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Friedel–Crafts alkylations of electron-rich aromatics with 3-hydroxy-2-oxindoles: scope and limitations†‡

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A Lewis acid-catalyzed nucleophilic addition of electron rich aromatics with 3-hydroxy-2-oxindoles **5** was developed. The reaction is believed to proceed through the 2*H*-indol-2-one ring system **9**, which eventually reacts with various electron-rich aromatics to afford a variety of 2-oxindoles with an all-carbon quaternary center at the pseudobenzylic position (**4**, **8**, **13**, and **16**) in high yields. The methodology provides an expeditious route to the tetracyclic core (**3**) of diazonamide (**1**), and azonazine (**2**) as well as the tricyclic core of asperazine (**6a**), idiospermuline (**6b**), and calycosidine (**6c**) *viz*. C(3a)-arylpyrroloindolines **7** having an all-carbon quaternary center on further synthetic elaboration.

Introduction

The development of efficient methodologies to construct an all-carbon quaternary stereocenter[1] remains a challenging task in organic chemistry. In this regard, alkaloids sharing an all-carbon quaternary stereocenter[2] at the pseudobenzylic position such as diazonamide A (**1**),[3] azonazine (**2**),[4] asperazine (**6a**),[5] idiospermuline (**6b**),[6] calycosidine (**6c**)[6] (Fig. 1) and many others[7] constitute an important class of those exhibiting a diverse range of biological activities and have hence gained much synthetic interest.[8] Consequently, the development of novel synthetic strategies to access 3,3-disubstituted oxindole derivatives which can eventually be utilized in the synthesis of these fascinating synthetic targets is of paramount importance.

Prominent methods for the synthesis of 3,3-disubstituted 2-oxindoles include the derivatization of other heterocycles,[9] intramolecular Heck type reactions,[10] arylation of amides,[11] variants of the Stolle reaction,[12] the Gassman sulfonium ylide reaction,[13] photoinduced studies,[14a,b] the hetero Claisen approach,[14c,d] radical cyclization approaches,[15] transition-metal-catalyzed reactions,[16] and oxidative coupling reaction.[17] Few enantioselective organocatalytic approaches to construct 3,3-disubstituted 2-oxindoles have also been reported in the literature. These include asymmetric reactions with prochiral 3-alkyl/aryl-2-oxindoles[18] as donors as well as some dipolar cycloaddition strategies using 3-alkylidene 2-oxindoles.[19] Other approaches involve photo-Fries rearrangement,[20] Hofmann–Martius rearrangement[21] and nucleophilic addition to the 3-halo-2-oxindoles through the formation of reactive 2*H*-indol-2-one rings.[22]

One of the classical ways to synthesize 3,3-disubstituted 2-oxindoles involves a Friedel–Crafts alkylation[23] of electron-rich aromatics with isatins[24] or 3-alkyl/aryl-3-hydroxy-2-oxindoles.[25] In fact, the total synthesis of diazonamide A (**1**)[25a] (Fig. 1) by Nicolaou *et al*. beautifully indicates the application of this strategy where the 3-hydroxy-2-oxindole compound could be activated under the influence of trifluoromethane sulfonic acid leading to the formation of an all-carbon quaternary center at the pseudobenzylic (3a)-position of the 2-oxindole derivative. Their pioneering work led to the efficient total synthesis of diazonamide A[3] (**1**) and related structures.

Towards this end, recently, we have reported an efficient reaction of 3-aryl-3-hydroxy-2-oxindoles **5** with a variety of 2-π electron rich substrates such as allyl/methallyl trimethylsilane, phenylacetylene, acetophenone (*via* keto–enol tautomerization), styrene, and indoles (see Scheme 1).[26]

An architecturally interesting indole alkaloid, azonazine[4] (**2**) (Fig. 1), has recently been isolated from a Hawaiian marine sediment-derived fungus *Aspergillus insulicola*, having a unique hexacyclic dipeptide structure with a similar tetracyclic core to that of diazonamide A (**1**) (Fig. 1). While working in the area of

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†This paper is dedicated to Professor Ganesh Pandey on the occasion of his 60th Birthday.

‡Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. CCDC 1007347–1007349 for (±)-**4q**, (±)-**16a**, and (±)-7. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01264j

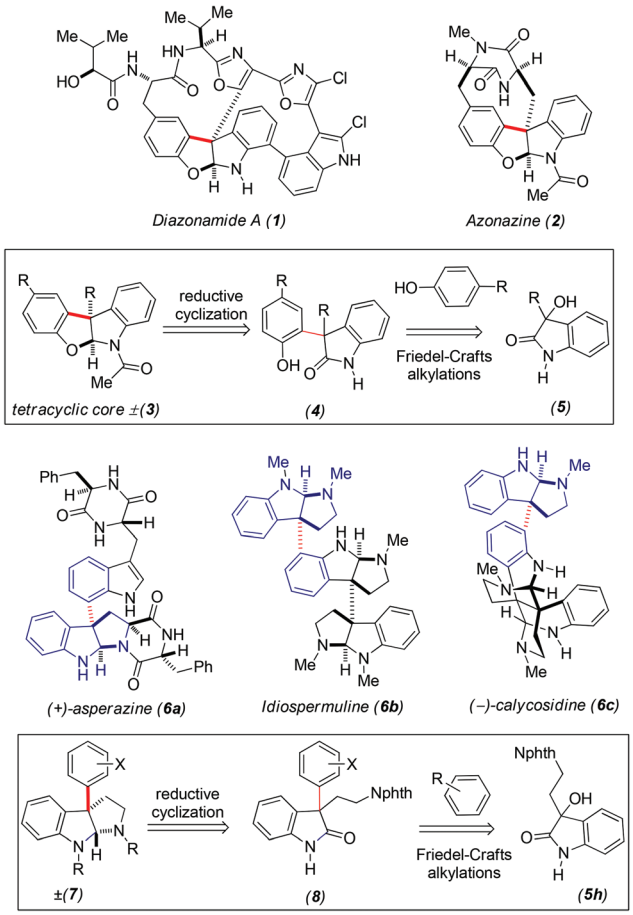
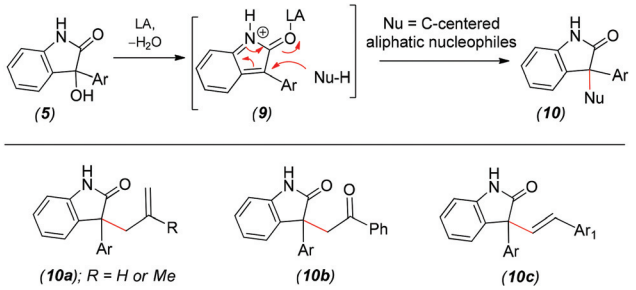
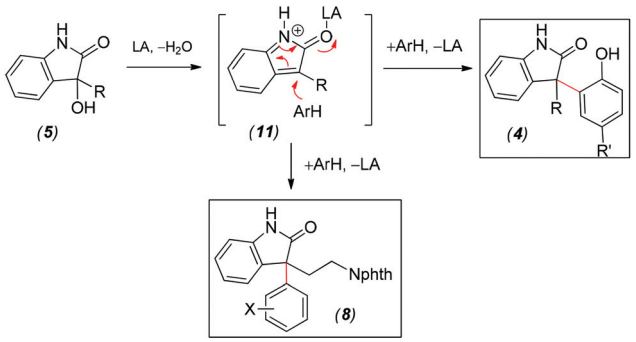


Fig. 1 Indole alkaloids (**1**, **2**, and **6a–c**) sharing an all-carbon quaternary stereocenter and our approach.



Scheme 1 Our report on C-centered nucleophiles.

development of methodologies for the synthesis of 2-oxindoles,[27,28] we have reported an efficient Lewis acid-catalyzed Friedel–Crafts alkylation of 4-substituted phenol[29] (Scheme 2) with 3-hydroxy 2-oxindoles to synthesize various 3,3-disubstituted 2-oxindoles having an all-carbon quaternary center at the pseudobenzylic position. We have also employed this methodology in the construction of the tetracyclic core (**3**) of azonazine (**2**) from an advanced 2-oxindole intermediate **4a** in two steps *viz*. reduction of 2-oxindole followed by MnO_2-promoted intramolecular oxidative cyclization.[30] We, herein, elaborate the scope and limitations of



Scheme 2 Lewis acid-catalyzed F–C alkylations of electron-rich aromatics.

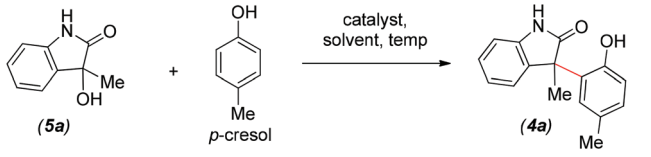
Lewis acid-catalyzed activation of 3-alkyl-3-hydroxy-2-oxindoles followed by nucleophilic attack with electron-rich aromatics.

Results and discussion

3-Hydroxy 2-oxindoles serve as versatile building blocks in the syntheses of various indole alkaloids of immense biological importance. Their ability to undergo a variety of nucleophilic substitution reactions has made them extensively used as powerful synthetic tools to realize different C–C bond forming events. Towards this end, the Lewis acid catalyzed Friedel–Crafts alkylations of aromatic compounds with electron-deficient partners has prevalently been utilized in the formation of C–C bonds in organic synthesis, but there are limited reports on similar transformations involving 3-hydroxy 2-oxindole for the synthesis of 3,3-disubstituted-2-oxindoles and, therefore, needs further exploration.

The reactivities of 2*H*-indol-2-one ring (**9**) were tested in the presence of Lewis acid-catalyzed activation of 3-alkyl/aryl-3-hydroxy 2-oxindoles followed by nucleophilic attack with various nucleophiles. At the outset, we carried out our studies taking 3-hydroxy 2-oxindole **5a** as the electron-deficient partner for the Friedel–Crafts alkylation of *p*-cresol. The optimization studies for the Friedel–Crafts alkylation were performed with *p*-cresol and **5a** using $BF_3{\cdot}OEt_2$ (Table 1) in different solvents under reflux. We could obtain products in 51–54% yields with 24–40% of recovered **5a** when the reactions were carried out in aromatic solvents such as xylene, toluene, mesitylene and benzene along with a multitude of spots on TLC (thin layer chromatography). Acetonitrile as the solvent afforded the product in only 56% yield with decomposition of the remaining reaction mixture. We hypothesized that there is a possibility of addition of acetonitrile to the intermediate **11** under a Ritter type process.[31] However, other solvents such as ethylacetate, diethylether, *N*,*N*-dimethylformamide, and tetrahydrofuran were found to be inefficient, leading to recovery of **5a** in 84–90% yields. Interestingly, chlorinated solvents were found to be good, and it was observed that 50 mol%, 25 mol%, and 10 mol% of $BF_3{\cdot}OEt_2$ in refluxing dichloromethane afforded product **4a** in 90%, 62%, and 38% yields, respectively, along

Table 1 Optimization of $BF_3{\cdot}OEt_2$–$HClO_4$-catalyzed F–C alkylations



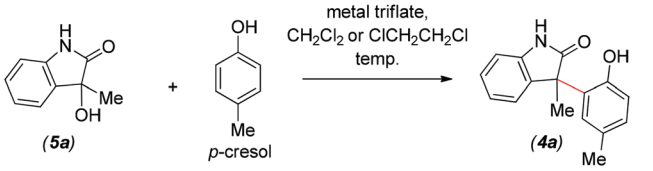
Entry	Cat. (mol%)	Solvent	Temp.	Time	Yield[a,b]	8a[c]
1.	50 mol% $BF_3{\cdot}OEt_2$	CH_2Cl_2	40 °C	06 h	90%	—
2.	25 mol% $BF_3{\cdot}OEt_2$	CH_2Cl_2	40 °C	16 h	62%	19%
3.	25 mol% $BF_3{\cdot}OEt_2$	CH_2Cl_2	40 °C	24 h	38%	32%
4.	10 mol% $BF_3{\cdot}OEt_2$	$ClCH_2CH_2Cl$	80 °C	04 h	97%	—
5.	20 mol% $BF_3{\cdot}OEt_2$	$CHCl_3$	50 °C	06 h	83%	—
6.	*10 mol% $BF_3{\cdot}OEt_2$*	*$ClCH_2CH_2Cl$*	*80 °C*	*04 h*	*93%*	—
7.	10 mol% $BF_3{\cdot}OEt_2$	$CHCl_3$	50 °C	10 h	70%	14%
8.	5 mol% $BF_3{\cdot}OEt_2$	$ClCH_2CH_2Cl$	80 °C	12 h	85%	09%
9.	5 mol% $BF_3{\cdot}OEt_2$	$CHCl_3$	50 °C	16 h	54%	33%
10.	20 mol% $HClO_4$	$ClCH_2CH_2Cl$	25 °C	16 h	75%	12%
11.	20 mol% $HClO_4$	$CHCl_3$	25 °C	16 h	69%	15%
12.	20 mol% $HClO_4$	CH_2Cl_2	25 °C	16 h	61%	19%
13.	10 mol% $HClO_4$	$ClCH_2CH_2Cl$	25 °C	16 h	62%	20%
14.	10 mol% $HClO_4$	$CHCl_3$	25 °C	16 h	54%	28%
15.	*10 mol% $HClO_4$*	*$ClCH_2CH_2Cl$*	*80 °C*	*5 h*	*96%*	—
16.	10 mol% $HClO_4$	$CHCl_3$	50 °C	5 h	89%	—
17.	5 mol% $HClO_4$	$ClCH_2CH_2Cl$	80 °C	8 h	89%	08%
18.	5 mol% $HClO_4$	$CHCl_3$	50 °C	8 h	78%	15%

[a] Reactions were carried out on a 0.5 mmol of **5a** with 1.5 mmol of *p*-cresol in 4 mL of solvent. [b] Isolated yields after column chromatography. [c] Isolated starting materials.

with 19–32% recovery of **5a** in two subsequent cases (entries 1–3, Table 1). On the other hand, refluxing chloroform also afforded products in synthetically useful yields of 54–83% (Table 1, entries 5, 7, and 9). Interestingly, changing the solvent to a high boiling dichloroethane afforded **4a** in high yields (20 mol% and 10 mol% of $BF_3{\cdot}OEt_2$ in refluxing dichloroethane afforded products in 97% and 93%, respectively (entries 4 and 6)) with faster rates. Further, the Friedel–Crafts alkylations of *p*-cresol with 3-methyl 3-hydroxy 2-oxindole (**5a**) were carried out in the presence of $HClO_4$ in dichloroethane and chloroform. We found that 10 mol% $HClO_4$ in refluxing dichloroethane and chloroform afforded products in 96% and 89%, respectively, whereas 5 mol% of $HClO_4$ afforded **4a** in 89% yields, along with 8% of recovered **5a** (entry 17, Table 1). These studies led us to conclude that 10 mol% $BF_3{\cdot}OEt_2$ and $HClO_4$ in refluxing dichloroethane were optimal to achieve **4a** in high yields (Table 1).

Further, we anticipated various metal triflate-catalyzed Friedel–Crafts alkylations of *p*-cresol with 3-hydroxy 2-oxindole (**5a**) (Table 2). It was observed that the reaction was sluggish despite higher catalyst loadings in dichloromethane at room temperature and 10–46% of yields were obtained (entries 1–7). However, under refluxing dichloromethane, 25–50 mol% of $In(OTf)_3$, $Cu(OTf)_2$, and $Bi(OTf)_3$ afforded **4a** in 91–95% yields (entries 8–9, 16–17, and 19–20). Further optimization (Table 2) showed that in refluxing dichloromethane 10 mol% of $In(OTf)_3$ (condition **A**), $Cu(OTf)_2$ (condition **B**), and $Bi(OTf)_3$ (condition **C**) provided the F–C alkylation product **4a** in 92% (entry 10), 91% (entry 18), and 94% (entry 21), respectively.

Table 2 Optimization using Lewis acids



Entry	Lewis acid	Solvent	Temp.	Time	Yield[a,b]
1.	$Sc(OTf)_3$ (50 mol%)	CH_2Cl_2	25 °C	24 h	10%
2.	$In(OTf)_3$ (50 mol%)	CH_2Cl_2	25 °C	24 h	46%
3.	$Zn(OTf)_2$ (50 mol%)	CH_2Cl_2	25 °C	24 h	Traces
4.	$Zn(OTf)_2$ (50 mol%)	CH_2Cl_2	45 °C	12 h	Traces
5.	$Cu(OTf)_2$ (50 mol%)	CH_2Cl_2	25 °C	24 h	24%
6.	$Sn(OTf)_2$ (50 mol%)	CH_2Cl_2	25 °C	18 h	42%
7.	$FeCl_3$ (50 mol%)	CH_2Cl_2	25 °C	24 h	40%
8.	$In(OTf)_3$ (50 mol%)	CH_2Cl_2	45 °C	4 h	95%
9.	$In(OTf)_3$ (25 mol%)	CH_2Cl_2	45 °C	5 h	92%
10.	*$In(OTf)_3$ (10 mol%)*	*CH_2Cl_2*	*45 °C*	*7 h*	*92%*
11.	$FeCl_3$ (50 mol%)	CH_2Cl_2	45 °C	18 h	56%
13.	$Ce(OTf)_3$ (50 mol%)	CH_2Cl_2	45 °C	12 h	90%
14.	$Ce(OTf)_3$ (25 mol%)	CH_2Cl_2	45 °C	12 h	82%
15.	$Ce(OTf)_3$ (10 mol%)	CH_2Cl_2	45 °C	16 h	53%
16.	$Cu(OTf)_2$ (50 mol%)	CH_2Cl_2	45 °C	12 h	92%
17.	$Cu(OTf)_2$ (25 mol%)	CH_2Cl_2	45 °C	14 h	91%
18.	*$Cu(OTf)_2$ (10 mol%)*	*CH_2Cl_2*	*45 °C*	*12 h*	*91%*
19.	$Bi(OTf)_3$ (50 mol%)	CH_2Cl_2	25 °C	12 h	94%
20.	$Bi(OTf)_3$ (25 mol%)	CH_2Cl_2	45 °C	12 h	93%
21.	*$Bi(OTf)_3$ (10 mol%)*	*CH_2Cl_2*	*45 °C*	*10 h*	*94%*
22.	$Sn(OTf)_2$ (50 mol%)	CH_2Cl_2	45 °C	14 h	86%
23.	$Sn(OTf)_2$ (25 mol%)	CH_2Cl_2	45 °C	14 h	79%
24.	$Sn(OTf)_2$ (10 mol%)	CH_2Cl_2	45 °C	15 h	65%
25.	$Sn(OTf)_2$ (10 mol%)	$ClCH_2CH_2Cl$	80 °C	3 h	89%
26.	*$Cu(OTf)_2$ (10 mol%)*	*$ClCH_2CH_2Cl$*	*80 °C*	*3 h*	*93%*
27.	*$In(OTf)_3$ (10 mol%)*	*$ClCH_2CH_2Cl$*	*80 °C*	*3 h*	*95%*
28.	*$Bi(OTf)_3$ (10 mol%)*	*$ClCH_2CH_2Cl$*	*80 °C*	*3 h*	*93%*
29.	$Cu(OTf)_2$ (5 mol%)	$ClCH_2CH_2Cl$	80 °C	4 h	83%
30.	$Sn(OTf)_2$ (5 mol%)	$ClCH_2CH_2Cl$	80 °C	4 h	87%
31.	$In(OTf)_3$ (5 mol%)	$ClCH_2CH_2Cl$	80 °C	4 h	90%
32.	$Bi(OTf)_3$ (5 mol%)	$ClCH_2CH_2Cl$	80 °C	4 h	92%
33.	$Cu(OTf)_2$ (2 mol%)	$ClCH_2CH_2Cl$	80 °C	6 h	73%
34.	$In(OTf)_3$ (2 mol%)	$ClCH_2CH_2Cl$	80 °C	6 h	85%
35.	$Bi(OTf)_3$ (2 mol%)	$ClCH_2CH_2Cl$	80 °C	6 h	82%

[a] Reactions were carried out on a 0.50 mmol of **5a** with 1.50 mmol of *p*-cresol in 4 mL of CH_2Cl_2 or $ClCH_2CH_2Cl$. [b] Isolated yields. Condition **A**: $In(OTf)_3$; condition **B**: $Cu(OTf)_2$; condition **C**: $Bi(OTf)_3$.

Although, under similar conditions, 25–50 mol% of $Ce(OTf)_3$ and $Sn(OTf)_2$ provided high yields of products (79–90% isolated yields) (entries 13, 14, 22, and 23), but 10 mol% of these catalysts afforded only 53% and 65% yields (entries 15 and 24), respectively, where 29–32% starting materials were recovered from the reaction mixture.

Changing the solvent to dichloroethane, 10 mol% of $Sn(OTf)_2$, $Cu(OTf)_2$, $In(OTf)_3$, and $Bi(OTf)_3$ furnished **4a** in 89%, 93%, 95%, and 93%, respectively (entries 25–28, Table 2). Interestingly, 5 mol% of these catalysts afforded **4a** in the range of 83–92% yields (entries 29–32, Table 2). It is important to note that 2 mol% of $Cu(OTf)_2$, $In(OTf)_3$, and $Bi(OTf)_3$ was also efficient and afforded products in refluxing dichloroethane in synthetically useful 73%, 85%, and 82% yields, respectively. However, based on our optimization studies, in practice, 5–10 mol% of these catalysts were used for efficient

Friedel–Crafts reaction of *p*-cresol with 3-hydroxy 2-oxindole **5a** in refluxing dichloroethane (Table 2). Thus, we considered revisiting our methodology in refluxing dichloroethane, and for that purpose a set of three different optimized conditions was chosen *viz*. $In(OTf)_3$ (condition **A**), $Cu(OTf)_2$ (condition **B**), and $Bi(OTf)_3$ (condition **C**).

With the optimized conditions in hand, the reaction was extended to a variety of substrates shown in Fig. 2. A range of 3-alkyl/aryl 3-hydroxy 2-oxindoles were synthesized directly from isatin. 3-Allyl-3-hydroxy 2-oxindoles **5d–f** and **5k** were synthesized in very good to excellent yields from *N*,*N*-dimethylformamide (DMF) catalyzed reactions of isatins and allyltrichlorosilane (Scheme 3).[32]

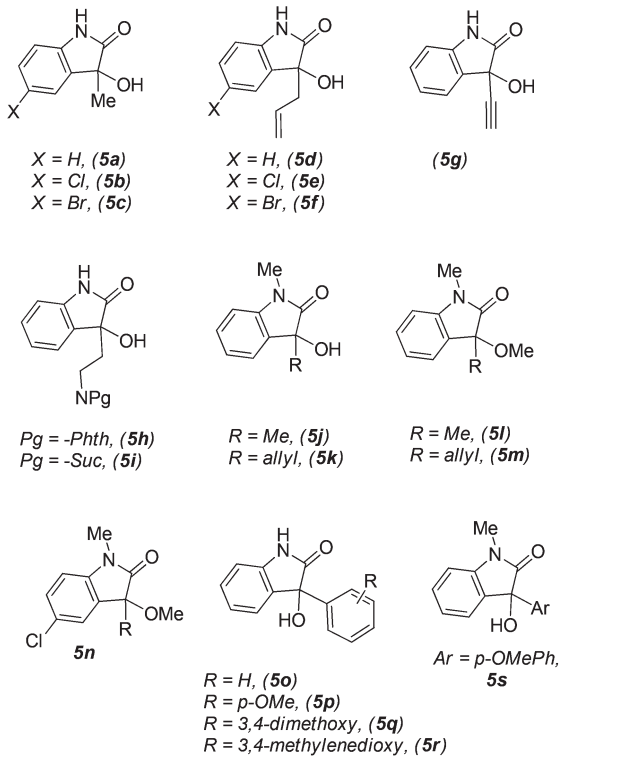
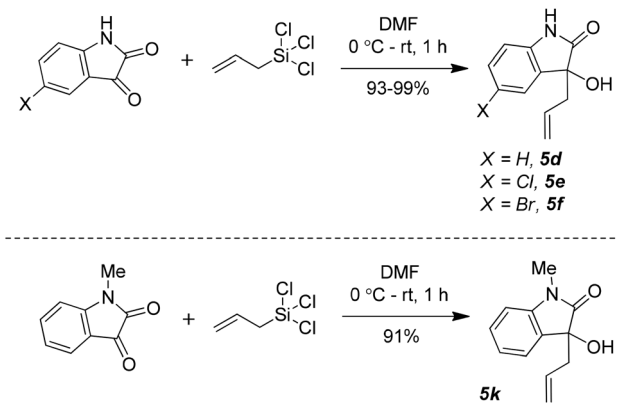


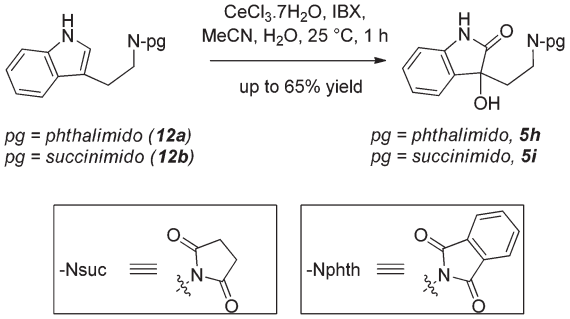
Fig. 2 3-Hydroxy-2-oxindoles **5a–s** used in this study.



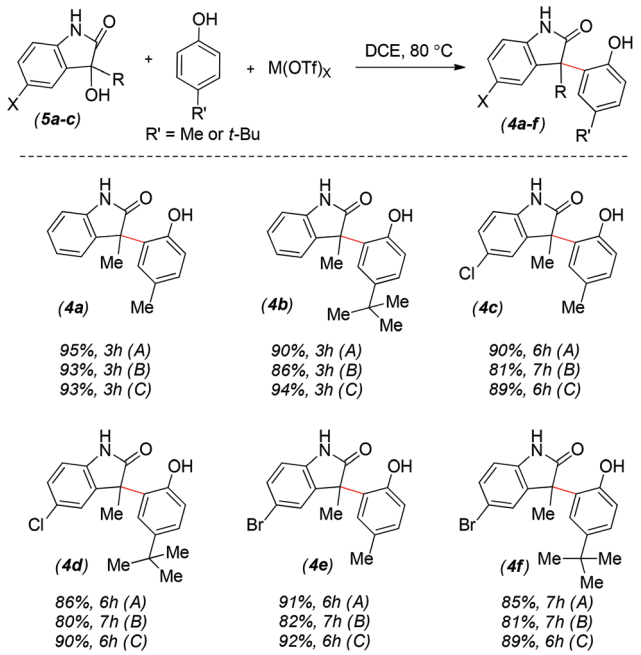
Scheme 3 Synthesis of allylated 3-hydroxy-2-oxindoles **5d–f**, and **5k**.

Phthalimido and succinimido protected 3-aminoethyl-3-hydroxy-2-oxindoles **5h–i**[28] were prepared in two steps *viz*. *N*-protection of tryptamine with phthalic anhydride and succinic anhydride in refluxing toluene to afford **12a–b** and the latter upon $CeCl_3{\cdot}7H_2O$-promoted oxidation using IBX afforded **5h–i** in 56–65% yields (Scheme 4).

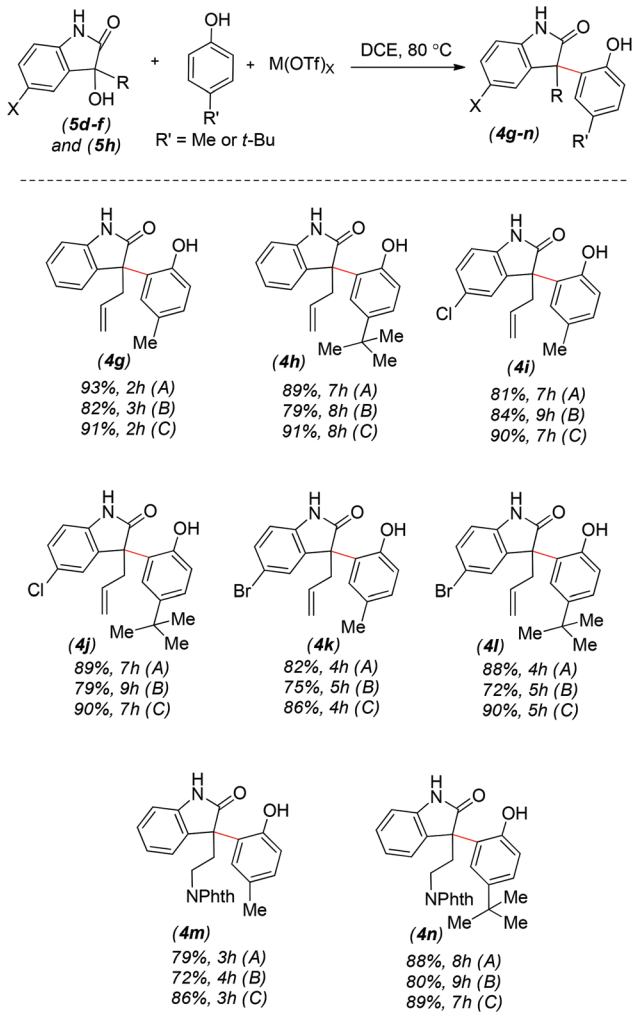
Under optimized conditions, substrates **5a–c** were treated with *p*-cresol and 4-*tert*-butyl phenol as electron-rich partners and the results are summarized in Scheme 5. We found that *p*-cresol and 4-*tert*-butyl phenol were efficiently added to **5a** under optimized conditions to furnish products **4a–b** in 86–95% yields only in 3 h (Scheme 5). In the case of halogen substituted 3-hydroxy-2-oxindoles **5b–c**, the reaction rates were a little slower than the one with no substitution (**5a**). Evidently, the electron-withdrawing halogen substituent hampers the for-



Scheme 4 Synthesis of 3-hydroxy-2-oxindole (±) **5h–i**.



Scheme 5 Substrates scope using 3-hydroxy-2-oxindoles **5a–c**. [Reactions were carried out on a 0.50 mmol of **5** with 1.50 mmol of *p*-cresol or 4-*tert*-butylphenol in 4 mL of $ClCH_2CH_2Cl$ (DCE) at 80 °C and isolated yields column chromatography. Condition **A**: 10 mol% $In(OTf)_3$; condition **B**: 10 mol% $Cu(OTf)_2$; condition **C**: 10 mol% $Bi(OTf)_3$.]

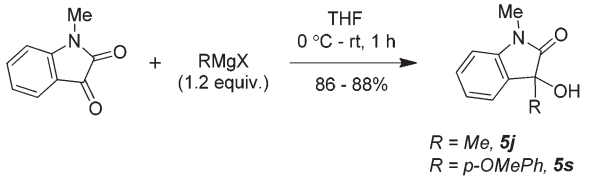


Scheme 6 Substrates scope using 3-hydroxy-2-oxindoles **5d–f** and **5h**. [Reactions were carried out on a 0.50 mmol of **5** with 1.50 mmol of *p*-cresol or 4-*tert*-butylphenol in 4 mL of $ClCH_2CH_2Cl$ (DCE) at 80 °C and isolated yields after column chromatography. Condition **A**: 10 mol% $In(OTf)_3$; condition **B**: 10 mol% $Cu(OTf)_2$; condition **C**: 10 mol% $Bi(OTf)_3$.]

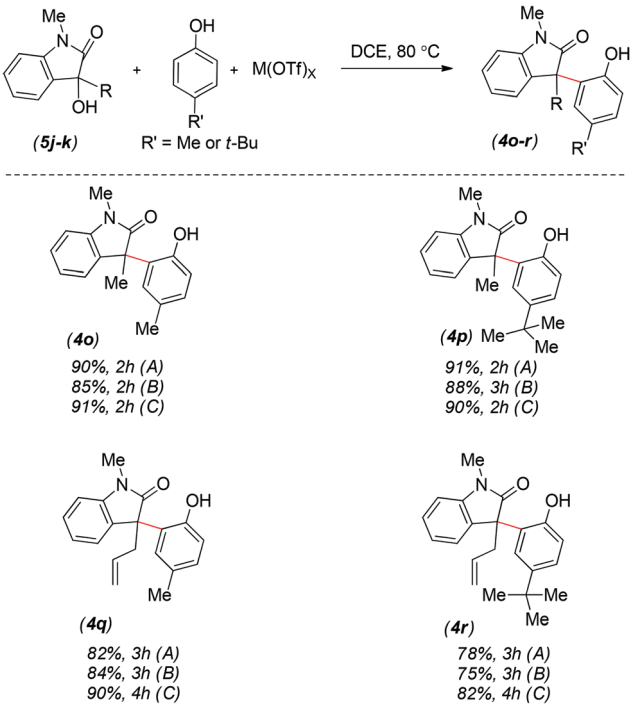
mation of the electron-deficient 2*H*-indol-2-one ring system of the type **11**.

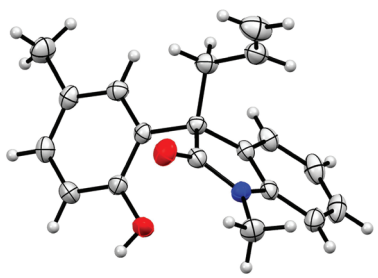
Further, 3-hydroxy-2-oxindoles **5d–f** were also tested with *p*-cresol and *p*-^{t}Bu-phenol and found as suitable electron-deficient partners furnishing Friedel–Crafts alkylation products **4g–l** in up to 93% isolated yields (Scheme 6). Similarly, 2-oxindole **5h** bearing an aminoethyl protected functionality afforded products **4m–n** in 72–89% yields under optimized conditions. These compounds could also serve as advanced intermediates for the core structure of diazonamide (**1**) and azonazine (**2**) as well as C(3a)-arylpyrroloindolines of the type **7** as shown in Fig. 1.

Later, to test whether *N*-methyl-3-hydroxy-2-oxindoles also shows similar reactivity towards Friedel–Crafts alkylations, we employed *N*-methyl-3-hydroxy-2-oxindoles **5j** and **5s** under optimized conditions. These oxindole substrates were synthesized in 86–88% yields *via* a direct Grignard reactions of *N*-methylisatin (Scheme 7).



Scheme 7 Synthesis of *N*-methyl-3-hydroxy-2-oxindoles **5j** and **5s**.

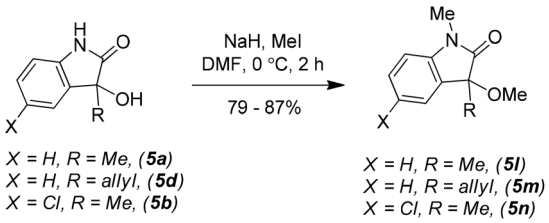




X-ray of (±)-**4q** (CCDC 1007347)

Scheme 8 Substrates scope using *N*-methyl-3-hydroxy-2-oxindoles **5j–k**. [Reactions were carried out on a 0.50 mmol of **5** with 1.50 mmol of *p*-cresol or 4-*tert*-butylphenol in 4 mL of $ClCH_2CH_2Cl$ at 80 °C and isolated yields are reported after column chromatography. Condition **A**: 10 mol% $In(OTf)_3$; condition **B**: 10 mol% $Cu(OTf)_2$; condition **C**: 10 mol% $Bi(OTf)_3$.]

Delightfully, we found that **5j–k** works equally well as electron-deficient partners in refluxing dichloroethane in the presence of 10 mol% of $In(OTf)_3$ (condition **A**), $Cu(OTf)_2$ (condition **B**), and $Bi(OTf)_3$ (condition **C**) and afforded products **4o–r** in 75–91% yields (Scheme 8). One of the F–C alkylation products (**4q**: CCDC 1007347) gave a suitable crystal for



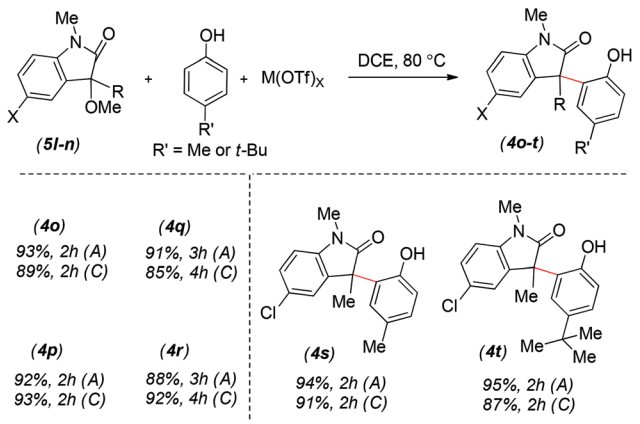
Scheme 9 Synthesis of *N*-methyl-3-methoxy-2-oxindoles **5l–n**.

X-ray analysis, which unambiguously proved the formation of all-carbon quaternary center.

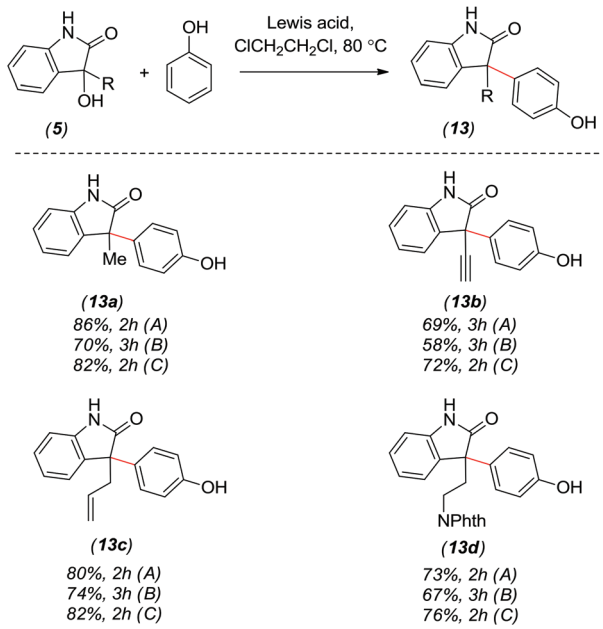
After the successful use of *N*-methyl substrates **5j–k**, we then probed the reactivity of 3-alkoxy-2-oxindoles such as **5l–n** as electron-deficient partners in Friedel–Crafts alkylations. Towards this, few *N*-methyl-3-alkyl-3-methoxy 2-oxindoles **5l–n** were prepared *via* *N*,*O*-dimethylation of 3-hydroxy-2-oxindoles **5a–b** and **5d** in the presence of NaH in DMF to afford products in 79–87% yields (Scheme 9).

We found that 2-oxindole substrates **5l–n** can also be activated in the presence of Lewis acids without event, to effect Friedel–Crafts reactions in the presence of 10 mol% of metal triflates in refluxing dichloroethane furnishing products **4o–t** in the range of 85–95% yields (Scheme 10).

Further, we set forth to investigate a general method for the reaction of phenol with 3-hydroxy-2-oxindoles **5a**, **5d** and **5g–h** as substrates in the presence of catalytic Lewis acids. We found that 10 mol% of metal triflates such as $In(OTf)_3$ (condition **A**), $Cu(OTf)_2$ (condition **B**), and $Bi(OTf)_3$ (condition **C**) afforded products **13a–d** in up to 86% yields under refluxing dichloroethane (Scheme 11). Notably, in all cases phenol reacts exclusively at the *p*-position to afford compounds **13a–d**. Also, 2-oxindole products having propargyl, allyl, and *N*-phthalimide protected 2-aminoethyl groups such as **13b–d** could serve as important intermediates for the synthesis of C-(3a)-pyrroloindoline of the type 7 in high yields (Fig. 1).

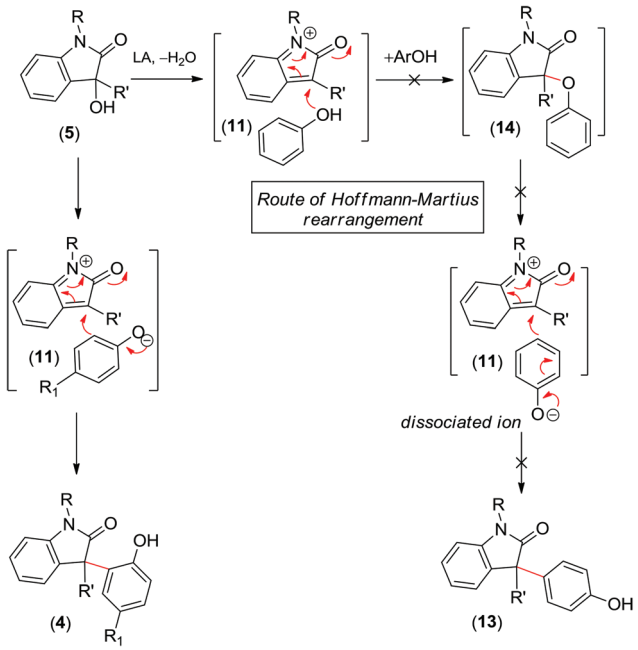


Scheme 10 Substrates scope using *N*,*O*-dimethyl-3-hydroxy-2-oxindoles **5l–n**. [Reactions were carried out on a 0.50 mmol of **5** with 1.50 mmol of *p*-cresol or 4-*tert*-butylphenol in 4 mL of $ClCH_2CH_2Cl$ at 80 °C and isolated yields are reported after column chromatography. Condition **A**: 10 mol% $In(OTf)_3$; condition **C**: 10 mol% $Bi(OTf)_3$.]



Scheme 11 Substrates scope of Friedel–Crafts alkylations using phenol. [Reactions were carried out on a 0.50 mmol of **5** with 1.5 mmol of *p*-cresol or 4-*tert*-butylphenol in 4 mL of $ClCH_2CH_2Cl$ at 80 °C and isolated yields are reported after column chromatography. Condition **A**: 5 mol% $In(OTf)_3$; condition **B**: 5 mol% $Cu(OTf)_2$; condition **C**: 5 mol% $Bi(OTf)_3$.]

Mechanistically, the reaction could proceed through the formation of 2*H*-indol-2-one (**11**) (Scheme 12) formed upon treatment of 3-hydroxy-2-oxindole (**5**) with a Lewis acid as per the literature report.[25c] The electron-rich *p*-position of phenol derivatives could easily react with 2*H*-indol-2-one (**11**) to afford

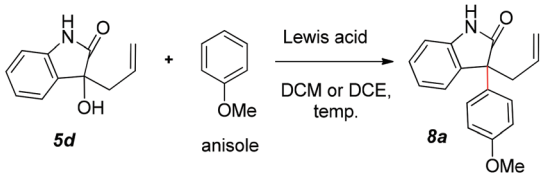


Scheme 12 Proposed mechanism for F–C alkylations of phenols.

the required products with excellent regioselectivity. Alternatively, the reaction could also follow a path where intermediate (**11**) forms twice during the course of the reaction, initially from the starting 3-hydroxy-2-oxindole (**5**) in the presence of Lewis acid and at a later stage from the 3-*O*-aryloxy-2-oxindoles (**14**) *via* a C–O bond breaking through a dissociated ion pair following a photo-Fries type rearrangement as reported by Magnus (Scheme 12).[20] In the latter case, one would expect a regioisomeric (*para* : *ortho*) mixture of products. However, the exclusive formation of *p*-substituted products (**13**) (Scheme 11), together with the literature report on the thermal and acid-catalyzed rearrangement of 3-*N*-aryl-2-oxindoles and 3-*O*-aryloxy-2-oxindoles (**14**) into 3-(*p*-aminoaryl)-2-oxindoles[21] and 3-(*p*-hydroxyaryl)-2-oxindoles (**13**),[20] respectively, following a photo-Fries[20] or Hofmann–Martius rearrangement[21] supports a direct attack of the *p*-position of electron-rich phenols to 2*H*-indol-2-one (**11**) simply leading to the final products.

Later, the Friedel–Crafts alkylation was extended to various electron-rich aromatics other than phenol derivatives such as anisole, veratrole, resorcinol dimethylether, furan, thioanisole, pyrroles, indoles, *etc*. with 3-hydroxy 2-oxindoles (**5**). Towards this end, we again initiated our optimization with 3-allyl 3-hydroxy 2-oxindole **5d** as a model substrate with 3 equiv. of anisole in the presence of various Lewis acids (Table 3). By refluxing dichloromethane and dichloroethane identified as optimal solvents of choice, we anticipate metal triflate-catalyzed Friedel–Crafts alkylations of anisole with 3-hydroxy 2-oxindole (**5d**) using $Zn(OTf)_2$, $Cu(OTf)_2$, $Sn(OTf)_2$, $Bi(OTf)_3$, $In(OTf)_3$, and these results are shown in Table 3. We found that 20 mol% of $Zn(OTf)_2$, $Cu(OTf)_2$, $Sn(OTf)_2$, $Bi(OTf)_3$, and $In(OTf)_3$ in refluxing dichloroethane (DCE) afforded the Friedel–Crafts alkylation product **8a** in 32%, 75%, 80%, 90%, and 92%, respectively (entries 2, 6, 10, 14, and 15). The results in Table 3 also clearly indicate that dichloroethane is a better choice than dichloromethane as a solvent. On further optimization, it was observed that 10 mol% of $In(OTf)_3$ (entry 16, condition **A**) and $Bi(OTf)_3$ (entry 19, condition **C**) in refluxing dichloroethane afforded **8a** in 89% and 90%, respectively. Thus, based on the optimized results, conditions **A** and **C** were chosen for further studies.

Table 3 Optimization of F–C alkylations of anisole in the presence of various Lewis acids



Entry	Cat. (mol%)	Solvent	Temp.	Time	Yield[a,b]	Recovered **5d**[c]
1.	20 mol% $Zn(OTf)_2$	CH_2Cl_2	40 °C	24 h	10%	72%
2.	20 mol% $Zn(OTf)_2$	DCE	80 °C	24 h	32%	55%
3.	10 mol% $Zn(OTf)_2$	CH_2Cl_2	40 °C	24 h	Trace	87%
4.	10 mol% $Zn(OTf)_2$	DCE	80 °C	24 h	25%	62%
5.	20 mol% $Cu(OTf)_2$	CH_2Cl_2	40 °C	24 h	12%	79%
6.	20 mol% $Cu(OTf)_2$	DCE	80 °C	24 h	75%	14%
7.	10 mol% $Cu(OTf)_2$	CH_2Cl_2	40 °C	24 h	Trace	90%
8.	10 mol% $Cu(OTf)_2$	DCE	80 °C	24 h	61%	24%
9.	20 mol% $Sn(OTf)_2$	CH_2Cl_2	40 °C	24 h	10%	78%
10.	20 mol% $Sn(OTf)_2$	DCE	80 °C	24 h	80%	9%
11.	10 mol% $Sn(OTf)_2$	CH_2Cl_2	40 °C	24 h	Trace	84%
12.	10 mol% $Sn(OTf)_2$	DCE	80 °C	24 h	69%	17%
13.	20 mol% $Bi(OTf)_3$	CH_2Cl_2	40 °C	24 h	71%	19%
14.	20 mol% $Bi(OTf)_3$	DCE	80 °C	24 h	90%	—
15.	20 mol% $In(OTf)_3$	DCE	80 °C	24 h	92%	—
16.	*10 mol% $In(OTf)_3$*	*DCE*	*80 °C*	*24 h*	*90%*	—
17.	5 mol% $In(OTf)_3$	DCE	80 °C	30 h	78%	10%
18.	10 mol% $Bi(OTf)_3$	CH_2Cl_2	40 °C	24 h	38%	53%
19.	*10 mol% $Bi(OTf)_3$*	*DCE*	*80 °C*	*24 h*	*89%*	—
20.	5 mol% $Bi(OTf)_3$	DCE	80 °C	30 h	76%	15%

[a] Reactions were carried out on a 0.2 mmol of **5d** with 0.6 mmol of anisole in 2.0 mL of solvent. [b] Isolated yields after column chromatography. [c] Condition **A**: 10 mol% $In(OTf)_3$; condition **C**: 10 mol% $Bi(OTf)_3$.

As expected, under optimized conditions (condition **A**: 10 mol% $In(OTf)_3$ and condition **C**: 10 mol% $Bi(OTf)_3$ in refluxing dichloroethane), **5a** and **5d** as electron-deficient substrates afforded a variety of Friedel–Crafts alkylation products in the presence of electron-rich partners such as anisole, catechol, dimethylether, resorcinol dimethylether, and quinol dimethylether (Fig. 3). In all cases 2-oxindole products having an all-carbon quaternary center were achieved in 82–93% yields (Fig. 3). The reaction could also be extended to substrates having an acetylinic group such as **5g** to afford products **8i–k** in 82–89% yields in 8–10 h. It is noteworthy that 2-oxindoles having allyl and propargyl groups at the C-3 position of 2-oxindoles such as **8a–d** and **8i–k** have the potential for further functionalization by exploiting allylic/acetylinic functional groups.[33]

Further, the reaction was extended to substrates **5h–i** having a phthalimido/succinimido-protected aminoethyl group at the 3-position of 2-oxindoles (Scheme 4). Under optimized conditions **A** and **C**, a variety of products possessing an all-carbon quaternary stereocenter at the pseudobenzylic C(3a)-position such as **8l–t** could be achieved in up to 92% yields from **5h–i** (Fig. 4). Importantly, 2-oxindoles having a furan scaffold at the C-(3a) position such as **8o** and **8t** could also be synthesized in 65–82% yields. The latter could serve as an excellent synthetic intermediate to access various indole alkaloids following oxidative cleavage of the furan moiety.[34]

Having established the practical viability of exploring the nucleophilic attack on 3-alkyl-3-hydroxy-2-oxindoles, we next investigated the reaction of 3-aryl-3-hydroxy-2-oxindoles **5o–s** (Fig. 2). Our interest in 3,3-diaryloxindoles **15a–c** (Fig. 5) is due to their immense biological activities such as mineralocorticoid receptor antagonists, anti-cancer, anti-bacterial, anti-protozoal, and anti-inflammatory activities.[25c,35,36] Few members of this group are also used as laxatives.[36e] It has also been identified that 3,3-diphenyl-2-oxindole **15a** (Fig. 5), could be used as Ca^{2+}-depleting translation initiation inhibitors as shown by Halperin and co-workers.[25b]

We found that, 3-hydroxy-3-aryl-2-oxindoles **5o–s** as electron-deficient partners resulted in comparatively faster and efficient reactions working in just 5 mol% of catalyst loading.

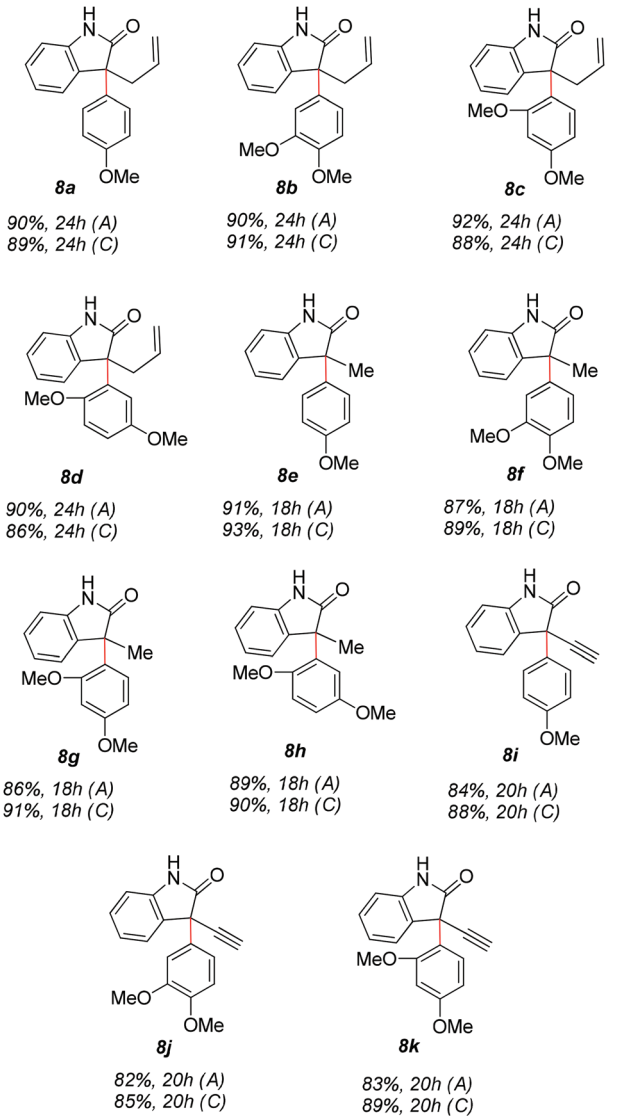


Fig. 3 Substrate scopes of Friedel–Crafts alkylations. [Reactions were carried out on a 0.2 mmol of **5** with 0.6 mmol of electron-rich arene in 2.0 mL of DCE (1,2-dichloroethane) at 80 °C. Isolated yields after purification. Condition **A**: 10 mol% $In(OTf)_3$; condition **C**: 10 mol% $Bi(OTf)_3$.]

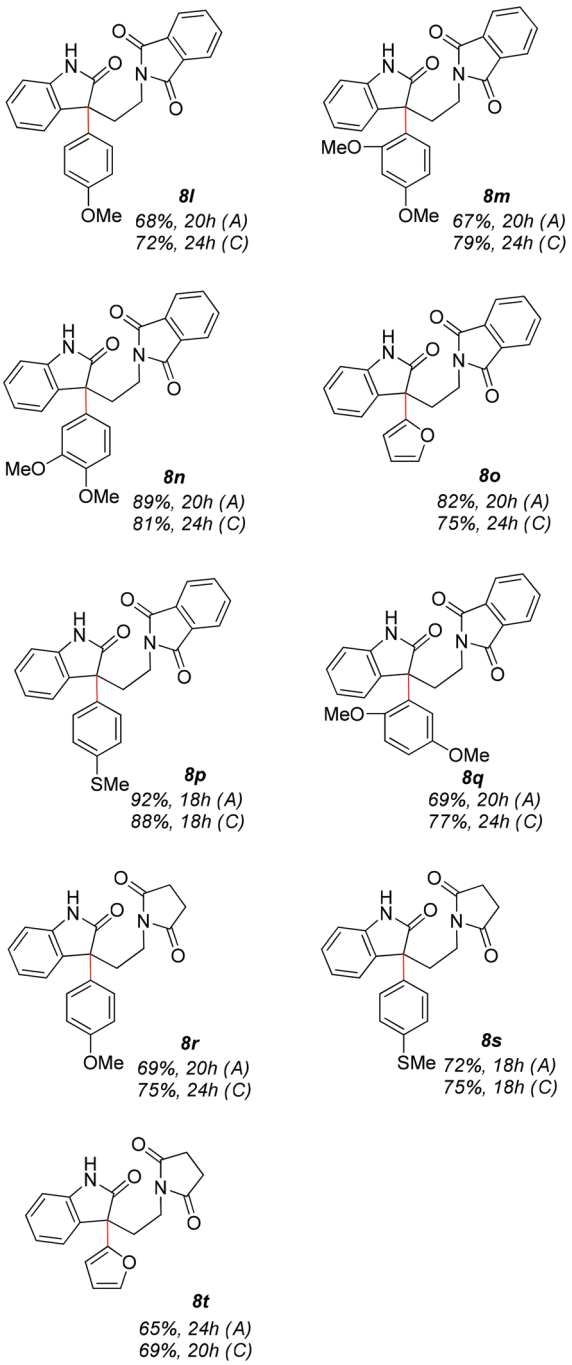


Fig. 4 Further substrate scopes of Friedel–Crafts alkylations. [Reactions were carried out on a 0.2 mmol of **5** with 0.6 mmol of electron-rich arene in 2.0 mL of DCE (1,2-dichloroethane) under reflux. Isolated yields after column chromatography. Condition **A**: 10 mol% $In(OTf)_3$; condition **C**: 10 mol% $Bi(OTf)_3$.]

N-Unsubstituted-3-aryl-2-oxindoles such as **5o–p** were used to effect the Friedel–Crafts alkylations of *p*-cresol, *p*-^{t}Bu-phenol, and phenol as electron-rich substrates. To our delight, we could synthesize a variety of products having unsymmetrical 3,3-diarylated 2-oxindoles **16a–f** in good to excellent yields (up to 95% yields) in the presence of only 5 mol% of Lewis acids in only 2–4 h under refluxing dichloroethane (Scheme 13). Similarly, *N*-methyl-3-hydroxy-2-oxindole **5s** was also found to be a good substrate for F–C alkylation reactions, which furnished 2-oxindoles **16g–i** in excellent yields in just 2 h in refluxing dichloroethane. Gratifyingly, one of the 3,3-diarylated 2-oxindoles (**16a:** CCDC 1007348) provided X-ray suitable for analysis, which unambiguously proved the structure of F–C alkylation adducts.

Further, the F–C alkylations were extended to 3-aryl-2-oxindoles such as **5o–r** in the presence of anisole as an electron-rich substrate, which afforded symmetrical and unsymmetrical 3,3-diarylated 2-oxindoles **16j–m** in 73–91% yields (Scheme 14). We also found that, pyrrole and *N*-tosylated pyrrole could also be used as electron-rich aromatics which

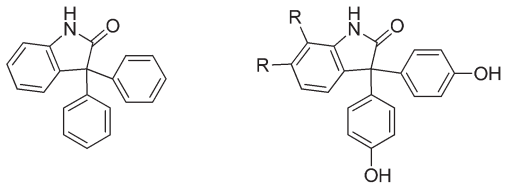


Fig. 5 Important 3,3-diaryl 2-oxindoles **15a–c**.

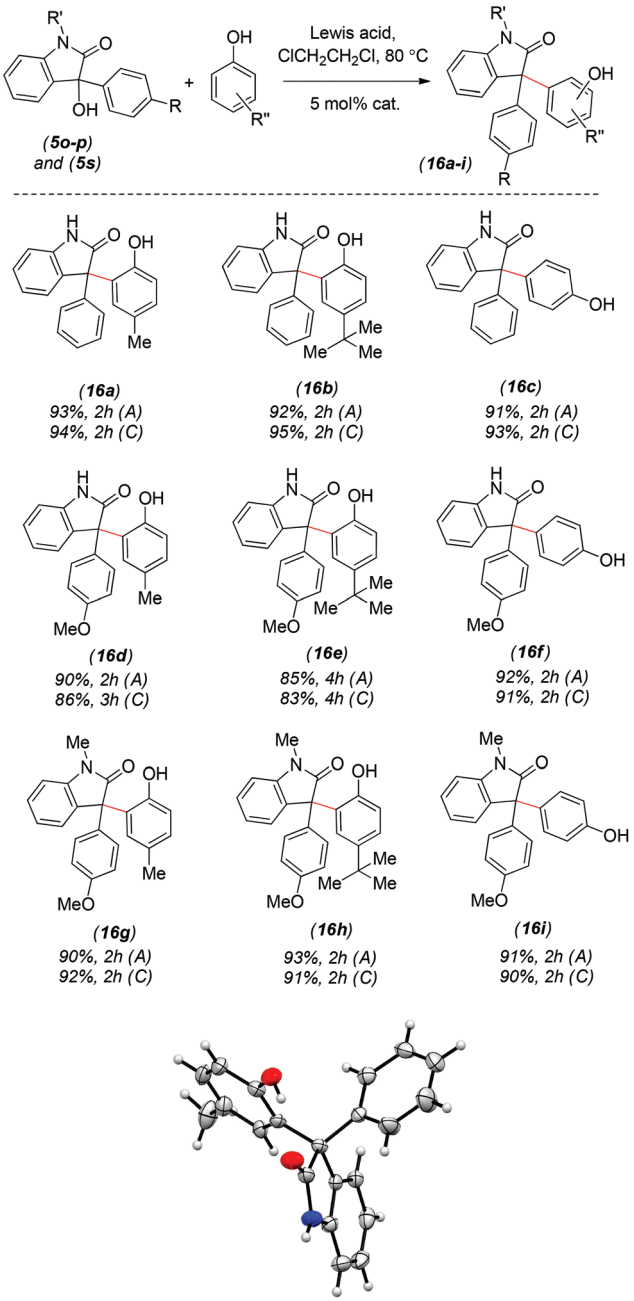
afforded F–C alkylation products **16n–o** in good yields in the presence of 5 mol% of $In(OTf)_3$ (condition **A**) and $Bi(OTf)_3$ (condition **C**). We found that indole could react with 3-hydroxy-2-oxindoles **5p–r** only in the presence of 2 mol% of metal triflates to afford **16p–r** in 82–91% yields (Scheme 14).[26] Along similar lines, *N*-methylindole furnished product **16s** in 82–84% yields in the presence of 5 mol% of metal triflates (Scheme 14).[37]

It is important to note that the reactions are faster when 3-hydroxy 3-aryl 2-oxindoles (**5o–s**) contain an aromatic group at the 3-position. We believe that this might be due to the pseudo dibenzylic nature of the 2*H*-indol-2-one ring system of the types **9a–b** (in the case of **5o–s**) as shown in Fig. 6, which gets further stabilized by the additional aromatic ring as compared to 3-hydroxy 3-alkyl 2-oxindoles **5a–d**.

We further checked the efficiency of Lewis acid catalyzed F–C alkylations with aromatic amines. We observed only 18–22% yield of **17a**, when reactions were carried out with 1 equiv. of *N*-methylaniline in the presence of 10 mol% catalysts under refluxing dichloroethane (Scheme 15). The inefficiency of F–C alkylations might be due to deactivation of metal triflates in the presence of the basic nature of aromatic amines. Therefore, it was decided to carry out the reactions using *N*-protected aniline, such as acetanilide,[37] where the basicity level of aniline is notably suppressed by an acetyl group. Interestingly, when acetanilide was used as an electron-rich partner, F–C alkylation products **17b–c** were isolated in 62–78% yields with just 5 mol% catalyst loading (Scheme 15).[37]

Eventually, we were interested in synthesizing few advanced intermediates from the 2-oxindole products such as the tetracyclic core of azonazine (**2**) through a reductive cyclization approach as shown in Scheme 16. Efforts in this direction led to either a multitude of products or incomplete reductions of the 2-oxindole moiety. In the case of reduction using $LiAlH_4$ we could isolate the over-reduced product **18** which on subsequent acetylation afforded bis acetylated product **19** in 72% yield over 2 steps (Scheme 16). Although it was disappointing at the first instance, this led us to consider exploiting intramolecular oxidative coupling of intermediate **18** to craft the tetracyclic core (**3**) as originally reported by Nicolaou for diazonamide A **1**.[30]

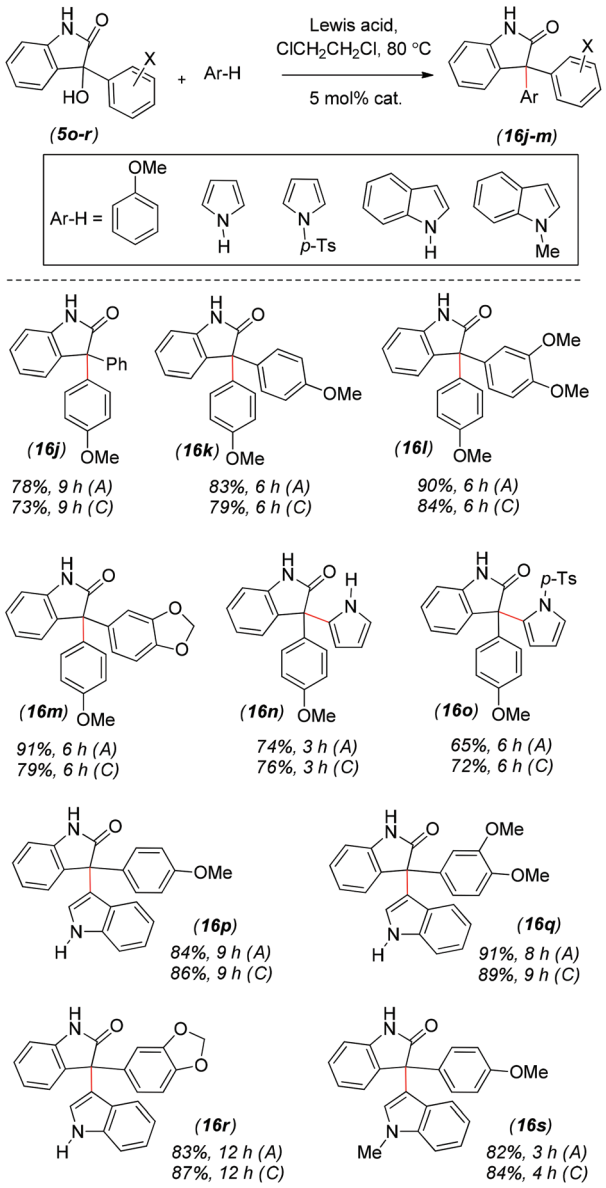
Gratifyingly, when compound **18** was treated with MnO_2 in refluxing benzene, it leads to the formation of tetracyclic core **3a** in 72% yield.[28] Mechanistically, α-elimination of intermediate Mn(IV)-complex **20a** under oxidative environment forms an



X-ray of (±)-**16a** (CCDC 1007348)

Scheme 13 Substrates scope of Friedel–Crafts alkylations using phenol. [Reactions were carried out on a 0.50 mmol of **5** with 1.50 mmol of *p*-cresol or 4-*tert*-butylphenol in 4 mL of $ClCH_2CH_2Cl$ at 80 °C and isolated yields are reported after column chromatography. Condition **A**: 5 mol% $In(OTf)_3$; condition **C**: 5 mol% $Bi(OTf)_3$.]

iminium intermediate **20c** *via* the intermediacy of **20b**. The phenoxide of **20c** then reacts with the iminium ion intramolecularly to afford the tetracyclic core **3a**.[28] On subsequent treatment with acetic anhydride and triethylamine, the tetracyclic core **3a** was converted to *N*-acetyl compound **3b** resembling the core structure of azonazine (**2**) in 85% yield (Scheme 17).



Scheme 14 Scopes using 3-aryl-3-hydroxy-2-oxindoles. [Reactions were carried out on a 0.2 mmol of **5** with 0.6 mmol of anisole in 2 mL of 1,2-dichloroethane. Isolated yields after column chromatography. Condition **A**: 5 mol% $In(OTf)_3$; condition **C**: 5 mol% $Bi(OTf)_3$.]

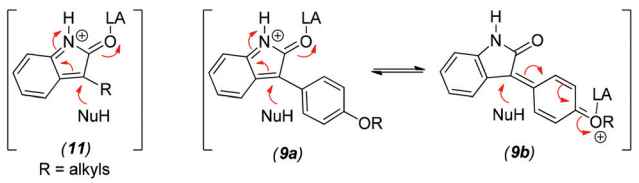
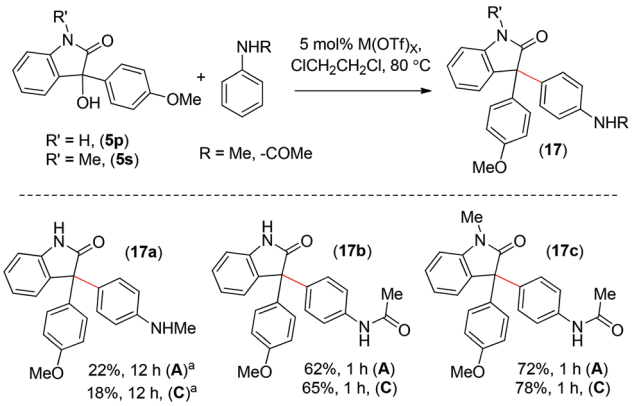
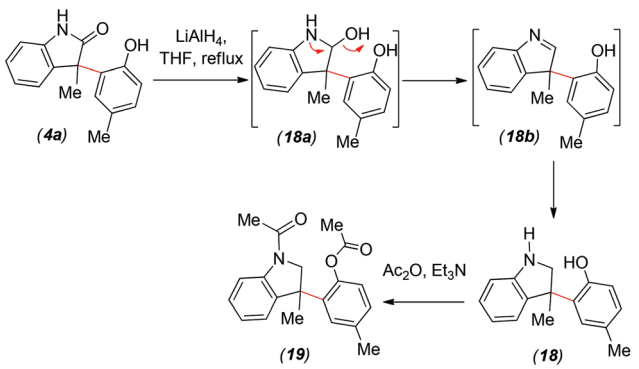


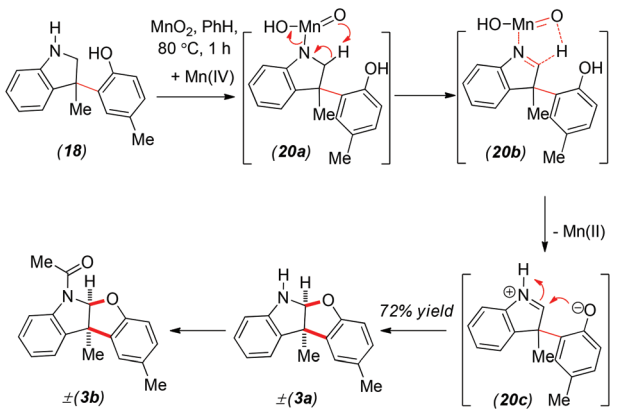
Fig. 6 Proposed reactive intermediates (**9a–b**).



Scheme 15 Friedel–Crafts alkylations using aromatic amine. [Reactions were carried out on a 0.3 mmol of **5** with 0.3 mmol of aniline derivatives in 2 mL of 1,2-dichloroethane. Condition **A**: 5 mol% $In(OTf)_3$; condition **C**: 5 mol% $Bi(OTf)_3$. [a]10 mol% Lewis acids were used.]

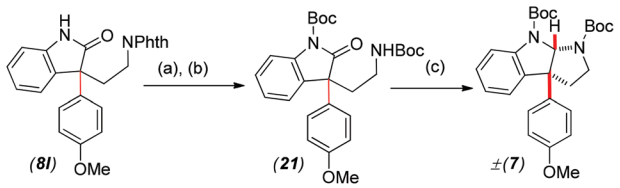


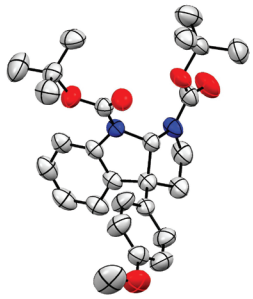
Scheme 16 Reductive cyclization approach to **3**.



Scheme 17 Crafting the tetracyclic core **3a** *via* oxidative coupling.

Further, in search of the core structure of naturally occurring alkaloids such as asperazine (**6a**), idiospermuline (**6b**), and calycosidine (**6c**) (Fig. 1), one of the F–C alkylation products was converted into C-(3a)-aryl pyrrolindoline[38] **7** as shown in Scheme 18. The cleavage of the phthalide group of **8l** using hydrazine hydrate followed by treatment with $(Boc)_2O$ leads to the bis-Boc protected compound **21** in 80% overall yields over 2 steps. The reduction of *N*-Boc protected amide





X-ray of (±)-7 (CCDC 1007349)
Hydrogen atoms are removed for clarity

Scheme 18 Synthesis of C-3(a)-aryl pyrroloindoline **7**. [Reaction conditions: (a) NH_2-NH_2·H_2O, MeOH–CH_2Cl_2, 25 °C, 12 h; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, DMAP (cat.), 25 °C, 24 h; (c) $NaBH_4$, THF–MeOH, 0 °C, 10 min then CSA, 25 °C, 4 h.]

functionality of 2-oxindole **21** in the presence of $NaBH_4$ led to the formation of lactol intermediate which upon cyclization in the presence of camphorsulfonic acid (CSA) constructs the tricyclic core **7** in 71% yield over 2 steps.[39] The X-ray structure of **7** (CCDC 1007349) unambiguously proved the formation of C-(3a)-aryl pyrroloindoline.[40]

Conclusion

In summary, we developed an efficient approach toward the Lewis acid-catalyzed Friedel–Crafts alkylations of phenol derivatives and electron-rich aromatics with a variety of 3-hydroxy-2-oxindoles. The current Friedel–Crafts alkylation strategy relies on the utility of the 2*H*-indol-2-one ring (**9**), formed in the presence of Lewis acids, to afford oxindole derivatives (**4**, **8**, **13**, and **16**) possessing an all-carbon quaternary stereocenter at the C(3a)-position. We applied this methodology in the synthesis of the tetracyclic core (**3**) of diazonamide A (**1**) and azonazine (**2**) through a late-stage intramolecular oxidative coupling. Further synthetic viability is shown by constructing C-(3a)-aryl pyrrolindoline subunits **3a**, which could be an advanced intermediate to access a variety of naturally occurring oxindole based alkaloids. We believe that nucleophilic addition to the 2*H*-indol-2-one ring (**9**) using a chiral Lewis acid-complex could be one of the promising platforms to accomplish these targets in an enantioenriched form. Further exploration towards this as well as its application in the synthesis of complex alkaloids is currently under active investigation.

Material and methods

Chemicals and reagents were purchased from commercial sources and used without further purification. Unless otherwise stated, reactions were performed in an oven-dried glassware fitted with rubber septa under an inert atmosphere and were stirred with Teflon-coated magnetic stirring bars. Tetrahydrofuran (THF) and toluene were distilled over sodium/benzophenone ketyl. Dichloromethane, chloroform, and dichloroethane were distilled over calcium hydride. All other solvents such as DMF, acetonitrile, methanol were used as received. Thin layer chromatography was performed using Silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, anisaldehyde stain and other stains. Silicagel of particle size 100–200 mesh was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on 400, 500 MHz spectrometers with ^{13}C operating frequencies of 100, 125 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent ($CDCl_3$) signal (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogen). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a FT-IR system (Spectrum BX) and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High-Resolution Mass Spectrometry (HRMS) and Low-Resolution Mass Spectrometry (LRMS) data were recorded on MicrOTOF-Q-II mass spectrometer using methanol as the solvent.

Caution! $HClO_4$ has a powerful oxidizing property. Although the use of 70% aqueous solution of $HClO_4$ as the catalyst could reduce the potential danger associated with $HClO_4$, it is important to take special care while carrying out the reaction. For important information, see: http://en.wikipedia.org/wiki/Perchloric_acid.

For synthesis and characterization of **5a–d**, **5g–h**, **4a–h**, **4m–n**, **13a–d**, **18**, **19**, **3a**, and **3b**, see ref. 28. For synthesis and characterization of **5o–r**, **8a–b**, and **16p–r** see ref. 26.

General procedure for DMF-catalyzed allylations to isatins (Scheme 3)

To a stirred solution of *N*-methyl isatin (11.0 mmol, 1.0 equiv.) in DMF (10 mL) at 0 °C was added allyltrichlorosilane (13.2 mmol, 1.2 equiv.). Then the mixture was stirred for 1 h at 0 °C. Upon completion of the reaction (Judged by running TLC), the reaction mixture was quenched by adding H_2O and extracted with 40% EtOAC–hexane (50 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography by using EtOAC and hexane to afford the desired product.

3-Allyl-5-chloro-3-hydroxyindolin-2-one (5e)

Yield 86%. The product was obtained as a yellowish solid, R_f = 0.43 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 9.49 (brs, 1H), 7.31–7.34 (m, 1H),

7.16–7.21 (m, 1H), 6.80 (t, J = 7.88 Hz, 1H), 5.57–5.69 (m, 1H), 5.07–5.11 (m, 2H), 4.98 (brs, 1H), 2.69–2.76 (m, 1H), 2.57–2.64 (m, 1H); **^{13}C NMR** (100 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 179.2, 140.1, 133.1, 130.8, 128.6, 126.8, 124.4, 119.4, 110.9, 75.9, 42.4; **IR** (film) ν_{max} 3248, 2663, 1708, 1469, 1180, 1088, 770 cm^{-1}; **HRMS** (ESI) m/z 224.0473 $[M + H]^+$; calculated for $[C_{11}H_{11}ClNO_2]^+$: 224.0458; **MP** 184–187 °C.

3-Allyl-5-bromo-3-hydroxyindolin-2-one (5f)

Yield 92%. The product was obtained as a yellowish solid, R_f = 0.45 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 9.58 (br, 1H), 6.99–7.19 (m, 2H), 6.44–6.52 (m, 1H), 5.28–5.38 (m, 1H), 4.79 (m, 2H), 3.93 (brs, 1H), 2.29–2.49 (m, 2H); **^{13}C NMR** (100 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 179.1, 140.5, 133.4, 131.6, 130.8, 127.3, 119.5, 114.2, 111.5, 75.9, 42.4; **IR** (film) ν_{max} 3665, 2355, 1700, 1446, 1181, 1119, 1080 cm^{-1}; **HRMS** (ESI) m/z 267.9940 $[M + H]^+$; calculated for $[C_{11}H_{11}BrNO_2]^+$: 267.9968; **MP** 192–195 °C.

3-Allyl-3-hydroxy-1-methylindolin-2-one (5k)

Yield 82%. The product was obtained as a reddish solid, R_f = 0.39 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.36 Hz, 1H), 7.31 (m, 1H), 7.08 (t, J = 7.48 Hz, 1H), 6.81 (d, J = 7.72 Hz, 1H), 5.57–5.68 (m, 1H), 5.05–5.10 (m, 2H), 3.16 (s, 1H), 2.56–2.75 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.9, 143.2, 130.5, 129.8, 129.6, 124.1, 123.1, 120.3, 108.4, 76.0, 42.9, 26.2; **IR** (film) ν_{max} 3575, 1696, 1612, 1465, 1384, 1307, 1213, 1092, 933, 754, 639, 426 cm^{-1}; **HRMS** (ESI) m/z 204.1020 $[M + H]^+$; calculated for $[C_{12}H_{14}NO_2]^+$: 204.1019; **MP** 132–137 °C.

Synthesis of 5i from 12b (Scheme 4)

A round-bottom flask was charged with *N*-succinimido protected tryptamine (5 mmol, 1.0 equiv.) in MeCN and H_2O (9 : 1) and then kept at 0 °C. IBX (12.5 mmol, 2.5 equiv.) was added in one portion followed by the addition of cerium(III) chloride heptahydrate, and then stirring was continued for 1 h. Upon completion of the reaction (as judged by TLC), the reaction mixture was quenched at 0 °C with saturated aqueous $NaHCO_3$ (15 mL for 5 mmol). Then the reaction mixture was diluted with 100 mL of CH_2Cl_2. The whole reaction mixture was taken in a separatory funnel and extracted with CH_2Cl_2 (50 mL × 2). The organic filtrate was dried over Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. The crude products were purified by flash chromatography (1 : 1–1 : 2 hexanes–EtOAc) to afford compound ±(**5i**) in 65% yield.

1-(2-(3-Hydroxy-2-oxoindolin-3-yl)ethyl)pyrrolidine-2,5-dione (5i) (Scheme 4)

The product was obtained as a white solid, R_f = 0.34 (EtOAc). **^{1}H NMR** (400 MHz, DMSO) δ: 10.25 (brs, 1H), 7.27–7.13 (m, 2H), 6.97–6.91 (m, 1H), 6.80–6.77 (m, 1H), 5.98 (s, 1H), 3.52–3.39 (m, 2H), 2.43 (m, 4H), 2.01–1.84 (m, 2H); **^{13}C NMR of one rotamer** (100 MHz, DMSO) δ: 183.8, 182.8, 147.9, 136.7, 134.2, 129.1, 126.9, 115.0, 79.3, 48.3, 39.6, 33.1; **^{13}C NMR of another rotamer** (100 MHz, DMSO) δ: 183.5, 182.6, 146.7, 134.3, 133.0, 129.0, 126.5, 114.6, 79.3, 40.4, 38.2, 33.1; **IR** (film) ν_{max} 3730, 3336, 2929, 2360, 1696, 1583, 1404, 1140, 1051, 745, 424 cm^{-1}; **HRMS** (ESI) m/z 297.0851 $[(M + Na)^+$; calculated for $[C_{14}H_{14}N_2O_4 + Na]^+$: 297.0846]; **MP** 188–191 °C.

General procedure for Grignard addition to isatins (Scheme 7)

To a stirred solution of *N*-methyl isatin (9.93 mmol, 1.0 equiv.) in dry THF (20 mL) at 0 °C was added RMgBr (11.92 mmol, 1.2 equiv.). Then the mixture was stirred for 1 h at 0 °C, allowed to warm to rt and stirred for 10 h. Upon completion of the reaction, the reaction mixture was quenched by adding saturated NH_4Cl solution and extracted with EtOAC. The combined organic layers were dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography by using EtOAC and a hexane mixture as eluents to afford the desired product.

3-Hydroxy-1,3-dimethylindolin-2-one (5j)

Yield 86%. The product was obtained as a yellowish solid, R_f = 0.49 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.28 Hz, 1H), 7.30 (t, J = 7.68 Hz, 1H), 7.08 (t, J = 7.48 Hz, 1H), 6.82 (d, J = 7.76 Hz, 1H), 3.53 (brs, 1H), 3.17 (s, 3H), 1.59 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.8, 142.8, 131.6, 129.6, 123.4, 123.3, 108.5, 73.7, 26.2, 24.8; **IR** (film) ν_{max} 3399, 1701, 1374, 1301, 1252, 1175, 1095, 1031, 943, 826, 757 cm^{-1}; **HRMS** (ESI) m/z 178.0860 $[M + H]^+$; calculated for $[C_{10}H_{12}NO_2]^+$: 178.0863; **MP** 154–159 °C.

3-Hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one (5s)

Yield 88%. The product was obtained as a yellowish solid, R_f = 0.49 (50% EtOAc in hexane). R_f = 0.48 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24–7.33 (m, 4H), 7.06 (t, J = 7.32 Hz, 1H), 6.85 (d, J = 7.76 Hz, 1H), 6.78–6.81 (m, 2H), 4.08 (brs, 1H), 3.73 (s, 3H), 3.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.8, 159.5, 143.4, 132.3, 131.8, 129.7, 127.0, 124.9, 123.5, 113.9, 108.6, 55.3, 26.5; **IR** (film) ν_{max} 3305, 1699, 1660, 1618, 1428, 1219, 1130, 750 cm^{-1}; **HRMS** (ESI) m/z 292.0930 $[M + Na]^+$; calculated for $[C_{16}H_{15}NO_3 + Na]^+$: 292.0944.

General procedure of *N*,*O*-dimethylations (Scheme 9)

A flame-dried round-bottom flask was charged with 3-substituted 3-hydroxy 2-oxindole (1.0 mmol, 1.0 equiv.) in DMF (6 mL) and then NaH (2.2 mmol, 2.2 equiv.) was added to it at 0 °C. After 5 minutes of stirring at the same temperature, MeI (2.5 mmol, 2.5 equiv.) was added. The reaction mixture was stirred at 0 °C for 2 h. Upon completion of the reaction (Judged by running TLC), the reaction mixture was quenched by adding a saturated NH_4Cl solution and extracted with EtOAC. The combined organic layers were dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography by using EtOAC and hexane as an eluent to afford the desired product.

3-Methoxy-1,3-dimethylindolin-2-one (5l)

Yield 81%. The product was obtained as a yellowish solid, R_f = 0.39 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.09–7.06 (m, 1H), 6.82 (d, J = 7.72 Hz, 1H), 3.19 (s, 3H), 2.97 (s, 3H), 1.50 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.5, 143.5, 129.7, 128.6, 123.7, 123.1, 108.4, 79.6, 53.0, 26.1, 23.8; **IR** (film) ν_{max} 3558, 2934, 1715, 1615, 1455, 1374, 1304, 1114, 1247, 1061, 1025, 820 cm^{-1}; **HRMS** (ESI) m/z 192.1022 $[M + H]^+$; calculated for $[C_{11}H_{14}NO_2]^+$: 192.1019; **MP** 79–82 °C.

3-Allyl-3-methoxy-1-methylindolin-2-one (5m)

Yield 79%. The product was obtained as a yellowish oil, R_f = 0.52 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28–7.34 (m, 2H), 7.07–7.10 (m, 1H), 6.82 (d, J = 7.76 Hz, 1H), 5.46–5.56 (m, 1H), 4.95–5.00 (m, 2H), 3.18 (s, 3H), 3.00 (s, 3H), 2.55–2.74 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.7, 143.9, 130.6, 129.8, 126.7, 124.5, 122.9, 119.6, 108.3, 82.5, 53.0, 41.9, 26.0; **IR** (film) ν_{max} 3546, 2935, 1715, 1615, 1469, 1374, 1307, 1250, 1119, 1032, 991, 924, 860, 755 cm^{-1}; **HRMS** (ESI) m/z 218.1175 $[M + H]^+$; calculated for $[C_{13}H_{16}NO_2]^+$: 218.1176.

5-Chloro-3-methoxy-1,3-dimethylindolin-2-one (5n)

Yield 87%. The product was obtained as a yellowish solid, R_f = 0.59 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25–7.29 (m, 2H), 6.75 (d, J = 8.20 Hz, 1H), 3.17 (m, 3H), 2.99 (m, 3H), 1.50 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 142.0, 130.4, 129.6, 128.6, 124.2, 109.4, 79.6, 53.2, 26.2, 23.7; **IR** (film) ν_{max} 3430, 2933, 1729, 1611, 1425, 1341, 1260, 1138 cm^{-1}; **HRMS** (ESI) m/z 226.0630 $[M + H]^+$; calculated for $[C_{11}H_{13}ClNO_2]^+$: 226.0629; **MP** 118–121 °C.

General procedure for Friedel–Crafts alkylations of electron-rich aromatics with 3-hydroxy-2-oxindoles in the presence of Lewis acids

A flame-dried round-bottom flask was charged with 3-substituted 3-hydroxy 2-oxindole (0.5 mmol, 1.0 equiv.) in dichloroethane (4 mL) and then Lewis acid was added to the reaction mixture at room temperature. After 5 minutes of stirring at room temperature, electron-rich aromatics (1.5 mmol, 3.0 equiv.) was added to it. The reaction mixture was stirred at room temperature for 5 minutes and then it was heated under reflux at 80 °C for the indicated time. Upon completion of the reaction (judged by running TLC), the reaction mixture was cooled to room temperature. Most of the volatile components were evaporated under reduced pressure and the crude materials were directly purified by flash chromatography using EtOAc and petroleum ether to afford Friedel–Crafts alkylation products.

3-Allyl-5-chloro-3-(2-hydroxy-5-methylphenyl)indolin-2-one (4i) (Scheme 6)

The product was obtained as a yellowish gel, R_f = 0.48 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.21 (br, 1H), 8.84 (br, 1H), 7.13 (s, 1H), 7.06 (d, J = 8.23 Hz, 1H), 6.97 (s, 1H), 7.06 (d, J = 8.23 Hz, 1H), 6.97 (s, 1H), 6.92 (d, J = 8.03 Hz, 1H), 6.71 (d, J = 8.17 Hz, 1H), 5.28–5.38 (m, 1H), 5.00 (d, J = 16.93 Hz, 1H), 4.93 (d, J = 10.20 Hz, 1H), 3.17 (dd, J = 13.25, 8.35 Hz, 1H), 2.95 (dd, J = 13.32, 6.12 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.8, 152.8, 139.2, 133.5, 131.1, 130.0, 129.7, 128.4, 128.3, 128.2, 125.4, 124.1, 120.1, 118.7, 111.5, 57.1, 39.8, 20.8; **IR** (film) ν_{max} 3281, 1699, 1621, 1479, 1332, 1234, 1182, 1117, 925, 895, 815, 740 cm^{-1}; **HRMS** (ESI) m/z 314.0955 $[M + H]^+$; calculated for $[C_{18}H_{17}ClNO_2]^+$: 314.0942.

3-Allyl-3-(5-(*tert*-butyl)-2-hydroxyphenyl)-5-chloroindolin-2-one (4j) (Scheme 6)

The product was obtained as a colorless gel, R_f = 0.52 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.20 (br, 2H), 7.17–7.23 (m, 3H), 7.13 (br, 1H), 6.84 (m, 1H), 6.80 (d, J = 8.19 Hz, 1H), 5.31–5.41 (m, 1H), 5.05 (d, J = 16.55 Hz, 1H), 4.95 (d, J = 10.07 Hz, 1H), 3.32 (dd, J = 13.63, 8.22 Hz, 1H), 2.96 (dd, J = 13.65, 6.33 Hz, 1H), 1.21 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.3, 153.5, 143.1, 138.9, 132.9, 131.3, 128.5, 128.3, 126.6, 126.42, 126.40, 125.0, 122.5, 120.1, 119.1, 58.3, 39.6, 34.3, 31.5; **IR** (film) ν_{max} 3352, 1697, 1620, 1479, 1241, 1133, 924, 887, 819, 740 cm^{-1}; **HRMS** (ESI) m/z 356.1427 $[M + H]^+$; calculated for $[C_{21}H_{23}ClNO_2]^+$: 356.1412.

3-Allyl-5-bromo-3-(2-hydroxy-5-methylphenyl)indolin-2-one (4k) (Scheme 6)

The product was obtained as a yellowish gel, R_f = 0.49 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (br, 1H), 8.82 (br, 1H), 7.25–7.29 (m, 2H), 6.93 (m, 2H), 6.73 (m, 1H), 6.67 (m, 1H), 5.28–5.39 (m, 1H), 5.02 (d, J = 16.96 Hz, 1H), 4.93 (d, J = 10.19 Hz, 1H), 3.21 (dd, J = 13.50, 8.15 Hz, 1H), 2.94 (dd, J = 13.47, 6.35 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.3, 153.0, 139.6, 133.7, 131.2, 131.1, 130.1, 129.7, 128.4, 128.3, 123.8, 120.1, 118.9, 115.6, 112.0, 57.2, 39.7, 20.8; **IR** (film) ν_{max} 3382, 1696, 1618, 1475, 1265, 1118, 1045, 926, 881, 815, 739 cm^{-1}; **HRMS** (ESI) m/z 358.0443 $[M + H]^+$; calculated for $[C_{18}H_{17}BrNO_2]^+$: 358.0437.

3-Allyl-5-bromo-3-(5-(*tert*-butyl)-2-hydroxyphenyl)indolin-2-one (4l) (Scheme 6)

The product was obtained as a colorless gel, R_f = 0.53 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.18 (brs, 1H), 8.36 (br, 1H), 7.38 (m, 2H), 7.19 (dd, J = 8.37, 1.94 Hz, 1H), 7.10 (m, 1H), 6.86 (d, J = 8.35 Hz, 1H), 6.80 (d, J = 7.87 Hz, 1H), 5.30–5.40 (m, 1H), 5.04 (d, J = 16.95 Hz, 1H), 4.95 (d, J = 10.17 Hz, 1H), 3.35 (dd, J = 13.45, 8.10 Hz, 1H), 2.92 (dd, J = 13.73, 6.39 Hz, 1H), 1.20 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.1, 153.4, 143.1, 139.4, 133.3, 131.4, 131.3, 129.2, 126.6, 125.0, 122.5, 120.2, 119.1, 115.5, 112.1, 58.1, 39.7, 34.3, 31.5; **IR** (film) ν_{max} 3289, 2964, 1699, 1475, 1273, 1131, 924, 885, 818, 740 cm^{-1}; **HRMS** (ESI) m/z 400.0927 $[M + H]^+$; calculated for $[C_{21}H_{23}BrNO_2]^+$: 400.0907.

3-(2-Hydroxy-5-methylphenyl)-1,3-dimethylindolin-2-one (4o) (Scheme 8)

The product was obtained as a light greenish gel, R_f = 0.52 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.35–7.41 (m, 2H), 7.22–7.26 (m, 1H), 6.96 (m, 2H), 6.89 (m, 1H), 6.78 (d, J = 1.53 Hz, 1H), 3.22 (s, 3H), 2.14 (s, 3H), 1.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 182.2, 154.5, 142.5, 132.7, 129.9, 129.1, 128.5, 128.3, 125.8, 124.9, 123.3, 119.8, 109.1, 52.9, 26.6, 22.4, 20.6; **IR** (film) ν_{max} 3318, 2929, 1676, 1447, 1268, 1122, 797, 742 cm^{-1}; **HRMS** (ESI) m/z 268.1319 $[M + H]^+$; calculated for $[C_{17}H_{18}NO_2]^+$: 268.1332.

3-(5-(*tert*-Butyl)-2-hydroxyphenyl)-1,3-dimethylindolin-2-one (4p) (Scheme 8)

The product was obtained as a white solid, R_f = 0.43 (15% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.37–7.41 (m, 2H), 7.24–7.27 (m, 1H), 7.19 (dd, J = 8.39, 2.32 Hz, 1H), 7.04 (s, 1H), 6.95 (m, 2H), 3.23 (s, 3H), 1.88 (s, 3H), 1.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 182.2, 154.4, 142.6, 132.7, 128.5, 126.3, 125.8, 124.9, 124.1, 123.1, 119.4, 109.2, 53.4, 34.2, 31.5, 26.6, 22.5; **IR** (film) ν_{max} 3340, 2959, 1675, 1614, 1455, 1376, 1280, 1149, 1025, 821, 745 cm^{-1}; **HRMS** (ESI) m/z 310.1804 $[M + H]^+$; calculated for $[C_{20}H_{24}NO_2]^+$: 310.1802; **MP** 189–194 °C.

3-Allyl-3-(2-hydroxy-5-methylphenyl)-1-methylindolin-2-one (4q) (Scheme 8)

The product was obtained as a white solid, R_f = 0.54 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.37–7.42 (m, 2H), 7.25 (m, 2H), 6.92–6.99 (m, 3H), 6.79 (s, 1H), 5.22–5.33 (m, 1H), 4.98 (d, J = 16.98 Hz, 1H), 4.89 (d, J = 10.08 Hz, 1H), 3.40 (dd, J = 13.72, 8.22 Hz, 1H), 3.20 (s, 3H), 2.95 (dd, J = 13.70, 6.21 Hz, 1H), 2.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.0, 154.7, 143.1, 132.1, 130.0, 129.9, 129.0, 128.8, 128.6, 126.6, 123.4, 123.1, 120.2, 119.5, 109.1, 57.8, 39.3, 26.5, 20.6; **IR** (film) ν_{max} 3318, 2921, 1681, 1611, 1470, 1378, 1269, 1140, 919, 820, 755 cm^{-1}; **HRMS** (ESI) m/z 294.1469 $[M + H]^+$; calculated for $[C_{19}H_{20}NO_2]^+$: 294.1489; **MP** 138–142 °C.

3-Allyl-3-(5-(*tert*-butyl)-2-hydroxyphenyl)-1-methylindolin-2-one (4r) (Scheme 8)

The product was obtained as a yellowish gel, R_f = 0.48 (15% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.39 (m, 2H), 7.26 (t, J = 7.29 Hz, 1H), 7.20 (dd, J = 8.37, 2.36 Hz, 1H), 7.07 (d, J = 2.35 Hz, 1H), 6.96 (t, J = 8.41 Hz, 2H), 5.22–5.32 (m, 1H), 4.99 (d, J = 16.75 Hz, 1H), 4.89 (d, J = 10.11 Hz, 1H), 3.45 (dd, J = 13.74, 8.11 Hz, 1H), 3.21 (s, 3H), 2.94 (dd, J = 13.76, 6.29 Hz, 1H), 1.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.0, 154.5, 143.2, 142.5, 132.1, 130.0, 128.7, 126.5, 126.4, 125.4, 122.9, 122.7, 119.7, 119.5, 109.2, 58.3, 39.5, 34.3, 31.5, 26.5; **IR** (film) ν_{max} 3399, 2963, 1678, 1614, 1469, 1376, 1244, 1135, 825, 754 cm^{-1}; **HRMS** (ESI) m/z 336.1954 $[M + H]^+$; calculated for $[C_{22}H_{26}NO_2]^+$: 336.1958.

5-Chloro-3-(2-hydroxy-5-methylphenyl)-1,3-dimethylindolin-2-one (4s) (Scheme 10)

The product was obtained as a white solid, R_f = 0.42 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (br, 1H), 7.31 (dd, J = 8.34, 1.43 Hz, 1H), 7.22 (m, 1H), 6.92 (d, J = 8.06 Hz, 1H), 6.82–6.85 (m, 2H), 6.73 (d, J = 8.03 Hz, 1H), 3.19 (s, 3H), 2.20 (s, 3H), 1.80 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.8, 153.5, 141.4, 135.2, 135.1, 129.9, 129.3, 128.5, 128.2, 128.0, 125.3, 124.7, 118.9, 109.7, 52.4, 26.7, 22.5, 20.7; **IR** (film) ν_{max} 3303, 2921, 1694, 1610, 1423, 1350, 1275, 1221, 1146, 739 cm^{-1}; **HRMS** (ESI) m/z 302.0980 $[M + H]^+$; calculated for $[C_{17}H_{17}ClNO_2]^+$: 302.0942; **MP** 213–217 °C.

3-(5-(*tert*-Butyl)-2-hydroxyphenyl)-5-chloro-1,3-dimethylindolin-2-one (4t) (Scheme 10)

The product was obtained as a white solid, R_f = 0.44 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.26 (br, 1H), 7.33 (dd, J = 8.33, 1.24 Hz, 1H), 7.27 (brs, 1H), 7.17 (dd, J = 8.38, 1.84 Hz, 1H), 7.07 (brs, 1H), 6.83–6.88 (m, 2H), 3.21 (s, 3H), 1.84 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.8, 153.7, 142.7, 141.3, 134.9, 128.5, 128.3, 126.4, 125.7, 124.4, 123.8, 118.9, 109.9, 53.0, 34.3, 31.5, 26.8, 22.6; **IR** (film) ν_{max} 3365, 2965, 1696, 1460, 1276, 1109, 824, 740 cm^{-1}; **HRMS** (ESI) m/z 344.1450 $[M + H]^+$; calculated for $[C_{20}H_{23}ClNO_2]^+$: 344.1412; **MP** 167–169 °C.

3-Allyl-3-(2,4-dimethoxyphenyl)indolin-2-one (8c) (Fig. 3)

The product was obtained as a light yellow gel, R_f = 0.64 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.91 (brs, 1H), 7.51 (d, J = 8.65 Hz, 1H), 7.15 (td, J = 7.52, 1.52 Hz, 1H), 6.92 (td, J = 7.48, 0.88 Hz, 1H), 6.86 (m, 2H), 6.58 (dd, J = 8.64, 2.54 Hz, 1H), 6.4 (d, J = 2.52 Hz, 1H), 5.49 (m, 1H), 5.06 (m, 1H), 4.95 (m, 1H), 3.86 (s, 3H), 3.46 (s, 3H), 3.01 (d, J = 7.12, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 182.2, 160.4, 158.2, 141.5, 134.2, 131.8, 128.1, 127.3, 122.8, 122.0, 121.8, 119.1, 109.0, 104.5, 100.1, 55.5, 55.4, 53.9, 40.8; **IR** (film) ν_{max} 3429, 3410, 1620, 1585, 1504, 1416, 1304, 1265, 1207, 1142, 1034, 926, 837, 791, 733 cm^{-1}; **HRMS** (ESI) m/z 310.1449 $[M + H]^+$; calculated $[C_{19}H_{20}NO_3]^+$: 310.1438.

3-Allyl-3-(2,5-dimethoxyphenyl)indolin-2-one (8d) (Fig. 3)

79% yield, white solid, R_f = 0.59 (50% EtOAc in hexane). **^{1}H NMR (400 MHz, $CDCl_3$)** δ: 8.55 (brs, 1H), 7.17 (d, J = 2.76 Hz, 1H), 7.12 (td, J = 7.4, 1.24 Hz, 1H), 6.91–6.83 (m, 3H), 6.79–6.71 (m, 2H), 5.53–5.42 (m, 1H), 5.06–5.01 (m, 1H), 4.95–4.92 (m, 1H), 3.81 (s, 3H), 3.37 (s, 3H), 2.97 (d, J = 8 MHz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 181.5, 153.9, 151.6, 141.5, 133.8, 131.6, 130.8, 127.5, 122.9, 122.1, 119.3, 115.0, 113.8, 112.4, 109.0, 56.5, 55.9, 54.3, 40.7; **IR** (film) ν_{max} 3184, 2358, 1704, 1616, 1471, 1289, 1230, 1057, 918, 803, 757, 665 cm^{-1}; **HRMS** (ESI) m/z 332.1224 $[(M + Na)^+$; calculated for $[C_{19}H_{19}NO_3 + Na]^+$: 332.1257]; **MP** 175–181 °C.

3-(4-Methoxyphenyl)-3-methylindolin-2-one (8e) (Fig. 3)

Yellow gel, R_f = 0.43 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.27 (brs, 1H), 7.13–7.16 (m, 2H), 7.11 (dd, J = 8.96, 1.26 Hz, 1H), 7.02 (dt, J = 7.36, 0.48 Hz, 1H), 6.95 (td, J = 7.46, 0.99 Hz, 1H), 6.86 (d, J = 7.69 Hz, 1H), 6.74 (m, 2H), 3.67 (s, 3H), 1.70 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 182.9, 158.8, 140.6, 135.8, 132.6, 128.0, 127.8, 124.3, 122.7, 114.0, 110.4, 55.3, 52.2, 23.5; **IR** (film) ν_{max} 3190, 1693, 1616, 1512, 1470, 1107, 1030, 745 cm^{-1}; **HRMS** (ESI) m/z 276.1048 [(M + Na)$^+$; calculated for [$C_{16}H_{15}NO_2$ + Na]$^+$: 276.0995].

3-(3,4-Dimethoxyphenyl)-3-methylindolin-2-one (8f) (Fig. 3)

Yellowish gel, R_f = 0.39 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.14 (brs, 1H), 7.14 (td, J = 7.67, 1.23 Hz, 1H), 7.06 (d, J = 6.95 Hz, 1H), 6.97 (td, J = 7.53, 0.94 Hz, 1H), 6.88 (d, J = 7.71 Hz, 1H), 6.76–6.78 (m, 2H), 6.70–6.72 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 182.6, 148.9, 148.4, 140.5, 135.6, 133.0, 128.1, 124.3, 122.7, 119.0, 111.1, 110.33, 110.32, 55.9, 55.8, 52.3, 23.7; **IR** (film) ν_{max} 3306, 1697, 1616, 1516, 1469, 1257, 1026, 756 cm^{-1}; **HRMS** (ESI) m/z 284.1281 [(M + H)$^+$; calculated for [$C_{17}H_{18}NO_3$]$^+$: 284.1281].

3-(2,4-Dimethoxyphenyl)-3-methylindolin-2-one (8g) (Fig. 3)

Yellowish gel, R_f = 0.40 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.26 (brs, 1H), 7.40 (d, J = 8.58 Hz, 1H), 7.03 (td, J = 7.70, 1.30 Hz, 1H), 6.80 (d, J = 7.68 Hz, 1H), 6.72–6.77 (m, 1H), 6.48 (dd, J = 8.56, 2.54 Hz, 1H), 6.28 (d, J = 2.49 Hz, 1H), 3.70 (s, 3H), 3.34 (s, 3H), 1.63 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.4, 160.5, 158.1, 140.9, 136.6, 128.2, 127.2, 122.3, 122.1, 122.0, 109.5, 104.6, 100.0, 55.5, 55.4, 50.1, 23.7; **IR** (film) ν_{max} 3248, 2927, 1712, 1612, 1504, 1211, 1030, 740 cm^{-1}; **HRMS** (ESI) m/z 284.1309 [(M + H)$^+$; calculated for [$C_{17}H_{18}NO_3$]$^+$: 284.1281].

3-(2,5-Dimethoxyphenyl)-3-methylindolin-2-one (8h) (Fig. 3)

88% yield, white solid, R_f = 0.60 (50% EtOAc in hexane). **^{1}H NMR (400 MHz, $CDCl_3$)** δ: 8.52 (brs, 1H), 7.11–7.06 (m, 2H), 6.85–6.81 (m, 2H), 6.78–6.76 (m, 1H), 6.74–6.71 (m, 1H), 6.67–6.65 (m, 1H), 3.76 (s, 3H), 3.32 (s, 3H), 1.65 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.9, 151.4, 140.6, 136.2, 132.7, 130.9, 127.4, 122.5, 122.3, 115.1, 113.5, 112.4, 109.3, 56.4, 55.8, 50.4, 23.6; **IR** (film) ν_{max} 3245, 2929, 1713, 1618, 1497, 1471, 1423, 1327, 1282, 1229, 1111, 1045, 927, 847, 803, 757, 696, 665, 594 cm^{-1}; **HRMS** (ESI) m/z 306.1107 [(M + Na)$^+$; calculated for [$C_{17}H_{17}NO_3$ + Na]$^+$: 306.1101]; **MP** 156–160 °C.

3-Ethynyl-3-(4-methoxyphenyl)indolin-2-one (8i) (Fig. 3)

The product was obtained as a light yellow-colored solid, R_f = 0.78 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.30 (brs, 1H), 7.36 (m, 2H), 7.28 (m, 2H), 7.11 (td, J = 7.59, 0.88 Hz, 1H), 6.99 (d, J = 7.76 Hz, 1H), 6.87 (m, 2H), 3.80 (s, 3H), 2.57 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.1, 159.5, 140.5, 132.2, 129.5, 129.2, 128.0, 125.0, 123.6, 114.2, 110.7, 81.1, 72.9, 55.3, 52.1; **IR** (film) ν_{max} 3414, 2928, 1713, 1616, 1508, 1470, 1254, 1180, 825, 748, 636 cm^{-1}; **HRMS** (ESI) m/z 286.0830 [M + Na]$^+$; calculated for [$C_{17}H_{13}NO_2$ + Na]$^+$: 286.0838; **MP** 163–165 °C.

3-(3,4-Dimethoxyphenyl)-3-ethynylindolin-2-one (8j) (Fig. 3)

The product was obtained as a light yellow-colored solid, R_f = 0.65 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.99 (brs, 1H), 7.28 (m, 2H), 7.12 (t, J = 7.56 Hz, 1H), 7.06 (d, J = 2.15 Hz, 1H), 7.0 (d, J = 7.69 Hz, 1H), 6.87 (m, 1H), 6.8 (m, 1H), 3.86 (s, 6H), 2.57 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 176.6, 149.1, 149.0, 140.3, 132.0, 129.7, 129.3, 125.1, 123.6, 119.0, 111.1, 110.6, 110.4, 81.1, 72.9, 55.94, 55.92, 52.2; **IR** (film) ν_{max} 3429, 2924, 1713, 1616, 1512, 1470, 1261, 1138, 1022, 752 cm^{-1}; **HRMS** (ESI) m/z 316.0947 [M + Na]$^+$; calculated for [$C_{18}H_{15}NO_3$ + Na]$^+$: 316.0944; **MP** 154–156 °C.

3-(2,4-Dimethoxyphenyl)-3-ethynylindolin-2-one (8k) (Fig. 3)

The product was obtained as a yellow-colored solid, R_f = 0.68 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.32 (brs, 1H), 8.01 (d, J = 8.56 Hz, 1H), 7.19 (m, 1H), 6.96 (m, 3H), 6.63 (dd, J = 8.58, 2.48 Hz, 1H), 6.38 (d, J = 2.44 Hz, 1H), 3.83 (s, 3H), 3.46 (s, 3H), 2.6 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.0, 161.2, 157.3, 140.8, 132.5, 130.6, 128.3, 123.2, 122.8, 118.2, 109.9, 104.6, 99.9, 80.8, 74.1, 55.5, 55.4, 50.7; **IR** (film) ν_{max} 3275, 2928, 2855, 1724, 1612, 1504, 1470, 1207, 1034, 845, 756 cm^{-1}; **HRMS** (ESI) m/z 316.0955 [M + Na]$^+$; calculated for [$C_{18}H_{15}NO_3$ + Na]$^+$: 316.0944; **MP** 180–183 °C.

2-(2-(3-(4-Methoxyphenyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (8l) (Fig. 4)

The product was obtained as a light yellow-colored solid, R_f = 0.62 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.60 (brs, 1H), 7.73 (m, 2H), 7.63 (m, 2H), 7.31 (m, 3H), 7.15 (td, J = 7.72, 1.24 Hz, 1H), 6.97 (td, J = 7.6, 1.0 Hz, 1H), 6.93 (d, J = 7.76, 1H), 6.82 (m, 2H), 3.75 (s, 3H), 3.68 (m, 2H), 2.72 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.2, 167.9, 158.9, 140.9, 133.7, 131.9, 131.8, 131.1, 128.3, 127.9, 125.1, 123.0, 122.6, 114.0, 110.5, 55.2, 54.8, 34.9, 34.5; **IR** (film) ν_{max} 3511, 2897, 1791, 1705, 1615, 1539, 1278, 1044, 901, 751 cm^{-1}; **HRMS** (ESI) m/z 435.1321 [M + Na]$^+$; calculated for [$C_{25}H_{20}N_2O_4$ + Na]$^+$: 435.1315; **MP** 156–159 °C.

2-(2-(3-(2,4-Dimethoxyphenyl)-2-oxoindolin-3-yl)ethyl)-isoindoline-1,3-dione (8m) (Fig. 4)

The product was obtained as a light yellow solid, R_f = 0.59 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.11 (brs, 1H), 7.79 (m, 2H), 7.67 (m, 3H), 7.06 (td, J = 7.6, 1.4 Hz, 1H), 6.90 (m, 2H), 6.84 (td, J = 7.4, 0.92 Hz, 1H), 6.62 (dd, J = 8.68, 2.52 Hz, 1H), 6.40 (d, J = 2.52 Hz, 1H), 3.82 (m, 2H), 3.81 (s, 3H), 3.52 (s, 3H), 2.63 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 182.0, 168.1, 160.4, 158.3, 141.1, 133.9, 133.8, 132.1, 128.3, 127.5, 123.1, 122.9, 122.3, 120.8, 109.5, 104.7, 100.2, 55.5, 55.4, 53.4, 52.5, 33.8; **IR** (film) ν_{max} 3521, 2900, 1798, 1699, 1616, 1260, 1051, 925, 754 cm^{-1}; **LRMS** (ESI) m/z 441.1531 [M − H]$^+$; calculated for [$C_{26}H_{21}N_2O_5$]$^+$: 441.1445; **MP** 172–175 °C.

2-(2-(3-(3,4-Dimethoxyphenyl)-2-oxoindolin-3-yl)ethyl)-isoindoline-1,3-dione (8n) (Fig. 4)

The product was obtained as a light yellow solid, R_f = 0.58 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.86 (brs, 1H), 7.73 (m, 2H), 7.63 (m, 2H), 7.37 (d, J = 7.36 Hz, 1H), 7.17 (td, J = 7.68, 1.12 Hz, 1H), 7.07 (d, J = 2.2 Hz, 1H), 7.0 (td, J = 7.56, 0.96 Hz, 1H), 6.95 (d, J = 7.64 Hz, 1H), 6.85 (dd, J = 8.48, 2.24 Hz, 1H), 6.72 (d, J = 8.56 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.74 (m, 1H), 3.69 (m, 1H), 2.82 (m, 1H), 2.61 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.3, 168.0, 149.0, 148.4, 140.9, 133.8, 131.9, 131.7, 131.2, 128.3, 125.3, 123.0, 122.6, 119.2, 110.9, 110.6, 110.3, 55.9, 55.8, 55.0, 34.9, 34.4; **IR** (film) ν_{max} 3514, 3317, 2931, 1775, 1705, 1616, 1516, 1261, 1026, 756 cm^{-1}; **HRMS** (ESI) m/z 441.1463 $[M - H]^+$; calculated for $[C_{26}H_{21}N_2O_5]^+$: 441.1445; **MP** 92–95 °C.

2-(2-(3-(Furan-2-yl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (8o) (Fig. 4)

The product was obtained as a light yellow solid, R_f = 0.69 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.34 (brs, 1H), 7.74 (m, 2H), 7.65 (m, 2H), 7.33 (m, 2H), 7.10 (td, J = 7.74, 1.22 Hz, 1H), 6.90 (m, 2H), 6.29 (m, 1H), 6.22 (m, 1H), 3.81 (m, 1H), 3.69 (m, 1H), 2.82 (m, 1H), 2.73 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.2, 167.9, 151.7, 142.9, 140.6, 133.7, 131.9, 129.8, 128.6, 124.6, 123.0, 122.7, 110.4, 110.3, 107.1, 52.2, 34.0, 33.2; **IR** (film) ν_{max} 3391, 3210, 2920, 2851, 1713, 1678, 1470, 1404, 1377, 1192, 1115, 1076, 1030, 748, 718 cm^{-1}; **HRMS** (ESI) m/z 395.1007 $[M + Na]^+$; calculated for $[C_{22}H_{16}N_2O_4 + Na]^+$: 395.1002; **MP** 210–214 °C.

2-(2-(3-(4-(Methylthio)phenyl)-2-oxoindolin-3-yl)ethyl)-isoindoline-1,3-dione (8p) (Fig. 4)

The product was obtained as a light yellow gel, R_f = 0.54 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, 0.5 mL $CDCl_3$ + 0.1 mL DMSO-d_6) δ: 10.38 (brs, 1H), 7.67 (m, 4H), 7.1 (m, 6H), 6.86 (m, 2H), 3.51 (m, 2H), 3.22 (brs, H_2O), 2.47–2.52 (m, 2H), 2.34 (brs, 3H); **^{13}C NMR** (100 MHz, 0.5 mL $CDCl_3$ + 0.1 mL DMSO-d_6) δ: 179.1, 167.6, 142.3, 137.5, 136.6, 134.1, 131.9, 131.7, 128.3, 127.3, 126.3, 124.8, 123.0, 122.0, 110.5, 54.8, 34.5, 34.2, 15.4; **IR** (film) ν_{max} 3391, 3256, 1713, 1647, 1396, 1184, 999, 825, 768, 714 cm^{-1}; **HRMS** (ESI) m/z 429.1267 $[M + H]^+$; calculated for $[C_{25}H_{21}N_2O_3S]^+$: 429.1267.

2-(2-(3-(2,5-Dimethoxyphenyl)-2-oxoindolin-3-yl)ethyl)-isoindoline-1,3-dione) (8q) (Fig. 4)

White solid, R_f = 0.32 (50% EtOAc in hexane). **^{1}H NMR (400 MHz, $CDCl_3$)** δ: 8.45 (brs, 1H), 7.77–7.75 (m, 2H), 7.65–7.63 (m, 2H), 7.36 (d, J = 2.76 Hz, 1H), 7.06–7.02 (m, 1H), 6.86–6.72 (m, 5H), 3.86 (s, 3H), 3.83–3.79 (m, 2H), 3.42 (s, 3H), 2.67–2.48 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 181.1, 168.0, 154.2, 151.5, 141.0, 133.8, 133.6, 132.1, 129.7, 127.7, 123.1, 123.0, 122.4, 114.5, 114.0, 113.3, 109.4, 56.4, 56.1, 52.8, 33.8, 33.7; **IR** (film) ν_{max} 3277, 2928, 1771, 1714, 1618, 1560, 1498, 1470, 1400, 1371, 1230, 1187, 1027, 870, 719 cm^{-1}; **HRMS** (ESI) m/z 443.1609 $[(M + H)^+$; calculated for $[C_{26}H_{22}N_2O_5]^+$: 443.1601]; **MP** 180–184 °C.

1-(2-(3-(4-Methoxyphenyl)-2-oxoindolin-3-yl)ethyl) pyrrolidine-2,5-dione (8r) (Fig. 4)

The product was obtained as a white coloured gel, R_f = 0.72 (75% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.51 (brs, 1H), 7.26–7.22 (m, 4H), 7.07 (t, J = 7.44 Hz, 1H), 6.94 (d, J = 7.68 Hz, 1H), 6.79 (m, 2H), 3.73 (S, 3H), 3.61–3.40 (m, 2H), 2.73–2.54 (m, 2H), 2.50–2.33 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.5, 177.1, 159.0, 141.1, 131.9, 131.2, 128.5, 127.8, 125.0, 122.6, 114.0, 110.6, 55.3, 54.9, 35.4, 33.6, 28.0; **IR** (film) ν_{max} 3405, 2850, 1700, 1509, 1406, 1252, 1185, 1029, 911, 825, 753 cm^{-1}; **HRMS** (ESI) m/z 387.1294 $[(M + Na)^+$; calculated for $[C_{21}H_{20}N_2O_4 + Na]^+$: 387.1315].

1-(2-(3-(4-(Methylthio)phenyl)-2-oxoindolin-3-yl)ethyl)-pyrrolidine-2,5-dione (8s) (Fig. 4)

The product was obtained as a white-colored foam, R_f = 0.61 (75% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.97 (brs, 1H), 7.21–7.27 (m, 4H), 7.13 (m, 2H), 7.06 (t, J = 7.50 Hz, 1H), 6.93 (d, J = 7.73 Hz, 1H), 3.54–3.61 (m, 1H), 3.40–3.47 (m, 1H), 2.67–2.73 (m, 1H), 2.52–2.59 (m, 1H), 2.41–2.46 (m, 2H), 2.39 (s, 3H), 2.34–2.38 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.0, 177.1, 141.3, 137.9, 136.1, 131.6, 128.6, 127.2, 126.6, 125.0, 122.6, 110.7, 55.1, 35.3, 33.4, 28.0, 15.7; **IR** (film) ν_{max} 3258, 1698, 1619, 1472, 1404, 1164, 1098, 911, 816, 733, 669 cm^{-1}; **HRMS** (ESI) m/z 403.1086 $[(M + Na)^+$; calculated for $[C_{21}H_{20}N_2O_3S + Na]^+$: 403.1087].

1-(2-(3-(Furan-2-yl)-2-oxoindolin-3-yl)ethyl)pyrrolidine-2,5-dione (8t) (Fig. 4)

The product was obtained as a yellow-colored gel, R_f = 0.65 (75% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.64 (brs, 1H), 7.32 (d, J = 1.05 Hz, 1H), 7.29 (d, J = 7.45 Hz, 1H), 7.23 (td, J = 7.66, 1.00 Hz, 1H), 7.04 (t, J = 7.49 Hz, 1H), 6.93 (d, J = 7.77 Hz, 1H), 6.25 (dd, J = 3.24, 1.87 Hz, 1H), 6.13 (d, J = 2.89 Hz, 1H), 3.61–3.69 (m, 1H), 3.41–3.48 (m, 1H), 2.71–2.78 (m, 1H), 2.57–2.63 (dt, J = 14.02, 5.87 Hz, 1H), 2.35–2.47 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.3, 177.0, 151.8, 142.9, 141.0, 129.9, 128.9, 124.4, 122.7, 110.5, 110.3, 107.0, 52.3, 34.9, 31.8, 27.9; **IR** (film) ν_{max} 3447, 1698, 1615, 1468, 1406, 1172, 1011, 736, 430 cm^{-1}; **HRMS** (ESI) m/z 347.1018 $[(M + Na)^+$; calculated for $[C_{18}H_{16}N_2O_4 + Na]^+$: 347.1002].

3-(2-Hydroxy-5-methylphenyl)-3-phenylindolin-2-one (16a) (Scheme 13)

The product was obtained as a white solid, R_f = 0.61 (30% EtOAc in hexane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.79 (brs, 1H), 7.29–7.32 (m, 4H), 7.18–7.20 (m, 2H), 7.14 (m, 2H), 7.09 (dd, J = 8.12, 1.74 Hz, 1H), 7.04 (d, J = 7.79 Hz, 1H), 6.94 (d, J = 8.10 Hz, 1H), 6.82 (d, J = 1.83 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 183.3, 154.4, 140.1, 139.1, 132.9, 130.6, 129.6, 129.3, 128.9, 128.5, 127.6, 127.3, 126.5, 124.8, 123.5, 119.9, 111.0, 62.8, 20.7; **IR** (film) ν_{max} 3865, 3334, 1698,

1608, 1484, 1235, 1038, 812, 750 cm^{-1}; **HRMS** (ESI) *m*/*z* 316.1332 $[M + H]^+$; calculated for $[C_{21}H_{18}NO_2]^+$: 280.1332; **MP** 258–260 °C.

3-(5-(*tert*-Butyl)-2-hydroxyphenyl)-3-phenylindolin-2-one (16b) (Scheme 13)

The product was obtained as a white solid, R_f = 0.67 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.23 (brs, 1H), 8.91 (s, 1H), 7.21–7.29 (m, 5H), 7.14 (m, 2H), 7.08 (m, 2H), 7.05 (d, *J* = 2.22 Hz, 1H), 7.00 (d, *J* = 7.77 Hz, 1H), 6.94 (d, *J* = 8.37 Hz, 1H), 1.18 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.7, 154.2, 142.8, 140.2, 139.3, 133.0, 128.9, 128.6, 127.6, 127.1, 126.9, 126.5, 126.3, 124.2, 123.3, 119.3, 111.3, 63.2, 34.3, 31.5; **IR** (film) ν_{max} 3303, 1694, 1610, 1472, 1494, 1266, 1244, 821, 740 cm^{-1}; **HRMS** (ESI) *m*/*z* 358.1836 $[M + H]^+$; calculated for $[C_{24}H_{24}NO_2]^+$: 358.1802; **MP** 216–218 °C.

3-(4-Hydroxyphenyl)-3-phenylindolin-2-one (16c) (Scheme 13)

The product was obtained as a light yellow solid, R_f = 0.52 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 9.73 (brs, 1H), 8.60 (brs, 1H), 6.77–7.10 (m, 11H), 6.59 (m, 2H); **^{13}C NMR** (100 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 184.7, 161.1, 147.3, 145.7, 138.8, 137.2, 134.3, 133.1, 133.0, 132.7, 131.7, 130.7, 126.9, 120.1, 115.0, 67.0; **IR** (film) ν_{max} 3420, 1673, 1241, 1026, 1002, 826, 763 cm^{-1}; **HRMS** (ESI) *m*/*z* 302.1191 $[M + H]^+$; calculated for $[C_{20}H_{16}NO_2]^+$: 302.1176; **MP** 209–212 °C.

3-(2-Hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)indolin-2-one (16d) (Scheme 13)

The product was obtained as a light yellow solid, R_f = 0.58 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.75 (s, 1H), 7.22–7.26 (m, 1H), 7.03–7.11 (m, 5H), 6.97 (d, *J* = 7.29 Hz, 1H), 6.88 (d, *J* = 8.10 Hz, 1H), 6.78–6.81 (m, 3H), 3.73 (s, 3H), 2.18 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.7, 158.9, 154.2, 139.3, 133.3, 132.0, 130.5, 129.3, 127.8, 127.0, 125.1, 123.4, 119.6, 114.3, 111.1, 62.1, 55.2, 20.7; **IR** (film) ν_{max} 3273, 2928, 1696, 1618, 1549, 1251, 1182, 1035, 750 cm^{-1}; **HRMS** (ESI) *m*/*z* 346.1457 $[M + H]^+$; calculated for $[C_{22}H_{20}NO_3]^+$: 346.1438; **MP** 190–194 °C.

3-(5-(*tert*-Butyl)-2-hydroxyphenyl)-3-(4-methoxyphenyl)indolin-2-one (16e) (Scheme 13)

The product was obtained as a yellowish gel R_f = 0.62 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.86 (s, 1H), 7.21–7.27 (m, 2H), 7.03–7.11 (m, 5H), 6.98 (d, *J* = 7.76 Hz, 1H), 6.92 (d, *J* = 8.39 Hz, 1H), 6.79 (d, *J* = 8.82 Hz, 2H), 3.73 (s, 3H), 1.17 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.8, 158.9, 154.2, 142.7, 139.2, 133.4, 132.1, 128.5, 127.8, 127.0, 126.8, 126.3, 124.2, 123.2, 119.2, 114.3, 111.2, 62.5, 55.2, 34.3, 31.5; **IR** (film) ν_{max} 3305, 2962, 1697, 1617, 1510, 1472, 1250, 1183, 1035, 750 cm^{-1}; **HRMS** (ESI) *m*/*z* 388.1919 $[M + H]^+$; calculated for $[C_{25}H_{26}NO_3]^+$: 388.1907.

3-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)indolin-2-one (16f) (Scheme 13)

The product was obtained as a light yellowish gel, R_f = 0.49 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 9.67 (br, 1H), 8.56 (br, 1H), 6.96–7.01 (m, 4H), 6.89 (d, *J* = 8.55 Hz, 2H), 6.81 (m, 1H), 6.75 (d, *J* = 7.67 Hz, 1H), 6.61 (d, *J* = 8.61, 2H), 6.56 (d, *J* = 8.56 Hz, 2H), 3.58 (s, 3H); **^{13}C NMR** (100 MHz, 0.4 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 180.1, 158.4, 156.3, 141.0, 134.4, 134.3, 132.7, 129.4, 129.3, 127.8, 125.8, 122.0, 115.2, 113.5, 110.1, 61.4, 55.1; **IR** (film) ν_{max} 3473, 1651, 1250, 1181, 1026, 1004, 826, 764 cm^{-1}; **HRMS** (ESI) *m*/*z* 332.1290 $[M + H]^+$; calculated for $[C_{21}H_{18}NO_3]^+$: 332.1281.

3-(2-Hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-1-methylindolin-2-one (16g) (Scheme 13)

The product was obtained as a white solid, R_f = 0.58 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.31–7.35 (m, 1H), 7.13 (m, 2H), 7.04 (dd, *J* = 8.11, 1.56 Hz, 1H), 6.96–7.01 (m, 3H), 6.89 (d, *J* = 8.10 Hz, 1H), 6.78 (m, 3H), 3.73 (s, 3H), 3.33 (s, 3H), 2.18 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.1, 158.8, 154.7, 142.1, 132.7, 132.4, 130.5, 129.4, 128.9, 128.4, 127.6, 127.0, 125.0, 123.5, 119.9, 114.2, 109.3, 61.8, 55.2, 26.9, 20.7; **IR** (film) ν_{max} 3366, 2934, 1682, 1608, 1510, 1493, 1251, 1183, 1035, 910, 733 cm^{-1}; **HRMS** (ESI) *m*/*z* 360.1609 $[M + H]^+$; calculated for $[C_{23}H_{21}NO_3]^+$: 360.1594; **MP** 188–193 °C.

3-(5-(*tert*-Butyl)-2-hydroxyphenyl)-3-(4-methoxyphenyl)-1-methylindolin-2-one (16h) (Scheme 13)

The product was obtained as a white crystalline solid, R_f = 0.67 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.34 (td, *J* = 7.77, 1.53 Hz, 1H), 7.26 (m, 1H), 7.10 (m, 2H), 7.02 (d, *J* = 2.20 Hz, 1H), 6.90–6.98 (m, 4H), 6.77 (d, *J* = 8.77 Hz, 2H), 3.73 (s, 3H), 3.34 (s, 3H), 1.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.1, 158.8, 154.6, 142.3, 142.0, 132.8, 132.6, 128.4, 127.6, 126.9, 126.8, 125.9, 124.1, 123.3, 119.5, 114.2, 109.3, 62.1, 55.2, 34.2, 31.5, 26.9; **IR** (film) ν_{max} 3291, 2958, 1679, 1614, 1505, 1470, 1359, 1274, 1185, 1035, 820, 749 cm^{-1}; **HRMS** (ESI) *m*/*z* 402.2065 $[M + H]^+$; calculated for $[C_{26}H_{28}NO_3]^+$: 402.2064; **MP** 136–142 °C.

3-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-1-methylindolin-2-one (16i) (Scheme 13)

The product was obtained as a white solid, R_f = 0.51 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (td, *J* = 7.73, 0.93 Hz, 1H), 7.21 (d, *J* = 7.18 Hz, 1H), 7.15 (d, *J* = 8.84 Hz, 2H), 7.08 (t, *J* = 7.15 Hz, 1H), 6.99 (d, *J* = 8.69 Hz, 2H), 6.90 (d, *J* = 7.79 Hz, 1H), 6.78 (M, 3H), 6.62 (d, *J* = 8.63 Hz, 2H), 3.73 (s, 3H), 3.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.8, 158.8, 155.5, 142.7, 133.8, 133.2, 129.52, 129.50, 128.2, 125.9, 123.1, 115.5, 113.8, 108.7, 61.5, 55.3, 26.7; **IR** (film) ν_{max} 3370, 2933, 1695, 1610, 1512, 1470, 1373, 1302, 1252, 1182, 1034, 945, 830, 749 cm^{-1}; **HRMS** (ESI) *m*/*z* 346.1433

$[M + H]^+$; calculated for $[C_{22}H_{20}NO_3]^+$: 346.1438; **MP** 141–143 °C.

3-(4-Methoxyphenyl)-3-phenylindolin-2-one (16j) (Scheme 13)

The product was obtained as a light yellow-colored solid, R_f = 0.81 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.11 (br, s, 1H), 7.31 (m, 5H), 7.22 (m, 4H), 7.06 (td, J = 7.56, 1.0 Hz, 1H), 6.98 (d, J = 7.72 Hz, 1H), 6.86 (m, 2H), 3.8 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.6, 158.9, 141.9, 140.2, 133.9, 133.5, 129.6, 128.5, 128.3, 128.2, 127.3, 126.2, 122.8, 113.8, 110.4, 62.4, 55.3; **IR** (film) ν_{max} 3244, 2920, 2851, 1709, 1612, 1504, 1470, 1250, 1030, 752, 690 cm^{-1}; **HRMS** (ESI) m/z 316.1321 $[M + H]^+$; calculated for $[C_{21}H_{18}NO_2]^+$: 316.1332; **MP** 119–121 °C.

3,3-Bis(4-methoxyphenyl)indolin-2-one (16k) (Scheme 14)

The product was obtained as a yellow-colored solid, R_f = 0.82 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.39 (br, s, 1H), 7.23 (m, 6H), 7.06 (m, 1H), 6.96 (d, J = 7.76 Hz, 1H), 6.86 (m, 4H), 3.79 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 181.0, 171.2, 158.8, 140.3, 134.3, 133.9, 129.5, 128.1, 126.0, 122.7, 113.9, 110.5, 61.8, 55.3; **IR** (film) ν_{max} 3491, 2916, 1643, 1508, 1465, 1250, 1180, 1034, 826, 752 cm^{-1}; **HRMS** (ESI) m/z 368.1255 $[M + Na]^+$; calculated for $[C_{22}H_{19}NO_3 + Na]^+$: 368.1257; **MP** 93–96 °C.

3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)indolin-2-one (16l) (Scheme 14)

The product was obtained as a light yellow gel, R_f = 0.62 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.18 (br, s, 1H), 7.22 (m, 4H), 7.06 (td, J = 7.55, 0.82 Hz, 1H), 6.96 (d, J = 7.76 Hz, 1H), 6.90 (d, J = 1.92 Hz, 1H), 6.84 (m, 2H), 6.79 (m, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.8, 158.8, 148.8, 148.4, 140.2, 134.1, 133.9, 133.8, 129.5, 128.1, 126.1, 122.7, 120.7, 113.8, 112.1, 110.7, 110.5, 61.9, 55.9, 55.8, 55.2; **IR** (film) ν_{max} 3395, 2932, 2839, 1713, 1609, 1512, 1250, 1138, 1030, 814, 744 cm^{-1}; **HRMS** (ESI) m/z 398.1364 $[M + Na]^+$; calculated for $[C_{23}H_{21}NO_4 + Na]^+$: 398.1368.

3-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)indolin-2-one (16m) (Scheme 14)

The product was obtained as a light yellow solid, R_f = 0.72 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.14 (br, s, 1H), 7.18 (m, 4H), 7.02 (td, J = 7.56, 0.98 Hz, 1H), 6.92 (d, J = 7.74 Hz, 1H), 6.79 (m, 3H), 6.69 (m, 2H), 5.89 (m, 2H), 3.74 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.6, 158.9, 147.8, 146.9, 140.2, 135.6, 134.0, 133.5, 129.5, 128.2, 126.1, 122.8, 121.7, 113.9, 110.5, 109.3, 107.9, 101.1, 62.0, 55.3; **IR** (film) ν_{max} 3414, 2924, 2851, 1705, 1612, 1477, 1242, 1180, 1034, 933, 806 cm^{-1}; **HRMS** (ESI) m/z 382.1051 $[M + Na]^+$; calculated for $[C_{22}H_{17}NO_4 + Na]^+$: 382.1050; **MP** 182–184 °C.

3-(4-Methoxyphenyl)-3-(1*H*-pyrrol-2-yl)indolin-2-one (16n) (Scheme 14)

The product was obtained as a brownish gel, R_f = 0.45 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (s, 2H), 7.25 (d, J = 8.19 Hz, 1H), 7.21 (td, J = 7.70, 1.01 Hz, 1H), 7.09 (t, J = 7.52 Hz, 1H), 6.98 (m, 2H), 6.91 (d, J = 7.72 Hz, 1H), 6.83 (m, 1H), 6.77 (m, 2H), 6.16 (m, 1H), 6.06 (m, 1H), 3.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.5, 158.9, 140.0, 133.9, 133.6, 128.3, 127.8, 125.5, 123.1, 119.1, 114.1, 110.5, 108.9, 107.9, 57.4, 55.3; **IR** (film) ν_{max} 3799, 1625, 1460, 1281, 1250, 1090, 1020, 749 cm^{-1}; **HRMS** (ESI) m/z 305.1278 $[M + H]^+$; calculated for $[C_{19}H_{17}N_2O_2]^+$: 305.1285.

3-(4-Methoxyphenyl)-3-(1-tosyl-1*H*-pyrrol-2-yl)indolin-2-one (16o) (Scheme 14)

The product was obtained as a white solid, R_f = 0.35 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, 0.5 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 9.25 (m, 1H), 7.67 (brs, 1H), 6.95–7.15 (7H), 6.80 (d, J = 7.58 Hz, 1H), 6.53–6.63 (m, 4H), 6.03 (m, 1H), 5.59 (m, 1H), 3.63 (s, 3H), 2.23 (s, 3H); **^{13}C NMR** (100 MHz, 0.5 mL $CDCl_3$, 0.1 mL DMSO-D_6) δ 179.6, 159.1, 144.1, 142.29, 142.26, 136.4, 135.0, 131.6, 130.9, 129.5, 128.2, 126.7, 125.6, 125.3, 121.1, 120.6, 111.2, 110.2, 57.4, 55.2, 21.5; **IR** (film) ν_{max} 1696, 1614, 1489, 1360, 1244, 1164, 1076, 808, 677, 591 cm^{-1}; **HRMS** (ESI) m/z 459.1399 $[M + H]^+$; calculated for $[C_{26}H_{23}N_2O_4S]^+$: 459.1373; **MP** 245–249 °C.

3-(4-Methoxyphenyl)-3-(1-methyl-1*H*-indol-3-yl)indolin-2-one (16s) (Scheme 14)

The product was obtained as a yellow solid, R_f = 0.35 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.19 (brs, 1H), 7.32–7.30 (m, 3H), 7.16–7.25 (m, 4H), 6.90–7.00 (m, 3H), 6.81–6.83 (m, 2H), 6.78 (s, 1H), 3.76 (s, 3H), 3.66 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.8, 158.8, 140.2, 137.8, 134.8, 132.3, 129.1, 128.7, 128.0, 126.3, 125.6, 122.6, 121.8, 121.7, 119.1, 114.9, 113.8, 110.4, 109.4, 57.4, 55.2, 32.7; **IR** (film) ν_{max} 3255, 2933, 1710, 1618, 1471, 1250, 1034, 826, 741 cm^{-1}; **HRMS** (ESI) m/z 369.1598 $[M + H]^+$; calculated for $[C_{24}H_{21}N_2O_2]^+$: 369.1598; **MP** 201–202 °C.

General procedure for Friedel–Crafts alkylations of *N*-methylaniline and acetanilide with 5p and 5s (Scheme 15)

A flame-dried round-bottom flask was charged with **5p** or **5s** (0.3 mmol, 1.0 equiv.) in dichloroethane (2 mL) and Lewis acid was added to the reaction mixture at room temperature. To this reaction mixture *N*-methylaniline or acetanilide (0.3 mmol, 1.0 equiv.) was added and it was heated under reflux at 80 °C for the indicated time. Upon completion (judged by running TLC), the reaction mixture was cooled to room temperature. Most of the volatiles were evaporated under reduced pressure and the crude materials were directly purified by flash chromatography using EtOAc and petroleum ether to afford **17a–c**.

(±)-3-(4-Methoxyphenyl)-3-(4-(methylamino)phenyl)-indolin-2-one (±)-17a

The product was obtained as a yellowish gel, R_f = 0.46 (40% EtOAc in hexane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.21–7.24 (m, 4H), 7.09–7.12 (m, 2H), 7.06 (td, J = 7.60, 1.02 Hz, 1H), 6.95 (d, J = 7.64 Hz, 1H), 6.84 (m, 2H), 6.56 (m, 2H), 4.33 (br, 1H), 3.79 (s, 3H), 2.82 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 180.5, 158.7, 148.5, 140.0, 134.5, 134.2, 130.0, 129.5, 129.2, 127.9, 126.2, 122.7, 113.8, 112.3, 110.0, 61.6, 55.3, 30.7; **IR** (film) ν_{max} 3702, 1689, 1514, 1243, 1175, 650 cm^{-1}; **HRMS** (ESI) m/z 345.1604 $[M + H]^+$; calculated for $[C_{22}H_{21}N_2O_2]^+$: 345.1598.

(±)-*N*-(4-(3-(4-Methoxyphenyl)-2-oxoindolin-3-yl)-phenyl)-acetamide (±)-17b

The product was obtained as a white solid, R_f = 0.43 (50% EtOAc in hexane). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.21–7.24 (m, 4H), 7.09–7.12 (m, 2H), 7.06 (td, J = 7.60, 1.02 Hz, 1H), 6.95 (d, J = 7.64 Hz, 1H), 6.84 (m, 2H), 6.56 (m, 2H), 4.33 (br, 1H), 3.79 (s, 3H), 2.82 (s, 3H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 180.5, 158.7, 148.5, 140.0, 134.5, 134.2, 130.0, 129.5, 129.2, 127.9, 126.2, 122.7, 113.8, 112.3, 110.0, 61.6, 55.3, 30.7; **IR** (film) ν_{max} 3666, 2844, 2546, 2329, 2142, 1660, 1516, 1242, 749 cm^{-1}; **HRMS** (ESI) m/z 395.1370 $[M + Na]^+$; calculated for $[C_{23}H_{20}N_2O_3 + Na]^+$: 395.1366; **MP** 121–124 °C.

(±)-*N*-(4-(3-(4-Methoxyphenyl)-1-methyl-2-oxoindolin-3-yl)-phenyl)acetamide (±)-17c

The product was obtained as a white solid, R_f = 0.32 (30% EtOAc in hexane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (brs, 1H), 7.39 (m, 2H), 7.33 (td, J = 7.70, 1.09 Hz, 1H), 7.23–7.25 (m, 1H), 7.15–7.18 (m, 4H), 7.10 (td, J = 7.56, 0.72 Hz, 1H), 6.94 (d, J = 7.76 Hz, 1H), 6.80–6.84 (m, 2H), 3.78 (s, 3H), 3.30 (s, 3H), 2.14 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.0, 168.4, 158.8, 142.9, 137.7, 137.1, 133.7, 133.2, 129.7, 129.0, 128.3, 125.5, 122.9, 119.9, 113.8, 108.6, 61.4, 55.3, 26.7, 24.5; **IR** (film) ν_{max} 3729, 2848, 2631, 2333, 1675, 1517, 1258, 1184, 1035, 913, 818 cm^{-1}; **HRMS** (ESI) m/z 409.1531 $[M + Na]^+$; calculated for $[C_{24}H_{22}N_2O_3 + Na]^+$: 409.1523; **MP** 145–149 °C.

Synthesis of Boc-protected 2-oxindole (21)

An oven dried round-bottom flask was charged with **8l** (2.0 mmol, 1.0 equiv.) in MeOH (6 mL) and dichloromethane (4 mL). To this reaction mixture was added hydrazine hydrate (8.0 mmol, 4.0 equiv.) at room temperature and it was stirred overnight. Upon completion of the reaction (judged by running TLC), saturated K_2CO_3 solution (2 mL) was added to the reaction mixture and the whole mixture was taken in a separatory funnel. The mixture was extracted with dichloromethane (10 mL × 2). The organic layer was dried over anhydrous $MgSO_4$ and most of the volatile components were evaporated under reduced pressure. The crude primary amine was used for the next step without isolation.

The crude amine was taken in dichloromethane (8 mL) in an oven-dried round-bottom flask and triethylamine (4.0 mmol, 2.0 equiv.) was added to this at room temperature. DMAP (0.4 mmol, 0.2 equiv.) was added to the reaction mixture and finally $(Boc)_2O$ (4.0 mmol, 2.0 equiv.) in dichloromethane (1 mL) was added drop-wise by a syringe. The reaction mixture was stirred at room temperature for 24 h (TLC showed complete conversion of starting material). Water (10 mL) was added to the reaction mixture and extracted with dichloromethane (10 mL × 2). The organic layer was dried over anhydrous $MgSO_4$ and most of the volatile components were evaporated under reduced pressure. The crude product was purified by flash chromatography using EtOAc and petroleum ether to afford bis-Boc 2-oxindole (**21**).

***tert*-Butyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-3-(4-methoxyphenyl)-2-oxoindoline-1-carboxylate (21)**

The product was obtained as a colorless gel (773 mg, 80%), 80% yield, R_f = 0.52 (10% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.94 (d, J = 8.08 Hz, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.22 (m, 2H), 6.84 (m, 2H), 4.44 (br, s, 1H), 3.78 (s, 3H), 2.94 (m, 2H), 2.68 (m, 1H), 2.40 (m, 1H), 1.64 (s, 9H), 1.40 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.0, 155.5, 149.2, 139.7, 131.6, 130.0, 128.7, 128.0, 124.9, 124.86, 124.8, 115.4, 114.0, 84.4, 79.3, 55.3, 53.4, 38.0, 37.0, 28.3, 28.1; **IR** (film): ν_{max} 3392, 2979, 2932, 1762, 1732, 1607, 1512, 1480, 1368, 1347, 1290, 1252, 1151, 1101, 1034, 830, 754, 580 cm^{-1}; **HRMS** (ESI) m/z 500.2758 $[M + NH_4]^+$; calculated for $[C_{27}H_{34}N_2O_6 + NH_4]^+$: 500.2755.

Synthesis of bis-Boc-protected pyrroloindoline ±(7)

An oven dried round-bottom flask was charged with **21** (0.5 mmol, 1.0 equiv.) in THF (2 mL) and the reaction mixture was cooled to 0 °C. To this reaction mixture was added a methanolic solution of $NaBH_4$ (0.6 mmol, 1.2 equiv. in 2 mL of MeOH) at 0 °C, and it was stirred for 10 min (TLC showed complete consumption of starting material). Then, camphorsulfonic acid (CSA) (10.0 mmol, 20.0 equiv.) was added to the reaction mixture and stirring was continued for 4 h. Upon completion of the reaction, it was then diluted with 5 mL of EtOAc and quenched with saturated $NaHCO_3$ solution (5 mL). The whole mixture was taken in a separatory funnel and extracted with EtOAc (5 mL × 2). The organic layer was dried over $MgSO_4$ and most of the volatile components were evaporated under reduced pressure. The crude pyrroloindoline was purified by flash chromatography using EtOAc and petroleum ether to afford bis-Boc pyrroloindole ±(7).

Di-*tert*-butyl 3a-(4-methoxyphenyl)-3,3a-dihydropyrrolo[2,3-*b*]-indole-1,8(2*H*,8a*H*)-dicarboxylate ±(7)

The product was obtained as a white-colored gel (166 mg, 71%), as 3.4 : 1 rotameric ratio, R_f = 0.41 (10% EtOAc in hexane), **^{1}H NMR** (400 MHz, $CDCl_3$) (major rotamer) δ: 7.28–7.30 (m, 1H), 7.22–7.24 (m, 1H), 7.13–7.15 (m, 2H), 7.11–7.13 (m, 1H), 7.02–7.04 (m, 1H), 6.81–6.86 (m, 2H), 6.36 (s, 1H), 3.88–3.92 (m, 1H), 3.78 (s, 3H, –OMe), 2.95 (td, J =

11.1, 6.0 Hz, 1H), 2.49–2.58 (m, 2H), 1.58 (s, 9H, Boc), 1.51 (s, 9H, Boc); **^{1}H NMR** (400 MHz, $CDCl_3$) (minor rotamer) δ: 7.24–7.28 (m, 1H), 7.11–7.14 (m, 2H), 7.07–7.09 (m, 1H), 6.84–6.86 (m, 2H), 6.77 (m, 1H), 6.70 (d, J = 7.7 Hz, 1H), 5.45 (s, 1H), 3.78 (s, 3H, –OMe), 3.73–3.75 (m, 1H), 3.10–3.15 (m, 1H), 2.58–2.64 (m, 2H), 1.55 (s, 9H, Boc), 1.48 (s, 9H, Boc); **IR** (film) ν_{max} 3410, 2929, 1706, 1514, 1480, 1395, 1367, 1253, 1165, 1038, 890, 751 cm^{-1}; **HRMS** (ESI) m/z 467.2543 $[M + H]^+$; calculated for $[C_{27}H_{35}N_2O_5]^+$: 467.2540.

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