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Synthesis of Dihydropyrrole Derivatives by Oxidative Functionalization of 2-Amino-4*H*-Chromenes Using Hypervalent Iodine Reagents

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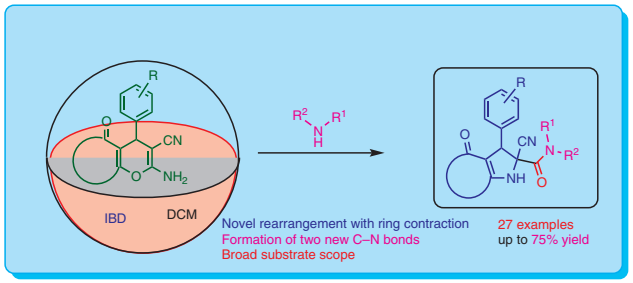

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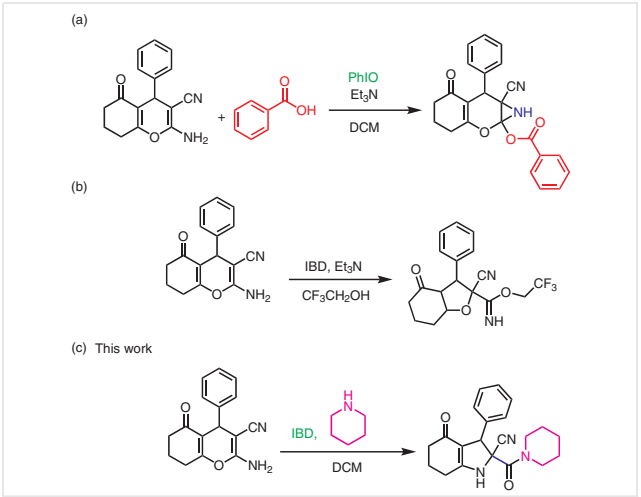
Abstract An efficient simple, metal-free, one-pot protocol for the synthesis of dihydropyrrole derivatives has been achieved via sequential addition of iodobenzenediacetate and secondary amine to 2-amino-4*H*-pyran derivatives. The one-pot protocol proceeds through tandem oxidative functionalization, rearrangement, and ring contraction to provide an entirely new strategy for the construction of the dihydropyrrole skeleton.

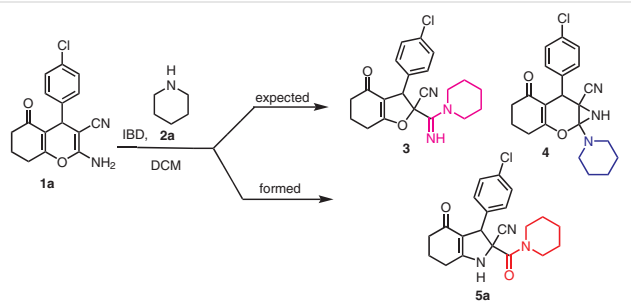
Key words one pot, metal free, oxidative functionalization, rearrangement, ring contraction

Hypervalent iodine (HVI) reagents have fascinated chemists over many years as versatile synthetic agents. HVIs are mildly oxidizing reagents, possessing electrophilic character, environmentally friendly behavior, and are commercially accessible.[1,2] Occasionally, they are found to be superior agents than metal catalysts.[3] HVI reagents mediate several group transformations on various scaffolds involving oxidative functionalization,[4] intermolecular rearrangements,[5] and cyclization/coupling reactions.[6,7] They have been known to be helpful in aminofluorination,[8] diamination,[9] dioxygenation,[10] halogenations,[11] 1,5-electrocyclization,[12] and acetoxylation.[13] The electrophilic and excellent ligand-exchange[14] nature of the iodine in HVI reagents makes them suitable for the generation of the cationic intermediates which can react with nucleophiles or form rearranged products with ring expansion, ring contraction, or migration of functional groups.[15] The geminal dialkoxylation and 1,2-migration of $-NH_2$ in 2-amino-4*H*-pyrans was reported by this group in the presence of iodobenzene diacetate (IBD) via an apparent intramolecular aziridination.[16a] The same study with *N*-chlorosuccinimide (NCS) shows both chlorination and alkoxylation at the double bond in the 2-amino-4*H*-pyrans.[16a] Yet another oxidative difunctionalization of amino pyrans leading to dihydrofurans through sequential addition of NCS in the presence of base has also been accomplished by this group.[16b] Zhao et al., demonstrated the conventional method for the conversion of enamines to 2-*H*-aziridines and their subsequent rearrangements by using IBD.[17] Recently, Das et al. have reported a synthetic route to construct the aziridine ring by exploiting the enamine fragment of 2-amino-4*H*-pyrans and their skeletal transformation in the presence of IBD (Scheme 1a).[18] Synthesis of 2,2,2-trifluoroethyl 2-cyano-4-oxo-3-phenyloctahydrobenzofuran-2-carbimidate from 2-amino-4*H*-pyrans has also been accomplished (Scheme 1b).[19a] The syntheses of dihydrofuran,[16b,19] pyridone,[20] aziridine,[21] and oxazine[22] derivatives through the rearrangement of 2-amino-4*H*-pyrans have also been accomplished.



Scheme 1 Previous and present approaches towards the oxidative functionalization of amino chromenes

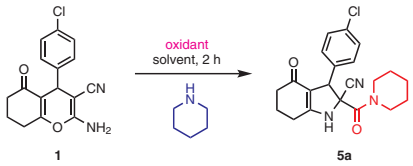
Fused heterocycles are formed by the union of two or more heterocyclic frameworks into a single molecular identity. They are found in many natural products which exhibit a broad variety of biological activities primarily owing to the presence of multiple pharmacophores in a single molecular entity.[23] Among these, fused pyrrole heterocycles are found in large variety of naturally occurring compounds.[24] Inherent diversity of dihydropyrrole derivatives and their distinct therapeutic response led to many researchers choosing them for exploring their maximum potential as medicinal and pharmaceutical agents,[25] as well as in materials science.[26] Owing to the importance of dihydropyrrole scaffolds, synthesis and/or derivatization of these compounds is of contemporary interest. Keeping this in consideration and as a part of our ongoing research program on the development of innovative and efficient synthetic protocols for the construction of biologically significant heterocycles, herein a report on the synthesis of functionalized dihydropyrroles through skeletal transformation of 2-amino chromenes is described for the first time under one-pot conditions mediated by HVI (Scheme 2).



Scheme 2 Synthesis of compound **5**

2-Amino-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile was synthesized from a method previously developed in our laboratory.[16] In an effort towards oxidative functionalization of 2-amino chromenes employing 2-amino-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile as model substrate the reaction with IBD (1 mmol) has been investigated in 4 mL of dichloromethane (DCM) at room temperature (rt) for 30 min, followed by addition of piperidine (1 mmol) to the reaction mixture. The complete consumption of the starting materials was monitored by TLC, and column chromatography of the reaction mixture gave white-colored solid in 65% yield (Table 1, entry 1). An anticipated structure of the product can be either compound **3** or **4**. Normally, imines on hydrolysis under acidic conditions result in the formation of the corresponding carbonyl compound.[16b] To confirm the structure of the compound, acidic hydrolysis of the product was performed. No change in the TLC and mass spectrum of the product was observed. Therefore structure **3** was ruled out. The ^{1}H NMR spectrum of the compound shows a singlet signal at δ = 5.49 ppm accounting for –NH, and the ^{13}C NMR spectra of compound a signal at δ = 164 ppm, likely due to the presence of C=O in the formed compound, firmly ruling out compound **4** as the product. Ultimately, the structure of the compound was confirmed by X-ray crystallographic studies and assigned as 3-(4-chlorophenyl)-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (**5a**).

Table1 Optimization of Reaction Conditions for the Synthesis of 3-(4-Chlorophenyl)-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (**5a**)[a]



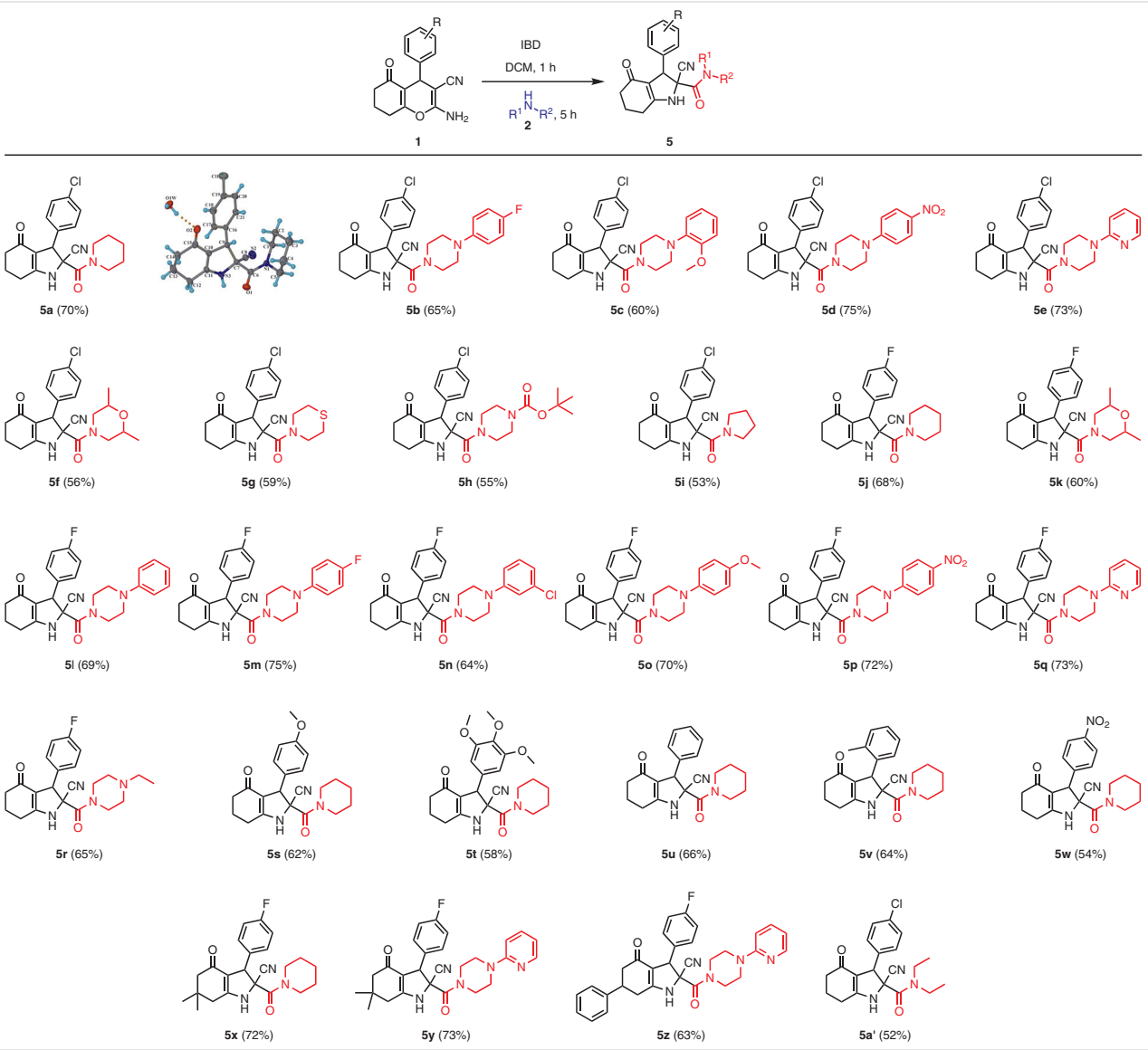
Entry	Solvent	Oxidant	Temp	Time (h)	Yield (%)[b]
1	DCM	IBD	rt	6	65
2	MeCN	IBD	rt	6	50
3	toluene	IBD	rt	6	45
4	DCE	IBD	rt	6	52
5	THF	IBD	rt	6	traces
6	dioxane	IBD	rt	6	30
7	DMF	IBD	rt	6	NR[c]
8	H_2O	IBD	rt	6	NR[c]
9	MeOH	IBD	rt	1	NR[c]
10	DCM	IBD (1.1)[d]	rt	6	70
11	DCM	IBD (1.2)[d]	rt	6	59
12	DCM	IBD (1.5)[d]	rt	6	50
13	DCM	IBD (1.1)[d]	0 °C	8	30
13	DCM	PIFA	rt	6	traces
14	DCM	HTIB	rt	6	NR[c]
15	DCM	PhIO	rt	6	NR[c]

[a] Reaction conditions: 2-amino-4-(4-chlorophenyl)-5-*oxo*-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (1 mmol), IBD (1 mmol), piperidine (1 mmol).
[b] Isolated yields.
[c] NR: no reaction.
[d] Equivalents of oxidant used in parentheses.

After the conformation of the product structure, work on identification of suitable reaction conditions for the synthesis of 3-(4- chlorophenyl)-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7- hexahydro-1*H*-indole-2-carbonitrile was initiated by altering various reaction parameters (Table 1). Firstly, the solvent effect was studied by changing solvents such as acetonitrile (MeCN), toluene, dichloroethane (DCE), tetrahydrofuran (THF), and dioxane. The reaction time as well as yield of the reaction and product distribution was greatly affected in all the cases and a decrease in the product yield was observed (Table 1, entries 2–6). In di-

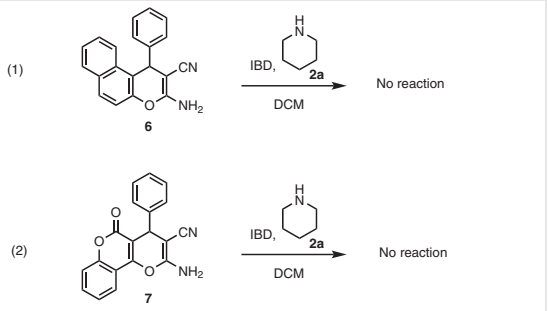
methylformamide (DMF) and water (H_2O), formation of the product **5** was not observed (Table 1, entries 7 and 8). Whereas in methanol the formation of 3-amino-4-(4-chlorophenyl)-2,2-dimethoxy-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-3-carbonitrile was observed, as mentioned in an earlier report[16a] (Table 1, entry 9). Alternative HVI reagents were studied. With iodosobenzene bis(trifluoroacetate) (PIFA, Table 1, entry 13) only traces of compound were formed, whereas with other reagents, HTIB and PhIO (hydroxyl (tosyloxy)iodobenzene and iodosobenzene, Table 1, entries 14 and 15), no product formation was observed (starting material recovered). Later ideal HVI load was determined and by changing the quantity of IBD. Raising the molar ratio to 1.1 equivalents in solvent DCM increased the product yield to 70% (Table 1 entry 10). Further increase in the mol equivalents of IBD (Table 1, entries 11 and 12) did not significantly increase the product yield.

After establishing the feasible reaction conditions for the preparation of compound **5**, an exploration of the substrate scope was taken up, using a variety of secondary amines as exemplified in Scheme 3. Secondary amines such as 1-phenylpiperazine derivatives with neutral, electron-donating (–OMe) and electron-withdrawing group (–NO_2) on the phenyl ring gave moderate to good yields (**5b–e**,**h**). Morpholine and thiomorpholine derivatives afforded moderate yields (**5f**,**g**). Similarly, the reaction with pyrrole afforded the product **5i** in moderate yield. Subsequently the substrate scope was extended to various neutral, electron-



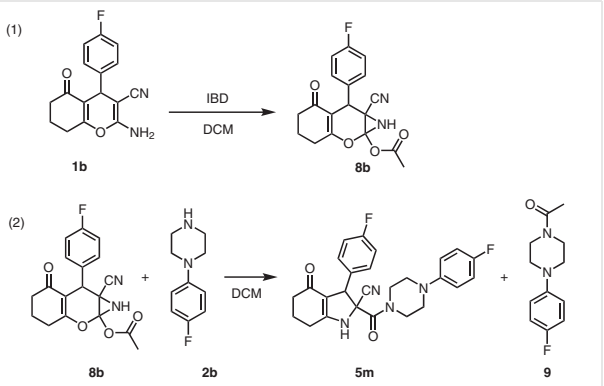
Scheme 3 Substrate scope

donating and electron-withdrawing substitutions on the fused phenyl ring of the 4*H*-pyran framework that were reacted with piperidine (**5j–w**). Gratifyingly, they were well tolerated, and the respective products were obtained in moderate to good yields. The scope of the reaction was evaluated with substitution change in chromenes. Both the substitutions dimethyl and phenyl at the 7-position of chromenes afforded the corresponding products in good yields (**5x–z**). The scope was extended to noncyclic secondary amine (diethylamine) which gives the corresponding product (**5a'**) in moderate yield. However, there is no progress in the reaction when the corresponding amino chromene derivatives with naphthol and 2-hydroxycoumarin (**6** and **7**, Scheme 4) were reacted (starting material unreacted).



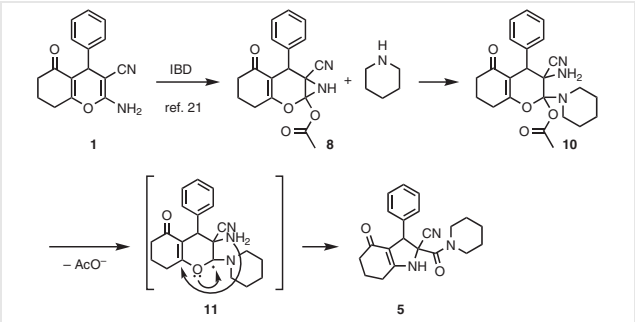
Scheme 4

To study the mechanistic aspects control experiments were carried out. A stepwise protocol was performed. The aziridine **8b** was isolated and characterized, followed by addition of secondary amines. The reaction gave a functionalized pyrrole derivative **5m**. A byproduct **9**, resulting from *N*-acetylation of secondary amine was also detected (Scheme 5).[26]



Scheme 5 Control experiments

Taking into consideration all the facts, it appears that a base-catalyzed aziridine ring opening and rearrangement is the most probable route for conversion into the product (Scheme 6). Firstly, 2-amino chromene reacts with IBD, resulting in the formation of compound **8**. The secondary amine attacks the aziridine ring resulting in the ring opening and the compound **10** is formed. Due to the steric crowding the acetate ion is eliminated and a charged complex **11** is formed, which further undergoes intramolecular rearrangements to give the title compound **5**.



Scheme 6 Plausible mechanism

In conclusion, a novel and one-pot methodology for the construction of dihydropyrrole derivatives has been accomplished by tandem oxidative functionalization, rearrangement, and ring contraction of aminopyrans.[27,28] This one pot methodology illustrates the reactivity of 2-amino-4*H*-pyran with sequentially added IBD and secondary amine. The protocol uses simple substrates and reagents for the synthesis of dihydropyrrole derivatives.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Acknowledgement

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1500-6863.

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(27) **General Procedure for the Preparation of Dihydropyrrole Derivatives**
A mixture of 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (1 mmol, 1 equiv) and IBD (1.1 mmol, 1.1 equiv) in anhydrous DCM (3 mL) was stirred for 60 min, then secondary amine derivatives were added. Stirring was continued at room temperature until the starting material was completely consumed (TLC monitoring). After completion, the reaction mixture was extracted with DCM (20 mL) and washed with water (10 mL). The combined organic layers were dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to dryness. The crude product thus obtained was purified by column chromatography (60–120 mesh, and EtOAc–hexane, 30:70) to afford the pure product.
(28) **Analytical Data**
3-(4-Chlorophenyl)-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5a)
Yield: 134 mg (70%); white solid; mp156–158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.4 Hz, 2 H), 7.25 (dd, *J* = 7.8, 5.4 Hz, 2 H), 5.53 (s, 1 H), 4.39 (s, 1 H), 3.58 (m, 4 H), 2.59 (q, *J* = 6.4 Hz, 2 H), 2.29–2.22 (m, 2 H), 2.11–2.03 (m, 2 H), 1.68–1.58 (m, 2 H), 1.30 (dt, *J* = 13.8, 7.0 Hz, 2 H), 0.88 (t, *J* = 7.1 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.38, 167.41, 163.51, 136.17, 134.48, 129.36, 115.88, 77.06, 67.33, 54.35, 47.59, 45.53, 36.44, 25.36, 25.13, 24.06, 23.70, 22.20. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{21}H_{23}O_2N_3Cl$: 384.14869; found: 384.14733.
3-(4-Chlorophenyl)-2-[4-(4-fluorophenyl)piperazine-1-carbonyl]-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5b)
Yield: 155 mg (65%); white solid; mp 212–214 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2 H), 7.28–7.25 (m, 2 H), 7.02–6.97 (m, 2 H), 6.92–6.88 (m, 2 H), 5.47 (s, 1 H), 4.44 (s, 1 H), 4.07–3.62 (m, 4 H), 3.31–3.01 (m, 4 H), 2.61 (dd, *J* = 13.8, 6.7 Hz, 2 H), 2.29–2.24 (m, 2 H), 2.10–2.07 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.40, 167.21, 163.92, 159.26, 156.80, 147.11, 135.86, 134.68, 129.40, 119.02, 115.99, 115.77, 67.28, 54.55, 50.40, 49.76, 46.59, 44.22, 36.43, 23.70, 22.20. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{26}H_{25}O_2N_4ClF$: 479.16507; found: 479.16446.
3-(4-Chlorophenyl)-2-[4-(2-methoxyphenyl)piperazine-1-carbonyl]-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5c)
Yield: 147 mg (60%); off-white solid; mp 204–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 5.4, 3.5 Hz, 2 H), 7.29–7.27 (m, 1 H), 7.21 (dt, *J* = 6.8, 1.9 Hz, 1 H), 7.06 (m, 1 H), 6.95–6.89 (m, 3 H), 5.51 (s, 1 H), 4.44 (s, 1 H), 3.95 (s, 1 H), 3.90 (s, 3 H),

3.87–3.75 (m, 3 H), 3.22 (dd, *J* = 10.3, 5.9 Hz, 3 H), 3.07–2.99 (m, 1 H), 2.66–2.57 (m, 2 H), 2.31–2.26 (m, 2 H), 2.12–2.08 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.36, 167.51, 163.83, 152.30, 139.97, 139.42, 135.02, 130.44, 129.02, 128.12, 126.37, 124.04, 121.16, 118.72, 115.76, 115.55, 111.46, 67.26, 55.55, 54.73, 50.24, 49.80, 46.98, 44.54, 36.44, 23.71, 22.18. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{27}H_{28}O_3N_4Cl$: 491.18498; found: 491.18444.

3-(4-Chlorophenyl)-2-[4-(4-nitrophenyl)piperazine-1-carbonyl]-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5d)

Yield: 189 mg (75%); yellow solid; mp 246–248 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18–8.16 (m, 1 H), 7.35 (dd, *J* = 4.7, 1.9 Hz, 1 H), 7.31–7.28 (m, 1 H), 7.24–7.21 (m, 1 H), 6.91–6.87 (m, 2 H), 5.42 (s, 1 H), 4.42 (s, 1 H), 4.20–4.07 (m, 1 H), 3.93 (s, 1 H), 3.70 (dd, *J* = 68.9, 29.8 Hz, 4 H), 3.49–3.31 (m, 2 H), 2.70–2.57 (m, 2 H), 2.31–2.26 (m, 2 H), 2.14–2.07 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$ + DMSO): δ = 189.86, 167.29, 162.23, 153.13, 139.11, 137.40, 132.97, 129.03, 127.10, 126.91, 125.60, 124.51, 114.81, 112.00, 110.84, 66.83, 52.69, 44.93, 35.20, 22.22, 20.96. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{26}H_{25}O_4N_5Cl$: 506.16003; found: 506.15896

3-(4-Chlorophenyl)-4-oxo-2-[4-(pyridin-2-yl)piperazine-1-carbonyl]-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5e)

Yield: 168 mg (73%); white solid; mp 204–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1 H), 7.57–7.50 (m, 1 H), 7.42–7.33 (m, 1 H), 7.29–7.24 (m, 2 H), 6.75–6.66 (m, 2 H), 5.52 (s, 1 H), 4.44 (s, 1 H), 4.01–3.41 (m, 8 H), 2.60 (m, 2 H), 2.30–2.24 (m, 2 H), 2.12–2.06 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.36, 167.27, 164.09, 158.70, 148.09, 137.89, 135.88, 134.66, 129.43, 115.84, 115.62, 114.57, 107.45, 77.06, 67.38, 54.51, 46.22, 44.95, 44.49, 43.98, 36.42, 23.69, 22.20. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{25}H_{25}O_2N_5Cl$: 462.17025; found: 462.16913.

3-(4-Chlorophenyl)-2-(2,6-dimethylmorpholine-4-carbonyl)-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5f)

Yield: 116 mg (56%); off-white solid; mp 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 2 H), 7.18 (dd, *J* = 36.9, 6.9 Hz, 2 H), 5.74 (s, 1 H), 4.34 (dd, *J* = 23.1, 13.8 Hz, 2 H), 3.81 (d, *J* = 12.8 Hz, 1 H), 3.67 (s, 2 H), 3.09–2.82 (m, 1 H), 2.59 (d, *J* = 27.8 Hz, 3 H), 2.26 (d, *J* = 6.3 Hz, 2 H), 2.13–2.01 (m, 2 H), 1.33–1.13 (m, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.33, 167.63, 163.92, 139.24, 134.97, 130.41, 129.07, 128.14, 126.26, 115.93, 115.21, 71.76, 71.12, 70.57, 67.35, 55.68, 53.83, 52.14, 51.79, 49.39, 48.95, 36.39, 23.65, 22.16, 18.65, 18.45. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{22}H_{25}O_3N_3Cl$: 414.15821; found: 414.15790.

3-(4-Chlorophenyl)-4-oxo-2-(thiomorpholine-4-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5g)

Yield: 118 mg (59%); white solid; mp 214–216 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (td, *J* = 4.6, 3.0 Hz, 2 H), 7.28–7.25 (m, 1 H), 7.21–7.17 (m, 1 H), 5.42 (s, 1 H), 4.35 (s, 1 H), 4.31 (d, *J* = 11.7 Hz, 1 H), 4.02 (d, *J* = 10.2 Hz, 1 H), 3.80–3.71 (m, 1 H), 3.64–3.53 (m, 1 H), 2.96–2.85 (m, 1 H), 2.80–2.71 (m, 1 H), 2.61 (m, 4 H), 2.28 (dd, *J* = 9.5, 4.0 Hz, 2 H), 2.12–2.05 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.37, 167.46, 164.06, 139.27, 135.07, 130.49, 129.12, 128.06, 126.27, 115.71, 67.36, 54.60, 48.96, 47.03, 36.40, 27.22, 26.65, 23.69, 22.17. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{20}H_{21}O_2N_3ClS$: 402.10532; found: 402.10509.

***tert*-Butyl 4-[3-(4-Chlorophenyl)-2-cyano-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonyl]piperazine-1-carboxylate (5h)**

Yield: 134 mg (55%); white solid; mp 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 5.45 (s, 1 H), 4.38 (s, 1 H), 3.96–3.25 (m, 8 H), 2.65–2.56 (m, 2 H), 2.29–2.24 (m, 2 H), 2.11–2.04 (m, 2 H), 1.48 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.40, 167.21, 164.17, 154.36, 135.76, 134.70, 129.50, 115.84, 115.65, 80.92, 77.06, 67.29, 54.48, 46.36, 44.13, 36.41, 28.37, 23.68, 22.18. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{25}H_{30}O_4N_4Cl$: 485.19561; found: 485.19501.

3-(4-Chlorophenyl)-4-oxo-2-(pyrrolidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5i)

Yield: 98 mg (53%); off-white solid; mp 258–260 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 5.47 (s, 1 H), 4.47 (s, 1 H), 3.75–3.40 (m, 4 H), 2.60 (t, *J* = 5.6 Hz, 2 H), 2.37–2.21 (m, 2 H), 2.12–2.02 (m, 4 H), 1.96 (dd, *J* = 13.1, 5.7 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.58, 167.69, 162.77, 136.22, 134.39, 129.30, 115.41, 77.06, 67.97, 53.43, 48.51, 47.56, 36.43, 26.70, 23.65, 23.34, 22.22. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{20}H_{21}O_2N_3Cl$: 370.13359; found: 370.13302.

3-(4-Fluorophenyl)-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5j)

Yield: 98 mg (73%); white solid; mp 210–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.12 (m, 2 H), 7.14–6.90 (m, 2 H), 5.44 (s, 1 H), 4.40 (s, 1 H), 3.84–3.36 (m, 4 H), 2.67–2.46 (m, 2 H), 2.34–2.17 (m, 2 H), 2.09 (dd, *J* = 12.3, 6.1 Hz, 2 H), 1.86–1.58 (m, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.36, 167.35, 163.89, 163.58, 161.43, 133.46, 129.65, 116.18, 115.96, 115.76, 67.51, 54.19, 47.56, 45.47, 36.43, 25.34, 25.11, 24.04, 23.66, 22.19. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{20}H_{21}O_2N_3Cl$: 354.17359; found: 354.17302

2-(2,6-Dimethylmorpholine-4-carbonyl)-3-(4-fluorophenyl)-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5k)

Yield: 119 mg (60%); off-white solid; mp 150–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 10.3 Hz, 2 H), 7.08 (t, *J* = 8.4 Hz, 2 H), 5.49 (s, 1 H), 4.47–4.24 (m, 2 H), 4.06 (dd, *J* = 83.5, 21.9 Hz, 1 H), 3.82 (d, *J* = 12.4 Hz, 1 H), 3.64 (d, *J* = 31.2 Hz, 2 H), 2.58 (tt, *J* = 23.9, 11.8 Hz, 3 H), 2.29 (t, *J* = 19.2 Hz, 2 H), 2.15–2.00 (m, 2 H), 1.21 (dd, *J* = 47.3, 12.0 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.47, 167.16, 164.01, 163.66, 133.14, 129.71, 116.34, 116.12, 71.81, 71.09, 70.64, 67.43, 55.45, 53.72, 52.16, 49.43, 36.45, 23.71, 22.21, 18.67. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{22}H_{25}O_3N_3F$: 398.18865; found: 398.18845.

3-(4-Fluorophenyl)-4-oxo-2-(4-phenylpiperazine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5l)

Yield: 153 mg (69%); white solid; mp 232–234 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 1 H), 7.12–7.07 (m, 1 H), 6.95 (dd, *J* = 7.7, 3.6 Hz, 1 H), 5.49 (s, 1 H), 4.47 (s, 1 H), 4.06–3.58 (m, 4 H), 3.48–2.89 (m, 4 H), 2.70–2.49 (m, 2 H), 2.42–2.19 (m, 2 H), 2.09 (t, *J* = 6.3 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.42, 167.18, 164.01, 161.54, 150.48, 133.24, 129.74, 129.37, 121.23, 117.05, 116.36, 116.14, 115.94, 67.49, 54.43, 49.41, 48.82, 46.54, 44.19, 36.45, 23.69, 22.21. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{26}H_{26}O_2N_4F$: 445.20385; found: 445.20343.

3-(4-Fluorophenyl)-2-[4-(4-fluorophenyl)piperazine-1-carbonyl]-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5m)

Yield: 173 mg (75%); white solid; mp 230–232 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2 H), 7.12–7.05 (m, 2 H), 7.03–6.96 (m, 2 H), 6.93–6.84 (m, 2 H), 5.46 (s, 1 H), 4.46 (s, 1 H), 4.03 (d, *J* = 12.5 Hz, 1 H), 3.90–3.57 (m, 3 H), 3.35–2.99 (m, 4 H), 2.60 (m, 2 H), 2.31–2.24 (m, 2 H), 2.09 (t, *J* = 6.2 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.45, 167.07, 164.03, 161.57, 159.22, 156.82, 147.11, 133.20, 129.81, 129.72, 119.04, 116.39, 116.18,

116.00, 115.78, 67.45, 54.47, 50.42, 49.79, 46.60, 44.22, 36.47, 23.73, 22.23. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{26}H_{25}O_2N_4F_2$: 463.19430; found: 463.19401.

2-[4-(3-Chlorophenyl)piperazine-1-carbonyl]-3-(4-fluorophenyl)-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5n)

Yield: 134 mg (64%); white solid; mp 248–250 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H), 7.22–7.18 (m, 1 H), 7.12–7.07 (m, 2 H), 6.92–6.89 (m, 2 H), 6.82–6.78 (m, 1 H), 5.44 (s, 1 H), 4.45 (s, 1 H), 4.13–3.57 (m, 4 H), 3.24 (dd, *J* = 71.6, 62.7 Hz, 4 H), 2.65–2.57 (m, 2 H), 2.28 (m, 2 H), 2.12–2.07 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.44, 167.13, 164.05, 161.56, 151.51, 135.17, 133.15, 130.30, 129.80, 129.72, 120.90, 116.89, 116.40, 116.18, 115.90, 115.84, 114.80, 77.06, 67.47, 54.42, 48.88, 48.30, 46.31, 43.99, 36.44, 23.70, 22.21. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{26}H_{25}O_2N_4ClF$: 479.16507; found: 479.16446.

3-(4-Fluorophenyl)-2-[4-(4-methoxyphenyl)piperazine-1-carbonyl]-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5o)

Yield: 166 mg (70%); off-white solid; mp 158–160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H), 7.11–7.06 (m, 2 H), 6.94–6.89 (m, 2 H), 6.87–6.83 (m, 2 H), 5.47 (s, 1 H), 4.46 (s, 1 H), 4.00 (d, *J* = 11.1 Hz, 1 H), 3.83 (s, 1 H), 3.78 (s, 3 H), 3.76–3.64 (m, 2 H), 3.27–2.97 (m, 4 H), 2.61 (q, *J* = 6.5 Hz, 2 H), 2.27 (dd, *J* = 11.3, 6.2 Hz, 2 H), 2.09 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.45, 167.20, 163.97, 161.53, 154.85, 144.66, 133.23, 129.73, 119.34, 116.35, 116.01, 114.62, 77.07, 67.47, 55.58, 54.43, 50.87, 50.22, 46.72, 44.32, 36.45, 23.70, 22.21. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{27}H_{28}O_3N_4F$: 475.21482; found: 475.21400.

3-(4-Fluorophenyl)-2-[4-(4-nitrophenyl)piperazine-1-carbonyl]-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5p)

Yield: 176 mg (72%); yellow solid; mp 242–244 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.11 (m, 2 H), 7.33–7.28 (m, 2 H), 7.16–7.06 (m, 2 H), 6.93–6.83 (m, 2 H), 5.42 (s, 1 H), 4.45 (s, 1 H), 4.14 (d, *J* = 10.5 Hz, 1 H), 3.92 (s, 1 H), 3.70 (d, *J* = 44.9 Hz, 4 H), 3.49–3.31 (m, 2 H), 2.66–2.57 (m, 2 H), 2.32–2.24 (m, 2 H), 2.09 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.94, 167.29, 162.04, 159.41, 152.98, 136.82, 132.53, 128.71, 124.29, 114.62, 114.19, 113.98, 111.69, 110.54, 66.89, 52.00, 44.51, 43.83, 41.95, 34.84, 21.86, 20.67. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{26}H_{25}O_4N_5F$: 490.18927; found: 490.18851

3-(4-Fluorophenyl)-4-oxo-2-[4-(pyridin-2-yl)piperazine-1-carbonyl]-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5q)

Yield: 162 mg (73%); off-white solid; mp 178–180 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23–8.19 (m, 1 H), 7.57–7.50 (m, 1 H), 7.33–7.28 (m, 2 H), 7.09 (t, *J* = 8.5 Hz, 2 H), 6.75–6.65 (m, 2 H), 5.69 (s, 1 H), 4.47 (s, 1 H), 4.12–3.39 (m, 8 H), 2.83–2.47 (m, 2 H), 2.37–2.18 (m, 2 H), 2.08 (dd, *J* = 12.4, 6.2 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.44, 167.13, 164.05, 151.51, 135.17, 133.12, 130.30, 129.80, 120.90, 116.89, 116.40, 115.84, 114.80, 67.47, 54.42, 48.88, 48.30, 46.31, 43.99, 36.44, 23.70, 22.21. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{25}H_{25}O_2N_5F$: 446.21482; found: 446.21400

2-(4-Ethylpiperazine-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5r)

Yield: 129 mg (65%); white solid; mp 142–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 1 H), 7.10–7.05 (m, 1 H), 5.54 (d, *J* = 3.8 Hz, 1 H), 4.42 (s, 1 H), 3.87 (d, *J* = 38.8 Hz, 1 H), 3.74–3.52 (m, 3 H), 2.69–2.55 (m, 4 H), 2.53–2.40 (m, 4 H), 2.29–2.24 (m, 2 H), 2.11–2.05 (m, 2 H), 1.11 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.42, 167.21, 163.76, 161.50, 133.28, 129.79, 116.29, 116.07, 115.90, 67.42, 54.36, 52.09, 51.51, 46.63, 44.21, 36.45, 23.69, 22.20, 11.93. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{22}H_{25}N_4O_2F$: 397.203979; found: 397.20519

3-(4-Methoxyphenyl)-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5s)

Yield: 117 mg (62%); white solid; mp 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 2 H), 6.93–6.87 (m, 2 H), 5.47 (s, 1 H), 4.38 (s, 1 H). 3.79 (s, 3 H), 3.78–3.71 (m, 1 H), 3.63 (d, *J* = 14.8 Hz, 1 H), 3.58–3.44 (m, 2 H), 2.59 (t, *J* = 8.0 Hz, 2 H), 2.28–2.23 (m, 2 H), 2.07 (dt, *J* = 11.9, 5.9 Hz, 2 H), 1.73 (s, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.51, 167.05, 163.88, 159.63, 129.60, 129.10, 116.15, 114.47, 77.06, 67.76, 55.23, 54.39, 47.61, 45.44, 36.51, 25.38, 25.14, 24.11, 23.73, 22.25. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{22}H_{26}N_3O_3$: 380.19720; found: 380.19687.

4-Oxo-2-(piperidine-1-carbonyl)-3-(3,4,5-trimethoxyphenyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5t)

Yield: 128 mg (58%); white solid; mp 198–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 (s, 2 H), 5.49 (s, 1 H), 4.34 (s, 1 H), 3.85 (d, *J* = 6.1 Hz, 9 H), 3.71–3.52 (m, 4 H), 2.66–2.54 (m, 2 H), 2.33–2.17 (m, 2 H), 2.12–2.06 (m, 2 H), 1.82–1.61 (m, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.47, 167.11, 163.82, 153.53, 138.34, 133.09, 115.96, 105.39, 67.63, 60.86, 56.27, 55.40, 47.59, 45.42, 36.54, 25.35, 24.09, 23.76, 22.30. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{22}H_{26}N_3O_3$: 440.218000; found: 440.21798.

4-Oxo-3-phenyl-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5u)

Yield: 115 mg (66%); white solid; mp 204–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38 (ddd, *J* = 7.5, 4.4, 1.3 Hz, 2 H), 7.34–7.29 (m, 3 H), 5.44 (s, 1 H), 4.41 (s, 1 H), 3.80–3.71 (m, 1 H), 3.67–3.44 (m, 3 H), 2.60 (dd, *J* = 11.5, 5.7 Hz, 2 H), 2.29–2.23 (m, 2 H), 2.12–2.05 (m, 2 H), 1.62 (dt, *J* = 16.2, 7.7 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.40, 167.30, 163.77, 137.55, 129.07, 128.63, 127.94, 116.01, 77.06, 67.61, 54.93, 47.59, 45.45, 36.47, 25.36, 25.11, 24.07, 23.69, 22.21. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{21}H_{24}N_3O_2$: 350.18630; found: 350.18632.

4-Oxo-2-(piperidine-1-carbonyl)-3-(*o*-tolyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5v)

Yield: 116 mg (64%); white solid; mp 162–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.5 Hz, 1 H), 7.24–7.14 (m, 3 H), 5.48 (s, 1 H), 4.67 (s, 1 H), 3.98 (s, 1 H), 3.44 (dd, *J* = 105.7, 41.0 Hz, 3 H), 2.58 (s, 3 H), 2.57–2.53 (m, 2 H), 2.21 (dt, *J* = 8.2, 4.6 Hz, 2 H), 2.03 (dd, *J* = 11.4, 5.2 Hz, 2 H), 1.68 (d, *J* = 21.4 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.31, 166.43, 164.05, 136.46, 135.59, 130.62, 128.19, 127.93, 126.78, 118.52, 116.44, 67.69, 50.22, 47.54, 45.61, 36.48, 25.31, 24.12, 23.74, 22.05, 19.72. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{22}H_{26}N_3O_2$: 364.20351; found: 364.20195.

3-(4-Nitrophenyl)-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5w)

Yield: 106 mg (54%); white solid; mp 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.22 (m, 2 H), 7.52–7.47 (m, 2 H), 5.57 (s, 1 H), 4.51 (s, 1 H), 3.82 (d, *J* = 13.0 Hz, 1 H), 3.51 (dt, *J* = 18.0, 12.1 Hz, 3 H), 2.63 (dd, *J* = 10.2, 5.5 Hz, 2 H), 2.27 (dd, *J* = 14.7, 6.9 Hz, 2 H), 2.10 (dd, *J* = 12.3, 6.1 Hz, 2 H), 1.62 (s, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.32, 167.84, 163.03, 147.97, 144.88, 129.16, 124.42, 115.61, 115.53, 66.87, 54.45, 47.63, 45.67, 36.34, 25.35, 25.15, 24.02, 23.73, 22.17. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{21}H_{22}N_4O_4$: 394.16420; found: 394.16340.

3-(4-Fluorophenyl)-6,6-dimethyl-4-oxo-2-(piperidine-1-carbonyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5x)

Yield: 142mg (72%); white solid; mp 160–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (ddd, *J* = 7.0, 4.5, 2.0 Hz, 2 H), 7.10–7.05

(m, 2 H), 5.35 (s, 1 H). 4.40 (s, 1 H), 3.79 (d, *J* = 13.2 Hz, 1 H), 3.61 (d, *J* = 13.4 Hz, 1 H), 3.47 (dd, *J* = 23.6, 14.8 Hz, 2 H), 2.44 (d, *J* = 5.8 Hz, 2 H), 2.14 (dd, *J* = 40.0, 16.4 Hz, 2 H), 1.73 (d, *J* = 4.7 Hz, 6 H), 1.10 (d, *J* = 2.3 Hz, 6 H).^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.83, 166.33, 163.92, 163.61, 161.46, 133.53, 129.64, 116.26, 116.05, 115.95, 114.47, 67.67, 54.11, 50.57, 47.60, 45.51, 37.42, 34.65, 29.07, 28.28, 25.37, 25.10, 24.06. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{23}H_{27}O_2N_3F$: 396.20818; found: 396.20904.

3-(4-Fluorophenyl)-6,6-dimethyl-4-oxo-2-[4-(pyridin-2-yl)piperazine-1-carbonyl]-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5y)

Yield: 172 mg (73%); white solid; mp 164–166 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23–8.19 (m, 1 H), 7.53 (ddd, *J* = 8.9, 7.2, 2.0 Hz, 1 H), 7.34–7.29 (m, 2 H), 7.13–7.07 (m, 2 H), 6.74–6.70 (m, 1 H), 6.68 (d, *J* = 8.6 Hz, 1 H), 5.41 (s, 1 H), 4.45 (s, 1 H), 3.98 (d, *J* = 12.9 Hz, 1 H), 3.84 (t, *J* = 9.0 Hz, 3 H), 3.75–3.55 (m, 3 H), 3.50–3.40 (m, 1 H), 2.46 (s, 2 H), 2.18–2.09 (m, 2 H), 1.11 (d, *J* = 4.3 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.79, 165.99, 164.21, 158.72, 148.08, 137.91, 133.24, 129.79, 116.42, 116.21, 115.92, 114.57, 107.46, 67.68, 54.35, 50.62, 46.23, 44.98, 44.50, 43.99, 37.46, 34.70, 28.97, 28.38. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{27}H_{29}O_2N_5F$: 474.23108; found: 474.22998.

3-(4-Fluorophenyl)-4-oxo-6-phenyl-2-[4-(pyridin-2-yl)piperazine-1-carbonyl]-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carbonitrile (5z)

Yield: 164 mg (63%); white solid; mp 210–212 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29–8.13 (m, 1 H), 7.60–7.48 (m, 1 H), 7.39–7.31 (m, 2 H), 7.25 (m, 5 H), 7.10 (m, 2 H), 6.72 (dd, *J* = 7.1, 4.9 Hz, 1 H), 6.69 (d, *J* = 8.5 Hz, 1 H), 5.58 (d, *J* = 15.4 Hz, 1 H), 4.50 (d, *J* = 7.9 Hz, 1 H), 3.98 (d, *J* = 12.5 Hz, 1 H), 3.80 (t, *J* = 18.3 Hz, 3 H), 3.76–3.56 (m, 3 H), 3.53–3.40 (m, 2 H), 2.90–2.79 (m, 2 H), 2.57–2.54 (m, 2 H).^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.03, 164.08, 158.68, 148.03, 142.26, 137.85, 129.84, 128.81, 127.18, 126.83, 126.72, 116.29, 116.08, 115.76, 114.52, 107.44, 77.06, 67.66, 54.36, 46.20, 44.94, 44.47, 43.93, 43.51, 41.07, 40.22, 31.28, 30.89. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{31}H_{29}O_2N_5F$: 522.23097; found: 522.22998.

3-(4-Chlorophenyl)-2-cyano-*N*,*N*-diethyl-4-oxo-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carboxamide (5a′)

Yield: 190 mg (52%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.27 (d, *J* = 2.6 Hz, 1 H), 7.23–7.19 (m, 1 H), 5.69 (s, 1 H), 4.38–4.35 (m, 1 H), 3.54 (dt, *J* = 13.5, 6.8 Hz, 1 H), 3.50–3.37 (m, 3 H), 2.59 (dd, *J* = 12.4, 6.2 Hz, 2 H), 2.28 (dd, *J* = 6.9, 4.7 Hz, 2 H), 2.08 (dt, *J* = 12.6, 6.2 Hz, 2 H), 1.33 (t, *J* = 6.9 Hz, 3 H), 1.19 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.33, 167.80, 164.26, 139.64, 134.89, 130.33, 128.91, 128.06, 126.25, 115.81, 115.20, 67.54, 54.56, 42.27, 41.64, 36.41, 23.65, 22.17, 12.82, 12.40. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{20}H_{23}N_3O_2Cl$: 372.14882; found: 372.14956.

1-[4-(4-Fluorophenyl)piperazin-1-yl]ethan-1-one (7)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.94 (m, 2 H), 6.92–6.83 (m, 2 H), 3.81–3.73 (m, 2 H), 3.67–3.57 (m, 2 H), 3.13–2.97 (m, 4 H), 2.14 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.05, 158.73, 156.35, 147.52, 118.59, 115.85, 115.53, 50.68, 50.32, 46.22, 41.35, 29.64, 21.30. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{12}H_{16}ON_2F$: 223.12412; found: 223.12470.

Crystal Data for 5a

$C_{24}H_{22}N_3O_2Cl_1$, *M* = 401.88, monoclinic, space group $P2_1/n$ (No.14), *a* =14.005(12)Å, *b* = 14.440(12)Å, *c* = 10.998(9)Å, *α* = 90°, *β* = 112.583(18)°, *γ* = 90°, *V* = 2054(3)Å^3, *Z* = 4, D_c = 1.300 g/cm^3, F_{000} = 848, Bruker D8 QUEST PHOTON-100, Mo Kα radiation, *λ* = 0.71073 Å, *T* = 293(2) K, $2\theta_{max}$ = 50°, μ = 0.212 mm^{-1}, 13591 reflections collected, 3595 unique (R_{int} = 0.0667), 265 parameters, *R1* = 0.0618, *wR2* = 0.1542, *R* indices based on 2598 reflections with I > 2σ(I) (refinement on F^2), final *GooF* = 1.025, largest difference hole and peak = –0.390 and 0.570 e Å^{-3} (Figure 1). CCDC 2065225 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

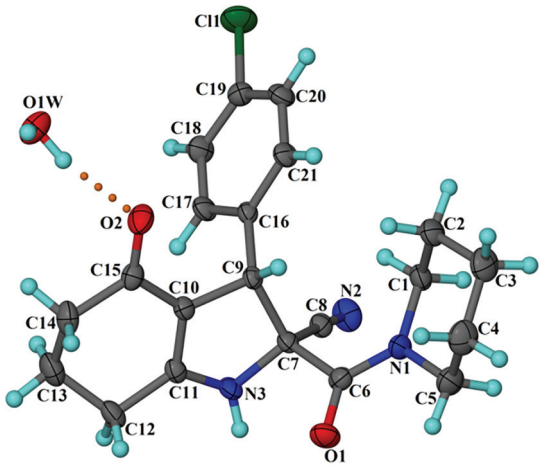

Figure 1 ORTEP diagram of compound **5a** with atom numbering. The compound crystallized as monohydrate. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radius. Hydrogen bonds are shown in dotted lines.