Synthesis P. Gandeepan et al. Special Topic

# Palladium-Catalyzed C–H Activation and Cyclization of Anilides with 2-Iodoacetates and 2-Iodobenzoates: An Efficient Method toward Oxindoles and Phenanthridones

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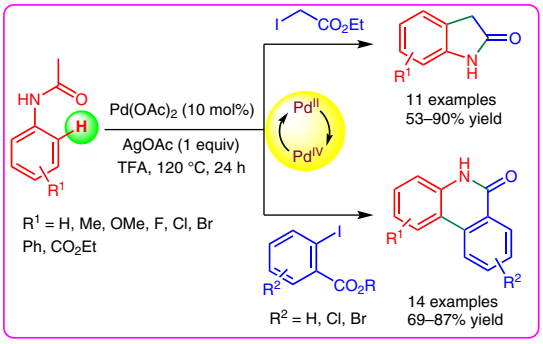


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**Abstract** A concise approach to the synthesis of oxindoles and phenanthridones from anilides is described. In the presence of catalytic amount of $Pd(OAc)_2$, 2-iodoacetates and 2-iodobenzoates can be used to functionalize *ortho* C–H bond of anilides, which subsequently undergo intramolecular cyclization to give the products. A possible reaction mechanism that involves a $Pd^{II}/Pd^{IV}$ catalytic cycle is proposed with the support of detailed mechanistic studies.

**Key words** palladium, C–H activation, alkylation, arylation, cyclization, oxindole, phenanthridone, heterocycle synthesis

Transition-metal-catalyzed hydrocarbon functionalization has become a powerful method in organic synthesis owing to their atom- and step-economy compared to the traditional methods.[1,2] In particular, palladium-catalyzed C–H activation and cyclization approach is emerging as a convenient tool for the synthesis of heterocycles.[3] Generally, the site selectivity of the C–H cleavage is controlled by a directing group (DG). However, often the introduction and removal of DG reduce the novelty of the transformation. Recently, our group has developed many methods for the synthesis of complex organic compounds that involve Pd-catalyzed C–H activation followed by cyclization with a directing functional group, which significantly reduce the synthetic steps and by-products.[4] As part of our continuing interest in the development of improved and novel C–H activation methods for highly useful compounds, we disclose in this report a palladium catalyzed C–H alkylation and cyclization route to the synthesis of oxindoles from anilides and 2-iodoacetates. It is worth noting that the C–H alkylation is much less familiar than that of C–H arylation.[5]

Oxindole (indolin-2-one) is an important heterocycle scaffold found as the core structure in many natural and bioactive compounds (Figure 1).[6] A variety of substituted oxindoles and their derivatives are recognized as a potential candidate for anticancer, antiviral, antibacterial, anti-inflammatory, and antihypertensive activities.[7] Furthermore, they are also known to be key intermediates in many heterocycles synthesis.[8] A number of methods have been developed for the synthesis of oxindoles, but most of them are based on the intramolecular cyclization of 2-haloacryloylanilides or acrylamides.[9] Palladium-catalyzed intramolecular amide α-arylation, and cyclocarbonylation of 2-aminostyrenes have also been known for the synthesis of oxindoles.[10] Nevertheless, considering the great biological applications of oxindoles, the development of new synthetic methods is sought after. The present method is concise, using readily available starting compounds and has a broad scope.

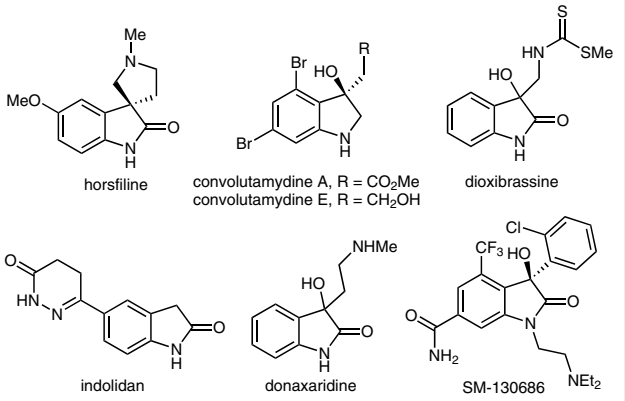
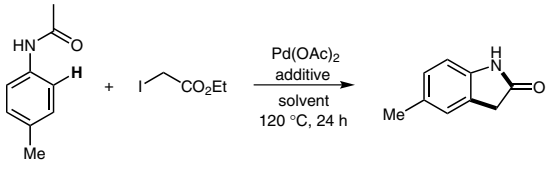



**Figure 1** Examples of oxindole cored natural and bioactive compounds

To begin the reaction optimization, we selected 4′-methylacetanilide (**1a**) and ethyl 2-iodoacetate (**2a**) as the starting substrates. At first several solvents were investigated for $Pd(OAc)_2$-catalyzed C–H activation and cyclization reaction of **1a** and **2a** with AgOAc as an additive (Table 1). Among the various solvents tested, TFA was found to be most suitable to give product **3a** in 88% isolated yield (Table 1, entry 10). The reaction was also effective with other silver additives; however, AgOAc was the most desired one.[11] The reaction gave 18% product yield in the absence of additives (entry 18). Finally, the controlled experiment revealed that no reaction occurred in the absence of $Pd(OAc)_2$ (entry 17).

**Table 1** Optimization Studies for the Pd-Catalyzed C–H Activation and Cyclization of 4′-Methylacetanilide (**1a**) and Ethyl 2-Iodoacetate (**2a**)[a]




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

| Entry | Solvent | Additive (equiv) | Yield (%)[b] |
|---|---|---|---|
| 1 | DCE | AgOAc (1) | 5 |
| 2 | AcOH | AgOAc (1) | 25 |
| 3 | 1,4-dioxane | AgOAc (1) | 32 |
| 4 | toluene | AgOAc (1) | – |
| 5 | DMF | AgOAc (1) | 64 |
| 6 | $EtCO_2H$ | AgOAc (1) | 11 |
| 7 | PivOH | AgOAc (1) | 21 |
| 8 | DMSO | AgOAc (1) | 7 |
| 9 | *t*-BuOH | AgOAc (1) | – |
| **10** | **TFA** | **AgOAc (1)** | **93 (88)[c]** |
| 11 | TFA | AgOAc (1) | 65[d] |
| 12 | TFA | $Ag_2O$ (0.5) | 88 |
| 13 | TFA | $Ag_2CO_3$ (0.5) | 72 |
| 14 | TFA | $AgNO_3$ (1) | 24 |
| 15 | TFA | NaOAc | 9 |
| 16 | TFA | $Na_2CO_3$ | 23 |
| 17 | TFA | AgOAc (1) | –[e] |
| 18 | TFA | – | 18 |
| 19 | TFA | AgOAc (1) | 66[f] |

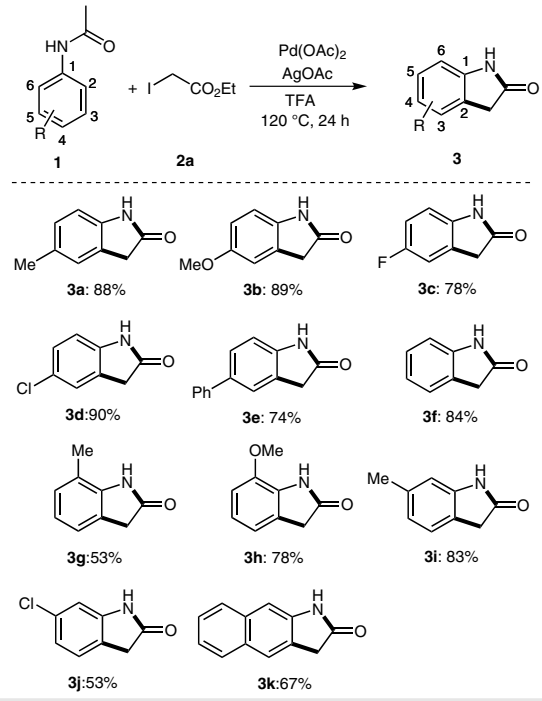
[a] All reactions were performed using **1a** (0.33 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (0.033 mmol, 10 mol%), and additive in solvent (3 mL) at 120 °C for 24 h.
[b] Yields were determined by the $^1H$ NMR integration method using mesitylene as the internal standard.
[c] Yield of isolated product.
[d] Reaction conducted at 100 °C.
[e] No $Pd(OAc)_2$ was used.
[f] $Pd(OAc)_2$ used: 5 mol%.

Next, the reactions of **1a** with 2-bromo- (**2b**) and 2-chloroacetates (**2c**) were examined (Scheme 1). The results revealed that **2b** gave **3a** in 32% yield and **2c** is ineffective. This is probably due to the difficulty of oxidative addition of the C–Br and C–Cl bonds to a palladium-centered reaction intermediate during the reaction.


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

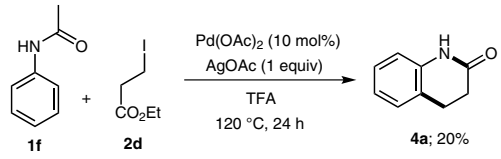
**Scheme 1** Reactivity of 2-haloacetates in the Pd-catalyzed C–H activation and cyclization reaction

With the optimized reaction conditions in hand, we then investigated the scope of the reaction (Scheme 2). A variety of *para*-substituted anilides were effectively transformed into the corresponding oxindole derivatives (products **3a**–**e**). Both the electron-donating group (EDG) and electron-withdrawing group (EWG) substituted substrates are tolerated under the reaction conditions. Sterically hindered *ortho*-substituted anilides are also effective to give



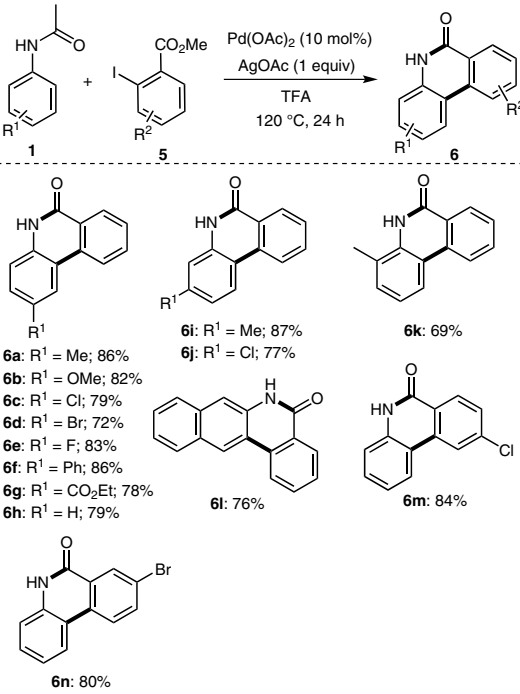

**Scheme 2** Scope of the Pd-catalyzed C–H activation and cyclization reaction of substituted anilides and 2-iodoacetate. *Reagents and conditions*: **1** (0.5 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (0.050 mmol, 10 mol%), AgOAc (0.50 mmol), in TFA (4 mL) at 120 °C for 24 h. Yields of isolated products are given.

the desired oxindole products in good yields (products **3g** and **3h**). The *meta*-substituted anilides regioselectively underwent C–H activation at the less hindered site (products **3i** and **3j**). The reaction also effective for *N*-(naphthalen-2-yl)acetamide to give the desired product **3k** in 67% yield. It is important to mention that compounds **3c** and **3j** were known to exhibit sedative activities.[12] Surprisingly, treatment of ethyl 3-iodopropanoate (**2d**) with *N*-phenylacetamide under the optimized reaction conditions gave 3,4-dihydroquinolinone (**4a**) in 20% yield (Scheme 3). Our attempt to improve the yield of this reaction was unsuccessful.




**Scheme 3** Synthesis of 3,4-dihydroquinolinone **4a**

Based on the results in Schemes 2 and 3, we think that it is possible to perform the C–H activation and cyclization reaction of **1** and 2-iodobenzoates to afford phenanthridones.[13] As an initial test of this hypothesis, we carried out the reaction using **1a** and methyl 2-iodobenzoate (**5a**). Gratifyingly, under the same conditions used in Schemes 1–3, the reaction proceeded smoothly to afford 2-methylphenanthridin-6(5*H*)-one (**6a**) in 86% isolated yield. Various substituted anilides and 2-iodobenzoates also proceeded efficiently to give the corresponding substituted phenanthridones in high yields (Scheme 4).




**Scheme 4** Scope of the Pd-catalyzed C–H activation and cyclization reaction of substituted anilides and 2-Iodobenzoates. *Reagents and conditions*: **1** (0.50 mmol), **5** (0.75 mmol), $Pd(OAc)_2$ (0.050 mmol, 10 mol%), AgOAc (0.50 mmol), in TFA (4 mL) at 120 °C for 24 h. Isolated yields are given.

To understand the mechanism of the catalytic reaction, we conducted a series of experiments as shown in Scheme 5. First, *N*-phenylacetamide was treated with a stoichiometric amount of $Pd(OAc)_2$ in TFA at 120 °C for three hours to give a palladacycle dimer **7** in 83% yield. The structure of **7** was thoroughly characterized by single crystal X-ray structure analysis (Figure 2).[14] Compound **7** was then treated with **2a** in TFA in the presence and absence of additives. The results revealed that the expected product **3f** was formed in all the three reaction conditions; however, with AgOAc the reaction was completed in less time and gave higher yields. The results imply that the $Ag^+$ ions act as the halide scavenger and thus prevent the coordination of halide ions and facilitate the reductive elimination step. Next, the reaction of **1a** and **2a** was conducted under the standard reaction conditions but at lower reaction temperature (80 °C). The reaction afforded products **3a** and **8a** in 21% and 38% yield, respectively. Compound **8a** is the alkylation product of **1a** by **2a**. Hence, it appears that in the present catalytic reaction, the *ortho* alkylation occurs prior to the cyclization. Treatment of **8a** in TFA at 120 °C for 12 hours afforded **3a** in 88% yield, which indicates that the intramolecular cyclization does not require Pd or Ag.

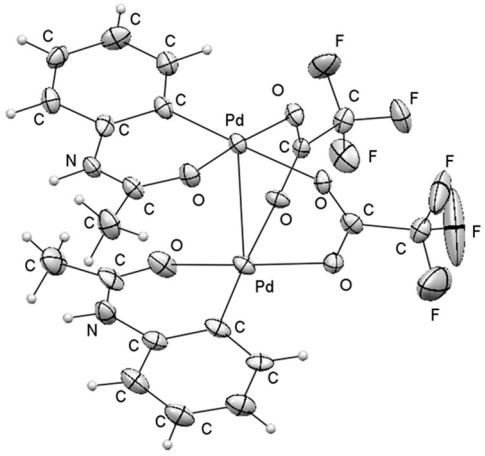
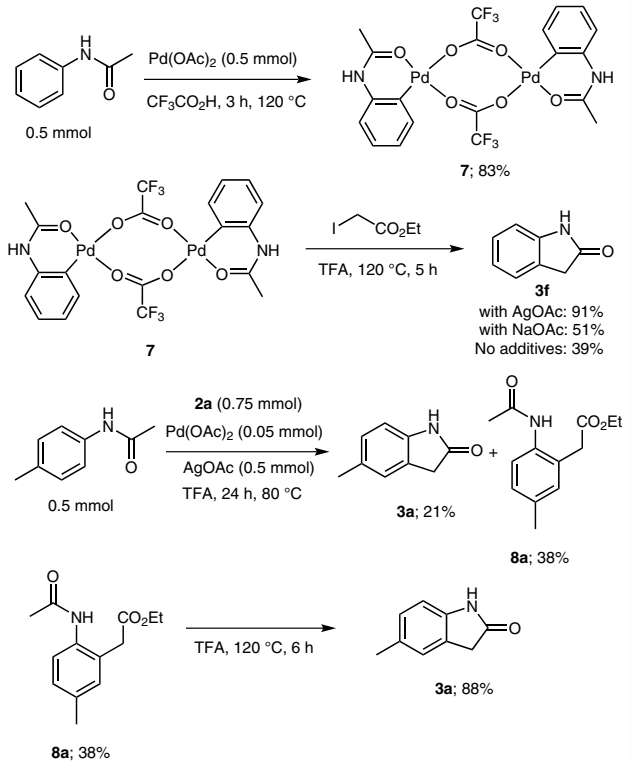


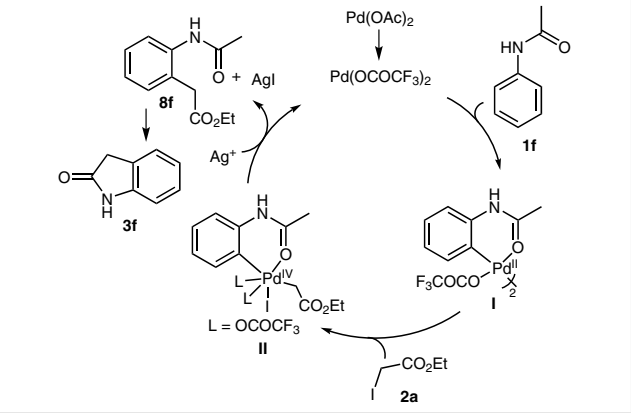

**Figure 2** ORTEP diagram of Pd dimer **7**

A plausible catalytic cycle to account for the Pd-catalyzed C–H activation reaction is proposed using **1f** and **2a** as the substrates on the basis of the above experimental results (Scheme 6). Initially, the coordination of anilide to $Pd^{II}$ species is followed by *ortho* C–H bond cleavage to give a six-membered palladacycle dimmer complex **I**. Next, oxidative addition of alkyl iodide to **I** to form $Pd^{IV}$intermediate **II**[4,15] Carbon–carbon bond forming reductive elimination of **II** af-




**Scheme 5** Mechanistic studies

fords *ortho*-alkylated anilide **8f**. Under the acidic reaction conditions, the intramolecular aminolysis of ester group provides the final oxindole product **3a**.[16]




**Scheme 6** Proposed reaction mechanism

In conclusion, we have successfully demonstrated a novel and concise approach to the synthesis of oxindoles and phenanthridones from anilides. The reaction tolerates a wide range of functional groups and affords good yields from both EDG and EWG substituted substrates. A possible reaction mechanism that involves $Pd^{IV}$ intermediate was proposed. The proposed mechanism was supported by the isolation of key organopalladium intermediate and other mechanistic studies.

Unless otherwise mentioned, all catalytic reactions were performed under a $N_2$ atmosphere on a dual-manifold Schlenk line and in oven-dried glassware. All commercially available reagents were purchased and used without further purification. NMR spectra ($^1H$ and $^{13}C$) were measured on a Varian MERCURY 400 MHz spectrometer. High-resolution (HR) mass data were measured with a JEOL AccuTOF-GCx spectrometer. IR spectra were recorded on a HORIBA FT-IR 720 using KBr plates.

### Anilides 1;[17] General Procedure

Arylamine (10.0 mmol; 1 equiv) was added to a round-bottom flask and fitted with a rubber septum. The flask was purged with $N_2$ and anhyd $CH_2Cl_2$ (3 mL/1 mmol) was added. $Ac_2O$ (12.0 mmol, 1.2 equiv) was added and the reaction was stirred at r.t. and monitored by TLC. Upon completion, the reaction mixture was washed with a sat. aq $Na_2CO_3$, the organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using EtOAc/*n*-hexane as eluent.

All anilides are known compounds.[17]

### Oxindoles 3 from Anilides 1 and Ethyl 2-Iodoacetate (2a); General Procedure

A seal-tube (15 mL) initially fitted with a septum containing anilide **1** (0.5 mmol), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol, 10 mol%), and AgOAc (83.5 mg, 0.5 mmol) was evacuated and purged with $N_2$ three times. TFA (4.0 mL), and ethyl 2-iodoacetate (**2a**; 160 mg, 0.75 mmol) were added to the system and the reaction mixture was stirred at 120 °C for 24 h. The mixture was cooled to r.t. and filtered through a short Celite pad and washed with $CH_2Cl_2$ several times. The filtrate was concentrated under vacuum and purified on a silica gel column using hexane/EtOAc as eluent to give the corresponding pure oxindole product **3**.

### Phenanthridones 6 from Anilides 1 and 2-Iodobenzoates 5; General Procedure

A seal-tube (15 mL) initially fitted with a septum containing anilide **1** (0.5 mmol), $Pd(OAc)_2$ (11.3 mg, 0.050 mmol, 10 mol%), and AgOAc (83.5 mg, 0.50 mmol) was evacuated and purged with $N_2$ three times. TFA (4.0 mL) and 2-iodobenzoate **5** (0.75 mmol) were added to the system and the reaction mixture was stirred at 120 °C for 24 h. The reaction mixture was cooled to r.t. and filtered through a short Celite pad and washed with $CH_2Cl_2$ several times. The filtrate was concentrated by vacuum and purified on a silica gel column using hexane/EtOAc as eluent to give the corresponding pure phenanthridone product **6**.

### Palladacycle 7 from $Pd(OAc)_2$ and *N*-Phenylacetamide (1f)

A seal-tube (15 mL) fitted with a septum containing $Pd(OAc)_2$ (167 mg, 0.74 mmol), *N*-phenylacetamide (**1f**; 100 mg, 0.74 mmol), and TFA (5.0 mL) was evacuated and purged with $N_2$ three times. The reaction mixture was stirred at 120 °C for 3 h. After cooling to r.t., the mixture was filtered through a short Celite pad and washed with $CH_2Cl_2$ several times. The filtrate was concentrated under vacuum and the residue was dissolved in $CHCl_3$. The addition of hexane to the

solution led to the precipitation of the corresponding palladium complex **7** as a brown solid. Recrystallization from $CHCl_3$ and hexane gave a single crystal suitable for X-ray analysis.

**5-Methylindolin-2-one (3a)**

Yield: 65 mg (88%); pale yellow solid; mp 172–175 °C.

IR (KBr): 2915, 1697, 1619, 1481, 1311, 1241, 1195, 817 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, NH), 7.01 (s, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 3.47 (s, 2 H), 2.28 (s, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 178.1 (C=O), 140.1 (C), 131.7 (C), 128.1 (CH), 125.3 (C), 125.3 (CH), 109.4 (CH), 36.3 ($CH_2$), 21.0 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_9NO$: 147.0684; found: 147.0683.

**5-Methoxyindolin-2-one (3b)**

Yield: 73 mg (89%); pale yellow solid; mp 176–178 °C.

IR (KBr): 2923, 1689, 1488, 1226, 1133, 1033, 786 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.08 (s, NH), 6.81 (s, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.72 (dd, *J* = 8.4, 2.4 Hz, 1 H), 3.74 (s, 3 H), 3.49 (s, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 177.8 (C=O), 155.6 (C), 136.1 (C), 126.6 (C), 112.5 (CH), 111.7 (CH), 110.0 (CH), 55.7 ($CH_3$), 36.7 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_9NO_2$: 163.0633; found: 163.0628.

**5-Fluoroindolin-2-one (3c)**

Yield: 59 mg (78%); pale yellow solid; mp 143–146 °C.

IR (KBr): 2915, 1689, 1481, 1311, 1265, 1187, 802, 740 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.54 (NH), 6.96–6.87 (m, 2 H), 6.81 (dd, *J* = 8.8, 4.0 Hz, 1 H), 3.53 (s, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 178.2 (C=O), 159.1 (d, $J_{C,F}$ = 237.9 Hz, C), 138.8 (C), 127.0 (d, $J_{C,F}$ = 9.1 Hz, C), 116.0 (C), 114.4 (d, $J_{C,F}$ = 23.5 Hz, CH), 112.6 (d, $J_{C,F}$ = 25.0 Hz, CH), 110.5 (d, $J_{C,F}$ = 8.3 Hz, CH), 36.9 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_6FNO$: 151.0433; found: 151.0428.

**5-Chloroindolin-2-one (3d)**

Yield: 75 mg (90%); pale brown solid; mp 195–197 °C.

IR (KBr): 2923, 2854, 1697, 1612, 1465, 809, 765 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, NH), 7.29–7.16 (m, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 3.51 (s, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 176.8 (C=O), 140.9 (C), 127.9 (CH), 127.9 (C), 126.8 (C), 125.0 (CH), 110.5 (CH), 36.1 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_6ClNO$: 167.0138; found: 167.0133.

**5-Phenylindolin-2-one (3e)**

Yield: 77 mg (74%); pale brown solid; mp 159–161 °C.

IR (KBr): 2923, 2854, 1727, 1689, 1481, 1311, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.70 (NH), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.44–7.39 (m, 4 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 7.6 Hz, 1 H), 3.59 (s, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 177.6 (C=O), 141.7 (C), 140.8 (C), 135.8 (C), 128.7 (2 CH), 126.9 (CH), 126.8 (CH), 126.7 (2 CH), 125.8 (C), 123.5 (CH), 109.8 (CH), 36.3 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}NO$: 209.0841; found: 209.0837.

**Indolin-2-one (3f)**

Yield: 56 mg (84%); pale yellow solid; mp 124–127 °C.

IR (KBr): 2923, 1727, 1681, 1619, 1473, 1334, 1234, 740 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, NH), 7.21–7.17 (m, 2 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 3.52 (s, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 178.3 (C=O), 142.6 (C), 127.8 (CH), 125.2 (C), 124.4 (CH), 122.1 (CH), 109.8 (CH), 36.2 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_7NO$: 133.0528; found: 133.0522.

**7-Methylindolin-2-one (3g)**

Yield: 39 mg (53%); pale brown solid; mp 203–205 °C.

IR (KBr): 2923, 1689, 1457, 1380, 1326, 1211, 748 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.70 (NH), 7.05–7.01 (m, 2 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 3.54 (s, 2 H), 2.29 (s, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 178.8 (C=O), 141.6 (C), 129.1 (CH), 124.8 (C), 122.2 (CH), 121.7 (CH), 119.4 (C), 36.7 ($CH_2$), 16.4 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_9NO$: 147.0684; found: 147.0679.

**7-Methoxyindolin-2-one (3h)**

Yield: 64 mg (78%); pale brown solid; mp 198–201 °C.

IR (KBr): 3178, 1689, 1627, 1496, 1465, 1288, 1211, 1072, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, NH), 6.95 (t, *J* = 8.0 Hz, 1 H), 6.82 (d, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 3.84 (s, 3 H), 3.53 (s, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 177.1 (C=O), 143.8 (C), 131.3 (C), 126.0 (C), 122.7 (CH), 116.8 (CH), 110.2 (CH), 55.6 ($CH_3$), 36.7 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_9NO_2$: 163.0633; found: 163.0628.

**6-Methylindolin-2-one (3i)**

Yield: 61 mg (83%); pale brown solid; mp 188–190 °C.

IR (KBr): 1658, 1621, 1457, 1334, 1249, 1203, 794 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.86 (s, NH), 7.11 (d, *J* = 8.0 Hz, 1 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 6.72 (s, 1 H), 3.47 (s, 2 H), 2.30 (s, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 178.6 (C=O), 142.6 (C), 137.9 (C), 124.1 (CH), 122.8 (CH), 122.1 (C), 110.7 (CH), 36.0 ($CH_2$), 21.5 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_9NO$: 147.0684; found: 147.0679.

**6-Chloroindolin-2-one (3j)**

Yield: 44 mg (53%); pale brown solid; mp 196–198 °C.

IR (KBr): 2915, 2854, 1697, 1619, 1457, 1064, 933, 771, 694 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.86 (s, NH), 7.11 (d, *J* = 8.0 Hz, 1 H), 6.97 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.89 (s, 1 H), 3.49 (s, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 177.4 (C=O), 143.4 (C), 133.6 (C), 125.4 (CH), 123.4 (C), 122.3 (CH), 110.3 (CH), 35.7 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_6ClNO$: 167.0138; found: 167.0132.

**1*H*-Benzo[*f*]indol-2(3*H*)-one (3k)**

Yield: 61 mg (67%); pale yellow solid; mp 172–175 °C.

IR (KBr): 2923, 2854, 1712, 1465, 863, 740 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, NH), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 7.65 (s, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.16 (s, 1 H), 3.65 (s, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.5 (C=O), 140.4 (C), 133.5 (C), 130.1 (C), 127.8 (CH), 126.9 (CH), 126.3 (CH), 126.0 (C), 124.2 (CH), 123.9 (CH), 104.9 (CH), 35.4 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_9NO$: 183.0684; found: 183.0679.

**3,4-Dihydroquinolin-2(1*H*)-one (4a)**

Yield: 15 mg (20%); pale yellow solid; mp 165–167 °C.

IR (KBr): 2923, 2854, 1681, 1388, 748 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, NH), 7.19-7.15 (m, 2 H), 6.99 (t, *J* = 7.2 Hz, 1 H), 6.78 (d, *J* = 7.6 Hz, 1 H), 2.97 (t, *J* = 7.2 Hz, 2 H), 2.64 (t, *J* = 7.2 Hz, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C=O), 137.3 (C), 128.2 (CH), 127.7 (CH), 123.9 (C), 123.4 (CH), 115.6 (CH), 29.9 ($CH_2$), 25.5 ($CH_2$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_9NO$: 147.0684; found: 147.0679

**2-Methylphenanthridin-6(5*H*)-one (6a)**

Yield: 90 mg (86%); pale yellow solid; mp 263–266 °C.

IR (KBr): 1658, 1612, 1558, 1504, 1465, 1365, 771 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 10.89 (s, NH), 8.57 (d, *J* = 7.0 Hz, 1 H), 8.27 (d, *J* = 8.0 Hz, 1 H), 7.99 (s, 1 H), 7.77 (t, *J* = 8.0 Hz, 1 H), 7.59 (t, *J* = 7.2 Hz, 1 H), 7.30–7.26 (m, 2 H), 2.46 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.8 (C=O), 134.7 (C), 133.8 (C), 132.6 (CH), 132.3 (C), 130.6 (CH), 128.2 (CH), 127.6 (CH), 125.7 (C), 122.7 (CH), 121.9 (CH), 118.4 (C), 116.5 (CH), 21.2 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}NO$: 209.0841; found: 209.0835.

**2-Methoxyphenanthridin-6(5*H*)-one (6b)**

Yield: 92 mg (82%); pale yellow solid; mp 227–230 °C.

IR (KBr): 1666, 1604, 1504, 1465, 1365, 1272, 1218, 1303, 763 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.55 (s, NH), 8.51 (d, *J* = 8.0 Hz, 1 H), 8.30 (d, *J* = 8.0 Hz,1 H), 7.84–7.79 (m, 2 H), 7.61 (t, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 9.2 Hz, 1 H), 7.11 (dd, *J* = 9.2, 2.4 Hz, 1 H), 3.85 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.0 (C=O), 155.4 (C), 134.7 (C), 133.2 (CH), 131.3 (C), 128.6 (CH), 128.1 (CH), 126.5 (C), 123.6 (CH), 118.9 (C), 118.4 (CH), 117.9 (CH), 106.8 (CH), 56.3 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}NO_2$: 225.0790; found: 225.0784.

**2-Chlorophenanthridin-6(5*H*)-one (6c)**

Yield: 90 mg (79%); pale yellow solid; mp 340–342 °C.

IR (KBr): 2861, 1689, 1612, 1473, 1365, 879, 809, 771 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.78 (s, NH), 8.53 (d, *J* = 8.0 Hz, 1 H), 8.44 (s, 1 H), 8.29 (d, *J* = 7.6 Hz, 1 H), 7.84 (t, *J* = 7.2 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.51 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.3 (C=O), 136.0 (C), 133.8 (C), 133.6 (CH), 130.1 (CH), 129.3 (CH), 128.1 (CH), 127.2 (C), 126.4 (C), 123.8 (CH), 123.5 (CH), 119.8 (C), 118.5 (CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_8ClNO$: 229.0294; found: 229.0289.

**2-Bromophenanthridin-6(5*H*)-one (6d)**

Yield: 98 mg (72%); pale yellow solid; mp 329–331 °C.

IR (KBr): 1673, 1349, 871, 763 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.77 (s, NH), 8.56 (s, 1 H), 8.53 (d, *J* = 8.0 Hz, 1 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 7.83 (t, *J* = 7.6 Hz, 1 H), 7.67–7.61 (m, 2 H), 7.28 (d, *J* = 8.4 Hz, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.3 (C=O), 136.3 (C), 133.7 (C), 133.6 (CH), 132.8 (CH), 129.3 (CH), 128.1 (CH), 126.4 (C), 126.4 (CH), 123.7 (CH), 120.2 (C), 118.8 (CH), 115.1 (C).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_8BrNO$: 272.9789; found: 272.9784.

**2-Fluorophenanthridin-6(5*H*)-one (6e)**

Yield: 88 mg (83%); pale yellow solid; mp 309–311 °C.

IR (KBr): 2861, 1689, 1504, 1265, 1149, 879, 763 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.71 (s, NH), 8.48 (d, *J* = 8.4 Hz, 1 H), 8.30 (d, *J* = 8.0 Hz, 1 H), 8.23 (d, *J* = 7.6 Hz, 1 H), 7.83 (t, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 6.0 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.4 (C=O), 157.8 (d, $J_{C,F}$ = 235.8 Hz, C), 133.5 (d, $J_{C,F}$ = 3.0 Hz, C), 133.1 (d, $J_{C,F}$ = 1.4 Hz, C), 132.8 (CH), 128.5 (CH), 127.4 (CH), 125.8 (C), 123.1 (CH), 118.8 (d, $J_{C,F}$ = 8.3 Hz, C), 117.7 (d, $J_{C,F}$ = 8.4 Hz, CH), 117.1 (d, $J_{C,F}$ = 23.8 Hz, CH), 109.1 (d, $J_{C,F}$ = 23.9 Hz, CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_8FNO$: 213.0590; found: 213.0584.

**2-Phenylphenanthridin-6(5*H*)-one (6f)**

Yield: 93 mg (86%); pale yellow solid; mp 321–323 °C.

IR (KBr): 1673, 1604, 1349, 1249, 871, 748 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.75 (s, NH), 8.71 (d, *J* = 8.0 Hz, 1 H), 8.63 (s, 1 H), 8.32 (d, *J* = 7.6 Hz, 1 H), 7.88–7.80 (m, 4 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.49–7.36 (m, 4 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.4 (C=O), 140.3 (C), 136.6 (C), 134.9 (2 × C), 133.4 (CH), 129.5 (2 × CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.4 (2 × CH), 126.4 (C), 123.7 (CH), 121.8 (CH), 118.6 (C), 117.4 (CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{13}NO$: 271.0997; found: 271.0992.

**Ethyl 6-Oxo-5,6-dihydrophenanthridine-2-carboxylate (6g)**

Yield: 104 mg (78%); pale yellow solid; mp 262–265 °C.

IR (KBr): 1673, 1612, 1558, 1357, 1249, 1110, 863 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.98 (s, NH), 8.84 (s, 1 H), 8.50 (d, *J* = 8.0 Hz, 1 H), 8.30 (d, *J* = 8.0 Hz, 1 H), 8.01 (dd, *J* = 8.4 Hz, *J* = 0.8 Hz, 1 H), 7.87 (t, *J* = 8.4 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 166.0 (C=O), 161 (C=O), 140.7 (C), 134.1 (C), 133.9 (CH), 130.7 (CH), 129.2 (CH), 128.2 (CH), 126.3 (C), 125.3 (CH), 124.3 (C), 123.4 (CH), 117.9 (C), 117.0 (CH), 61.4 ($CH_2$), 14.9 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{13}NO_3$: 267.0895; found: 267.0890.

**Phenanthridin-6(5*H*)-one (6h)**

Yield: 77 mg (79%); pale yellow solid; mp 290–291 °C.

IR (KBr): 1666, 1544, 1457, 1349, 717 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.47 (s, NH), 8.29 (t, *J* = 8.0 Hz, 2 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.37–730 (m, 2 H), 7.17 (t, *J* = 7.6 Hz, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.3 (C=O), 136.3 (C), 134.3 (C), 132.5 (CH), 129.2 (CH), 127.5 (2 CH), 125.6 (C), 122.6 (CH), 122.2 (CH), 122.0 (CH), 117.7 (C), 116.3 (CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_9NO$: 195.0684; found: 195.0679.

**3-Methylphenanthridin-6(5*H*)-one (6i)**

Yield: 91 mg (87%); pale yellow solid; mp 248–250 °C.

IR (KBr): 1650, 1604, 1550, 1465, 1357, 1149, 856, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 11.36 (s, NH), 8.56 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 8.4 Hz, 1 H), 7.20 (s, 1 H), 7.08 (dd, *J* = 8.0, 0.8 Hz, 1 H), 2.45 (s, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 163.2 (C=O), 139.8 (C), 136.0 (C), 135.0 (C), 132.7 (CH), 128.2 (CH), 127.2 (CH), 125.2 (C), 124.2 (CH), 122.6 (CH), 121.7 (CH), 116.7 (CH), 116.1 (C), 21.4 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}NO$: 209.0841; found: 209.0835.

**3-Chlorophenanthridin-6(5*H*)-one (6j)**

Yield: 88 mg (77%); pale yellow solid; mp 297–299 °C.

IR (KBr): 2854, 1666, 1604, 1558, 1388, 1234, 1149, 879, 763 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 11.76 (s, NH), 8.47 (d, *J* = 8.0 Hz, 1 H), 8.39 (d, *J* = 8.8 Hz, 1 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 7.85 (td, *J* = 8.4, 1.2 Hz, 1 H), 7.64 (t, *J* = 8.0 Hz, 1 H), 7.37 (s, 1 H), 7.27 (dd, *J* = 8.4, 2.0 Hz, 1 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 161.4 (C=O), 138.3 (C), 134.4 (C), 134.2 (C), 133.7 (CH), 129.0 (CH), 128.1 (CH), 126.1 (C), 126.0 (CH), 123.5 (CH), 122.8 (CH), 117.2 (C), 115.9 (CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_8ClNO$: 229.0294; found: 229.0289.

**4-Methylphenanthridin-6(5*H*)-one (6k)**

Yield: 72 mg (69%); pale yellow solid; mp 252–255 °C.

IR (KBr): 2923, 1658, 1604, 1481, 1442, 1365, 825, 748 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.07 (s, NH), 8.50 (d, *J* = 7.6 Hz, 1 H), 8.26 (d, *J* = 8.4 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.77 (t, *J* = 8.0 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 2.50 (s, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 162.0 (C=O), 135.0 (C), 134.2 (C), 132.9 (CH), 130.7 (CH), 128.2 (CH), 127.7 (CH), 125.4 (C), 123.2 (C), 122.3 (CH), 122.2 (CH), 121.0 (CH), 118.3 (C), 17.0 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}NO$: 209.0841; found: 209.0835.

**Benzo[*b*]phenanthridin-5(6*H*)-one (6l)**

Yield: 93 mg (76%); pale yellow solid; mp 331–333 °C.

IR (KBr): 1650, 1604, 1519, 1434, 1373, 833 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 11.74 (s, NH), 9.04 (s, 1 H), 8.67 (d, *J* = 8.0 Hz, 1 H), 8.32 (d, *J* = 7.6 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.91–7.85 (m, 2 H), 7.70 (s, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 161.5 (C=O), 135.4 (C), 134.7 (C), 133.9 (C), 133.6 (CH), 129.6 (C), 129.1 (2 CH), 128.3 (CH), 127.8 (CH), 127.1 (CH), 126.5 (C), 125.1 (CH), 123.7 (2 CH), 119.4 (C), 111.5 (CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{11}NO$: 245.0841; found: 245.0835.

**9-Chlorophenanthridin-6(5*H*)-one (6m)**

Yield: 96 mg (84%); pale yellow solid; mp 310–312 °C.

IR (KBr): 1673, 1349, 1280, 856, 740 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 11.75 (s, NH), 8.57 (s, 1 H), 8.41 (d, *J* = 8.0 Hz, 1 H), 8.27 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 8.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.23 (t, *J* = 7.2 Hz, 1 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 160.8 (C=O), 138.9 (C), 137.6 (C), 136.7 (C), 131.0 (CH), 130.3 (CH), 128.7 (CH), 125.0 (C), 124.4 (CH), 123.1 (CH), 123.0 (CH), 117.2 (C), 116.8 (CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_8ClNO$: 229.0294; found: 229.0289.

**8-Bromophenanthridin-6(5*H*)-one (6n)**

Yield: 110 mg (80%); pale yellow solid; mp 325–327 °C.

IR (KBr): 1666, 1596, 1465, 1403, 1349, 1257, 817, 725 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 11.8(s, NH), 8.44 (d, *J* = 8.4 Hz, 1 H), 8.36 (s, 1 H), 8.35 (d, *J* = 7.6 Hz, 1 H), 7.98 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.34 (d, *J* = 7.6 Hz, 1 H), 7.25 (t, *J* = 7.2 Hz, 1 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 160.3 (C=O), 137.1 (C), 136.2 (CH), 134.0 (C), 130.7 (CH), 130.3 (CH), 128.0 (C), 125.9 (CH), 124.0 (CH), 123.2 (CH), 121.7 (C), 117.5 (C), 116.9 (CH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_8BrNO$: 272.9789; found: 272.9784.

**Ethyl 2-(2-Acetamido-5-methylphenyl)acetate (8a)**

Yield: 45 mg (38%); white solid; mp 79–81 °C.

IR (KBr): 2985, 1735, 1658, 1527, 1295, 1257, 1157, 1033, 809, 709 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, NH), 7.63 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 6.99 (s, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 3.54 (s, 2 H), 2.27 (s, 3 H), 2.16 (s, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 172.7 (C=O), 168.6 (C=O), 135.0 (C), 133.9 (C), 131.2 (CH), 128.9 (CH), 125.8 (C), 124.9 (CH), 61.5 ($CH_2$), 38.8 ($CH_2$), 24.1 ($CH_3$), 20.7 ($CH_3$), 14.0 ($CH_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1203.

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## Supporting Information

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(14) CCDC 1443927 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk.

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