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Multicomponent Strategy to Indeno[2,1-*c*]pyridine and Hydroisoquinoline Derivatives through Cleavage of Carbon-Carbon Bond

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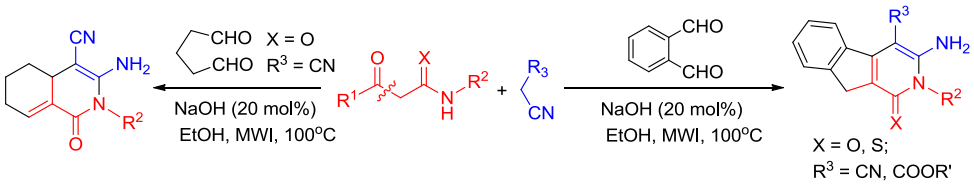


ABSTRACT: A concise and efficient three-component domino reaction has been developed for the synthesis of polyfunctionalized indenopyridine and hydroisoquinoline derivatives via the cleavage of a C–C bond under transition-metal-free conditions. This reaction provides facile access to complex nitrogen-containing heterocycles by simply mixing three common starting materials in EtOH in the presence of 20 mol% NaOH under microwave irradiation conditions.

INTRODUCTION

Nitrogen-containing heterocyclic skeletons can be found in a broad range of natural products and synthetic molecules, and many of these compounds have been reported to exhibit important biological activities.[1] Indenopyridines, for example, represent an important structural class of nitrogen-containing compounds, with numerous applications in biological and medicinal chemistry.[2] The 4-azafluorenone (5*H*-indeno[1,2-*b*]pyridine-5-one) alkaloids (Figure 1, structure **A**), which were originally isolated from plants belonging to the *Annonaceae* family, are a small group of alkaloids with interesting biological properties.[3] For example, 4-azafluorenone

derivatives have been reported to exhibit cytotoxic, phosphodiesterase inhibitory, adenosine A2a receptor antagonistic, coronary dilating, anti-inflammatory and calcium modulating activities.[4] It has also been reported that the pharmacological profiles of **B** and **C** are both similar to that of the antidepressant desmethylimipramine.[5] In 2003, Garrido et al.[6] identified haouamine A (Figure 1, structure **D**) during their chemical study of the ascidian *Aplidium haouarianum*. The cytotoxic activity of this compound was tested against several human tumor cell lines, where it was found it to be highly cytotoxic towards HT-29 cells, with an IC_{50} value of 0.1 mg/mL.[6] Although several studies have been published pertaining to the synthesis of indenopyridine derivatives,[7] the overall applicability of these methods has been limited by their use for toxic catalysts and solvents, narrow substrate scope, harsh reaction conditions and operational complexity. The development of new methods for the concise and efficient construction of haouamine A and its analogues is therefore highly desired.[8]

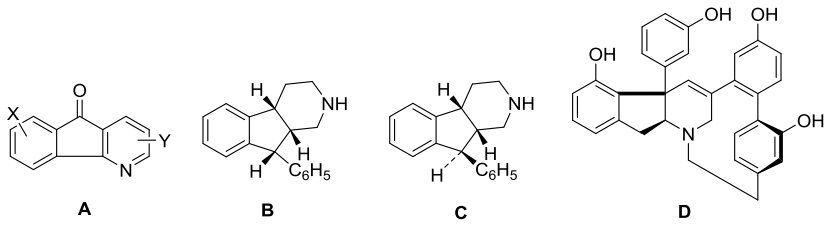


Figure 1. Naturally occurring and medicinally important indenopyridine derivatives

The development of concise and effective one-pot transformations for the construction of complex molecule libraries represents a major challenge in modern organic synthetic chemistry.[9] Several novel strategies have been developed to meet this challenge, and multicomponent domino reactions (MDRs), in particular, have received considerable attention. MDRs eliminate the need for the isolation and purification of multiple reaction intermediates, which can lead to an increase in the overall yield of the desired product and a reduction in the amount of waste, making MDRs

ideal candidates for the construction of complex molecules from readily available starting materials.[10] For these reasons, MDRs have been used as synthetic tools to deliver high levels of diversity in the construction of targeted compound libraries.[11] We recently reported the development of several new MDRs that provided rapid access to a variety of nitrogen-containing heterocyclic skeletons of chemical and pharmaceutical interest.[12] In this study, we have developed a novel three-component domino reaction for the synthesis of polyfunctionalized indenopyridine and hydroisoquinoline derivatives under transition-metal-free and microwave irradiation conditions. There are several attractive features to this newly developed MDR, including the novel strategy used for the construction of the indenopyridine skeleton and the direct C–C bond cleavage of a β-ketoamide, both of which were easily achieved without the need for multistep operations.

RESULTS AND DISCUSSION

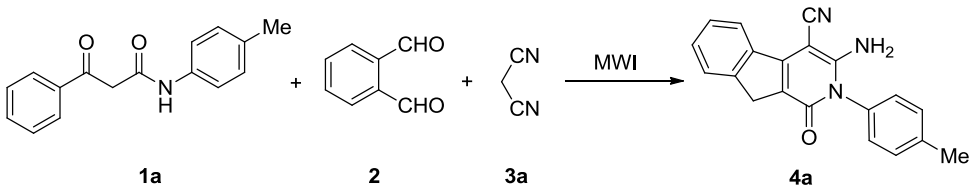
3-Oxo-3-phenyl-*N*-(*p*-tolyl)-propanamide (**1a**), phthalaldehyde (**2**) and malononitrile (**3a**) were selected as model substrates for this MDR to establish the feasibility of the strategy and to optimize the reaction conditions (Table 1). Initial optimization experiments revealed that the desired reaction did not proceed in ethanol under catalyst-free conditions (Table 1, entry 1). Pleasingly, however, the desired indeno[2,1-*c*]pyridine product **4a** was formed in 55% yield when the reaction was conducted in the presence of NaOH (10 mol%) in ethanol (Table 1, entry 2). The effect of different solvents on the yield of the reaction was investigated, and the results showed that the use of ethanol gave a much better yield than dimethylformamide, acetonitrile, toluene or tetrahydrofuran (Table 1, entries 2–6). Several bases were evaluated in the reaction, including NaOH, Cs_2CO_3, piperidine and pyridine, which were all added in catalytic quantities (10 mol%), and the reactions themselves were conducted in ethanol at 100 ℃ under microwave irradiation

conditions. The results of these screening experiments revealed that NaOH provided superior catalytic efficiency compared with all of the other catalysts tested (Table 1, entries 2 and 7–9).

Having identified NaOH as the best catalyst for the transformation, we proceeded to evaluate the amount of catalyst required for this reaction. The results of these screening experiments revealed that increasing the amount of NaOH from 10 to 20 mol% led to an increase in the yield from 55 to 85% (Table 1, entries 2 and 10). The use of a 20 mol% charge of NaOH in ethanol was determined to be most effective way of pushing this reaction towards completion, with the addition of even larger amounts of this catalyst failing to provide any further improvements in the yield. Last, the reaction was conducted at a variety of temperatures to identify the optimum reaction temperature, The reaction was carried out with 20 mol% NaOH in EtOH at 80, 90, and 100 ℃, with the desired product **4a** being formed in yields of 70, 79, and 85% (Table 1, entries 12–13 and 10), respectively. These results therefore revealed that the best reaction temperature was 100 ℃.

Taken together, the results of these screening experiments have shown that the optimum reaction conditions for this transformation are 20 mol% NaOH in EtOH at 100 ℃ under microwave irradiation conditions. It is noteworthy that the desired product was only formed in 71% yield when the same reaction was carried out in EtOH under refluxing conditions for 3 h without microwave irradiation (Table 1, entry 14). This result clearly shows that this reaction was occurring at a faster rate under microwave irradiation conditions.

Table 1. Optimization of the Reaction Conditions for the Synthesis of **4a**

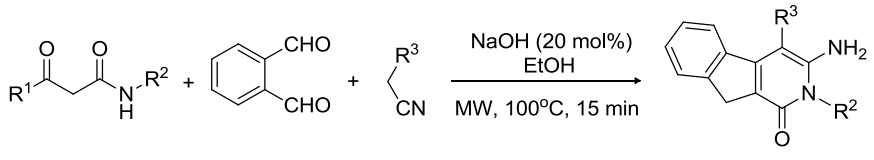


1a 2 3a 4a

entry	solvent	catalyst (mol%)	temp (^{o}C)	time (min)	isolated yield (%)
1	EtOH	No	100	15	Trace
2	EtOH	NaOH (10)	100	15	55
3	DMF	NaOH (10)	100	15	Trace
4	CH_3CN	NaOH (10)	100	15	24
5	toluene	NaOH (10)	100	15	Trace
6	THF	NaOH (10)	100	15	28
7	EtOH	Cs_2CO_3(10)	100	15	48
8	EtOH	Piperidine (10)	100	15	50
9	EtOH	Pyridine (10)	100	15	Trace
10	EtOH	NaOH (20)	100	15	85
11	EtOH	NaOH (30)	100	15	82
12	EtOH	NaOH (20)	80	15	70
13	EtOH	NaOH (20)	90	15	79
14	EtOH	NaOH (20)	reflux	180 (without MWI)	71

With the optimal reaction conditions in hand, we proceeded to evaluate the scope of this novel strategy using a variety of different β-ketoamides. As shown in Table 2, a variety of mono- and disubstituted phenyl rings bearing either electron-withdrawing or electron-donating substituents were well tolerated on the amide nitrogen of the β-ketoamide (i.e., R^2), with the corresponding products being formed in satisfactory yields. Furthermore, the replacement of malononitrile with ethyl cyanoacetate gave the corresponding ester substituted products in good yields (Table 2, entries 15–19).

Table 2. Synthesis of 1*H*-Indeno[2,1-*c*]pyridine-1-one Derivatives **4a-v**

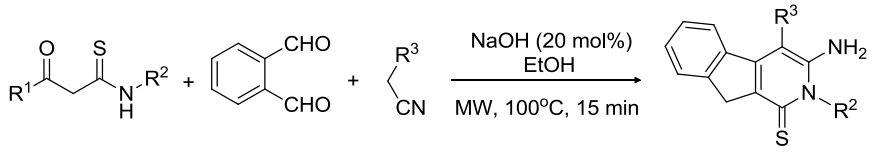


1 2 3 4

entry	product	R^1	R^2	R^3	isolated yield (%)
1	**4a**	Me	4-$CH_3C_6H_4$	CN	85
2	**4b**	Me	4-$(CH_3)_3CC_6H_4$	CN	83
3	**4c**	Me	4-$(CH_3)_2CHC_6H_4$	CN	79
4	**4d**	Me	4-$CH_3OC_6H_4$	CN	81
5	**4e**	Me	C_6H_5	CN	66
6	**4f**	Me	4-FC_6H_4	CN	70
7	**4g**	Me	4-ClC_6H_4	CN	73
8	**4h**	Me	4-BrC_6H_4	CN	78
9	**4i**	Me	4-$CF_3C_6H_4$	CN	77
10	**4j**	Me	3,5-$(CH_3)_2C_6H_3$	CN	73
11	**4k**	Me	3-Cl-4-$CH_3C_6H_3$	CN	69
12	**4l**	Me	$CH_3CH_2CH_2CH_2$	CN	64
13	**4m**	Ph	4-$CH_3OC_6H_4CH_2$	CN	75
14	**4n**	Ph	$C_6H_5CH_2$	CN	67
15	**4o**	Me	4-$CH_3OC_6H_4$	COOEt	68
16	**4p**	Me	4-$CH_3C_6H_4$	COOEt	62
17	**4q**	Me	4-FC_6H_4	COOEt	76
18	**4r**	Me	4-ClC_6H_4	COOEt	71
19	**4v**	Me	4-BrC_6H_4	COOEt	71

β-Ketothioamide (**5**) was also investigated as a substrate for this reaction, to further expand the scope of this transformation. Pleasingly, the desired 1*H*-indeno[2,1-*c*]pyridine-1-thione derivatives (**6a**–**g**) were obtained in satisfactory yields under the optimal reaction conditions.

Table 3. Synthesis of 1*H*-Indeno[2,1-*c*]pyridine-1-thione Derivatives **6a**–**g**



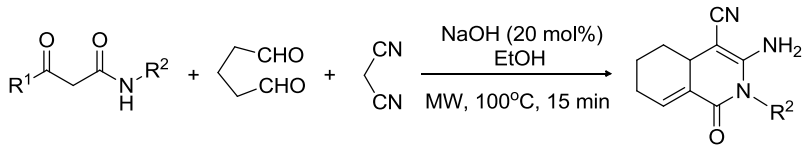
5 **2** **3** **6**

entry	product	R^1	R^2	R^3	isolated yield (%)
1	**6a**	Ph	C_6H_5	CN	78
2	**6b**	Ph	4-$CH_3C_6H_4$	CN	75
3	**6c**	Ph	3-$CH_3C_6H_4$	CN	72
4	**6d**	Ph	C_6H_5	COOEt	67
5	**6e**	Ph	4-$CH_3C_6H_4$	COOEt	66
6	**6f**	Ph	C_6H_5	COOMe	60
7	**6g**	Ph	4-$CH_3C_6H_4$	COOMe	58

Interestingly, the replacement of phthalaldehyde (**2**) with glutaraldehyde (**7**) gave the corresponding hydroisoquinolines (**8a–i**) in good yields when it was reacted with a series of

β-ketoamides (**1**) and malononitrile (**3**) under the optimal conditions (Table 4). In this particular case, the C–C double bond formed in a different position. However, none of the desired product was formed when β-ketothioamide (**5**) and ethyl cyanoacetate were used as the starting materials in this reaction.

Table 4. Synthesis of Hydroisoquinoline Derivatives **8a–i**



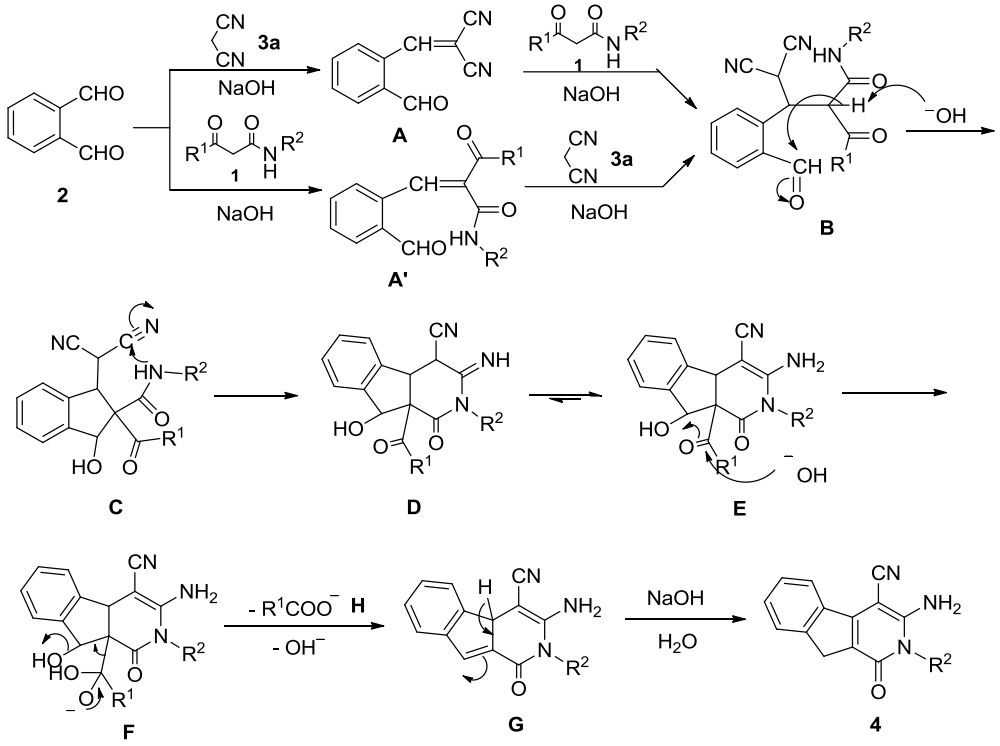
1 **7** **3** **8**

entry	product	R^1	R^2	isolated yield (%)
1	**8a**	Ph	4-$(CH_3)_3CC_6H_4$	75
2	**8b**	Ph	4-$(CH_3)_2CHC_6H_4$	74
3	**8c**	Ph	4-$CH_3CH_2OC_6H_4$	67
4	**8d**	Ph	4-$CH_3OC_6H_4$	71
5	**8e**	Me	4-$CH_3C_6H_4$	69
6	**8f**	Ph	3,5-$(CH_3)_2C_6H_3$	68
7	**8g**	Ph	3-Cl-4-$CH_3C_6H_3$	60
8	**8h**	Ph	4-FC_6H_4	52
9	**8i**	Ph	4-ClC_6H_4	50

The structures of these products were determined from their IR, ^{1}H NMR, ^{13}C NMR and HRMS spectra. The structures of compounds **4h**, **6a** and **8a** were further confirmed by X-ray diffraction analysis (see Supporting Information).

Based on the results of this study, we have proposed mechanism for the synthesis of compound **4**, which is shown in Scheme 1. The initial NaOH-catalyzed Knoevenagel condensation of phthalaldehyde (**2**) with malononitrile (**3**) or β-ketoamide (**1**) would give intermediate **A** or **A'**. The subsequent Michael addition of β-ketoamide (**1**) or malononitrile (**3**) to intermediate **A** or **A'** would give intermediate **B**, which could undergo an intramolecular nucleophilic addition reaction catalyzed by NaOH to form intermediate **C**. The cyclization and subsequent isomerization of Intermediate **C** would give intermediate **E**, which would undergo a NaOH-catalyzed C-C bond

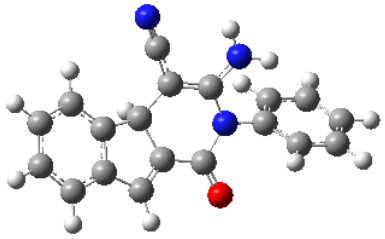
cleavage reaction to give intermediate **G** via the loss of its R^1COO^- (intermediate **H**) and hydroxy groups. In the last step, intermediate **G** would undergo a NaOH-catalyzed isomerization reaction to generate the desired product **4**. Notably, it would not be possible for the final isomerization reaction to occur when phthalaldehyde (**2**) was replaced by glutaraldehyde (**7**), which explains why intermediate **G** was obtained as the final product in these cases. Intermediate **H** could be detected by HPLC-MS in the reaction mixture after aciding with HCl to pH 1~2.



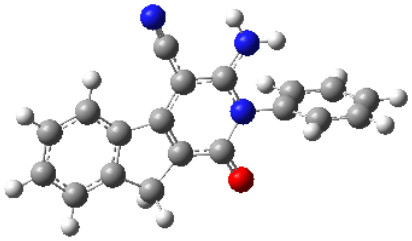
Scheme 1. Proposed Mechanism for the Synthesis of Compound **4**

Density functional theory calculations were carried out at the B3LYP/6-31G level to determine the energy associated with the different conformations of intermediate **G** and product **4e** and evaluate the energy barrier associated with the final isomerization in this system. The geometries of the two possible configurations were initially optimized and their lowest energy minima were then calculated (Figure 2). The results revealed that the most stable configuration of **4e** was 98.22 kJ/mol lower in energy than that of intermediate **G**. This result therefore suggested that

intermediate **G** could be readily transformed to the more stable product **4**.



Intermediate **G**: E = –970.758832 hartree



Product **4e**: E = –970.796244 hartree

Figure 2. Lowest energy minimum of intermediate **G** and product **4e**

CONCLUSION

In conclusion, we have developed a facile and efficient method for the synthesis of indenopyridine and hydroisoquinoline derivatives using a novel three-component domino reaction. This method allowed for the rapid construction of a diverse collection of polyfunctionalized indenopyridine and hydroisoquinoline derivatives in good yields by simply heating a mixture of a β-ketoamide, a phthalaldehyde (or glutaraldehyde) and a malononitrile (or alkyl 2-cyanoacetate) in EtOH under microwave irradiation conditions in the presence of 20 mol% NaOH.

EXPERIMENTAL SECTION

General Methods. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured by infrared detector (external sensor type) during microwave heating.

General Experimental Procedures for the Synthesis of Compounds 1. Compounds **1** were

synthesized according to the procedure reported in the literature[13]. A mixture of ethyl acetoacetate (10 mmol), an appropriate amine (10 mmol) and a catalytic amount of potassium *tert*-butoxide was taken into a 250 mL Pyrex beaker with an inverted glass funnel and irradiated in a domestic microwave oven for 3-5 min with 30 s pulses at 480 W while monitoring the progress of the reaction by TLC. On completion of the reaction, the reaction mixture was cooled and triturated with ice-cold ether. The product separated was filtered, washed with small portions of ice-cold ether and dried. Purification by recrystallization from ethanol afforded a colorless crystalline solid.

3-Oxo-N-(p-tolyl)butanamide ***(1a)***: white solid, yield 60%; mp 95-96 ℃ (Lit.[14] 95 °C); ^{1}H NMR (400 MHz, $CDCl_3$, *δ*, ppm) 9.10 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 3.54 (s, 2H), 2.90-2.83 (m, 1H), 2.27 (s, 3H), 1.22 (s, 3H) , 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, *δ*, ppm) 204.9, 163.9, 135.0, 134.2, 129.5, 120.3, 50.2, 31.0, 20.9; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{13}NNaO_2$ 214.0844 $[M+Na]^+$, found 214.0840.

N-(4-(tert-butyl)phenyl)-3-oxobutanamide ***(1b)***: colourless oil, yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$, *δ*, ppm) 9.08 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 3.56 (s, 2H), 2.29 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, *δ*, ppm) 205.0, 163.7, 147.6, 134.9, 125.8, 120.1, 50.1, 34.4, 31.4; HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{19}NNaO_2$ 256.1313 $[M+Na]^+$, found 256.1290.

N-(4-isopropylphenyl)-3-oxobutanamide ***(1c)***: white solid, yield 53%; mp 86-87 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, *δ*, ppm) 9.10 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 3.52 (s, 2H), 2.29 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, *δ*, ppm) 205.0, 163.8, 145.3, 135.2, 126.9, 120.4, 50.2, 33.6, 31.0, 24.0; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{17}NNaO_2$ 242.1157 $[M+Na]^+$, found 242.1155.

N-(4-methoxyphenyl)-3-oxobutanamide ***(1d)***: gray solid, yield 66%; mp 118-119 ℃ (Lit.[14] 118°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.00 (s, 1H), 7.41 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.53 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 205.2, 163.6, 156.6, 130.6, 122.0, 114.1, 55.5, 49.9, 31.1; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{13}NNaO_3$ 230.0793 $[M+Na]^+$, found 230.0796.

3-Oxo-N-phenylbutanamide ***(1e)***: white solid, yield 57%; mp 86-87 ℃ (Lit.[15] 86°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.23 (s, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.32-7.28 (m, 2H), 7.13-7.09 (m, 1H), 3.55 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 204.9, 164.2, 137.6, 129.0, 124.7, 120.3, 50.3, 31.0; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{11}NNaO_2$ 200.0687 $[M+Na]^+$, found 200.0687.

N-(4-fluorophenyl)-3-oxobutanamide ***(1f)***: white solid, yield 64%; mp 110-111 ℃ (Lit.[16] 110°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.21 (s, 1H), 7.46-7.43 (m, 2H), 6.97-6.92 (m, 2H), 3.52 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 204.9, 164.1, 159.5 (d, J_{CF} = 242.3 Hz), 133.6, 133.5, 122.1 (d, J_{CF} = 7.9 Hz), 115.6 (d, J_{CF} = 22.3 Hz), 50.0, 31.0; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{10}FNNaO_2$ 218.0593 $[M+Na]^+$, found 218.0595.

N-(4-chlorophenyl)-3-oxobutanamide ***(1g)***: white solid, yield 55%; mp 133-134 ℃ (Lit.[17] 132-133°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.26 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 3.59 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 205.3, 163.7, 136.1, 129.5, 129.0, 121.4, 49.6, 31.3; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{10}ClNNaO_2$ 234.0298 $[M+Na]^+$, found 234.0296.

N-(4-bromophenyl)-3-oxobutanamide ***(1h)***: white solid, yield 61%; mp 132-133 ℃ (Lit.[18] 132-135°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.26 (s, 1H), 7.52-7.50 (m, 2H), 7.30-7.28 (m,

2H), 3.59 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 205.3, 163.6, 136.1, 129.5, 129.0, 121.4, 49.5, 31.3; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{10}BrNNaO_2$ 277.9793 $[M+Na]^+$, found 277.9795.

3-Oxo-N-(4-(trifluoromethyl)phenyl)butanamide ***(1i)***: white solid, yield 51%; mp 155-156 ℃ (Lit.[19] 157°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.46 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 3.62 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 205.4, 163.7, 140.5, 130.6, 130.4, 126.5, 126.3, 126.2, 126.1, 122.7, 119.8, 114.5, 49.2, 31.4; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{10}F_3NNaO_2$ 268.0561 $[M+Na]^+$, found 268.0557

N-(3,5-dimethylphenyl)-3-oxobutanamide ***(1j)***: white solid, yield 64%; mp 81-82 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.02 (s, 1H), 7.16 (s, 2H), 6.75 (s, 1H), 3.54 (s, 2H), 2.29-2.27 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 205.0, 163.8, 138.7, 137.4, 126.4, 118.0, 50.2, 31.1, 21.3; HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{15}NNaO_2$ 228.1000 $[M+Na]^+$, found 228.0998.

N-(3-chloro-4-methylphenyl)-3-oxobutanamide ***(1k)***: white solid, yield 53%; mp 116-117 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.17 (s, 1H), 7.63 (s, 1H), 7.28 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 3.56 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 205.2, 163.6, 136.2, 134.4, 132.1, 131.0, 120.8, 118.5, 49.6, 31.2, 19.5; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{12}ClNNaO_2$ 248.0454 $[M+Na]^+$, found 248.0451.

N-butyl-3-oxobutanamide ***(1l)***: colourless oil, yield 48%; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 8.46 (s, 1H), 4.30(s, 2H), 3.11-3.06 (m, 2H), 1.80 (s, 3H), 1.46-1.40 (m, 2H), 1.32-1.27 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 170.5, 161.7, 81.7, 58.0, 42.5, 32.4, 19.9, 13.6; HRMS (ESI-TOF) *m/z* calcd for $C_8H_{15}NNaO_2$ 180.1000 $[M+Na]^+$, found 180.0996.

N-(4-methoxybenzyl)-3-oxo-3-phenylpropanamide ***(1m)***: white solid, yield 66%; mp 86-87 ℃;

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.96 (d, J = 8.4 Hz, 2H), 7.61-7.58 (m, 1H), 7.48-7.44 (m, 3H), 7.19 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.40-4.38 (m, 2H), 3.94 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 195.9, 165.8, 159.0, 136.2, 134.0, 130.0, 129.1, 128.9, 128.6, 114.1, 55.3, 45.4, 43.1; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}NNaO_3$ 306.1106 $[M+Na]^+$, found 306.1099.

N-benzyl-3-oxo-3-phenylpropanamide ***(1n)***: white solid, yield 60%; mp 84-85 ℃ (Lit.[20] 85-86°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.99 (d, J = 8.8 Hz, 2H), 7.65-7.63 (m, 1H), 7.52-7.48 (m, 2H), 7.35-7.26 (m, 6H), 4.51-4.49 (m, 2H), 3.98 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 195.9, 165.9, 138.0, 136.2, 134.1, 128.9, 128.7, 128.6, 127.7, 127.5, 45.4, 43.6; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{15}NNaO_2$ 276.1000 $[M+Na]^+$, found 276.0984.

N-(4-(tert-butyl)phenyl)-3-oxo-3-phenylpropanamide ***(1o)***: white solid, yield 64%; mp 132-133 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.32 (s, 1H), 8.01-7.98 (m, 2H), 7.61-7.58 (m, 1H), 7.51-7.44 (m, 4H), 7.35-7.26 (m, 2H), 4.09 (s, 2H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.2, 164.2, 147.6, 136.1, 135.0, 134.2, 128.9, 128.6, 125.8, 120.1, 45.9, 34.4, 31.4; HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{21}NNaO_2$ 334.1242 $[M+Na]^+$, found 334.1235.

N-(4-isopropylphenyl)-3-oxo-3-phenylpropanamide ***(1p)***: white solid, yield 68%; mp 130-131 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.28 (s, 1H), 8.01-7.98 (m, 2H), 7.63-7.60 (m, 1H), 7.50-7.48 (m, 4H), 7.18-7.16 (m, 2H), 4.09 (s, 2H), 2.89-2.86 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 163.9, 145.3, 136.1, 135.3, 134.2, 128.9, 128.6, 126.9, 120.4, 45.7, 33.6, 24.0; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{19}NNaO_2$ 320.1085 $[M+Na]^+$, found 320.1080.

N-(4-ethoxyphenyl)-3-oxo-3-phenylpropanamide ***(1q)***: white solid, yield 59%; mp

139-140 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.18 (s, 1H), 8.00-7.98 (m, 2H), 7.61-7.59 (m, 1H), 7.50-7.44 (m, 4H), 6.84-6.81 (m, 2H), 4.07 (s, 2H), 4.01-3.96 (m, 2H), 1.39 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 163.8, 155.9, 136.1, 134.2, 130.6, 128.9, 128.6, 122.0, 114.7, 63.7, 45.6, 14.8; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}NNaO_3$ 306.1106 $[M+Na]^+$, found 306.1098.

N-(4-methoxyphenyl)-3-oxo-3-phenylpropanamide ***(1r)***: white solid, yield 62%; mp 123-124 ℃ (Lit.[21] 123°C); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 10.1 (s, 1H), 8.039 (d, J = 7.2 Hz, 2H), 7.67-7.64 (m, 2H), 7.57-7.52 (m, 4H), 6.94-6.88 (m, 2H), 4.14 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 195.1, 165.3, 155.8, 136.8, 134.0, 132.7, 129.2, 128.9, 125.7, 121.1, 55.6, 48.4; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{15}NNaO_3$ 308.0721 $[M+Na]^+$, found 308.0734.

N-(3,5-dimethylphenyl)-3-oxo-3-phenylpropanamide ***(1s)***: white solid, yield 56%; mp 113-114 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.30 (s, 1H), 7.97-7.94 (m, 2H), 7.59-7.55 (m, 1H), 7.45-7.41 (m, 2H), 7.21-7.18 (m, 2H), 6.74 (s, 1H), 4.04 (s, 2H), 2.26 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 195.9, 164.6, 138.6, 137.5, 136.1, 134.1, 128.9, 128.6, 126.4, 118.1, 46.2, 21.3; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}NNaO_2$ 306.0929 $[M+Na]^+$, found 306.0911.

N-(3-chloro-4-methylphenyl)-3-oxo-3-phenylpropanamide ***(1t)***: white solid, yield 58%; mp 141-142 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 9.36 (s, 1H), 8.01 (d, J = 7.2 Hz, 2H), 7.68-7.62 (m, 2H), 7.53-7.49 (m, 2H), 7.34-7.32 (m, 1H), 7.16-7.14 (m, 1H), 4.10 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.5, 163.8, 136.3, 136.0, 134.5, 132.1, 131.0, 129.0, 128.6, 120.8, 118.4, 45.2, 19.5; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{14}NNaO_2$ 326.0382 $[M+Na]^+$, found

326.0356.

N-(4-fluorophenyl)-3-oxo-3-phenylpropanamide ***(1u)***: white solid, yield 63%; mp 153-154 ℃ (Lit.[22] 153°C); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 10.28 (s, 1H), 8.02 (d, J = 7.6 Hz, 2H), 7.67-7.60 (m, 3H), 7.57-7.51 (m, 2H), 7.17-7.13 (m, 2H), 4.16 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 195.0, 165.7, 158.5 (J = 238Hz), 136.7, 134.1, 129.3, 128.8, 125.8, 121.3, 121.2, 115.8 (J = 22Hz), 48.4; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{12}FNNaO_2$ 296.0521 $[M+Na]^+$, found 296.0510.

N-(4-chlorophenyl)-3-oxo-3-phenylpropanamide ***(1v)***: white solid, yield 66%; mp 158-159 ℃ (Lit.[23] 157-158°C); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 10.35 (s, 1H), 8.01 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.58-7.56 (m, 3H), 7.52-7.48 (m, 3H), 4.17 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 194.9, 166.0, 138.8, 136.7, 134.1, 132.1, 129.3, 128.8, 125.8, 121.4, 48.6; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{12}ClNNaO_2$ 312.0226 $[M+Na]^+$, found 312.0214.

Representative Synthesis of 4: 3-Amino-1-oxo-2-(*p*-tolyl)-2,9-dihydro-*1H*-indeno[2,1-*c*] pyridine-4-carbonitrile (4a). 3-Oxo-3-phenyl-*N*-(*p*-tolyl)propanamide **1a** (1.0 mmol), phthalaldehyde **2** (1.0 mmol) and malononitrile **3a** (1.0 mmol) were placed in a 5 mL Initiator reaction vial, followed by NaOH (0.2 mmol) and EtOH (2 mL). The reaction vial was then sealed and prestirred for 20 s before being irradiated in the microwave (time, 15 min; temperature, 100 ℃; absorption level, high; fixed hold time) until TLC (2:1 mixture of petroleum ether and ethyl acetate) revealed the complete consumption of the starting materials. The reaction mixture was then cooled to room temperature to give a precipitate, which was collected by Büchner filtration. The solid material was then purified by recrystallization from 95% EtOH to afford the

desired product **4a** as a gray solid, 0.266 g, yield 85%; mp 242-243 ℃; IR (KBr, *v*, cm^{-1}) 3433, 3173, 2922, 2199, 1669, 1586, 1511, 1423, 1314, 1294, 1197, 1102, 822, 778, 753, 645; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.21-8.18 (m, 1H), 7.66-7.64 (m, 1H), 7.51-7.48 (m, 2H), 7.39-7.37 (m, 2H), 7.21-7.19 (m, 2H), 6.74 (s, 2H), 3.65 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.3, 157.7, 148.5, 146.1, 139.4, 139.0, 132.8, 131.2, 129.5, 129.1, 127.5, 125.8, 122.3, 118.0, 116.9, 64.7, 35.0, 21.3; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{16}N_3O$ 314.1293 $[M+H]^+$, found 314.1297.

3-Amino-2-(4-(tert-butyl)phenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4b)***: Yellow solid, 0.295 g, yield 83%; mp 206-208 ℃; IR (KBr, *v*, cm^{-1}) 3412, 3316, 3235, 2963, 2196, 1675, 1618, 1521, 1400, 1385, 1112, 1051, 748, 715. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.21-8.19 (m, 1H), 7.67-7.65 (m, 1H), 7.60-7.58(m, 2H), 7.51-7.49 (m, 2H), 7.24-7.22 (m, 2H), 6.73 (s, 2H), 3.66 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.2, 157.5, 148.5, 146.1, 139.9, 139.0, 135.2, 131.3, 129.5, 127.5, 126.7, 125.8, 122.3, 118.0, 116.9, 64.6, 56.5, 35.0, 21.2, 19.0; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{22}N_3O$ 356.1763 $[M+H]^+$, found 356.1792.

3-Amino-2-(4-isopropylphenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4c)***: Brown solid, 0.270 g, yield 79%; mp 235-236 ℃; IR (KBr, *v*, cm^{-1}) 3459, 3316, 3210, 2946, 2869, 2201, 1682, 1621, 1568, 1528, 1153, 1126, 1018, 828, 747, 716; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.22-8.19 (m, 1H), 7.66-7.64 (m, 1H), 7.52-7.49(m, 2H), 7.46-7.43 (m, 2H), 7.24-7.21 (m, 2H), 6.72 (s, 2H), 3.65 (s, 2H), 3.00-2.97 (m, 1H) , 1.29-1.26 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.3, 157.7, 149.9,148.5, 146.1, 138.9, 133.0, 129.4, 129.1, 128.5, 127.5, 125.7, 122.3, 118.0, 116.9, 64.8, 35.0, 33.7, 24.2; HRMS (ESI-TOF) *m/z* calcd for

$C_{22}H_{20}N_3O$ 342.1606 $[M+H]^+$, found 342.1617.

3-Amino-2-(4-methoxyphenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4d)***: Gray solid, 0.266 g, yield 81%; mp 208-209 ℃; IR (KBr, *v*, cm^{-1}) 3430, 3014, 2972, 2936, 2840, 2203, 1672, 1503, 1439, 1422, 1304, 1251, 1176, 1102, 1027, 832, 778, 754, 640; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.20-8.18 (m, 1H), 7.66-7.64 (m, 1H), 7.51-7.48(m, 2H), 7.24-7.22 (m, 2H), 7.12-7.10 (m, 2H), 6.80 (s, 2H) , 3.83 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 160.2, 159.5, 157.9, 148.5, 146.1, 139.0, 130.5, 129.5, 127.8, 127.5, 125.8, 122.3, 118.0, 116.8, 115.8, 64.6, 55.9, 35.0; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{15}N_3O_2$ 328.1086 $[M-H]^-$, found 328.1085.

3-Amino-1-oxo-2-phenyl-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4e)***: Yellow solid, 0.197 g, yield 66%; mp 257-259 ℃ (Lit.[24] 263-265 °C); IR (KBr, *v*, cm^{-1}) 3451, 3307, 2945, 2845, 2344, 2208, 1674, 1629, 1525, 1450, 1384, 1290, 1126, 1074, 959, 753; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.21-8.19 (m, 1H), 7.67-7.65 (m, 1H), 7.61-7.49 (m, 5H), 7.34-7.32 (m, 2H), 6.80 (s, 2H), 3.66 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.3, 157.6, 148.6, 146.1, 138.9, 135.5, 130.6, 129.9, 129.5, 129.5, 127.5, 125.8, 122.3, 118.0, 116.9, 64.8, 35.0; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{12}N_3O$ 298.0980 $[M-H]^-$, found 298.0990.

3-Amino-2-(4-fluorophenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4f)***: Yellow solid, 0.222 g, yield 70%; mp 244-246 ℃; IR (KBr, *v*, cm^{-1}) 3453, 3340, 2897, 2201, 1667, 1618, 1508, 1295, 1227, 1155, 1094, 1050, 844, 752, 717, 663; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.20-8.18 (m, 1H), 7.66-7.64 (m, 1H), 7.52-7.47(m, 2H), 7.40-7.39 (m, 4H), 6.97 (s, 2H), 3.64 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 163.0 (J = 243 Hz), 159.3, 157.8, 148.8, 146.1, 138.9, 131.8 (J = 9 Hz), 131.7, 129.5, 127.5, 125.8, 122.3, 118.0, 117.5 (J = 23 Hz), 116.6,

64.7, 34.9; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{12}FN_3O$ 316.0886 $[M-H]^-$, found 316.0900.

3-Amino-2-(4-chlorophenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4g)***: Green solid, 0.243 g, yield 73%; mp 270-272 ℃ (Lit.[24] 275-278 °C); IR (KBr, *v*, cm^{-1}) 3455, 3309, 3207, 2205, 1683, 1621, 1530, 1490, 1399, 1296, 1198, 1154, 1089, 1016, 940, 836, 792, 748, 716, 661; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.21-8.19 (m, 1H), 7.66-7.61 (m, 3H), 7.51-7.49 (m, 2H), 7.38-7.36 (m, 2H), 7.00 (s, 2H), 3.64 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.2, 157.7, 148.9, 146/1, 138.9, 134.6, 134.5, 131.5, 130.7, 129.5, 127.5, 125.8, 122.4, 118.0, 116.6, 64.8, 34.9; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{13}ClN_3O$ 334,0747 $[M+H]^+$, found 334.0756.

3-Amino-2-(4-bromophenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4h)***: Brown solid, 0.294 g, yield 78%; mp 252-253 ℃; IR (KBr, *v*, cm^{-1}) 3449, 3314, 3211, 2202, 1677, 1628, 1525, 1488, 1396, 1296, 1263, 1153, 1068, 1013, 826, 790, 748, 716; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.21-8.18 (m, 1H), 7.76-7.74 (m, 2H), 7.66-7.64 (m, 1H), 7.51-7.47 (m, 2H), 7.31-7.29 (m, 2H), 7.01 (s, 2H), 3.64 (s, $2H_2$); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.1, 157.6, 148.9, 146.1, 138.9, 135.0, 133.6, 131.8, 129.5, 127.5, 125.8, 123.3, 122.3, 117.9, 116.6, 64.8, 34.9; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{13}BrN_3O$ 378.0242 $[M+H]^+$, found 378.0270.

3-Amino-1-oxo-2-(4-(trifluoromethyl)phenyl)-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonit rile ***(4i)***: Yellow solid, 0.283 g, yield 77%; mp 255-256 ℃; IR (KBr, *v*, cm^{-1}) 3451, 2207, 1676, 1632, 1529, 1400, 1330, 1296, 1163, 1101, 1068, 1020, 771, 747, 658; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.23-8.20 (m, 1H), 7.95-7.93 (m, 2H), 7.67-7.63(m, 1H), 7.61-7.60 (m, 2H), 7.54-7.48 (m, 2H), 7.07 (s, 2H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.1, 157.5, 149.1, 146.1, 139.5, 138.8, 130.8, 130.3 (J = 32 Hz), 129.5, 128.6, 127.7 (J = 4 Hz), 127.5, 126.1, 125.7, 124.5 (J = 271 Hz), 122.4, 120.1, 117.9, 116.5, 65.0, 34.9; HRMS (ESI-TOF) *m/z*

calcd for 367.0932 $C_{20}H_{12}F_3N_3O$ $[M]^+$, found 367.0946.

3-Amino-2-(3,5-dimethylphenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4j)***: Brown solid, 0.328 g, yield 73%; mp 218-219 ℃; IR (KBr, *v*, cm^{-1}) 3316, 3210, 2918, 2201, 1678, 1611, 1587, 1523, 1466, 1272, 1153, 1043, 852, 751, 714, 689; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.20-8.18 (m, 1H), 7.66-7.64 (m, 1H), 7.51-7.48(m, 2H), 7.16 (s, 1H), 6.92 (s, 2H), 6.75 (s, 2H) , 3.64 (s, 2H), 3.33 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.4, 157.7, 152.2, 148.5, 146.1, 138.9, 132.7, 129.5, 128.8, 127.5, 127.4, 125.8, 122.3, 118.0, 117.0, 64.7, 35.0, 31.6; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{17}N_3O$ 326.1293 $[M-H]^-$, found 326.1299.

3-Amino-2-(3-chloro-4-methylphenyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4k)***: Brown solid, 0.238 g, yield 69%, mp 223-225 ℃; IR (KBr, *v*, cm^{-1}) 3465, 3314, 3203, 2202, 1681, 1567, 1520, 1444, 1389, 1342, 1268, 1153, 1053, 870, 752, 718, 700; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.21-8.19 (m, 1H), 7.65-7.64 (m, 1H), 7.55-7.48 (m, 4H), 7.22-7.20 (m, 1H), 7.00 (s, 2H), 3.64 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.2, 157.7, 148.8, 146.1, 138.9, 137.3, 134.6, 134.4, 132.9, 129.9, 129.5, 128.2, 127.5, 125.8, 122.4, 118.0, 116.6, 64.7, 34.9, 19.9; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{14}ClN_3O$ 348.0904 $[M+H]^+$, found 348.0915.

3-Amino-2-butyl-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4l)***: Yellow solid, 0.178 g, yield 64%; mp 230-231 ℃; IR (KBr, *v*, cm^{-1}) 3396, 3152, 2956, 2931, 2868, 2198, 1743, 1666, 1641, 1585, 1520, 1440, 1184, 1101, 1060, 777, 752, 717; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.13-8.11 (m, 1H), 7.63-7.60 (m, 1H), 7.51 (s, 2H), 7.47-7.44 (m, 2H), 4.03 (t, J = 7.6 Hz, 2H), 3.65(s, 2H), 1.52-1.46(m, 2H), 1.37-1.28(m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 158.9, 156.9, 147.8, 146.0, 138.9, 129.3, 127.4, 125.7, 122.2, 118.3,

116.0, 64.8, 41.3, 34.9, 29.5, 19.8, 14.2; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}N_3O$ 278.1293 $[M-H]^-$, found 278.1285.

3-Amino-2-(4-methoxybenzyl)-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4m)***: Yellow solid 0.258 g, yield 75%; mp 248-249 ℃; IR (KBr, *v*, cm^{-1}) 3388, 3220, 3179, 2897, 2835, 2344, 2209, 2158, 1662, 1629, 1612, 1526, 1518, 1439, 1251, 1179, 1030, 984, 818, 755, 745; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.15-8.13 (m, 1H), 7.63-7.61 (m, 1H), 7.47-7.45(m, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.31 (s, 2H), 3.70 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.1, 158.9, 157.1, 148.2, 146.1, 138.9, 129.4, 128.6, 128.1, 127.4, 125.7, 122.3, 118.1, 116.1, 114.3, 65.1, 55.5, 43.5, 35.0; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{16}N_3O_2$ 342.1243 $[M-H]^-$, found 342.1251.

3-Amino-2-benzyl-1-oxo-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(4n)***: Gray solid, 0.210 g, yield 67%; mp 257-258 ℃; IR (KBr, *v*, cm^{-1}) 3420, 3026, 2202, 1663, 1619, 1566, 1519, 1455, 1384, 1068, 748, 693; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.17-8.15 (m, 1H), 7.64-7.63 (m, 1H), 7.51-7.46(m, 4H), 7.34-7.31 (m, 2H), 7.27-7.23 (m, 1H), 7.19-7.17 (m, 2H), 5.38 (s, 2H), 3.66 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 159.0, 157.2, 148.3, 146.1, 138.9, 136.2, 129.4, 128.9, 127.5, 127.4, 126.9, 125.7, 122.3, 118.1, 116.0, 65.1, 44.1, 35.0; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{14}N_3O$ 312.1137 $[M-H]^-$, found 312.1140.

Ethyl 3-amino-2-(4-methoxyphenyl)-1-oxo-2,9-dihydro-1H-indeno [2,1-c]pyridine-4-carboxylate ***(4o)***: Yellow solid, 0.255 g, yield 68%; mp 191-193 ℃; IR (KBr, *v*, cm^{-1}) 3367, 2971, 2835, 1890, 1736, 1676, 1483, 1368, 1301, 1166, 1028, 1109, 866, 837, 752, 716; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.97-7.95 (m, 1H), 7.60-7.58 (m, 1H), 7.41-7.38(m, 2H), 7.27-7.25(m, 2H), 7.15-7.12(m, 2H), 7.02 (s, 2H), 4.39-4.34 (m, 2H), 3.84 (s, 3H), 3.66 (s, 2H), 1.29 (t, *J* = 7.2

Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 167.8, 160.1, 159.7, 155.9, 149.8, 146.2, 140.9, 130.6, 128.4, 128.0, 126.5, 126.4, 125.1, 119.2, 115.8, 85.0, 60.7, 55.9, 35.5, 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{20}N_2O_4$ 375.1345 $[M-H]^-$, found 375.1334.

Ethyl 3-amino-1-oxo-2-(p-tolyl)-2,9-dihydro-1H-indeno [2,1-c] pyridine-4-carboxylate ***(4p)***: Yellow solid, 0.224 g, yield 62%; mp 186-188 ℃; IR (KBr, *v*, cm^{-1}) 3378, 3253, 2973, 2922, 1677, 1638, 1548, 1513, 1484, 1401, 1366, 1315, 1301, 1239, 1108, 1019, 817, 792, 753; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.96-7.94 (m, 1H), 7.59-7.58 (m, 1H), 7.41-7.39(m, 4H), 7.22-7.20 (m, 2H), 6.95 (s, 2H), 4.39-4.33 (m, 2H), 3.66 (s, 2H), 2.41 (s, 3H) , 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 167.8, 159.6, 155.6, 149.9, 146.2, 140.9, 139.2, 133.1, 131.2, 129.2, 128.4, 126.5, 126.4, 125.1, 119.2, 85.1, 60.7, 35.5, 21.3, 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{21}N_2O_3$ 361.1552 $[M+H]^+$, found 361.1562.

Ethyl 3-amino-2-(4-fluorophenyl)-1-oxo-2,9-dihydro -1H-indeno[2,1-c]pyridine-4-carboxylate ***(4q)***: Yellow solid, 0.278 g, yield 76%; mp 206-208 ℃; IR (KBr, *v*, cm^{-1}) 3239, 3123, 3073, 2978, 2929, 1680, 1548, 1506, 1395, 1369, 1314, 1245, 1217, 1110, 1016, 843, 757, 716; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.96-7.94 (m, 1H), 7.59-7.58 (m, 1H), 7.43-7.39(m, 6H), 7.12 (s, 2H), 4.39-4.34 (m, 2H), 3.66 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 167.8, 166.9, 162.8 (*J* = 244 Hz), 159.6, 158.1, 155.7, 150.1, 146.2, 140.8, 132.1, 132.0, 131.9 (*J* = 9 Hz), 128.5, 126.5, 126.4, 125.1, 121.8, 119.1, 117.5 (*J* = 23 Hz), 117.1, 85.2, 61.8, 60.7, 35.4, 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{17}FN_2O_3$ 363.1145 $[M-H]^-$, found 363.1161.

Ethyl 3-amino-2-(4-chlorophenyl)-1-oxo-2,9-dihydro -1H-indeno[2,1-c]pyridine-4-carboxylate ***(4r)***: Yellow solid, 0.270 g, yield 71%; mp 220-222 ℃; IR (KBr, *v*, cm^{-1}) 3412, 2973, 2922, 1674, 1631, 1542, 1488, 1391, 1368, 1301, 1150, 1111, 1099, 1059, 837, 747, 713; ^{1}H NMR (400 MHz,

DMSO-d_6, δ, ppm) 7.96-7.94 (m, 1H), 7.68-7.64 (m, 2H), 7.61-7.59(m, 1H), 7.43-7.39 (m, 4H), 7.15 (s, 2H), 4.39-4.34 (m, 2H), 3.66 (s, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 167.8, 159.4, 155.5, 150.1, 146.2, 140.8, 134.7, 134.5, 131.6, 130.7, 128.5, 126.6, 126.4, 125.1, 119.0, 85.2, 60.7, 35.4, 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{17}ClN_2O_3$ 379.0849 $[M-H]^-$, found 379.0838.

Ethyl 3-amino-2-(4-bromophenyl)-1-oxo-2,9-dihydro -1H-indeno[2,1-c]pyridine-4-carboxylate ***(4s)***: Yellow solid, 0.302 g, yield 71%; mp 220-221 ℃; IR (KBr, v, cm^{-1}) 3411, 3124, 2975, 1671, 1662, 1595, 1558, 1543, 1486, 1393, 1301, 1112, 1012, 877, 748, 712; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.96-7.94 (m, 1H), 7.80-7.78 (m, 2H), 7.60-7.58(m, 1H), 7.41-7.39(m, 2H), 7.34-7.32(m, 2H), 7.14 (s, 2H), 4.39-4.33 (m, 2H), 3.66 (s, $2H_2$), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 167.8, 159.4, 155.5, 150.2, 146.2, 140.8, 135.2, 133.6, 131.9, 128.5, 126.6, 126.4, 125.1, 123.2, 119.0, 85.2, 60.7, 35.4, 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{17}BrN_2O_3$ 423.0344 $[M-H]^-$, found 423.0351.

General Experimental Procedures for Compounds 5. A mixture of 40 mmol NaH, 30 mL 1,4-dioxane, 40 mmol acetophenone was stirred at RT. 40 mmol isothiocyanatobenzene was added dropwise and stirring was continued at RT for 2 h. The solids were collected by filtration, washed with 1,4-dioxane. The solids were dissolved with water then slowly neutraliazed under stirring with HCl. After filtration , the filter cake was dried to yield product as a light yellow solid. *3-Oxo-N,3-diphenylpropanethioamide* ***(5a)***: yellow solid, yield 47%; mp 79-80 ℃ (Lit.[25] 79-81°C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 10.98 (s, 1H), 8.06-8.02 (m, 2H), 7.80-7.78 (m, 3H), 7.42-7.40 (m, 5H), 4.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 197.0, 190.8, 137.8, 135.8, 134.5, 129.0, 128.9, 128.8, 128.7, 123.6, 54.3; HRMS (ESI-TOF) *m/z* calcd for

$C_{15}H_{13}NNaOS$ 278.0616 $[M+Na]^+$, found 278.0606.

3-Oxo-3-phenyl-N-(p-tolyl)propanethioamide ***(5b)***: yellow solid, yield 50%; mp 99-100 ℃ (Lit.[25] 102-103°C); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 10.93 (s, 1H), 7.08 (d, J = 7.6 Hz, 2H), 7.55-7.51 (m, 1H), 7.47-7.40 (m, 4H), 7.22-7.20 (m, 2H), 4.65 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 197.1, 191.0, 137.0, 134.5, 129.5, 129.0, 128.8, 128.6, 123.6, 54.0, 21.2; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{15}NNaOS$ 292.0772 $[M+Na]^+$, found 292.0768.

3-Oxo-3-phenyl-N-(m-tolyl)propanethioamide ***(5c)***: yellow oil, yield 43%; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 10.93 (s, 1H), 8.06-8.04 (m, 2H), 7.53-7.49 (m, 2H), 7.42-7.38 (m, 3H), 7.31-7.27 (m, 2H), 4.64 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.8, 190.8, 138.9, 137.8, 135.9, 134.4, 129.0, 128.9, 128.7, 127.9, 126.3, 124.1, 54.5, 21.4; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{15}NNaOS$ 292.0772 $[M+Na]^+$, found 292.0767.

Representative Synthesis of 6: 3-Amino-2-phenyl-1-thioxo-2,9-dihydro-*1H*-indeno[2,1-*c*] pyridine-4-carbonitril (6a). 3-Oxo-N,3-diphenylpropanethioamide **5a** (1.0 mmol), phthalaldehyde **2** (1.0 mmol) and malononitrile **3a** (1.0 mmol) were placed in a 5 mL Initiator reaction vial, followed by NaOH (0.2 mmol) and EtOH (2 mL). The reaction vial was then sealed and prestirred for 20 s before being irradiated in the microwave (time, 15 min; temperature, 100 ^oC; absorption level, high; fixed hold time) until TLC (2:1 mixture of petroleum ether and ethyl acetate) revealed the complete consumption of the starting materals. The reaction mixture was then cooled to room temperature to give a precipitate, which was collected by Büchner filtration. The solid material was then purified by recrystallization from 95% EtOH to afford the desired product **6a** as a yellow solid, 0.247 g, yield 78%; mp 274-275 ℃ (Lit.[24] 277-278 °C); IR (KBr, ν, cm^{-1}) 3461, 2205, 1631, 1566, 1473, 1361, 1276, 1186, 104, 743, 710; ^1H NMR (400 MHz,

DMSO-d_6, δ, ppm) 8.24-8.22 (m, 1H), 7.68-7.67 (m, 1H), 7.62-7.58 (m, 2H), 7.56-7.51 (m, 3H), 7.30-7.28 (m, 2H), 7.03 (s, 2H), 3.76 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 178.4, 156.9, 146.8, 143.8, 139.0, 138.3, 131.9, 130.9, 130.4, 130.0, 129.1, 127.9, 125.7, 123.4, 117.1, 72.0; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{13}N_3NaS$ 338.0728 $[M+Na]^+$, found 338.0716.

Methyl 3-amino-1-thioxo-2-(p-tolyl)-2,9-dihydro-1H- indeno[2,1-c] pyridine-4-carboxylate ***(6b)***: Brown solid, 0.246 g, yield 75%; mp 240-241 ℃ (Lit.[24] 245 °C); IR (KBr, *v*, cm^{-1}) 3318, 2203, 1542, 1464, 1404, 1359, 1312, 1185, 1106, 1037, 886, 774, 737; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.18 (d, *J* = 7.2 Hz, 1H), 7.64-7.62 (m, 1H), 7.51-7.47 (m, 2H), 7.40-7.38 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.97 (s, 2H), 3.70 (s, 2H), 2.4 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 178.5, 157.1, 146.8, 143.7, 139.4, 138.3, 136.4, 131.9, 131.4, 130.4, 128.7, 127.9, 125.7, 123.4, 117.1, 71.9, 21.4; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{16}N_3S$ 330.1065 $[M+H]^+$, found 330.1042.

3-Amino-1-thioxo-2-(m-tolyl)-2,9-dihydro-1H-indeno[2,1-c]pyridine-4-carbonitrile ***(6c)***: Yellow solid, 0.237 g, yield 72%; mp 236-238 ℃; IR (KBr, *v*, cm^{-1}) 3304, 3214, 2212, 1719, 1637, 1542, 1475, 1359, 1276, 1185, 1062, 791, 737, 684; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.14 (d, *J* = 7.2 Hz, 1H), 7.61-7.59 (m, 1H), 7.50-7.44 (m, 3H), 7.34-7.32 (m, 1H), 7.09-7.07 (m, 2H), 6.91 (s, 2H), 3.67 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 178.3, 157.0, 146.9, 146.8, 143.8, 140.7, 139.0, 138.3, 132.1, 131.0, 130.9, 130.6, 129.4, 128.0, 126.1, 125.8, 123.5, 117.2, 72.2, 21.6; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{15}N_3SNa$ 352.0884 $[M+Na]^+$, found 352,0877.

Ethyl 3-amino-2-phenyl-1-thioxo-2,9-dihydro-1H-indeno [2,1-c]pyridine-4-carboxylate ***(6d)***: Yellow solid, 0.244 g, yield 67%; mp 184-185 ℃; IR (KBr, *v*, cm^{-1}) 3431, 2968, 2876, 1659, 1590, 1349, 1309, 1275, 1205, 1118, 1014, 763, 732, 696; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.94

(d, *J* = 7.6 Hz, 1H), 7.64-7.60 (m, 3H), 7.56-7.52 (m, 1H), 7.46-7.37 (m, 2H), 7.30 (d, *J* = 7.2 Hz, 2H), 6.87 (s, 2H), 4.44-4.39 (m, 2H), 3.81 (s, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 194.6, 167.6, 154.8, 147.2, 144.8, 139.9, 139.5, 133.1, 131.1, 130.1, 129.7, 129.2, 127.2, 127.1, 125.3, 92.7, 61.8, 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{18}N_2O_2S$ 362.1089 $[M]^+$, found 362.1089.

Ethyl 3-amino-1-thioxo-2-(p-tolyl)-2,9-dihydro-1H- indeno[2,1-c]pyridine-4-carboxylate ***(6e)***: Brown solid, 0.248 g, yield 66%; mp 159-161 ℃; IR (KBr, *v*, cm^{-1}) 3415, 1719, 1659, 1589, 1537, 1349, 1273, 1241, 1099, 1014, 868, 820, 767, 735; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 7.94 (d, *J* = 7.5 Hz, 1H), 7.62-7.59 (m, 1H), 7.46-7.36 (m, 4H), 7.17-7.14 (m, 2H), 6.87 (s, 2H), 4.45-4.38 (m, 2H), 3.80 (s, 2H), 2.41 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 177.5, 167.4, 154.7, 147.0, 144.6, 139.7, 139.3, 136.8, 132.8, 131.4, 129.5, 129.0, 128.7, 127.0, 126.9, 125.1, 92.5, 61.6, 21.4, 14.3; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{21}N_2O_2S$ 377.1324 $[M+H]^+$, found 377.1312.

Methyl 3-amino-2-phenyl-1-thioxo-2,9-dihydro-1H- indeno[2,1-c] pyridine-4-carboxylate ***(6f)***: Brown solid, 0.210 g, yield 60%; mp 184-185 ℃; IR (KBr, *v*, cm^{-1}) 3454, 1656, 1581, 1535, 1316, 1246, 1216, 1154, 1120, 948, 783, 767, 706; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.94 (d, *J* = 7.6 Hz, 1H), 7.64-7.60 (m, 3H), 7.56-7.52 (m, 1H), 7.46-7.37 (m, 2H), 7.30 (d, *J* = 7.2 Hz, 2H), 6.87 (s, 2H), 3.91 (s, 3H), 3.80 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 177.6, 167.9, 154.7, 147.2, 144.8, 139.9, 139.5, 133.1, 131.1, 129.7, 129.2, 127.4, 127.0, 125.3, 92.6, 52.5, 52.4; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{17}N_2O_2S$ 349.1011 $[M+H]^+$, found 349,0998.

Methyl 3-amino-1-thioxo-2-(p-tolyl)-2,9-dihydro-1H- indeno[2,1-c]pyridine-4-carboxylate ***(6g)***: Brown solid, 0.211 g, yield 58%; mp 148-150 ℃; IR (KBr, *v*, cm^{-1}) 3415, 1719, 1656, 1587, 1535,

1316, 1276, 1216, 1154, 1199, 948, 820, 767, 736;^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.87-7.85 (m, 1H), 7.63-7.61 (m, 1H), 7.47-7.40 (m, 4H), 7.16-7.14 (m, 2H), 6.85 (s, 2H), 3.91 (s, 3H), 3.79 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 177.6, 167.7, 154.6, 147.0, 144.5, 139.7, 139.3, 136.8, 132.8, 131.4, 129.7, 129.5, 128.7, 127.2, 126.8, 125.1, 92.3, 52.3, 21.4; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{17}N_2O_2S$ 361.1011 $[M-H]^-$, found 361.1012.

Representative Synthesis of 8: 3-Amino-2-(4-(tert-butyl)phenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile (8a). 3-(4-(tert-Butyl)phenyl)-3-oxo-*N*-phenyl propanamide **1b** (1.0 mmol), glutaraldehyde **7** (1.0 mmol) and malononitrile **3a** (1.0 mmol) were placed in a 5 mL Initiator reaction vial, followed by NaOH (0.2 mmol) and EtOH (2 mL). The reaction vial was then sealed and prestirred for 20 s before being irradiated in the microwave (time, 15 min; temperature, 100 ^{o}C; absorption level, high; fixed hold time) until TLC (2:1 mixture of petroleum ether and ethyl acetate) revealed the complete consumption of the starting materials. The reaction mixture was then cooled to room temperature to give a precipitate, which was collected by Büchner filtration. The solid material was then purified by recrystallization from 95% EtOH to afford the desired product **8a** as a yellow solid, 0.240 g, yield 75%; mp 209-210 ℃; IR (KBr, *v*, cm^{-1}) 3452, 3307, 3199, 2964, 2183, 1696, 1641, 1592, 1414, 1310, 1255, 1128, 821, 753; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.51 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.84-6.83(m, 1H), 5.38(s, 2H), 3.33-3.32(m, 1H), 2.29-2.27 (m, 2H), 2.16-2.13 (m, 1H), 1.87-1.84 (m, 1H), 1.59-1.54 (m, 1H), 1.42-1.39 (m, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 164.0, 153.3, 151.7, 139.0, 132.9, 129.8, 129.6, 126.7, 120.6, 100.0, 59.7, 34.9, 31.5, 30.2, 28.5, 25.8, 20.7; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{22}N_3O$ 320.1763 $[M-H]^-$, found 320.1771.

3-Amino-2-(4-isopropylphenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8b)***:

Yellow solid, 0.228 g, yield 74%; mp 190-192 ℃; IR (KBr, *v*, cm^{-1}) 3463, 3306, 3197, 2962, 2869, 2813, 2217, 2186, 1693, 1643, 1592, 1527, 1413, 1310, 1257, 1202, 1129, 823, 759, 719; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.36 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.84-6.83(m, 1H), 5.38(s, 2H), 3.33-3.32(m, 1H), 3.00-2.93 (m, 1H), 2.29-2.24 (m, 2H), 2.17-2.13 (m, 1H), 1.87-1.84 (m, 1H), 1.60-1.53 (m, 1H), 1.41-1.35 (m, 1H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 164.0, 153.3, 149.4, 139.0, 133.1, 129.9, 129.8, 127.7, 120.6, 59.6, 33.6, 30.3, 28.5, 25.8, 24.2, 20.7; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{20}N_3O$ 306.1606 $[M-H]^-$, found 306.1600.

3-Amino-2-(4-ethoxyphenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8c)***:

White solid, 0.206 g, yield 67%; mp 250-251 ℃; IR (KBr, *v*, cm^{-1}) 3469, 3325, 2981, 2938, 2183, 1690, 1647, 1591, 1510, 1410, 1313, 1257, 1176, 1114, 1043, 920, 839, 806, 746; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.14 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.83-6.82(m, 1H), 5.43(s, 2H), 4.10-4.04(m, 2H), 3.35-3.30 (m, 1H), 2.28-2.26 (m, 2H), 2.16-2.12 (m, 1H), 1.86-1.83 (m, 1H), 1.61-1.51 (m, 1H), 1.40-1.32 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 164.1, 159.1, 153.5, 138.9, 131.2, 129.8, 127.7, 120.7, 115.5, 63.8, 59.3, 30.3, 28.5, 25.8, 20.7, 15.1; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{18}N_3O_2$ 308.1399 $[M-H]^-$, found 308.1417.

3-amino-2-(4-methoxyphenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8d)***:

Brown solid, 0.210 g, yield 71%; mp 217-218 ℃; IR (KBr, *v*, cm^{-1}) 3461, 3316, 3244, 3201, 2933, 2859, 2836, 2361, 2182, 1688, 1645, 1591, 1509, 1414, 1314, 1254, 1131, 1023, 967, 826, 761; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.16 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.83-6.82(m, 1H), 5.44(s, 2H), 3.81(s, 3H), 3.34-3.30 (m, 1H), 2.28-2.27 (m, 2H), 2.17-2.13 (m, 1H), 1.87-1.84 (m, 1H), 1.60-1.54 (m, 1H), 1.41-1.32 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ,

ppm) 164.1, 159.8, 153.5, 138.9, 131.2, 129.8, 127.8, 120.7, 115.0, 59.3, 55.8, 30.3, 28.5, 25.8, 20.7; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}N_3O_2$ 294.1243 $[M-H]^-$, found 294.1257.

3-Amino-1-oxo-2-(p-tolyl)-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8e)***: Yellow solid, 0.193 g, yield 69%; mp 269-270 ℃; IR (KBr, *v*, cm^{-1}) 3447, 3329, 2934, 2863, 2804, 2365, 2180, 1680, 1643, 1583, 1416, 1314, 1261, 1203, 1136, 1080, 806, 743; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.28 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 2H), 6,82(s, 1H), 5.41(S, 2H), 3.32-3.30(m, 1H), 2.35 (s, 3H), 2.26 (s, 2H), 2.14-2.11 (m, 1H), 1.86-1.82 (m, 1H), 1.57-1.50 (m, 1H) , 1.39-1.33 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 164.0, 153.3, 138.9, 138.8, 132.9, 130.4, 129.8, 129.7, 120.6, 59.5, 30.3, 28.5, 25.8, 21.2, 20.7; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}N_3O$ 278.1293 $[M-H]^-$, found 278.1300.

3-Amino-2-(3,5-dimethylphenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8f)***: White solid, 0.199 g, yield 68%; mp 203-205 ℃; IR (KBr, *v*, cm^{-1}) 3368, 2938, 2182, 1692, 1649, 1591, 1412, 1323, 1260, 1128, 841, 745; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.09 (s, 1H), 6.86 (s, 2H), 6.82-6.81(m, 1H), 5.42(s, 2H), 3.33-3.30(m, 1H), 2.30 (s, 6H), 2.28-2.26 (m, 2H), 2.16-2.12 (m, 2H), 1.86-1.83 (m, 1H), 1.59-1.53 (m, 1H), 1.41-1.31 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 163.9, 153.2, 139.8, 139.1, 138.8, 135.3, 130.8, 129.8, 127.5, 120.6, 59.4, 30.2, 28.5, 25.8, 21.2, 20.7; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{18}N_3O$ 292.1450 $[M-H]^-$, found 292.1445.

3-Amino-2-(3-chloro-4-methylphenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8g)***: Yellow solid, 0.189 g, yield 60%; mp 144-145 ℃; IR (KBr, *v*, cm^{-1}) 3508, 3387, 2892, 2841, 2218, 2162, 1714, 1673, 1614, 1557, 1508, 1368, 1337, 1288, 1279, 1216, 1182, 956, 867; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.45-7.36 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 1H),6,82(s, 1H),

5.62(S, 2H), 3.31-3.29(m, 1H), 2.37 (s, 3H), 2.26 (s, 2H), 2.14-2.11 (m, 1H), 1.85-1.82 (m, 1H), 1.60-1.50 (m, 1H), 1.40-1.30 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 164.0, 153.2, 139.2, 136.8, 134.5, 133.8, 132.1, 130.6, 129.7, 128.9, 120.6, 59.7, 30.2, 28.4, 25.9, 20.7, 19.8; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{15}ClN_3O$ 312.0904 $[M-H]^-$, found 312.0893.

3-Amino-2-(4-fluorophenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8h)***: Yellow solid, 0.148 g, yield 52%; mp 156-158 ℃; IR (KBr, *v*, cm^{-1}) 3379,3316, 3213, 3076, 2936, 2808, 2178, 1689, 1650, 1579, 1506, 1420, 1313, 1258, 1152, 833, 762; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.29 (d, *J* = 7.2 Hz, 4H), 6.83-6.82(m, 1H), 5.57(s, 2H), 3.33-3.30 (m, 1H), 2.28-2.26 (m, 2H), 2.15-2.11 (m, 1H), 1.86-1.83 (m, 1H), 1.58-1.52 (m, 1H), 1.40-1.34 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 164.0, 162.4 (*J* = 244 Hz), 153.3, 139.1, 132.4 (*J* = 9 Hz), 131.8, 131.7, 129.7, 120.6, 116.6 (*J* = 23 Hz), 59.5, 30.2, 28.5, 25.8, 20.7; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{13}FN_3O$ 282.1043 $[M-H]^-$, found 282.1050.

3-Amino-2-(4-chlorophenyl)-1-oxo-1,2,4a,5,6,7-hexahydroisoquinoline-4-carbonitrile ***(8i)***: White solid, 0.150 g, yield 50%; mp 180-181 ℃; IR (KBr, *v*, cm^{-1}) 3386, 3310, 3210, 2923, 2864, 2816, 2175, 1688, 1650, 1597, 1490, 1309, 1257, 1199, 1089, 812; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.52 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H),6.83-6.82(m, 1H), 5.63(s, 2H), 3.33-3.30 (m, 1H), 2.28-2.24 (m, 2H), 2.15-2.11 (m, 1H), 1.86-1.83 (m, 1H), 1.58-1.52 (m, 1H), 1.40-1.30 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 163.9, 153.2, 139.2, 134.6, 133.9, 132.1, 129.8, 129.7, 120.6, 59.6, 30.2, 28.5, 25.9, 20.7; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{13}ClN_3O$ 298.0747 $[M-H]^-$, found 298.0744.

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Supporting Information

Characterization, ^{1}H and ^{13}C NMR spectra, crystallographic data for the products **4h**, **6a** and **8a** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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