl furan. All reactions in PEG 400 proceeds smoothly to completion in a short time to afford the corresponding product, in excellent yield and with high region selectivity. This is just preliminary data and scope expansion work of use of PEG 400 as green reaction media has also been explored for the synthesis of Schiff bases of isatins with various aromatic amines like aniline, 2-aminopyridine, and 2-aminothiazole. Work is currently underway in our laboratory results and will be published soon. All reactions were pursued *via* both conventional and PEG-mediated method, and the comparative study of the results confirms the superiority of the developed method.

Table 4

Solvent-free direct synthesis of 3-methylene-2-oxindoles (**4a–j**).

Product no.	X	Ar	Reaction time[a] (min)	Yield[b] (%)
4a	H	Phenyl	7	97
4b	F	Phenyl	9	95
4c	Cl	Phenyl	8	94
4d	Br	Phenyl	9	96
4e	CH_3	Phenyl	7	96
4f	H	2-Pyridyl	9	94
4g	F	2-Pyridyl	8	93
4h	Cl	2-Pyridyl	10	94
4i	Br	2-Pyridyl	12	95
4j	CH_3	2-Pyridyl	9	96

[a]Isatin **1** (1 mmol) and ketone **2** (2 mmol) stirred at 120°C for the specified time.
[b]Isolated yield.

CONCLUSION

A facile tandem route for the synthesis of a series of biological potential isatin-linked chalcones (**4a–j**) and their 3-hydroxy precursors (**3a–j**) using green solvent PEG 400 has been developed. Use of eco-friendly solvent, catalyst-free mild reaction conditions, short reaction times, high atom economy, and easy workup procedure are the key features of this method deserving

attention from a sustainable standpoint. This is just the preliminary data as scope expansion work with other isatins and ketones is currently underway in our laboratory. Developed method will be of great use to researchers seeking these bioactive motifs as precursors or intermediates for the synthesis of numerous pharmaceutically active drugs including spiro-oxindoles.

MATERIALS AND METHODS

All fine chemicals like substituted isatins, acetophenone, and acetylpyridine were purchased from Aldrich Chemicals Co., USA. Solvents used in this study were of analytical grade and purchased from Thermo Fisher Scientific India Pvt. Ltd. Elemental analysis was performed using a Heraeus CHN-O-rapid analyzer. Melting points were determined using open capillary tubes in scientific melting point apparatus and are uncorrected. Infrared (IR) spectra in KBr were scanned using a Perkin-Elmer model 557 grating IR spectrophotometer (ν_{max} in cm^{-1}). ^1H and ^{13}C NMR were recorded on Bruker Advance 400 spectrophotometer (chemical shift in δ ppm downfield from tetramethylsilane as an internal reference). The mass spectra were recorded on Jeol SX-102 mass spectrophotometer. The progress of the reaction was monitored by TLC using Merck silica gel coated alumina plates (0.25 mm) using solvent systems of different polarity. All the products were purified by simple filtration of the reaction mixture and crystallization except in few cases where the purification was accomplished by a short column chromatography. All synthesized compounds were characterized based on their ^1H NMR, ^{13}C NMR, Fourier transform infrared, mass spectroscopy, and elemental analyses.

EXPERIMENTAL

Representative general procedure for synthesis of 3-hydroxy-3-(2-oxo-2-arylethyl)-1,3-dihydro-2*H*-indol-2-ones (3a–j) (route A). Isatin **1a** (1 mmol) and acetophenone **2** (1 mmol) in PEG 400 (5 mL) were mixed thoroughly and stirred at 50°C for 8 min. The progress of the reaction was monitored by TLC using pet ether : ethyl acetate (3:1) as the solvent system. After completion of the reaction, the mixture was extracted with ethyl acetate (5–10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was filtered, dried, and recrystallized from ethanol as shining white crystals of **3a**, which were found to be TLC pure. However, in the case of compounds **3c** and **3i**, a short column chromatography on silica gel was used to purify the desired product. All compounds, **3f–j**, were synthesized in a similar manner with slight variation in reaction time as reported in Table 2. Physical and spectral data of compounds, **3a–e**, were comparable with earlier reported compounds in our published paper [40].

3-Hydroxy-3-[2-oxo-2-(2-pyridinyl)ethyl]-1,3-dihydro-2H-indol-2-one (3f). This compound was obtained as shining white flakes, mp: 200–202°C; IR (KBr, ν cm^{-1}): 3400 (OH), 3258 (NHCO), 1715 (CO–Ar), 1682 (NHCO), 1617, 1475, 1399, 1216, 755; ^1H NMR (DMSO, 300 MHz, δ ppm): 10.23 (s, 1H), 7.86 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.12–6.77 (d, *J* = 7.3 Hz, 1H), 6.77–6.80 (t, *J* = 7.4 Hz, 2H), 6.02 (s, 1H, OH), 4.05 (d, *J* = 17.6 Hz, 1H), 3.54 (d, *J* = 17.6 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 197.39, 178.8, 153.2, 47.8, 141.2, 136, 131.5, 129, 127.7, 123.2, 120.9, 120.3, 110.2, 74, 44.9; HRMS *m/z*: 267 (M^+) for $C_{15}H_{12}N_2O_3$.

5-Fluoro-3-hydroxy-3-[2-oxo-2-(2-pyridinyl)ethyl]-1,3-dihydro-2H-indol-2-one (3g). This compound was obtained as cream colored shining crystals, mp 198°C; IR (KBr, ν cm^{-1}): 3410 (OH), 3282 (NHCO), 1721 (CO), 1668 (NHCO), 1523, 1452, 1336, 1216, 1183, 748; ^1H NMR (DMSO, 300 MHz, δ ppm): 10.23 (s, 1H, NH), 7.91 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 6.82–6.74 (m, 2H), 6.64 (d, *J* = 7.8, 1H), 6.08 (s, 1H, OH), 4.05 (d, *J* = 17.1 Hz, 1H), 3.55 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 194.2, 174.8, 152.2, 147.2, 142.8, 138.2, 134.6, 132.2, 131.1, 129.5, 128.4, 124.2, 110.5, 72.7, 45.4; HRMS *m/z*: 285 (M^+) for $C_{15}H_{11}FN_2O_3$.

5-Chloro-3-hydroxy-3-[2-oxo-2-(2-pyridinyl)ethyl]-1,3-dihydro-2H-indol-2-one (3h). This compound was obtained as yellow solid, mp 209°C; IR (KBr, ν cm^{-1}): 3451 (OH), 3380 (NHCO), 1715 (CO), 1683 (NHCO), 1604, 1448, 1219, 1175, 820, 767; ^1H NMR (DMSO, 300 MHz, δ ppm): 10.17 (s, 1H, NH), 7.22 (d, *J* = 7.4 Hz, 1H), 7.11 (d, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.95–6.74 (m, 2H), 6.13 (d, *J* = 7.8 Hz, 1H), 6.03 (d, *J* = 7.22, 1H), 5.96 (s, 1H), 3.7 (d, *J* = 17.3 Hz, 1H), 3.25 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 196.9, 177.8, 150.3, 147.3, 141.6, 139, 135.7, 134.4, 132.2, 130.5, 129.9, 129.2, 109.4, 74.8, 44.7; HRMS *m/z*: 301 (M^+) for $C_{15}H_{11}ClN_2O_3$.

5-Bromo-3-hydroxy-3-[2-oxo-2-(2-pyridinyl)ethyl]-1,3-dihydro-2H-indol-2-one (3i). This compound was obtained as lemon yellow shining flakes, mp 218°C; IR (KBr, ν cm^{-1}): 3410 (OH), 3316 (NHCO), 1712 (CO), 1676 (NHCO), 1476, 1216, 990, 748; ^1H NMR (DMSO, 300 MHz, δ ppm): 10.32 (s, 1H, NH), 8.19 (d, *J* = 7.3 Hz, 1H), 8.18 (d, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.75–7.16 (m, 2H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8, 1H), 6.16 (s, 1H), 4.15 (d, *J* = 17.3 Hz, 1H), 3.65 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 191.9, 176.7, 152.3, 148.3, 141.6,

139, 137.7, 134.4, 133.2, 130.5, 129.9, 126.3, 109.4, 74.8, 45.2; HRMS *m/z*: 346 (M^+) for $C_{15}H_{11}BrN_2O_3$.

3-Hydroxy-5-methyl-3-[2-oxo-2-(2-pyridinyl)ethyl]-1,3-dihydro-2H-indol-2-one (3j). This compound was obtained as light yellow solid, mp 186–187°C; IR (KBr, ν cm^{-1}): 3374 (OH), 3280 (NHCO), 1715 (CO), 1680 (NHCO), 1469, 1354, 1227, 750; ^{1}H NMR (DMSO, 300 MHz, δ ppm): 10.26 (s, 1H, NH), 8.71 (d, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.2–7.12 (m, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.8, 1H), 6.10 (s, 1H), 4.27 (d, *J* = 17.3 Hz, 1H), 3.64 (d, *J* = 17.3 Hz, 1H), 2.48 (s, 3H, CH_3); ^{13}C NMR (DMSO, 75 MHz): δ 196.9, 177.8, 150.3, 147.3, 141.6, 139, 135.7, 134.4, 132.2, 130.5, 129.9, 129.2, 109.4, 74.8, 44.7, 24.8; HRMS *m/z*: 281 (M^+) for $C_{16}H_{14}N_2O_3$.

Representative procedure for synthesis of 3-(2-oxo-2-arylethylidene)-1,3-dihydro-2*H*-indol-2-one (4a–j) (route B). 3-Hydroxy-2-oxindole **3a** (1 mmol) generated, *in situ*, was further heated in the same vessel in PEG 400 at 100 °C with constant stirring for 6 min. The reaction was monitored by TLC when solution turned dark red. On completion, the reaction mixture was cooled and poured in cold water to obtain the desired bright colored compound. The crude product was recrystallized from hot ethanol as shining red crystals of pure chalcone, **4a**. Physical and spectral data of compounds, **4a**–**e**, were comparable with earlier reported compounds in our published paper [40]. All compounds, **4f**–**j**, were synthesized in a similar manner with slight variation in reaction time as reported in Table 3.

3-[2-(2-Pyridinyl)-2-oxoethylidene]-1,3-dihydro-2H-indol-2-one (4f). This compound was obtained as bright red shining needles, mp 189–190°C; IR (KBr, ν cm^{-1}): 3189 (NHCO), 1712 (CO), 1644 (NHCO), 1616 (C=C),1617, 1460, 1333, 1290, 1023, 998, 750; ^{1}H NMR (DMSO-d_6, δ ppm): 10.77 (s, 1H, NH), 8.07 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.99 (t, *J* = 7.8 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 191.3, 169.8, 141.2, 137.8, 137.3, 134.4, 133.5, 132.5, 129.0, 128.7, 126.2, 120.9, 124.3, 120.7, 109.4; HRMS m/z: 249 (M^+) for $C_{15}H_{10}N_2O_2$.

5-Fluoro-3-[2-(2-pyridinyl)-2-oxoethylidene]-1,3-dihydro-2H-indol-2-one (4g). This compound was obtained as shining brown needles, mp 236°C; IR (KBr, ν cm^{-1}): 3220 (NHCO), 1700 (CO), 1656 (NHCO), 1605 (C=C), 1425, 1334, 1216, 994, 748; ^{1}H NMR (DMSO, δ ppm): 11.0 (s, 1H, NH), 7.57 (d, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 2H), 6.88 (d, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 192.9, 168.2, 145.6, 142.3, 140.3, 138.8, 136.7, 133.2, 132.6, 132.3, 129.4, 126.3, 122.3, 121.5, 109.4; HRMS *m/z*: 267 (M^+) for $C_{15}H_9FN_2O_2$.

5-Chloro-3-[2-(2-pyridinyl)-2-oxoethylidene]-1,3-dihydro-2H-indol-2-one (4h). This compound was obtained as red fluffy solid, mp 254°C; IR (KBr, ν cm^{-1}): 3200 (NHCO), 1690 (CO), 1655 (NHCO), 1590 (C=C), 1620, 1421, 1320, 1284, 1013, 760; ^{1}H NMR (DMSO-d_6, δ ppm): 10.78 (s, 1H, NH), 8.46 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H) 6.78 (s, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 190.6, 168.2, 143.6, 142.3, 139.4, 138.8, 136.7, 133.2, 133.6, 132.7, 129.4, 125.1, 121.3, 119.5, 111.3; HRMS *m/z*: 283 (M^+) for $C_{15}H_9ClN_2O_2$.

5-Bromo-3-[(2-(2-pyridinyl)-2-oxoethylidene]-1,3-dihydro-2H-indol-2-one (4i). This compound was obtained as dark red needles, mp 270°C; IR (KBr, ν cm^{-1}): 3280 (NHCO), 1702 (CO–Ar), 1683 (NHCO), 1621, 1445, 1343, 1297, 1025, 1011, 760; ^{1}H NMR (DMSO-d_6, δ ppm): 10.93 (s, 1H, NH), 8.79 (s, 1H), 8.68 (d, *J* = 7.4 Hz, 1H), 8.43 (d, *J* = 7.1 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.7 (d, *J* = 7.3 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR (DMSO, 75 MHz): δ 190.8, 166.7, 147.8, 143.5, 137.4, 134.6, 130.6, 128.2, 126.6, 125.9, 125.3, 122.8, 121.9, 121.4, 110.4; HRMS *m/z*: 228 (M^+) for $C_{15}H_9BrN_2O_2$.

5-Methyl-3-[2-(2-pyridinyl)-2-oxoethylidene]-1,3-dihydro-2H-indol-2-one (4j). This compound was obtained as dark red fluffy flakes, mp 220°C; IR (KBr, ν cm^{-1}): 3190 (NHCO), 1690 (CO), 1655 (NHCO), 1590 (C=C), 1604 (C=C), 1334, 1216, 1014, 748; ^{1}H NMR (DMSO-d_6, δ ppm): 10.68 (s, 1H, NH), 8.83 (s, 1H), 8.64 (d, *J* = 8.2 Hz, 1H), 8.56 (d, *J* = 8.2 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 8.14 (d, 1H), 8.02 (d, *J* = 7.3 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 6.86 (s, 1H), 2.27 (s, 3H, CH_3); ^{13}C NMR (DMSO, 75 MHz): δ 189.8, 168.5, 143.8, 140.5, 136.4, 132.6, 132.4, 129.3, 127.7, 126.6, 125.3, 122.8, 121.9, 121.4, 110.4, 21.5; HRMS *m/z*: 263 (M^+) for $C_{16}H_{12}N_2O_2$.

Representative procedure for direct synthesis of 3-(2-oxo-2-arylethylidene)-1,3-dihydro-2*H*-indol-2-one (4a–j) (route C). Isatin (1 mmol) and acetophenone (3 mmol) were mixed thoroughly using a pestle and mortar without any solvent or catalyst, and the mixture was heated at 120°C with stirring for 7 min. The reaction was monitored by TLC, and on completion, reaction mixture was cooled to obtain the desired bright colored compound. The crude product was recrystallized from hot ethanol as shining red crystals of pure chalcone, **4a**. All compounds, **4b**–**j**, were synthesized in a similar manner with slight variation in reaction time as reported in Table 4.

Representative general procedure for conventional thermal synthesis of 3a–j and 4a–j. An equimolar concentration of the corresponding isatin (10 mmol) and ketone (10 mmol) in the presence of catalytic amount of diethylamine (0.5 mL) was refluxed in absolute ethanol (20 mL) on a

steam bath for 40–80 min. The progress of the reaction was monitored by TLC. The solution was then kept at room temperature for 2–3 days when 3-hydroxy-2-oxindole, **3**, precipitated out. The crude compound was recrystallized from hot ethanol as a light colored shining compound.

In the second step, compound, **3**, was heated on a steam bath for 20–30 min at 95°C in the presence of glacial acetic acid (10 mL) and few drops of concentrated HCl (0.5 mL). On cooling, the reaction mixture was filtered, and chalcone, **4**, obtained as the bright color compound, was purified by recrystallization from hot ethanol. The results are reported in Tables 1 and 2.

Acknowledgment. Financial support from the Department of Science and Technology (DST), New Delhi, India (DST scheme no. SR/WOS-A/CS-26/2014) is gratefully acknowledged by the first author Alpana K. Gupta.

REFERENCES AND NOTES

[1] Gupta, A. K.; Bharadwaj, M.; Kumar, A.; Mehrotra, R. Top Curr Chem 2017, 375, 1.

[2] Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M. Expert Opin Ther Pat 2016, 26, 149.

[3] Prakash, C. R. Pharmacol Pharm 2012, 3, 62.

[4] Vine, K. L.; Matesic, L.; Locke, J. M.; Ranson, M.; Skropeta, D. Anticancer Agents Med Chem 2009, 9, 397.

[5] Vine, K. L.; Matesic, L.; Locke, J. M. Advances Anti Canc Agents Med Chem 2013, 254.

[6] Yu, B.; Yu, D. Q.; Liu, H. M. Eur J Med Chem 2015, 97, 673.

[7] Peddibhotla, S. Curr Bioact Compd 2009, 5, 20.

[8] Ziarani, G. M.; Moradi, R.; Lashgari, N. ARKIVOC 2016, 1, 1.

[9] Karthikeyan, C.; Solomon, V. R.; Lee, H.; Trivedi, P. Biomed Prev Nutr 2013, 3, 325.

[10] Albuquerque, H.; Santos, C.; Cavaleiro, J.; Silva, A. Curr Org Chem 2014, 18, 2750.

[11] Abo-Ashour, M. F.; Eldehna, W. M.; Nocentini, A.; Ibrahim, H. S.; Bua, S.; Abou-Seri, S. M.; Supuran, C. T. Eur J Med Chem 2018, 157, 28.

[12] Azizi, N.; Dezfooli, S.; Khajeh, M.; Hashemi, M. J Mol Liq 2013, 186, 76.

[13] Azizi, N.; Dezfooli, S.; Khajeh, M.; Hashemi, M. J Mol Liq 2014, 194, 62.

[14] Singh, G. S.; Desta, Z. Y. Chem Rev , 112, 6104.

[15] Yu, B.; Xing, H.; Yu, D. Q.; Liu, H. M. Beilstein J Org Chem 2016, 12, 1000.

[16] Amin, M. A.; Youssef, M. M.; Abdel-hafez, S. H. J Chemica Acta 2012, 1, 35.

[17] Hajinasiri, R.; Hossaini, Z.; Torshizi, H.; Rostami-charati, F. Iranian J Org Chem 2011, 3, 695.

[18] Zhang, F.; Li, C.; Qi, C. Tetrahedron Asymmetry 2013, 24, 380.

[19] Duan, Z.; Han, J.; Qian, P.; Zhang, Z.; Wang, Y.; Pan, Y. Org Biomol Chem 2013, 11, 6456.

[20] Kumar, T. P.; Manjula, N.; Katragunta, K. Tetrahedron Asymmetry 2015, 26, 1281.

[21] Chen, W. B.; Liao, Y. H.; Du, X. L.; Zhang, X. M.; Yuan, W. C. Green Chem 2009, 11, 1465.

[22] Chen, J. R.; Liu, X. P.; Zhu, X. Y. Tetrahedron 2007, 63, 10437.

[23] Bañn-Caballero, A.; Flores-Ferrándiz, J.; Guillena, G.; Nájera, C. Molecules 2015, 20, 12901.

[24] Sheldon, R. A. Green Chem 2005, 7, 267.

[25] Zhang, W.; Cue, B. W. Green Techniques for Organic Synthesis and Medicinal Chemistry; John Wiley: London, 2012.

[26] Meshram, H. M.; Nageswara, R. N.; Chandrasekhara, R. L.; Satish, K. N. Tetrahedron Lett 2012, 53, 3963.

[27] Dong, H.; Liu, J.; Ma, L.; Ouyang, L. Catalysts 2016, 6, 186.

[28] Tiwari, K. N.; Bora, D.; Chauhan, G.; et al. Synth Commun 2016, 46, 620.

[29] Huang, Y. Monatshefte Für Chemie 2000, 131, 521.

[30] Acharya, A. P.; Kamble, R. D.; Patil, S. D.; Hese, S. V.; Yemul, O. S.; Dawane, B. S. Res Chem Intermed 2015, 41, 2953.

[31] Dandia, A.; Singh, R.; Kumar, G.; Arya, K.; Sachdeva, H. Heterocycl Commun 2001, 7, 571.

[32] Vafaeezadeh, M.; Hashemi, M. M. J Mol Liq 2015, 207, 73.

[33] Liu, Y.; Liang, J.; Liu, X. H.; Fan, J. C.; Shang, Z. C. Chin Chem Lett 2008, 19, 1043.

[34] Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. Green Chem 2005, 7, 64.

[35] Cao, Y.; Dai, Z.; Zhang, R.; Chen, B. Synth Commun 2005, 35, 1045.

[36] Chandrasekhar, S.; Narsihmulu, C.; Reddy, N. R.; Sultana, S. Tetrahedron Lett 2004, 45, 4581.

[37] Tanemura, K.; Suzuki, T.; Nishida, Y.; Horaguchi, T. Chem Lett 2005, 34, 576.

[38] Gupta, A. K.; Kalpana, S.; Malik, J. K. Indian J Pharm Sci 2012, 74, 481.

[39] Lashgari, N. ARKIVOC 2012, 1, 277.

[40] MacDonald, J. P.; Badillo, J. J.; Arevalo, G. E.; Silva-García, A.; Franz, A. K. ACS Comb Sci 2012, 14, 285.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.