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# Highly regioselective and metal-free γ-addition of β-keto esters to isatins, catalyzed by DABCO: direct access to novel class of diversely functionalized 3-hydroxy-2-oxindole scaffolds

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ABSTRACT

DABCO catalyzed, highly regioselective γ-addition of β-keto esters has been achieved in the aldol reaction with isatins to afford γ-(3-hydroxy-2-oxindole)-β-keto ester structural framework under metal-free condition. The generality of the method has been demonstrated by screening series of isatin electrophiles as well as linear and cyclic β-keto esters. Compare to the dianion method, the present method is very simple and handy, which provides straightforward access for the new diversely functionalized 3-β-keto ester substituted-3-hydroxy-2-oxindole structural scaffolds in very good yields from readily available starting materials.



## 1. Introduction

3-Substituted-3-hydroxy-2-oxindole framework is a privileged structural motif persistently occurs in many biologically active compounds and natural products.[1] Selective representative example includes donaxaridine, maremycin A, maremycin B, convolutamydine A, B, C, D, E, welwitindolinone C, SM-130686, and dioxibrassinine (Fig. 1). As a result of this prevalence and prominence of 3-substituted-3-hydroxy-2-oxindole moiety, enormous research is promoted in the development of synthesis of such structural framework. Among the different reported protocols, direct addition of various nucleophiles to isatin is very general and straightforward approach used for the synthesis of this structural scaffold due to the fact that highly reactive β-carbonyl group of isatin is much susceptible to nucleophilic attack.[2] From the various nucleophiles, enolizable ketones[3] and aldehydes[4] have been explored extensively with isatins. However, only a handful of reports are available on direct nucleophilic addition of other enolizable carbonyl components[5–8] on isatin.

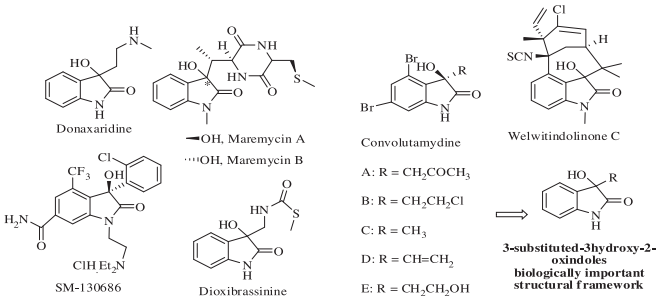


**Fig. 1.** Selected representative examples of natural products and pharmaceuticals possessing 3-substituted-3-hydroxy-2-oxidole structural framework.

In the class of carbonyl compounds, β-keto esters are well recognized as simple, easily available, and versatile starting material in the chemical synthesis for the construction of diversely functionalized complex molecular system.[9] Additionally, β-keto esters also explored in the aldol reaction,[10] which is one of the most important C–C bonds forming reaction of carbonyl compound in organic synthesis. In general, aldol reaction of β-keto esters with carbonyl compounds in the presence of organic bases affords α-addition products.[11] The formation of α-addition product is logical because, α-

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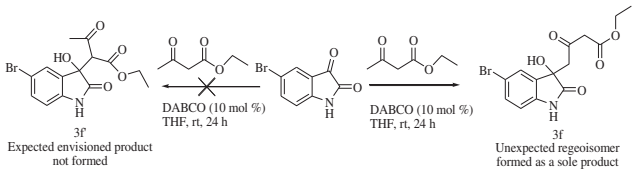
proton of β-keto ester is more acidic than γ-proton. Alternately, Huckin and Weiler developed aldol reaction of β-keto esters with aldehyde, which undergoes regioselective γ-addition reaction to give γ-hydroxy β-keto ester structural motifs by using dianion method.[12] The dianion protocol was also applied on ketones,[13] however the scope of this method is not tested on other electrophilic systems.

A search of literature revealed that β-keto ester having enolizable protons both at α and γ position remains totally unexplored for the aldol reaction with isatins. So far only one example of aldol reaction of β-keto ester[14] with isatin is reported in which β-keto ester having enolizable proton only at γ-position is employed. In this context, as a part of our efforts in the synthesis of 3-substituted 3-hydroxy-2-oxindoles,[15] we herein wish to report a DABCO catalyzed, metal-free, highly efficient, and novel method for regioselective γ-addition of β-keto esters to isatins for the synthesis of β-keto esters substituted 3-hydroxy-2-oxindole frameworks by using aldol reaction.

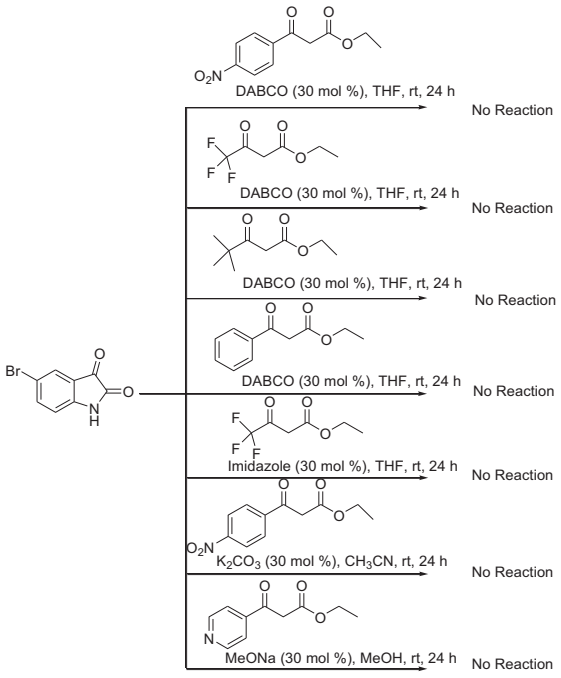
## 2. Results and discussions

In continuation of our ongoing interest in the development of 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed organic transformation,[15c,16] we planned to explore the potential of DABCO as a catalyst in the aldol reaction of β-keto ester with isatin. As a model reaction, we first attempted the reaction of ethyl acetoacetate with 5-bromo isatin in tetrahydrofuran (THF) in the presence of 10 mol % DABCO (Scheme 1). The reaction proceeded smoothly at room temperature to afford the new product as a white solid. Both crude and pure products were subjected for $^1$H NMR spectral analysis. To our surprise, we have not observed the formation of α-addition product **3f′** even in trace amount. Indeed, the reaction afforded γ-addition product **3f** as a sole product. The $^1$H NMR spectra of the product showed signal for the characteristic quaternary hydroxy at δ 6.1 ppm but, does not showed the anticipated singlet at approx. δ 2.3 ppm for three hydrogen of acetyl group and singlet at approx. δ 3.9 ppm for one α-hydrogen of ethyl acetoacetate group in expected product **3f′**. Moreover, $^1$H NMR shows the multiplet for four protons at δ 3.77–3.22 ppm consistent to the two α-protons and two γ-protons present in ethyl acetoacetate group of product **3f**. Thus, our observation showed that, the reaction of β-keto ester with isatin in the presence of 10 mol % DABCO affords single regioisomer, i.e., γ-(3-hydroxyoxindol)-β-keto ester (**3f**) instead of α-(3-hydroxyoxindol)-β-keto ester (**3f′**).



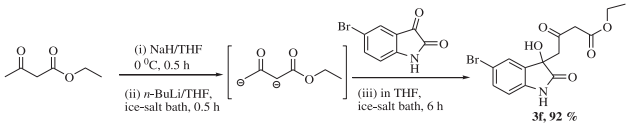

**Scheme 1.** Synthesis of β-keto esters substituted 3-hydroxy-2-oxindole framework.

To authenticate the observed γ-regioselectivity, further study was planned. In this regard, we performed the reaction of 5-bromo isatin with those β-keto esters having no enolizable proton at γ-position under different conditions (Scheme 2). First we screened β-keto esters like, ethyl 3-(4-nitrophenyl)-3-oxopropanoate, ethyl 4,4,4-trifluoro-3-oxobutanoate, ethyl 4,4-dimethyl-3-oxopentanoate, ethyl 3-oxo-3-phenylpropanoate with 5-bromo isatin in the presence of DABCO in THF. However we have not observed the formation of new product under this reaction condition. Latter we carried out reaction of 5-bromo isatin with ethyl 3-(4-nitrophenyl)-3-oxopropanoate, ethyl 4,4,4-trifluoro-3-oxobutanoate in the presence of other catalyst like imidazole and $K_2CO_3$, which also failed to form new product. Finally we tried to explore the catalytic activity of MeONa in the reaction of ethyl 3-oxo-3-(pyridin-4-yl)propanoate with 5-bromo isatin in MeOH. As like previous results, reaction does not proceed to afford the desired product even after longer reaction time. From these results it is understandable that, β-keto esters having no enolizable proton at γ-position, does not to undergo aldol reaction with isatin.




**Scheme 2.** Reaction of 5-bromo isatin with those β-keto esters having no enolizable protons at γ-position; Reaction conditions: 5-bromo isatin (1 mmol), β-keto esters (1 mmol) in 5 mL solvent at room temperature.

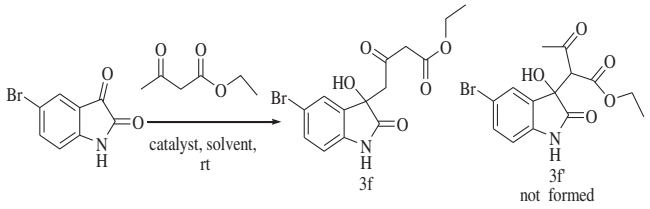
In addition to these, the observed γ-regioselectivity of the reaction obtained with DABCO was also confirmed by spectral analysis of the product obtained under dianion method[17] (Scheme 3). The $^1$H NMR signal pattern observed for the crude reaction mixture obtained by using DABCO was in good agreement with one that observed for the crude reaction mixture obtained under dianion method. All this above experiments validates the formation of regioselective γ-(3-hydroxy-2-oxindole)-β-keto ester (**3f**) instead of α-(3-hydroxy-2-oxindole)-β-keto ester (**3f′**) in the presence of DABCO. In dianion method, use of excess of base and combination of metallic bases, sodium hydride, and *n*-butyllithium is mandatory to get γ-hydroxy β-keto ester structural framework. Our extensive literature search does not showed any report regarding the γ-regioselective addition of β-keto ester on carbonyl component under the metal-free condition. To the best of our knowledge, this is the first study on metal-free, tertiary amine base (DABCO) catalyzed aldol reaction of β-keto ester with isatin to provide regioselective γ-(3-hydroxy-2-oxindole)-β-keto ester structural framework.




**Scheme 3.** Aldol reaction of 5-bromo isatin with ethyl acetoacetate under dianion method.

With these cheering observations, next we studied the reaction in detail to get optimized reaction condition. In this context, we tested the scope of different organic catalyst for the aldol reaction of 5-bromo isatin with ethyl acetoacetate and results are summarized in Table 1 (entries 1–9). As a part of study, we have also screened some other catalyst like $K_2CO_3$, $Cs_2CO_3$, MeONa, and

**Table 1**
Optimization of reaction conditions[a]




| Entry | Catalyst (mol %) | Solvent | Time (h) | Conversion[b] **3f**/**3f'** |
|---|---|---|---|---|
| 1 | DABCO (10) | THF | 24 | 94:0 |
| 2 | DABCO (30) | THF | 8 | 95:0 |
| 3 | TEA (30) | THF | 8 | 71:0 |
| 4 | DIPEA (30) | THF | 8 | 76:0 |
| 5 | DBU (30) | THF | 8 | 68:0 |
| 6 | DBN (30) | THF | 8 | 65:0 |
| 7 | Piperidine (30) | THF | 8 | 63:0 |
| 8 | Imidazole (30) | THF | 8 | 72:0 |
| 9 | DMAP (30) | THF | 8 | 61:0 |
| 10 | $K_2CO_3$ (30) | $CH_3CN$ | 8 | 74:0 |
| 11 | $Cs_2CO_3$ (30) | $CH_3CN$ | 8 | 67:0 |
| 12 | MeONa (30) | MeOH | 8 | 82:0 |
| 13 | EtONa (30) | EtOH | 8 | 81:0 |
| 14 | — | THF | 24 | 0:0 |

[a] Reaction conditions: 5-bromo isatin (1 mmol), ethyl acetoacetate (1 mmol) in 5 mL of solvent.
[b] By $^1$H NMR analysis. TEA=triethylamine, DIPEA=diisopropylethylamine, DBU=1,8-diazabicyclo[5.4.0]undec-7-ene, DBN=1,5 diazabicyclo[4.3.0]non-5-ene, DMAP=4-dimethylaminopyridine.

EtONa (entries 10–13). All the catalysts screened in this study showed their potential to afford the desired products; however they differ in the degrees of conversions as obtained by $^1$H NMR analysis. It is notable from the above results that, both the organic and inorganic catalysts have given only regioselective γ-addition product **3f** and the formation of α-addition product **3f'** was not observed. Control reaction without catalyst was also performed, but the formation of product was not observed even after stretching reaction time up to 24 h (entry 14). After extensive screening of various bases and solvents, 30 mol % DABCO in THF (entry 2, Table 1) was eventually preferred as set of optimized reaction condition for the efficient aldol reaction of 5-bromo isatin with ethyl acetoacetate. In that case, the desired product **3f** was obtained within 8 h with 95% conversion.

With this established optimum condition, we were keen to explore the scope of γ-regioselectivity of the reaction with respect to various other β-keto esters and isatins and results are depicted in Table 2. To our delight, we found that, array of β-keto esters and isatins with diverse functional groups including halogens were well-tolerated and afforded desired products with complete regioselectively in very good yields under optimized condition (Table 2). Encouraged by these results, next we screened some *N*-alkylated isatins, which also afforded the moderate to good yield of desired product (Table 2, **3g**,**h**,**q**). Moreover, β-keto esters having substituents at α-&/γ-carbon atom were also reacted smoothly with isatins under standard reaction condition and given desired γ-addition products in good to excellent yield as a mixture of inseparable diastereomers (Table 2, products **3l**–**u**). Similarly, the reaction of ethyl 2-benzyl-3-oxobutanoate with isatin carried out in optimized condition afforded corresponding γ-(3-hydroxy-2-oxindole)-β-keto ester adduct **3k**, with complete γ-regioselectivity. The desired γ-regioselectivity of the reaction was also confirmed by X-ray crystallographic structure[18] obtained for product **3k** (Fig. 2, also see Supplementary data file for detail single crystal X-ray data).

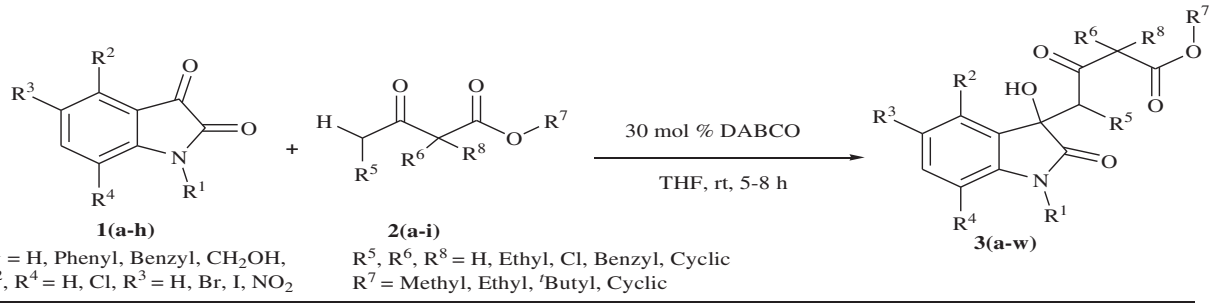
It is worthy to mention that α-halogenated β-keto ester like ethyl 2-chloro-3-oxobutanoate was reacted in the same fashion under optimized reaction condition to give γ-regioselective aldol product (Table 2, products **3n**–**q**). The reaction was successful not only with linear β-keto esters but also with cyclic β-keto esters, which reacted smoothly with isatins and afforded their respective γ-regioselective aldol products as mixture of diastereomers (Table 2, products **3s**–**u**). Further to rule out any rearrangement, we have also screened those β-keto esters having no enolizable proton at α carbon atom. In that case, we observed that the reaction of ethyl 2,2-diethyl-3-oxobutanoate with isatin and 5-chloro isatin under optimized reaction condition proceeds smoothly to afford desired product in good yield (products **3v**,**w**, respectively).

All the screened structurally varied β-keto esters underwent efficient γ-addition on different isatin electrophiles to provide γ-(3-hydroxy-2-oxindole)-β-keto ester structural scaffolds in mild reaction condition. Results depicted in Table 2 also showed that, aldol reaction of β-keto esters with isatins does not hold the definite correlation between the electronic nature of substituent on isatin and efficiency of the reaction.

To understand the detailed mechanistic pathways of this regioselective γ-addition aldol reaction, we screened other active methylene compound, such as malononitrile and 3-oxopentanenitrile under optimized reaction condition. By the obtained spectral data, we found that reaction of 5-chloro isatin with malononitrile afforded Knoevenagel condensation product **3x** as a sole product in quantitative yield. Similarly the reaction of 5-chloro isatin with 3-oxopentanenitrile afforded Knoevenagel condensation product **3y** as a major product with trace amount of aldol addition product (Scheme 4). This results encouraged us to undertake the detailed NMR study for better understanding of reaction mechanism for γ-regioselective aldol reaction of β-keto ester with isatins.

On the basis of NMR study, the reaction mechanism for γ-regioselective aldol reaction of β-keto ester with isatins is shown in Scheme 5 (see Supplementary data file for details). The formation of γ-regioselective products can be rationalized on the basis of the transition state between enolate of β-keto ester and isatin. When we recorded $^1$H NMR spectrum of ethyl acetoacetate in absence of DABCO in $CDCl_3$ with $D_2O$, we found signal at 2.310 ppm (s, 3γ-H), 3.490 (s, 2α-H) 4.237–4.213 (q, 2H), 1.336–1.302 (t, 3H) and not found any deuteration under this condition. However when we recorded $^1$H NMR spectrum of ethyl acetoacetate in presence of 30 mol % DABCO in $CDCl_3$ with $D_2O$, we found the two active α-proton get quickly deuterated due to which signal obtained at 3.490 ppm in previous experiment get disappeared. In this case we found signal at 2.310 ppm (s, 3γ-H), 4.265–4.211 (q, 2H), 1.337–1.302 (t, 3H). Additionally and more importantly, we found the extra signal at 2.822 ppm under this condition. Signal at 2.822 ppm corresponds to the partial deuteration on γ-H due to acidic nature of 3γ-H. Occurrence of partial deuteration on γ-H can be rationalized only by formation of kinetic enolate. With this study, we believe that the reaction get initiated by formation of enolate of β-keto ester with the aid of DABCO. When β-keto ester like ethyl acetoacetate is treated with DABCO, along with major thermodynamic enolate, small amount of kinetic enolate also formed due to acidic nature of protons present on γ-carbon atom. Further we propose the formation of disfavored transition state due to high steric interaction between thermodynamic enolate of ethyl acetoacetate and isatin. This high steric interaction might have reduced the nucleophilicity of thermodynamic enolate. As a result of such high steric interaction and reduction in nucleophilicity, thermodynamic enolate does not react with isatin to give α-addition product (Scheme 5, Path 1). However as depicted in Path 2, the steric interaction with isatin is much avoided with kinetic enolate of ethyl acetoacetate, which form favored transition state with isatin. Consequence of this, nucleophilicity of kinetic enolate might have increased and hence it reacts effectively with isatin to afford γ-addition product **3f** exclusively (Scheme 5, Path 2). Even the kinetic enolate present in minor amount, it shifts the equilibrium to

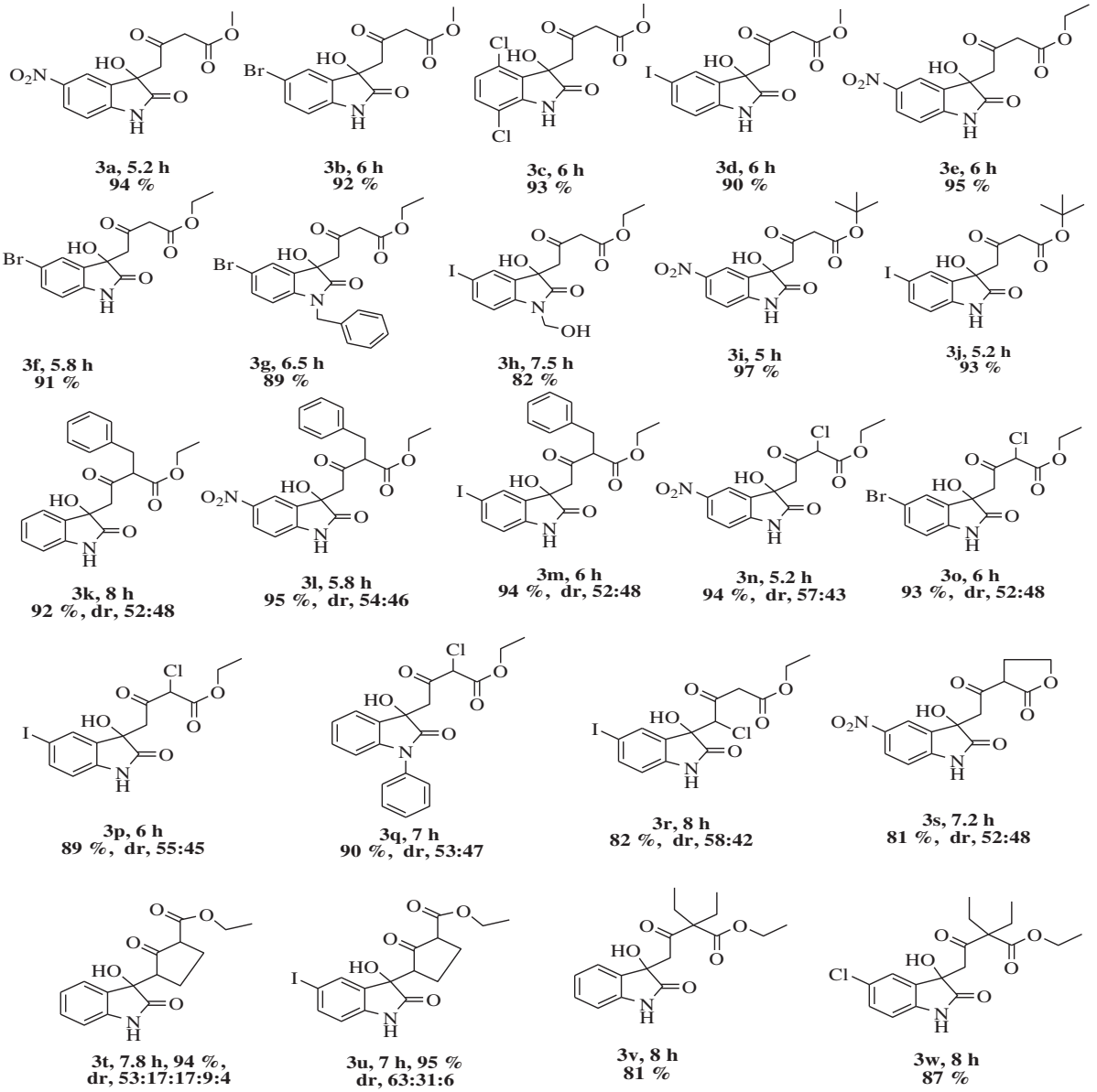
**Table 2**
Scope of aldol reaction of β-keto esters with isatins under optimized reaction condition[a]




**1(a-h)**
$R^1$ = H, Phenyl, Benzyl, $CH_2OH$,
$R^2$, $R^4$ = H, Cl, $R^3$ = H, Br, I, $NO_2$

**2(a-i)**
$R^5$, $R^6$, $R^8$ = H, Ethyl, Cl, Benzyl, Cyclic
$R^7$ = Methyl, Ethyl, $^t$Butyl, Cyclic

**3(a-w)**



**3a, 5.2 h**
**94 %**

**3b, 6 h**
**92 %**

**3c, 6 h**
**93 %**

**3d, 6 h**
**90 %**

**3e, 6 h**
**95 %**

**3f, 5.8 h**
**91 %**

**3g, 6.5 h**
**89 %**

**3h, 7.5 h**
**82 %**

**3i, 5 h**
**97 %**

**3j, 5.2 h**
**93 %**

**3k, 8 h**
**92 %, dr, 52:48**

**3l, 5.8 h**
**95 %, dr, 54:46**

**3m, 6 h**
**94 %, dr, 52:48**

**3n, 5.2 h**
**94 %, dr, 57:43**

**3o, 6 h**
**93 %, dr, 52:48**

**3p, 6 h**
**89 %, dr, 55:45**

**3q, 7 h**
**90 %, dr, 53:47**

**3r, 8 h**
**82 %, dr, 58:42**

**3s, 7.2 h**
**81 %, dr, 52:48**

**3t, 7.8 h, 94 %,**
**dr, 53:17:17:9:4**

**3u, 7 h, 95 %**
**dr, 63:31:6**

**3v, 8 h**
**81 %**

**3w, 8 h**
**87 %**

[a] Reaction conditions: isatin **1**(**a**–**h**) (1 mmol), β-keto esters **2**(**a**–**i**) (1 mmol) in 5 mL THF in the presence of 30 mol % DABCO and yields are given as isolated yields. All products **3**(**a**–**w**) are characterized by NMR, Mass, and IR spectroscopic techniques. (See Supplementary data file for characterization data and copies of $^1$H and $^{13}$C NMR spectrum).

forward direction by reacting with isatin and hence the reaction proceeds to completion to form new product. We believe that this NMR study has provided reasonable explanation for the formation of γ-addition product under our reaction condition. The further study for in-depth understanding of this reaction, which will also throw a light on described mechanistic pathway is currently in progress in our laboratory and results will be published in due course.

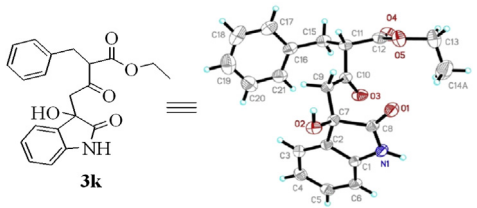
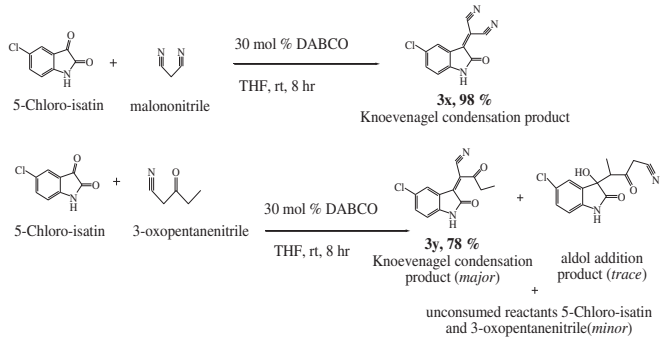
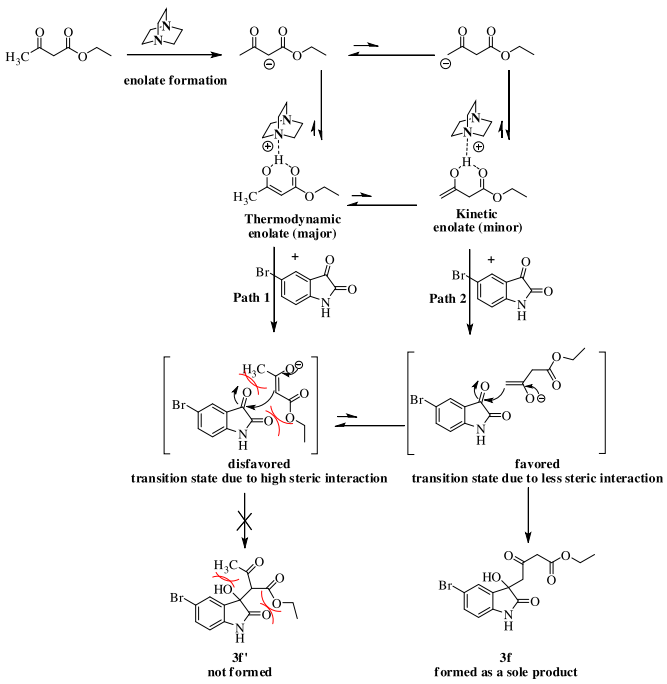



**Fig. 2.** ORTEP diagram of product **3k**.




**Scheme 4.** Reaction of 5-chloro isatin with malononitrile and 3-oxopentanenitrile under optimized reaction condition.




**Scheme 5.** Plausible mechanism for the formation of γ-addition product in the aldol reaction of β-keto esters with isatins.

## 3. Conclusion

In summary, we have demonstrated DABCO catalyzed, novel, regioselective γ-addition of β-keto esters to isatins under metal-free condition for the efficient synthesis of diversely functionalized 3-substituted 3-hydroxy-2-oxindoles framework. The discovery and development of this method led to a general route for the straightforward preparation of new class of 3-hydroxy-2-oxindole structural scaffolds in very good yields under mild reaction condition from readily available starting materials. In addition to simplicity, this method has one salient feature in its ability to tolerate a variety of functionalized isatins as well as β-keto esters. Such a 3-hydroxy-2-oxindole framework with intact β-keto ester structural motif provides an additional functional handle for further transformations, which can be effectively utilize in natural products synthesis and preparation of library of pharmaceutically important compounds. The preliminary study on an asymmetric version of this regioselective γ-addition of β-keto esters on isatins is initiated and results will be reported in due course.

## 4. Experimental section

### 4.1. General remarks

All materials used in this study were obtained from commercial supplier and used without further purification as received. Reaction involving moisture and/or air sensitive reagents were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Tetrahydrofuran (THF) was distilled over $Na/Ph_2CO$ under nitrogen atmosphere. Commercial grade solvents and reagents were used without further purification. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates (AL SIL G/UV, aluminum back) and one or more of the following methods were used for visualization: 254 nm UV light fluorescence quenching; iodine staining; anisaldehyde stain (ethanol (135 mL)/$H_2SO_4$ (5 mL)/AcOH (1.5 mL)/*p*-anisaldehyde 3.7 mL). Evaporation of solvents was performed at reduced pressure on a BUCHI rotary evaporator. Column chromatography was carried out with acme's silica gel grade 60–120 and 100–200 mesh. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Ethyl acetate and hexane were the common eluents used. All $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$/DMSO-$d_6$/$CDCl_3$+DMSO-$d_6$ on Gemini 200, Avance 300 or Inova 500 spectrometers. Chemical shifts ($\delta$) are reported in parts per million (ppm) relative to either residual $CHCl_3$ ($^1H$: $\delta$ 7.26 ppm, $^{13}C$: $\delta$ 77.00 ppm) or DMSO-$d_6$ ($^1H$: $\delta$ 2.50 ppm, $^{13}C$: $\delta$ 39.43 ppm) as an internal reference. The number of protons (*n*) for a given resonance is indicated by *n*H. Coupling constants (*J*) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s—singlet, d—doublet, t—triplet, q—quartet, br—broad, m—multiplet, dd—doublet of doublet, and br s—broad singlet. Melting points were measured on a BUCHI melting point machine. IR spectra were recorded on Thermo Nicolet FT/IR-5700 spectrometer. Mass spectra were recorded using Waters mass spectrometers. High resolution mass spectra (HRMS) were recorded using Applied Bio-Sciences HRMS spectrometer at national center for mass spectroscopy-IICT.

### 4.2. General procedure for DABCO catalyzed regioselective γ-addition of β-keto esters to isatins

To the stirred solution of β-keto ester **2**(**a**–**i**) (1.0 mmol) and DABCO (30 mol %) in 5 mL THF was added isatin **1**(**a**–**h**) (1 mmol). The mixture was then stirred at room temperature for stipulated time (5–8 h). After completion of reaction as indicated by TLC, the solvent was removed at reduced pressure on a BUCHI rotary evaporator. The residue was then purified by column chromatography on silica gel (hexane/ethyl acetate=4:1 to 1:1) to afford the desired product **3**(**a**–**w**).

*4.2.1. Methyl 4-(3-hydroxy-5-nitro-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3a**, Table 2).* Yield: 94%; Time 5.2 h; $R_f$ (50% EtOAc/hexanes) 0.13; Pale yellow solid; mp 161–163 °C; $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$: 10.85 (br s, 1H), 8.23–8.11 (m, 2H), 6.98 (d, $J$=9.1 Hz, 1H), 6.41 (br s, 1H), 3.67 (s, 3H), 3.62–3.27 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, DMSO-$d_6$) $\delta$: 199.39, 178.29, 166.74, 148.76, 142.28, 131.55, 126.12, 119.48, 109.63, 72.28, 51.83, 49.39, 48.80 ppm; IR (KBr): $\nu$=3256, 1713, 1626, 1526, 1480, 1338, 1254,

1188, 1107, 1072, 908, 841, 747, 592 $cm^{-1}$; MS (ESI): $m/z$=331 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{13}H_{12}N_2O_7Na$ $[M+Na]^+$=331.05367, found 331.05412.

*4.2.2. Methyl 4-(5-bromo-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3b**, Table 2).* Yield: 92%; Time 6 h; $R_f$ (50% EtOAc/hexanes) 0.13; White solid; mp 112–114 °C; $^1H$ NMR (200 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 10.27 (br s, 1H), 7.35 (d, $J$=1.1 Hz, 1H), 7.26 (dd, $J$=8.1, 1.1 Hz, 1H), 6.75 (d, $J$=8.1 Hz, 1H), 6.11 (br s, 1H), 3.67 (s, 3H), 3.61–3.12 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 200.31, 177.51, 167.25, 141.91, 133.68, 131.68, 130.05, 126.79, 111.50, 72.53, 51.80, 49.27, 48.98 ppm; IR (KBr): $\nu$=3235, 2960, 1698, 1618, 1446, 1349, 1258, 1184, 1062, 825, 729, 635 $cm^{-1}$; MS (ESI): $m/z$=364 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{13}H_{12}BrNO_5Na$ $[M+Na]^+$=363.97911, found 363.97952.

*4.2.3. Methyl 4-(4,7-dichloro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3c**, Table 2).* Yield: 93%; Time 6 h; $R_f$ (50% EtOAc/hexanes) 0.30; White solid; mp 134–136 °C; $^1H$ NMR (500 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 10.67 (br s, 1H), 7.17 (d, $J$=9.0 Hz, 1H), 6.85 (d, $J$=9.0 Hz, 1H), 6.32 (br, 1H), 3.83 (d, $J$=18.0 Hz, 1H), 3.64 (s, 3H), 3.52–3.45 (m, 2H), 3.42–3.39 (d, $J$=18.0 Hz, 1H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 199.32, 177.05, 166.52, 142.05, 130.13, 128.52, 123.07, 113.19, 107.02, 73.98, 51.77, 48.61, 47.76 ppm; IR (KBr): $\nu$=3424, 2926, 1743, 1621, 1468, 1104, 801, 466 $cm^{-1}$; MS (ESI): $m/z$=354 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{13}H_{11}Cl_2NO_5Na$ $[M+Na]^+$=353.99065, found 353.99098.

*4.2.4. Methyl 4-(3-hydroxy-5-iodo-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3d**, Table 2).* Yield: 90%; Time 6 h; $R_f$ (50% EtOAc/hexanes) 0.28; White solid; mp 162–164 °C; $^1H$ NMR (200 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 10.30 (br s, 1H), 7.57–7.43 (m, 2H), 6.65 (d, $J$=8.1 Hz, 1H), 6.12 (br s, 1H), 3.67 (s, 3H), 3.57–3.21 (m, 4H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 198.29, 175.71, 165.44, 140.66, 135.71, 132.10, 130.36, 110.40, 82.07, 70.72, 50.18, 48.82, 47.40 ppm; IR (KBr): $\nu$=3252, 1699, 1616, 1477, 1333, 1186, 1058, 827, 731, 531 $cm^{-1}$; MS (ESI): $m/z$=412 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{13}H_{12}NO_5INa$ $[M+Na]^+$=411.96524, found 411.96595.

*4.2.5. Ethyl 4-(3-hydroxy-5-nitro-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3e**, Table 2).* Yield: 95%; Time 6 h; $R_f$ (50% EtOAc/hexanes) 0.22; Pale yellow solid; mp 142–144 °C; $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$: 10.89 (br s, 1H), 8.21–8.09 (m, 2H), 6.97 (d, $J$=9.2 Hz, 1H), 6.29 (br s, 1H), 4.09 (q, $J$=7.2 Hz, 2H), 3.69–3.19 (m, 4H), 1.21 (t, $J$=7.2 Hz, 3H) ppm; $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$: 199.80, 178.59, 166.55, 149.03, 142.43, 131.78, 126.37, 119.62, 109.91, 72.41, 61.03, 49.57, 49.19, 13.87 ppm; IR (KBr): $\nu$=3260, 2927, 1749, 1712, 1626, 1526, 1479, 1337, 1255, 1188, 1107, 1072, 841, 747, 587 $cm^{-1}$; MS (ESI): $m/z$=345 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{14}N_2O_7Na$ $[M+Na]^+$=345.06932, found 345.07007.

*4.2.6. Ethyl 4-(5-bromo-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3f**, Table 2).* Yield: 91%; Time 5.8 h; $R_f$ (50% EtOAc/hexanes) 0.24; White solid; mp 153–155 °C; $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$: 10.28 (br s, 1H), 7.35 (d, $J$=1.5 Hz, 1H), 7.27 (dd, $J$=8.1, 1.5 Hz, 1H), 6.75 (d, $J$=8.1 Hz, 1H), 6.10 (br s, 1H), 4.10 (q, $J$=7.0 Hz, 2H), 3.77–3.22 (m, 4H), 1.21 (t, $J$=7.0 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, DMSO-$d_6$) $\delta$: 199.58, 177.68, 166.45, 141.60, 133.29, 131.70, 126.87, 113.60, 111.65, 72.96, 60.73, 49.60, 49.43, 14.02 ppm; IR (KBr): $\nu$=3344, 2985, 1739, 1711, 1621, 1479, 1344, 1278, 1184, 1062, 813, 577 $cm^{-1}$; MS (ESI): $m/z$=378 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{14}BrNO_5Na$ $[M+Na]^+$=377.99476, found 377.99470.

*4.2.7. Ethyl 4-(1-benzyl-5-bromo-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3g**, Table 2).* Yield: 89%; Time 6.5 h; $R_f$ (50% EtOAc/hexanes) 0.50; White solid; mp 105–108 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 7.56 (br s, 1H), 7.47–7.29 (m, 7H), 6.62 (d, $J$=8.4 Hz, 1H), 5.00 (d, $J$=15.1 Hz, 1H), 4.88 (d, $J$=15.1 Hz, 1H), 4.22 (q, $J$=7.5 Hz, 2H), 3.67–3.62 (m, 4H), 1.33 (t, $J$=7.4 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 199.91, 176.22, 166.44, 141.92, 134.74, 132.57, 131.35, 128.76, 127.68, 127.05, 115.70, 111.19, 73.51, 61.56, 49.61, 49.06, 43.94, 13.95 ppm; IR (KBr): $\nu$=3296, 2973, 2929, 1741, 1699, 1607, 1484, 1364, 1276, 1172, 1034, 951, 802, 698, 560, 475 $cm^{-1}$; MS (ESI): $m/z$=468 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{21}H_{20}BrNO_5Na$ $[M+Na]^+$=468.04171, found 468.04211.

*4.2.8. Ethyl 4-[3-hydroxy-1-(hydroxymethyl)-5-iodo-2-oxo-2,3-dihydro-1H-indol-3-yl]-3-oxobutanoate (**3h**, Table 2).* Yield: 82%; Time 7.5 h; $R_f$ (50% EtOAc/hexanes) 0.22; White solid; mp 104–106 °C; $^1H$ NMR (200 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 7.65–7.48 (m, 2H), 6.67 (d, $J$=8.3 Hz, 1H), 6.51 (br s, 1H), 6.11 (br s, 1H), 4.16 (q, $J$=7.8 Hz, 2H), 3.66–3.14 (m, 6H), 1.26 (t, $J$=7.8 Hz, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 200.19, 176.71, 163.96, 141.89, 136.55, 132.78, 131.11, 111.19, 82.44, 71.81, 64.30, 60.13, 49.87, 48.91, 13.81 ppm; IR (KBr): $\nu$=3248, 2981, 1443, 1698, 1616, 1477, 1347, 1185, 1089, 1025, 826, 729, 530 $cm^{-1}$; MS (ESI): $m/z$=456 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{15}H_{16}INO_6Na$ $[M+Na]^+$=455.99145, found 455.99179.

*4.2.9. tert-Butyl 4-(3-hydroxy-5-nitro-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3i**, Table 2).* Yield: 97%; Time 5 h; $R_f$ (50% EtOAc/hexanes) 0.18; Pale yellow solid; mp 155–157 °C; $^1H$ NMR (500 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 10.66 (br s, 1H), 8.09–7.98 (m, 2H), 6.86 (d, $J$=9.0 Hz, 1H), 6.21 (br s, 1H), 3.41 (d, $J$=17.0 Hz, 1H), 3.28 (d, $J$=15.0 Hz, 1H), 3.24–3.17 (m, 2H), 1.30 (s, 9H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 198.87, 177.62, 164.71, 148.25, 141.63, 131.06, 125.42, 118.80, 108.89, 80.88, 71.64, 49.80, 48.86, 26.91 ppm; IR (KBr): $\nu$=3265, 2980, 1712, 1626, 1526, 1480, 1336, 1256, 1187, 1071, 841, 746, 589 $cm^{-1}$; MS (ESI): $m/z$=373 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{16}H_{18}N_2O_7Na$ $[M+Na]^+$=373.10062, found 373.10173.

*4.2.10. tert-Butyl 4-(3-hydroxy-5-iodo-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3j**, Table 2).* Yield: 93%; Time 5.2 h; $R_f$ (50% EtOAc/hexanes) 0.14; White solid; mp 159–161 °C; $^1H$ NMR (500 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 10.19 (br s, 1H), 7.53 (d, $J$=2.0 Hz, 1H), 7.49 (dd, $J$=8.0, 2.0 Hz, 1H), 6.67 (d, $J$=8.0 Hz, 1H), 6.10 (br s, 1H), 3.40 (d, $J$=16.0 Hz, 1H), 3.36–3.30 (m, 2H), 3.16 (d, $J$=17.0 Hz, 1H), 1.44 (s, 9H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$: 198.28, 175.87, 164.18, 140.86, 136.02, 132.28, 130.76, 110.58, 82.15, 79.64, 71.10, 49.21, 48.07, 26.27 ppm; IR (KBr): $\nu$=3249, 2980, 1737, 1697, 1616, 1552, 1477, 1346, 1186, 1085, 1050, 829, 730, 534 $cm^{-1}$; MS (ESI): $m/z$=454 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{16}H_{18}INO_5Na$ $[M+Na]^+$=454.01219, found 454.01203.

*4.2.11. Ethyl 2-benzyl-4-(3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3k**, Table 2).* Yield: 92%; Time 8 h; $R_f$ (50% EtOAc/hexanes) 0.40; White solid; mp 170–172 °C; $^1H$ NMR (200 MHz, $CDCl_3$+DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 52:48, * denotes minor diastereomer peaks) $\delta$: 10.09 (br s, 1H), 10.09* (br s, 1H), 7.27–6.96 (m, 7H), 7.27–6.96* (m, 7H), 6.93–6.76 (m, 2H), 6.93–6.76* (m, 2H), 5.90 (br s, 1H), 5.88* (br s, 1H), 4.04 (q, $J$=7.0 Hz, 2H), 4.04* (q, $J$=7.0 Hz, 2H), 3.87–3.82* (m, 1H), 3.80–3.76 (m, 1H), 3.39–3.22 (m, 2H), 2.97–2.91 (m, 2H), 2.97–2.91* (m, 2H), 1.16 (t, $J$=7.0 Hz, 3H), 1.13* (t, $J$=7.0 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$+DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 54:46, * denotes minor diastereomer peaks) $\delta$: 200.85*, 200.75, 177.95, 177.87*, 168.06*, 167.91, 142.45*, 142.31, 137.76*, 137.63, 130.66*, 130.51, 128.94*, 128.43, 128.09, 126.18*, 123.47*, 123.21, 121.26*, 121.20, 109.63, 72.65*, 72.51, 60.90*, 60.87, 60.12*, 59.90, 49.22, 49.08*, 33.05, 13.67 ppm; IR (KBr): $\nu$=3068,

2937, 2876, 2717, 1703, 1636, 1591, 1508, 1457, 1333, 1112, 995, 833, 761, 632, $cm^{-1}$; MS (ESI): $m/z$=390 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{21}H_{21}NO_5Na$ $[M+Na]^+$=390.13119, found 390.13172.

*4.2.12. Ethyl 2-benzyl-4-(3-hydroxy-5-nitro-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3l**, Table 2).* Yield: 95%; Time 5.8 h; $R_f$ (50% EtOAc/hexanes) 0.34; White solid; mp 174–176 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 54:46, * denotes minor diastereomer peaks) $\delta$: 10.81* (br s, 1H), 10.80 (br s, 1H), 8.18–8.08 (m, 1H), 8.18–8.08* (m, 1H), 8.03* (d, $J$=1.2 Hz, 1H), 7.87 (d, $J$=1.2 Hz, 1H), 7.29–7.06 (m, 4H), 7.29–7.06* (m, 4H), 7.03–6.93 (m, 2H), 7.03–6.93* (m, 2H), 6.21* (br s, 1H), 6.16 (br s, 1H), 4.08 (q, $J$=7.2 Hz, 2H), 4.03* (q, $J$=7.2 Hz, 2H), 3.90–3.84 (m, 1H), 3.82–3.76* (m, 1H), 3.57 (d, $J$=18.1 Hz, 1H), 3.37* (d, $J$=18.1 Hz, 1H), 3.33* (d, $J$=18.0 Hz, 1H), 3.18 (d, $J$=18.0 Hz, 1H), 2.98–2.92 (m, 2H), 2.98–2.92* (m, 2H), 1.19(t, $J$=7.2 Hz, 3H), 1.13*(t, $J$=7.2 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 54:46, * denotes minor diastereomer peaks) $\delta$: 201.92, 201.84*, 178.16, 168.26*, 168.12, 149.53, 149.44*, 141.91*, 141.85, 137.86*, 137.78, 132.13, 132.10*, 128.67*, 128.58, 128.23*, 128.12, 126.63*, 126.55, 126.43*, 126.31, 119.36, 119.24*, 109.70*, 109.59, 71.91*, 71.85, 61.00, 59.31*, 59.03, 49.17, 48.99*, 32.90*, 32.81, 13.79, 13.70* ppm; IR (KBr): $\nu$=3257, 1711, 1626, 1525, 1457, 1336, 1258, 1188, 1104, 844, 748, 698, 594 $cm^{-1}$; MS (ESI): $m/z$=435 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{21}H_{20}N_2O_7Na$ $[M+Na]^+$=435.11627, found 435.11667.

*4.2.13. Ethyl 2-benzyl-4-(3-hydroxy-5-iodo-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3m**, Table 2).* Yield: 94%; Time 6 h; $R_f$ (50% EtOAc/hexanes) 0.36; White solid; mp 259–261 °C; $^1$H NMR (200 MHz, $CDCl_3$+DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 52:48, * denotes minor diastereomer peaks) $\delta$: 10.27 (br s, 1H), 10.27* (br s, 1H), 7.54–7.30 (m, 2H), 7.54–7.30* (m, 2H), 7.27–7.14 (m, 3H), 7.27–7.14* (m, 3H), 7.09–7.01 (m, 2H), 7.09–7.01* (m, 2H), 6.67 (d, $J$=8.0 Hz, 1H), 6.65* (d, $J$=8.0 Hz, 1H), 6.05 (br s, 1H), 6.01* (br s, 1H), 4.08 (q, $J$=6.98 Hz, 2H), 4.08* (q, $J$=6.98 Hz, 2H), 3.91–3.84 (m, 1H), 3.82–3.75* (m, 1H), 3.52–3.28 (m, 2H), 2.98–2.94 (m, 2H), 2.98–2.94* (m, 2H), 1.18 (t, $J$=7.0 Hz, 3H), 1.18* (t, $J$=7.0 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$+DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 52:48,* denotes minor diastereomer peaks) $\delta$: 200.73*, 200.61, 177.23, 177.17*, 166.77*, 167.62, 142.34*, 142.28, 137.66*, 137.40, 133.38*, 133.32, 131.93, 131.78*, 128.35, 128.15, 128.06*, 126.23, 126.17*, 112.09*, 112.03, 83.43*, 83.32, 72.46*, 72.38, 60.91, 60.86*, 60.04, 59.93*, 52.10, 52.01*, 33.25*, 33.05, 13.87*, 13.73 ppm; IR (KBr): $\nu$=3241, 1742, 1699, 1616, 1444, 1348, 1186, 827, 698, 582 $cm^{-1}$; MS (ESI): $m/z$=516 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{21}H_{20}INO_5Na$ $[M+Na]^+$=516.02784, found 516.02797.

*4.2.14. Ethyl 2-chloro-4-(3-hydroxy-5-nitro-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3n**, Table 2).* Yield: 94%; Time 5.2 h; $R_f$ (50% EtOAc/hexanes) 0.22; Pale yellow solid; mp 122–124 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 57:43, * denotes minor diastereomer peaks) $\delta$: 10.84 (br s, 1H), 10.83* (br s, 1H), 8.18–8.09 (m, 2H), 8.18–8.09* (m, 2H), 6.97 (d, $J$=9.0 Hz, 1H), 6.97* (d, $J$=9.0 Hz, 1H), 6.38 (br s, 1H), 6.33* (br s, 1H), 5.24–5.16 (m, 1H), 5.11–5.06* (m, 1H), 4.21 (q, $J$=7.0 Hz, 2H), 4.24* (q, $J$=7.0 Hz, 2H), 3.67 (dd, $J$=17.8, 1.97 Hz, 1H), 3.64* (d, $J$=17.8 Hz, 1H), 3.43 (d, $J$=17.8 Hz, 1H), 3.37* (dd, $J$=17.8, 1.97 Hz, 1H), 1.30* (t, $J$=7.0 Hz, 3H), 1.26 (t, $J$=7.0 Hz, 3H) ppm; $^{13}$C NMR (50 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 57:43, * denotes minor diastereomer peaks) $\delta$: 195.93, 195.65*, 177.97, 177.96*, 164.44, 164.41*, 149.38, 149.29*, 142.06, 132.13*, 131.70, 126.69, 126.53*, 119.75*, 119.66, 109.85, 109.73*, 72.18*, 72.05, 62.86*, 62.78, 61.12*, 60.89, 46.76*, 46.39, 13.67 ppm; IR (KBr): $\nu$=3263, 1715, 1626, 1526, 1477, 1338, 1253, 1185, 1101, 1017, 843, 745, 588 $cm^{-1}$; MS (ESI): $m/z$=379 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{13}ClN_2O_7Na$ $[M+Na]^+$=379.03035, found 379.03147.

*4.2.15. Ethyl 4-(5-bromo-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-2-chloro-3-oxobutanoate (**3o**, Table 2).* Yield: 93%; Time 6 h; $R_f$ (50% EtOAc/hexanes) 0.27; White solid; mp 134–136 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 52:48, * denotes minor diastereomer peaks) $\delta$: 10.36* (br s, 1H), 10.34 (br s, 1H), 7.37 (d, $J$=1.7 Hz, 1H), 7.37* (d, $J$=1.7 Hz, 1H), 7.29 (dd, $J$=8.1, 1.7 Hz, 1H), 7.29* (dd, $J$=8.1, 1.7 Hz, 1H), 6.75 (d, $J$=8.1 Hz, 1H), 6.75* (d, $J$=8.1 Hz, 1H), 6.27* (br s, 1H), 6.20 (br s, 1H), 5.36 (s, 1H), 5.20* (s, 1H), 4.25 (q, $J$=7.0 Hz, 2H) 4.21* (q, $J$=7.0 Hz, 2H), 3.57–3.55 (m, 2H), 3.30–3.20* (m, 2H), 1.32* (t, $J$=7.0 Hz, 3H), 1.28 (t, $J$=7.0 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 52:48, * denotes minor diastereomer peaks) $\delta$: 195.73, 195.61*, 177.28, 164.66, 164.57*, 142.11, 142.05*, 133.18, 132.10, 131.96*, 126.89*, 126.84, 113.28, 113.25*, 111.80, 72.73*, 72.53, 63.01*, 62.95, 61.26*, 61.15, 46.89, 46.46*, 13.84 ppm; IR (KBr): $\nu$=3251, 1697, 1619, 1480, 1447, 1348, 1260, 1188, 1062, 1019, 827, 729, 539 $cm^{-1}$; MS (ESI): $m/z$=412 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{13}BrClNO_5Na$ $[M+Na]^+$=411.95578, found 411.95597.

*4.2.16. Ethyl 2-chloro-4-(3-hydroxy-5-iodo-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3p**, Table 2).* Yield: 89%; Time 6 h; $R_f$ (50% EtOAc/hexanes) 0.31; White solid; mp 154–156 °C; $^1$H NMR (500 MHz, $CDCl_3$+DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 55:45, * denotes minor diastereomer peaks) $\delta$: 10.26* (br s, 1H), 10.22 (br s, 1H), 7.50 (d, $J$=2.0 Hz, 1H), 7.50* (d, $J$=2.0 Hz, 1H), 7.47 (dd, $J$=7.9, 2.0 Hz, 1H), 7.47* (dd, $J$=7.9, 2.0 Hz, 1H), 6.67 (d, $J$=7.9 Hz, 1H), 6.67* (d, $J$=7.9 Hz, 1H), 6.17* (br, s, 1H), 6.09 (br, s, 1H), 5.21 (s, 1H), 5.02* (s, 1H), 4.26* (q, $J$=7.9 Hz, 2H), 4.22 (q, $J$=7.9 Hz, 2H), 3.48* (d, $J$=16.8 Hz, 1H), 3.44 (d, $J$=16.8 Hz, 1H), 3.28* (d, $J$=16.8 Hz, 1H), 3.21 (d, $J$=16.8 Hz, 1H), 1.31 (t, $J$=7.9 Hz, 3H), 1.28* (t, $J$=7.9 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 55:44,* denotes minor diastereomer peaks) $\delta$: 194.13*, 194.04, 176.23, 163.49, 141.47*, 141.30, 136.87, 132.25, 131.99*, 131.52, 111.42, 82.79, 71.97, 71.88*, 61.82, 61.70*, 60.19, 60.01*, 45.84*, 45.35, 13.03, 12.97* ppm; IR (KBr): $\nu$=3194, 1759, 1697, 1615, 1478, 1443, 1346, 1186, 1018, 827, 729, 637, 532 $cm^{-1}$; MS (ESI): $m/z$=460 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{13}ClINO_5Na$ $[M+Na]^+$=459.94191, found 459.94235.

*4.2.17. Ethyl 2-chloro-4-(3-hydroxy-2-oxo-1-phenyl-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3q**, Table 2).* Yield: 90%; Time 7 h; $R_f$ (50% EtOAc/hexanes) 0.54; Yellow semi solid; mp 50 °C; $^1$H NMR (200 MHz, $CDCl_3$) (inseparable diastereomeric ratio, *major*/*minor*, 53:47, * denotes minor diastereomer peaks) $\delta$: 7.71–7.33 (m, 7H), 7.71–7.33* (m, 7H), 7.25–7.18 (m, 1H), 7.25–7.18* (m, 1H), 7.08–7.01 (m, 1H), 7.08–7.01* (m, 1H), 6.75 (br s, 1H), 6.72* (br s, 1H), 4.78* (s, 1H), 4.75 (s, 1H), 4.19 (q, $J$=7.2 Hz, 2H), 4.14* (q, $J$=7.2 Hz, 2H), 3.82–3.68* (m, 2H), 3.60–3.41 (m 2H), 1.22 (t, $J$=7.2 Hz, 3H), 1.71* (t, $J$=7.2 Hz, 3H) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$) (inseparable diastereomeric ratio, *major*/*minor*, 53:47, * denotes minor diastereomer peaks) $\delta$: 195.69*, 195.32, 176.14*, 175.89, 169.09*, 168.72, 144.04, 143.99*, 133.85, 129.96*, 129.49, 128.20, 128.09*, 126.51, 126.22*, 123.83*, 123.79, 123.36, 109.79, 109.60*, 73.58, 63.19*, 63.16, 61.03*, 60.86, 46.55, 46.41*, 13.70*, 13.67 ppm; IR (KBr): $\nu$=3250, 1729, 1613, 1500, 1463, 1372, 1296, 1253, 1207, 1023, 757, 700, 578 $cm^{-1}$; MS (ESI): $m/z$=410 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $C_{20}H_{18}ClNO_5Na$ $[M+Na]^+$=410.07657, found 410.07611.

*4.2.18. Ethyl 4-chloro-4-(3-hydroxy-5-iodo-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3r**, Table 2).* Yield: 82%; Time 8 h; $R_f$ (50% EtOAc/hexanes) 0.40; Light orange solid; mp 102–104 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio,

*major*/*minor*, 58:42, * denotes minor diastereomer peaks) $\delta$: 10.57 (br s, 1H), 10.50* (br s, 1H), 7.77* (d, $J$=1.5 Hz, 1H), 7.58–7.55 (m, 1H), 7.54–7.52* (m, 1H), 7.49 (d, $J$=1.5 Hz, 1H), 7.13 (br s, 1H), 6.69* (br s, 1H), 6.69 (d, $J$=8.1 Hz, 1H), 6.67* (d, $J$=8.1 Hz, 1H), 5.04* (s, 1H), 4.96 (s, 1H), 4.22 (q, $J$=7.2 Hz, 2H), 4.19* (q, $J$=7.2 Hz, 2H), 4.16–4.09* (m, 2H), 4.06–3.92 (m, 2H), 1.31(t, $J$=7.2 Hz, 3H), 1.25* (t, $J$=7.2 Hz, 3H) ppm; $^{13}$C NMR (50 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 58:42,* denotes minor diastereomer peaks) $\delta$: 195.62, 195.28*, 175.20, 175.02*, 166.28, 166.24*, 142.44, 142.25*, 138.52, 138.30*, 134.15, 133.16*, 131.01*, 129.13, 112.37*, 112.33, 84.07, 83.97*, 76.68, 75.58*, 67.04*, 62.80, 60.97, 60.90*, 49.12, 47.08*, 13.98, 13.87* ppm; IR (KBr): $\nu$=3324, 1732, 1615, 1472, 1436, 1324, 1181, 1132, 819, 625 cm$^{-1}$; MS (ESI): $m/z$=460 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{13}ClINO_5Na$ [M+Na]$^+$=459.94191, found 459.94243.

*4.2.19. 3-Hydroxy-5-nitro-3-[2-oxo-2-(2-oxotetrahydro furan-3-yl) ethyl]-1,3-dihydro-2H-indol-2-one (**3s**, Table 2).* Yield: 81%; Time 7.2 h; $R_f$ (50% EtOAc/hexanes) 0.33; White solid; mp 247–249 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 52:48, * denotes minor diastereomer peaks) $\delta$: 10.79 (br s, 1H), 10.79* (br s, 1H), 8.20–8.05 (m, 2H), 8.20–8.05* (m, 2H), 6.96 (d, $J$=7.0 Hz, 1H), 6.96* (d, $J$=7.0 Hz, 1H), 6.31* (br s, 1H), 6.28 (br s, 1H), 4.30–4.19 (m, 2H), 4.30–4.19* (m, 2H), 3.99–3.94 (m, 1H), 3.99–3.94* (m, 1H), 3.89* (d, $J$=17.8 Hz, 1H), 3.68 (d, $J$=17.8 Hz, 1H), 3.55* (d, $J$=17.8 Hz, 1H), 3.40 (d, $J$=17.8 Hz, 1H), 2.42–2.29 (m, 2H), 2.26–2.12* (m, 2H) ppm; $^{13}$C NMR (50 MHz, DMSO-$d_6$) (inseparable diastereomeric ratio, *major*/*minor*, 52:48,* denotes minor diastereomer peaks) $\delta$: 200.06*, 200.05, 178.20*, 178.12, 172.44, 149.28*, 149.23, 141.98, 132.06*, 132.04, 126.16, 119.61*, 119.32, 109.42, 72.05*, 71.98, 66.73*, 66.61, 51.92*, 51.42, 48.74, 48.55*, 23.30*, 23.14 ppm; IR (KBr): $\nu$=3246, 1763, 1713, 1628, 1526, 1459, 1336, 1148, 1109, 1017, 911, 749, 639 cm$^{-1}$; MS (ESI): $m/z$=343 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{12}N_2O_7$ [M+Na]$^+$=343.05367, found 343.05393.

*4.2.20. Ethyl 3-(3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-2-oxocyclopentanecarboxylate (**3t**, Table 2).* Yield: 94%; Time 7.8 h; $R_f$ (50% EtOAc/hexanes) 0.37; Yellow solid; mp 101–103 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) (complex inseparable diastereomeric ratio, 53:17:17:9:4, spectral data given only for major isomer) $\delta$: 8.97 (br s, 1H), 7.34 (d, $J$=7.4 Hz, 1H), 7.26 (t, $J$=7.4 Hz, 1H), 7.06 (t, $J$=7.4 Hz, 1H), 6.91 (d, $J$=7.4 Hz, 1H), 5.34 (br s, 1H), 4.21 (q, $J$=7.2 Hz, 2H), 3.34 (dd, $J$=11.8, 8.5 Hz, 1H), 2.95 (dd, $J$=11.1, 8.7 Hz, 1H), 2.29–2.08 (m, 4H), 1.28 (q, $J$=7.2 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$) (complex inseparable diastereomeric ratio, 53:17:17:9:4, spectral data given only for major isomer) $\delta$: 209.85, 178.16, 168.67, 142.49, 129.37, 124.48, 121.78, 110.11, 75.84, 60.80, 55.87, 54.49, 24.49, 22.51, 14.02 ppm; IR (KBr): $\nu$=3327, 2929, 1722, 1620, 1365, 1195, 1099, 1026, 938, 752, 672 cm$^{-1}$; MS (ESI): $m/z$=326 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{16}H_{17}NO_5Na$ [M+Na]$^+$=326.09989, found 326.09978.

*4.2.21. Ethyl 3-(3-hydroxy-5-iodo-2-oxo-2,3-dihydro-1H-indol-3-yl)-2-oxocyclopentanecarboxylate (**3u**, Table 2).* Yield: 95%; Time 7 h; $R_f$ (50% EtOAc/hexanes) 0.41; White solid; mp 200–202 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) (complex inseparable diastereomeric ratio, 63:31:6, spectral data given only for major isomer) $\delta$: 10.31 (br s, 1H), 7.63 (d, $J$=1.7 Hz, 1H), 7.51 (dd, $J$=8.1, 1.70 Hz, 1H), 6.66 (d, $J$=8.1 Hz, 1H), 5.93 (br s, 1H), 4.15 (q, $J$=7.2 Hz, 2H), 3.24–3.10 (m, 2H), 2.41–2.18 (m, 4H), 1.25 (t, $J$=7.2 Hz, 3H) ppm; $^{13}$C NMR (50 MHz, DMSO-$d_6$) (complex inseparable diastereomeric ratio, 63:31:6, spectral data given only for major isomer) $\delta$: 208.12, 176.11, 167.25, 141.05, 136.71, 131.79, 130.85, 111.04, 82.63, 74.31, 59.51, 54.52, 53.10, 23.20, 21.19, 12.74 ppm; IR (KBr): $\nu$=3252, 2978, 1729, 1697, 1615, 1472, 1439, 1336, 1185, 1129, 1098, 947, 830, 688 cm$^{-1}$. MS (ESI): $m/z$=452 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{16}H_{16}INO_5Na$ [M+Na]$^+$=451.99654, found 451.99671.

*4.2.22. Ethyl 2,2-diethyl-4-(3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-oxobutanoate (**3v**, Table 2).* Yield: 81%; Time 8 h; $R_f$ (50% EtOAc/hexanes) 0.25; White solid; mp 105–107 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 9.98 (br s, 1H), 7.30–7.06 (m, 2H), 7.03–6.79 (m, 2H), 5.86 (br s, 1H), 4.31–4.05 (m, 2H), 3.30 (d, $J$=17.9 Hz, 1H), 3.26 (d, $J$=17.9 Hz, 1H), 1.94–1.65 (m, 4H), 1.23 (t, $J$=7.2 Hz, 3H), 0.67 (t, $J$=7.6 Hz, 3H), 0.48 (t, $J$=7.6 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 203.46, 177.92, 171.41, 142.70, 131.11, 128.93, 123.33, 120.99, 109.31, 72.21, 62.78, 60.87, 46.05, 22.70, 22.49, 13.82, 7.60, 7.47 ppm; IR (KBr): $\nu$=3264, 2976, 1739, 1700, 1627, 1474, 1211, 1028, 756 cm$^{-1}$; MS (ESI): $m/z$=356 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{18}H_{23}NO_5Na$ [M+Na]$^+$=356.14739, found 356.14746.

*4.2.23. Ethyl 4-(5-chloro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2-diethyl-3-oxobutanoate (**3w**, Table 2).* Yield: 87%; Time 8 h; $R_f$ (50% EtOAc/hexanes) 0.26; White solid; mp 172–174 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 10.36 (br s, 1H), 7.32 (d, $J$=1.2 Hz, 1H), 7.22 (dd, $J$=8.2, 1.2 Hz, 1H), 6.79 (d, $J$=1.2 Hz, 1H), 6.12 (br s, 1H), 4.18–4.08 (m, 2H), 3.43 (d, $J$=18.2 Hz, 1H), 3.13 (d, $J$=18.2 Hz, 1H), 1.81–1.60 (m, 4H), 1.17 (t, $J$=7.1 Hz, 3H), 0.60 (t, $J$=7.5 Hz, 3H), 0.45 (t, $J$=7.5 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 203.77, 177.61, 171.25, 148.84, 133.24, 128.66, 125.09, 123.74, 110.72, 72.34, 62.73, 60.89, 45.95, 22.72, 22.42, 13.79, 7.55, 7.40 ppm; IR (KBr): $\nu$=3242, 2974, 1701, 1622, 1478, 1238, 1183, 1132, 833 cm$^{-1}$; MS (ESI): $m/z$=390 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{18}H_{22}ClNO_5Na$ [M+Na]$^+$=390.10842, found 390.10851.

*4.2.24. (5-Chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)propanedinitrile (**3x**, Scheme 4).* Yield: 98%; Time 8 h; $R_f$ (50% EtOAc/hexanes) 0.34; Red solid; mp 224–226 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 10.62 (br s, 1H), 7.48 (d, $J$=1.1 Hz, 1H), 7.37 (dd, $J$=8.3, 1.1 Hz, 1H), 6.61 (d, $J$=1.1 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 171.26, 170.01, 147.14, 134.54, 131.11, 126.01, 124.24, 113.8, 113.3, 109.94, 76.21 ppm; IR (KBr): $\nu$=3258, 2230, 2169, 2109, 1716, 1619, 1587, 1465, 1340, 1185, 754 cm$^{-1}$; MS (ESI): $m/z$=252 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{11}H_4ClN_3ONa$ [M+Na]$^+$=251.99406, found 251.99417.

*4.2.25. 2-(5-Chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-3-oxopentanenitrile (**3y**, Scheme 4).* Yield: 78%; Time 8 h; $R_f$ (50% EtOAc/hexanes) 0.38; Orange red solid; mp 203–205 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 10.61 (br s, 1H), 7.49 (d, $J$=1.2 Hz, 1H), 7.36 (dd, $J$=8.2, 1.2 Hz, 1H), 6.59 (d, $J$=1.2 Hz, 1H), 3.16–3.05 (m, 2H), 1.51 (t, $J$=7.3 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 203.78, 171.23, 148.82, 140.11, 133.21, 128.65, 125.08, 123.73, 116.3, 115.8, 110.71, 31.14, 8.10 ppm; IR (KBr): $\nu$=3258, 2261, 1716, 1701, 1622, 1617, 1588, 1466, 1341, 1239, 1186, 833, 755 cm$^{-1}$; MS (ESI): $m/z$=283 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for $C_{13}H_9ClN_2O_2Na$ [M+Na]$^+$=283.02502, found 283.02511.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.101. These data include MOL files and InChiKeys of the most important compounds described in this article.

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17. Reaction of 5-bromo isatin with ethyl acetoacetate under dianion method: to a suspension of sodium hydride (80%, 54 mg, 1.8 mmol) in dry THF (2 mL) was added ethyl acetoacetate (1.5 mmol) under nitrogen, after 30 min stirring at room temperature, *n*-butyllithium (in hexane 1.6 M, 1.13 mL, 1.8 mmol) was added at −15 to −10 °C (ice-salt bath). The mixture was kept this temperature for 30 min and then 5-bromo isatin (1.5 mmol) dissolved in 3 mL dry THF was added at this temperature. Reaction was monitored by TLC and after 6 h, as completion of reaction indicated by TLC, saturated $NH_4Cl$ (5 mL) was added to the reaction mixture and the reaction mixture was extracted with ethyl acetate (3×5 mL). The combined extract was dried and evaporated in vacuum and crude reaction mixture was subjected for $^1H$ NMR analysis.
18. X-ray crystallographic data for compound **3k**: crystal data for compound ethyl 2-benzyl-4-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3-oxobutanoate (**3k**, Table 2): $C_{21}H_{21}NO_5$, $M$=367.39, colorless block, 0.40×0.30×0.20 mm$^3$, monoclinic, space group $P2_1/c$ (No. 14), $a$=13.0027(8), $b$=9.9994(6), $c$=18.3895(8) Å, $\beta$=128.820(3)°, $V$=1862.86(18) Å$^3$, $Z$=4, $D_c$=1.310 g/cm$^3$, $F_{000}$=776, CCD area detector, Mo Kα radiation, $\lambda$=0.71073 Å, $T$=294(2) K, $2\theta_{max}$=50.0°, 17,355 reflections collected, 3273 unique ($R_{int}$=0.0225). Final *GoF*=1.020, $R1$=0.0371, $wR2$=0.0999, $R$ indices based on 2899 reflections with $I>2\sigma(I)$ (refinement on $F^2$), 257 parameters, $\mu$=0.094 mm$^{-1}$. CCDC 890261 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].