Tetrahedron 67 (2011) 5469–5476

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A convergent construction of 1,4-dihydropyridine scaffold containing indole fragment

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ARTICLE INFO

Article history:
Received 8 March 2011
Received in revised form 7 May 2011
Accepted 17 May 2011
Available online 25 May 2011

Keywords:
One-pot
Multi-component reaction
Indole
Hexahydroquinoline/dihydropyridine derivatives

ABSTRACT

Accompanying with the construction of 1,4-dihydropyridine scaffold, indol-3-yl-5-oxo-1,4,5,6,7,8-hexahydroquinoline, and indol-3-yl-1,4-dihydropyridine derivatives were facilely synthesized through three-component reactions of aromatic aldehydes, 3-cyanoacetyl indoles with 3-amino-2-enones in the presence of ammonium acetate. The 1,4-dihydropyridine core structure can be efficiently aromatized in the presence of stoichiometric 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). This chemistry provides an efficient and promising synthetic strategy to diversity-oriented construction of unaromatized and aromatized desired products. The advantages of the present protocol are atom-economy, simple work-up and easy purification of products by non-chromatographic methods.

1. Introduction

4-Aryl-1,4-dihydropyridines are analogues of NADH coenzymes, which have been explored for their calcium channel activity.[1a–c] This specific heterocyclic rings is common in many biological activities such as antihypertension,[1d] antioxidant,[1e] antiviral,[1f] and anticancer activity.[1g] For example, Nifedipine[2] (Fig. 1) represents the prototype 1,4-dihydropyridine structure found useful in both antianginal and antihypertensive treatments. The 1,4-dihydropyridine structures have been introduced in condensed systems, such as quinoline scaffolds.[3] Quinoline derivatives have played a unique role in the design and synthesis of novel biologically active compounds serving as antiinflammatory,[4a] antiasthmatic,[4b] antituberculosis,[4c] antibacterial,[4d] antihypertensive,[4e] antitumor,[4f] and most notably, antimalarial agents.[4g]

3-substituted indoles are privileged medicinal scaffolds, which have been found in a fascinating array of bioactive natural products and pharmaceutical compounds.[5,6] New indole alkaloids with a broad spectrum of biological properties are being discovered rapidly as marine invertebrate metabolites.[7–10] For examples, nortopsentins A–C exhibit in vitro cytotoxicity against P388 cells;[11] hamacanthin B reveals cytotoxic activities against a wide range of human tumor cell lines with GI50 values at micromolar concentration;[12] meridianins A–E show cytotoxicity toward murine tumor cell lines and have potent inhibition against several protein kinases.[13] It is valuable to synthesize libraries of diverse compounds containing 3-substituted indole scaffold for biomedical screenings.

A wide range of advantages offered by multi-component reactions (MCRs), such as high degree of atom-economy, convergence, ease of execution, and access to complex molecules has been recognized in the past many years.[14] The diversity generating potential of MCRs and their utility in preparing libraries for screening

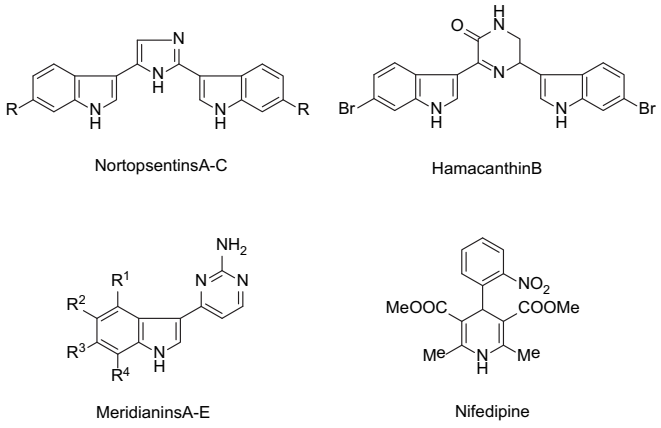

Fig. 1. Representatives of important indol-3-yl substituted heterocycles and 1,4-dihydropyridines.

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doi:10.1016/j.tet.2011.05.065

functional molecules have also been well-appreciated.[14d,15,16] Due to the potent and diverse biological activities of indoles, polyhydroquinolinone and 1,4-dihydropyridine derivatives, out of our interest in the multi-component syntheses,[17] and guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably,[18] herein, we report the synthesis of indol-3-yl substituted polyhydroquinolinone and 1,4-dihydropyridine derivatives via a facile, atom-economical, one-pot, three-component condensation reaction.

2. Results and discussion

The reaction of equimolar amount 4-bromobenzaldehyde **1**{1}, 3-cynaoacetyl indole **2**{1}, and 3-amino-5,5-dimethylcyclohex-2-enone **3**{1} as a model system was examined to establish the feasibility of the strategy and optimize the reaction conditions (Scheme 1). The results are summarized in Table 1. In this reaction, only unaromatized product **4**{1, 1, 1} was isolated; the aromatized product **5**{1, 1, 1} was not detected. However, some literatures[3u,17j] reported that only aromatized products or mixed products (unaromatized and aromatized products) were obtained in the absence of an additional oxidant in open vessels. It is indicated that unaromatized product **4**{1, 1, 1} is stable and cannot easily be oxidized by oxygen. In the absence of any catalyst, the product **4**{1, 1, 1} was obtained in a low yield of 27% even though the reaction was carried out in ethanol for 12 h when the oil bath temperature is 80 °C (Table 1, entry 1). Then some classical acids and bases were screened for this model reaction. However, product yields were less than 67% (Table 1, entries 2–6). When 1 equiv NH_4OAc was used in this reaction, the yield was improved to 80%. Afterward, various solvents were examined for this reaction. When the reaction solvent was changed from DMF to 1,4-dioxane, acetonitrile, MeOH or *n*-PrOH, the compound **4**{1, 1, 1} was produced in moderate yields (Table 1, entries 8–12). When H_2O was used as the reaction solvent, the compound **4**{1, 1, 1} was obtained in trace amount (Table 1, entry 13). Finally, it was found that *n*-BuOH was the most suitable solvent for this reaction (Table 1, entry 14). The reaction time was reduced to 8 h and the yield of **4**{1, 1, 1} was 90% when the oil bath temperature is 120 °C (Table 1, entry 15).

Encouraged by this success, we extended this reaction to commercially available aldehydes, a range of 3-cyanoacetyl indoles with electron-withdrawing or electron-donating substituents in indole heterocycles, cyclic and acyclic 3-amino-2-enones (Fig. 2) under the same conditions, resulting in moderate to high yields of the corresponding new indol-3-yl substituted heterocycles (Scheme 2). The results are summarized in Table 2. As shown in Table 2, when aromatic aldehydes with electron-withdrawing groups (such as halide groups) (Table 2, entries 1–5, entries 10–13 and entry 32) were used, the corresponding products were obtained in high yield. However, when the electron-withdrawing group was nitro (Table 2, entries 6–9), the yields of products were a little lower. When aromatic aldehydes

Table 1
Optimization of reaction conditions

Entry	Catalyst	Temperature[a] (°C)	Time (h)	Solvent	Yield[b] (%)
1	None	80	12	EtOH	27
2	*p*-TSA·H_2O (0.2 equiv)	80	12	EtOH	51
3	CAN (0.2 equiv)	80	12	EtOH	35
4	$InCl_3$ (0.2 equiv)	80	12	EtOH	63
5	NaOH (0.2 equiv)	80	12	EtOH	Trace
6	DABCO (0.2 equiv)	80	12	EtOH	67
7	NH_4OAc (1.0 equiv)	80	12	EtOH	80
8	NH_4OAc (1.0 equiv)	80	12	DMF	56
9	NH_4OAc (1.0 equiv)	80	12	1,4-Dioxane	67
10	NH_4OAc (1.0 equiv)	80	12	CH_3CN	69
11	NH_4OAc (1.0 equiv)	70	12	MeOH	70
12	NH_4OAc (1.0 equiv)	80	12	*n*-PrOH	65
13	NH_4OAc (1.0 equiv)	80	12	H_2O	Trace
14	NH_4OAc (1.0 equiv)	80	12	*n*-BuOH	82
15	NH_4OAc (1.0 equiv)	120	8	*n*-BuOH	90

[a] Oil bath temperature.
[b] Isolated yield.

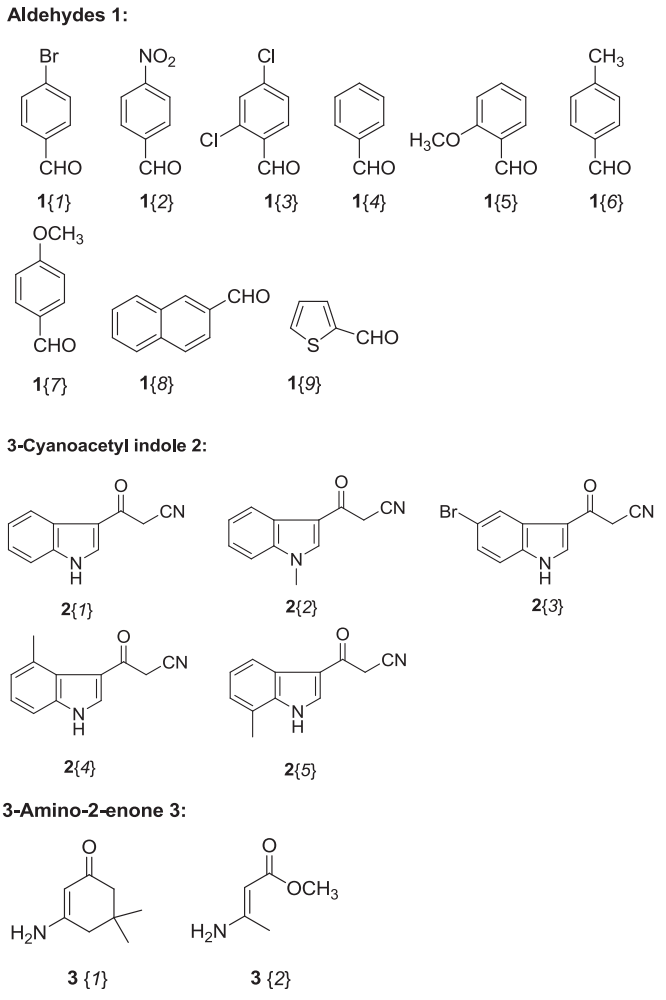
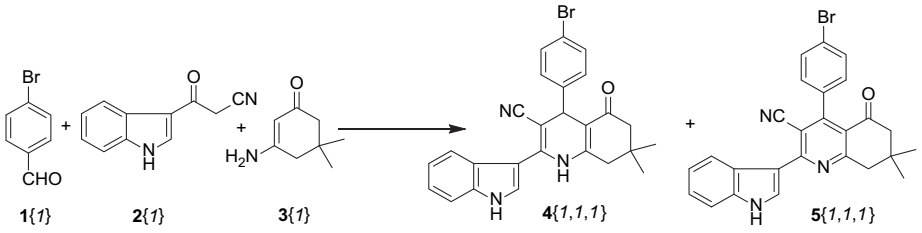
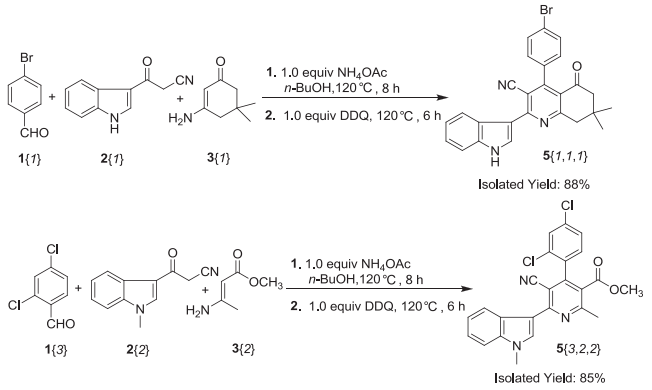


Fig. 2. Diversity of reagents.



Scheme 1. Model reaction.

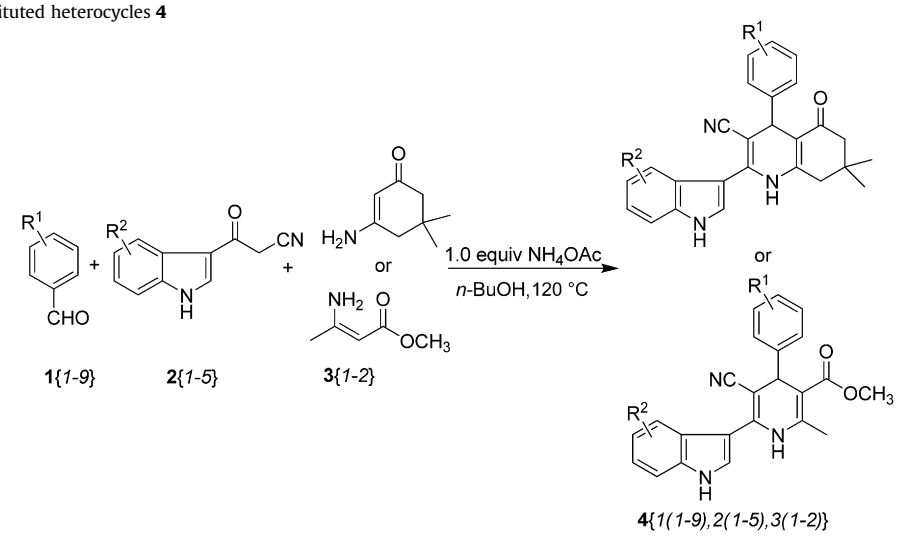


Scheme 2. One-pot, two-step synthesis of 2-(1*H*-indol-3-yl)-tetrahydroquinoline and 3-(pyridin-2-yl)-1*H*-indole derivatives.

with electron-donating groups (such as methyl and methoxyl groups), benzaldehyde, 2-naphthaldehyde or heterocyclic aldehyde were used, the reaction time needed to be prolonged to 12 h and the yields of the corresponding products were mostly moderate (Table 2, entries 14–31).

Considering that pyridine is also a core skeleton in bioactive molecules, the aromatization of the product **4** was attempted by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant. It was fortunately found that products **5**{1,1,1} and **5**{3,2,2} could be attained in high yield via one-pot, two-step reactions (Scheme 2). It provided an effective route to synthesis of 1,4-dihydropyridine and pyridine scaffold in a controlled manner. In this work, the products were characterized by melting point, IR, NMR and HRMS (or LC–MS). Furthermore, the structure of **4**{1,3,1} was established by X-ray crystallographic analysis (see Supplementary data).

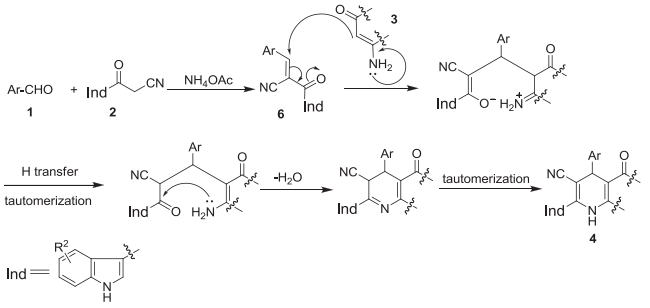
Table 2
Synthesis of 3-indol-yl-substituted heterocycles **4**



Entry	Product	Time (h)	Yield[a] (%)
1	**4**{1,1,1}	8	90
2	**4**{1,2,1}	8	87
3	**4**{1,3,1}	8	88
4	**4**{1,4,1}	8	82
5	**4**{1,5,1}	8	84
6	**4**{2,1,1}	8	80
7	**4**{2,2,1}	8	77
8	**4**{2,4,1}	8	75
9	**4**{2,5,1}	8	79
10	**4**{3,1,1}	8	93
11	**4**{3,2,1}	8	90
12	**4**{3,3,1}	8	89
13	**4**{3,4,1}	8	85
14	**4**{4,1,1}	12	83
15	**4**{4,2,1}	12	81
16	**4**{4,4,1}	12	77
17	**4**{4,5,1}	12	79
18	**4**{5,1,1}	12	80
19	**4**{5,2,1}	12	79
20	**4**{5,4,1}	12	76
21	**4**{5,5,1}	12	78
22	**4**{6,1,1}	12	81
23	**4**{6,2,1}	12	77
24	**4**{6,5,1}	12	73
25	**4**{7,1,1}	12	75
26	**4**{7,2,1}	12	72
27	**4**{7,4,1}	12	70
28	**4**{7,5,1}	12	71
29	**4**{8,1,1}	12	66
30	**4**{8,2,1}	12	61
31	**4**{9,2,1}	12	74
32	**4**{3,2,2}	12	85

[a] Isolated yield.

Although the detailed mechanism of the above reaction remains to be fully clarified, according to the experimental observation, the intermediate **6** could be obtained rapidly from substrates **1** and **2** in the presence of NH_4OAc and compound **4** could be formed from the intermediate **6** via Michael addition reaction with substrate **3** followed by intramolecular cyclization and tautomerization (Scheme 3).



Scheme 3. Possible mechanism for the formation of product **4**.

3. Conclusion

In summary, we have demonstrated a simple, atom-economical, and efficient approach for the synthesis of new indol-3-yl substituted derivatives via one-pot, three-component reactions using readily available starting materials and catalyst. It provides a promising synthetic strategy to construct unaromatized and aromatized products. This method incorporates both indole and other *N*-containing heterocycle moieties into one single molecule. In view of those molecules having either functionality, these novel compounds may potentially have enhanced biological activities. Prominent among the advantages of this method are atom-economy, operational simplicity, simple work-up procedures and easy product purification using non-chromatographic methods. Further reactivity studies and synthetic applications of this methodology are in progress in our laboratory.

4. Experimental section

4.1. General experimental method

All reactions were carried out in oven-dried glassware. Progresses of reactions were monitored by Thin Layer Chromatography. Melting points are uncorrected. IR spectra were recorded on an FT-IR spectrometer using KBr optics. NMR spectra were recorded at room temperature in DMSO-d_6 at 300/400 Hz for ^{1}H NMR and 75/100 Hz for ^{13}C NMR. High resolution mass spectra (HRMS) were obtained on a TOF-MS instrument with EI source. Liquid chromatography-mass spectra (LC–MS) were obtained on LC–MS instrument with ESI source. X-ray diffraction data were recorded with graphite monochromatic Mo Kα radiation.

4.2. Procedures and analytical data

Typical procedure for the synthesis of **4**. Aldehyde **1** (0.5 mmol), 3-cynaoacetyl indole **2** (0.5 mmol), and 3-amino-2-enone **3** (0.5 mmol) at 120 °C was stirred for 8 h or 12 h in 2 mL *n*-BuOH in the presence of NH_4OAc (0.5 mmol). After the completion (monitored by TLC), water (50 mL) was added. The mixture was filtered and the solid product was washed with water (3×5 mL). The crude product was purified by recrystallization from EtOH to give **4**.

Typical procedure for the synthesis of **5**. Aldehyde **1** (0.5 mmol), 3-cynaoacetyl indole **2** (0.5 mmol), and 3-amino-2-enone **3** (0.5 mmol) at 120 °C was stirred for 8 h or 12 h in 2 mL *n*-BuOH in the presence of NH_4OAc (0.5 mmol). After the completion (monitored by TLC), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.5 mmol) was added. The reaction was stirred for another 6 h at 120 °C. After the complete oxidation (monitored by TLC), water (50 mL) was added. The mixture was filtered and the solid product was washed with water (3×5 mL). The crude product was purified by recrystallization from EtOH to give **5**.

*4.2.1. 4-(4-Bromophenyl)-2-(1H-indol-3-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{1, 1, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): *ν* 3421, 3277, 3061, 2958, 2191, 1626, 1386 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 11.76 (s, 1H, NH), 9.63 (s, 1H, NH), 7.79 (s, 1H, ArH), 7.55 (d, 2H, *J*=7.6 Hz, ArH), 7.48 (d, 2H, *J*=7.2 Hz, ArH), 7.26 (d, 2H, *J*=8.0 Hz, ArH), 7.18–7.22 (m, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 4.59 (s, 1H, CH), 2.04–2.60 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (*δ*, ppm): 194.6, 150.4, 145.5, 143.5, 136.0, 131.4, 129.5, 127.7, 124.9, 122.2, 120.9, 120.1, 119.9, 119.8, 112.3, 107.7, 107.3, 84.1, 50.2, 39.6, 38.4, 32.0, 29.2, 26.6. LC–MS: calculated for $C_{26}H_{23}BrN_3O$ [MH$^+$]: 472.1019, found 472.1012.

*4.2.2. 4-(4-Bromophenyl)-7,7-dimethyl-2-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{1, 2, 1}).* Cream yellow solid; mp 149–149.5 °C. IR (KBr): *ν* 3412, 3276, 3076, 2957, 2196, 1635, 1369 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 9.67 (s, 1H, NH), 7.84 (s, 1H, ArH), 7.55 (d, 3H, *J*=8.0 Hz, ArH), 7.48 (d, 1H, *J*=7.6 Hz, ArH), 7.24–7.29 (m, 3H, ArH), 7.18 (t, 1H, *J*=7.6 Hz, ArH), 4.58 (s, 1H, CH), 3.86 (s, 3H, CH_3), 2.04–2.60 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (*δ*, ppm): 194.7, 150.4, 145.5, 143.0, 136.5, 131.5, 131.5, 129.5, 125.3, 122.3, 120.8, 120.4, 120.1, 119.8, 110.6, 107.7, 106.3, 84.1, 50.2, 38.4, 32.9, 32.0, 29.2, 26.6. LC–MS: calculated for $C_{27}H_{25}BrN_3O$ [MH$^+$]: 486.1176, found 486.1198.

*4.2.3. 2-(5-Bromo-1H-indol-3-yl)-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{1, 3, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): *ν* 3280, 3212, 3075, 2959, 2199, 1630, 1382 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 11.98 (s, 1H, NH), 9.68 (s, 1H, NH), 7.86 (s, 1H, ArH), 7.62 (s, 1H, ArH), 7.55 (d, 2H, *J*=8.0 Hz, ArH), 7.47 (d, 1H, *J*=8.4 Hz, ArH), 7.33 (d, 1H, *J*=8.4 Hz, ArH), 7.27 (d, 2H, *J*=8.0 Hz, ArH), 4.59 (s, 1H, CH), 2.03–2.62 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (*δ*, ppm): 194.6, 150.3, 145.4, 142.8, 134.8, 131.4, 129.5, 129.3, 126.6, 124.8, 122.0, 120.6, 119.8, 119.8, 114.3, 112.7, 107.7, 106.9, 84.7, 50.1, 38.3, 32.0, 29.2, 26.5. LC–MS: calculated for $C_{26}H_{22}Br_2N_3O$ [MH$^+$]: 550.0124, found 550.0110.

*4.2.4. 4-(4-Bromophenyl)-7,7-dimethyl-2-(4-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{1, 4, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): *ν* 3402, 3268, 3069, 2957, 2197, 1613, 1381 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 11.61 (s, 1H, NH), 9.85 (s, 1H, NH), 7.54–7.60 (m, 3H, ArH), 7.24–7.31 (m, 3H, ArH), 7.08 (s, 1H, ArH), 6.88 (s, 1H, ArH), 4.60 (s, 1H, CH), 2.06–2.45 (m, 7H, CH_2+CH_3), 1.04 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (*δ*, ppm): 194.5, 150.2, 145.1, 144.8, 136.3, 131.4, 129.6, 129.4, 127.1, 124.8, 122.2, 121.4, 120.4, 119.9, 110.0, 107.8, 87.0, 50.2, 38.4, 32.3, 28.7, 27.1, 19.3. LC–MS: calculated for $C_{27}H_{25}BrN_3O$ [MH$^+$]: 486.1176, found 486.1160.

*4.2.5. 4-(4-Bromophenyl)-7,7-dimethyl-2-(7-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{1, 5, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): *ν* 3270, 3201, 3057, 2946, 2191, 1612, 1385 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 11.78 (s, 1H, NH), 9.64 (s, 1H, NH), 7.78 (s, 1H, ArH), 7.55 (d, 2H, *J*=8.0 Hz, ArH), 7.25–7.31 (m, 3H, ArH), 6.99–7.03 (m, 2H, ArH), 4.58 (s, 1H,

CH), 2.03–2.61 (m, 7H, CH_2+CH_3), 1.06 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.6, 150.4, 145.5, 143.6, 135.6, 131.4, 129.5, 127.4, 127.1, 124.7, 122.6, 121.5, 120.9, 120.3, 119.8, 117.5, 107.7, 84.1, 50.2, 38.4, 32.0, 29.2, 26.6, 16.8. HRMS: calculated for $C_{27}H_{24}BrN_3O$ [M^+]: 485.1103, found 485.1097.

*4.2.6. 2-(1H-Indol-3-yl)-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{2, 1, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3349, 3273, 3074, 2955, 2197, 1626, 1350 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.81 (s, 1H, NH), 9.76 (s, 1H, NH), 8.25 (d, 2H, *J*=7.6 Hz, ArH), 7.83 (s, 1H, ArH), 7.59 (d, 2H, *J*=8.0 Hz, ArH), 7.49 (d, 2H, *J*=7.2 Hz, ArH), 7.13–7.22 (m, 2H, ArH), 4.78 (s, 1H, CH), 2.05–2.63 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.4, 153.1, 150.8, 146.3, 143.9, 136.0, 128.5, 127.8, 124.8, 123.8, 122.1, 120.5, 120.0, 119.8, 112.2, 107.2, 107.1, 83.3, 50.1, 32.0, 29.0, 26.6. LC–MS: calculated for $C_{26}H_{23}N_4O_3$ [MH^+]: 439.1770, found 439.1754.

*4.2.7. 7,7-Dimethyl-2-(1-methyl-1H-indol-3-yl)-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{2, 2, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3264, 3199, 3074, 2953, 2199, 1641, 1378 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.77 (s, 1H, NH), 8.25 (d, 2H, *J*=8.4 Hz, ArH), 7.86 (s, 1H, ArH), 7.55–7.59 (m, 3H, ArH), 7.49 (d, 1H, *J*=8.0 Hz, ArH), 7.28 (t, 1H, *J*=7.6 Hz, ArH), 7.18 (t, 1H, *J*=7.6 Hz, ArH), 4.77 (s, 1H, CH), 3.87 (s, 3H, CH_3), 2.05–2.63 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.6, 153.2, 150.9, 146.4, 143.5, 136.5, 131.7, 128.5, 125.2, 124.0, 122.3, 120.5, 120.4, 120.1, 110.6, 107.2, 106.1, 83.3, 50.1, 32.9, 32.0, 29.1, 26.7. LC–MS: calculated for $C_{27}H_{25}N_4O_3$ [MH^+]: 453.1921, found 453.1921.

*4.2.8. 7,7-Dimethyl-2-(4-methyl-1H-indol-3-yl)-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{2, 4, 1}).* Cream yellow solid; mp 288–289 °C. IR (KBr): ν 3415, 3237, 3056, 2956, 2199, 1614, 1386 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.63 (s, 1H, NH), 9.96 (s, 1H, NH), 8.25 (d, 2H, *J*=7.6 Hz, ArH), 7.57–7.63 (m, 3H, ArH), 7.31 (d, 1H, *J*=7.6 Hz, ArH), 7.09 (s, 1H, ArH), 6.88 (s, 1H, ArH), 4.80 (s, 1H, CH), 2.08–2.48 (m, 7H, CH_2+CH_3), 1.05 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.6, 152.8, 150.7, 146.4, 145.4, 136.3, 129.4, 128.7, 127.6, 124.7, 123.9, 122.3, 121.5, 120.2, 110.0, 107.6, 106.9, 86.3, 50.1, 32.4, 28.6, 27.2, 19.3. LC–MS: calculated for $C_{27}H_{25}N_4O_3$ [MH^+]: 453.1921, found 453.1903.

*4.2.9. 7,7-Dimethyl-2-(7-methyl-1H-indol-3-yl)-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{2, 5, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3273, 3061, 2947, 2192, 1619, 1385 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.81 (s, 1H, NH), 9.75 (s, 1H, NH), 8.25 (d, 2H, *J*=8.4 Hz, ArH), 7.80 (s, 1H, ArH), 7.58 (d, 2H, *J*=8.0 Hz, ArH), 7.31 (d, 1H, *J*=7.2 Hz, ArH), 7.01–7.05 (m, 2H, ArH), 4.77 (s, 1H, CH), 2.05–2.63 (m, 7H, CH_2+CH_3), 1.07 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.4, 153.1, 150.8, 146.3, 144.0, 135.5, 128.5, 127.4, 124.6, 123.8, 122.5, 121.4, 120.5, 120.2, 117.4, 107.5, 107.1, 83.3, 50.0, 39.6, 38.9, 31.9, 29.0, 26.6, 16.7. HRMS: calculated for $C_{27}H_{24}N_4O_3$ [M^+]: 452.1848, found 452.1841.

*4.2.10. 4-(2,4-Dichlorophenyl)-2-(1H-indol-3-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{3, 1, 1}).* Cream yellow solid; mp 286–288 °C. IR (KBr): ν 3410, 3284, 3081, 2958, 2196, 1629, 1385 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.77 (s, 1H, NH), 9.67 (s, 1H, NH), 7.77 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.47 (t, 3H, *J*=8.0 Hz, ArH), 7.39 (d, 1H, *J*=8.0 Hz, ArH), 7.17–7.21 (m, 1H, ArH), 7.12 (t, 1H, *J*=7.2 Hz, ArH), 5.11 (s, 1H, CH), 2.00–2.60 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.4, 151.3, 143.8, 142.7, 136.0, 132.7, 132.0, 128.8, 127.9, 127.7, 125.0, 122.2, 120.3, 120.1, 120.0, 112.3, 107.2, 83.6, 50.1, 39.6, 36.2, 32.0, 29.2, 26.7. HRMS: calculated for $C_{26}H_{21}Cl_2N_3O$ [M^+]: 461.1062, found 461.1059.

*4.2.11. 4-(2,4-Dichlorophenyl)-7,7-dimethyl-2-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{3, 2, 1}).* Cream yellow solid; mp 186–188 °C. IR (KBr): ν 3411, 3277, 3074, 2956, 2196, 1638, 1397 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.68 (s, 1H, NH), 7.81 (s, 1H, ArH), 7.53–7.58 (m, 2H, ArH), 7.46 (d, 2H, *J*=7.6 Hz, ArH), 7.38 (d, 1H, *J*=8.4 Hz, ArH), 7.26 (t, *J*=7.6 Hz, 1H, ArH), 7.16 (t, 1H, *J*=7.6 Hz, ArH), 5.11 (s, 1H, CH), 3.85 (s, 3H, CH_3), 2.00–2.60 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.3, 151.1, 143.3, 142.6, 136.4, 132.6, 131.9, 131.8, 131.4, 128.7, 127.9, 125.2, 122.2, 120.3, 120.2, 120.1, 110.6, 107.2, 106.2, 83.4, 50.0, 36.1, 32.9, 32.0, 29.2, 26.7. HRMS: calculated for $C_{27}H_{23}Cl_2N_3O$ [M^+]: 475.1218, found 475.1226.

*4.2.12. 2-(5-Bromo-1H-indol-3-yl)-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (compound **4**{3, 3, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3283, 3065, 2959, 2193, 1631, 1385 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.96 (s, 1H, NH), 9.69 (s, 1H, NH), 7.83 (s, 1H, ArH), 7.61 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.40–7.47 (m, 3H, ArH), 7.32 (d, 1H, *J*=8.8 Hz, ArH), 5.12 (s, 1H, CH), 1.99–2.61 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.4, 151.2, 143.2, 142.5, 134.7, 132.6, 132.0, 131.9, 129.2, 128.7, 127.9, 126.6, 124.8, 122.0, 120.0, 114.3, 112.7, 107.2, 106.8, 84.1, 50.1, 36.0, 32.0, 29.2, 26.7. LC–MS: calculated for $C_{26}H_{21}BrCl_2N_3O$ [MH^+]: 540.0245, found 540.0256.

*4.2.13. 4-(2,4-Dichlorophenyl)-7,7-dimethyl-2-(4-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (compound **4**{3, 4, 1}).* Cream yellow solid; mp 210–211 °C. IR (KBr): ν 3399, 3277, 3080, 2957, 2201, 1633, 1383 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.60 (s, 1H, NH), 9.88 (s, 1H, NH), 7.57 (s, 2H, ArH), 7.47 (d, 1H, *J*=8.0 Hz, ArH), 7.37 (d, 1H, *J*=8.0 Hz, ArH), 7.29 (d, 1H, *J*=8.0 Hz, ArH), 7.08 (t, 1H, *J*=6.8 Hz, ArH), 6.87 (s, 1H, ArH), 5.15 (s, 1H, CH), 2.02–2.54 (m, 7H, CH_2+CH_3), 1.04 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.1, 150.8, 145.0, 142.4, 136.2, 132.4, 131.8, 131.5, 129.3, 128.5, 127.8, 126.9, 124.6, 122.1, 121.3, 119.6, 109.9, 107.6, 107.0, 86.8, 50.1, 39.6, 38.4, 35.6, 28.6, 27.0, 19.2. HRMS: calculated for $C_{27}H_{23}Cl_2N_3O$ [M^+]: 475.1218, found 475.1216.

*4.2.14. 2-(1H-Indol-3-yl)-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{4, 1, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3397, 3278, 3056, 2954, 2187, 1633, 1386 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.77 (s, 1H, NH), 9.62 (s, 1H, NH), 7.79 (s, 1H, ArH), 7.48 (s, 2H, ArH), 7.32 (s, 4H, ArH), 7.10–7.22 (m, 3H, ArH), 4.59 (s, 1H, CH), 2.04–2.61 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.6, 150.3, 146.2, 143.3, 136.1, 128.5, 127.6, 127.2, 126.7, 125.0, 122.2, 121.1, 120.0, 119.9, 112.3, 108.1, 107.4, 84.6, 50.3, 32.0, 29.3, 26.6. HRMS: calculated for $C_{26}H_{23}N_3O$ [M^+]: 393.1841, found 393.1840.

*4.2.15. 7,7-Dimethyl-2-(1-methyl-1H-indol-3-yl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{4, 2, 1}).* Cream yellow solid; mp 224–226 °C. IR (KBr): ν 3268, 3059, 2957, 2196, 1638, 1369 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.63 (s, 1H, NH), 7.83 (s, 1H, ArH), 7.55 (d, 1H, *J*=8.4 Hz, ArH), 7.48 (d, 1H, *J*=7.6 Hz, ArH), 7.15–7.36 (m, 7H, ArH), 4.58 (s, 1H, CH), 3.86 (s, 3H, CH_3), 2.04–2.61 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.6, 150.2, 146.2, 142.8, 136.5, 131.5, 128.5, 127.2, 126.7, 125.3, 122.2, 121.0, 120.3, 120.1, 110.6, 108.1, 106.4, 84.5, 50.2, 32.9, 32.0, 29.3, 26.5. HRMS: calculated for $C_{27}H_{25}N_3O$ [M^+]: 407.1998, found 407.1996.

*4.2.16. 7,7-Dimethyl-2-(4-methyl-1H-indol-3-yl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{4, 4, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3256, 3046, 2944, 2188, 1609, 1386 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.59 (s, 1H, NH), 9.80 (s, 1H, NH), 7.58 (s, 1H, ArH), 7.29–7.34 (m, 5H, ArH), 7.21–7.24 (m, 1H, ArH), 7.07 (s, 1H, ArH), 6.87 (s, 1H, ArH), 4.60 (s, 1H, CH), 2.06–2.53 (m, 7H, CH_2+CH_3), 1.04 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.5, 150.1, 145.8, 144.5, 136.3, 129.4, 128.5, 127.3, 126.7, 124.8, 122.2, 121.4, 120.6, 110.0, 107.9, 87.6, 50.3, 32.3, 28.8, 27.1, 19.3. HRMS: calculated for $C_{27}H_{25}N_3O$ [M^+]: 407.1998, found 407.1997.

*4.2.17. 7,7-Dimethyl-2-(7-methyl-1H-indol-3-yl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{4, 5, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3259, 3058, 2947, 2190, 1613, 1386 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.77 (s, 1H, NH), 9.60 (s, 1H, NH), 7.76 (d, 1H, J=7.6, ArH), 7.30–7.36 (m, 5H, ArH), 7.22 (t, 1H, J=6.0 Hz, ArH), 6.98–7.04 (m, 2H, ArH), 4.59 (s, 1H, CH), 3.86 (s, 3H, CH_3), 2.03–2.61 (m, 7H, CH_2+CH_3), 1.06 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.6, 150.3, 146.2, 143.4, 135.6, 128.5, 127.2, 126.7, 124.8, 122.6, 121.5, 121.1, 120.2, 117.5, 108.1, 107.9, 84.6, 50.3, 32.0, 29.3, 26.6, 16.8. HRMS: calculated for $C_{27}H_{25}N_3O$ [M^+]: 407.1998, found 407.1999.

*4.2.18. 2-(1H-Indol-3-yl)-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{5, 1, 1}).* Cream yellow solid; mp 270–271 °C. IR (KBr): ν 3336, 3060, 2958, 2199, 1610, 1383 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.65 (s, 1H, NH), 9.43 (s, 1H, NH), 7.67 (s, 1H, ArH), 7.41–7.47 (m, 2H, ArH), 7.09–7.18 (m, 4H, ArH), 7.00 (d, 1H, J=7.2 Hz, ArH), 6.89 (s, 1H, ArH), 4.96 (s, 1H, CH), 3.80 (s, 3H, CH_3), 1.99–2.59 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.2, 156.6, 151.0, 143.1, 135.9, 134.1, 128.9, 127.8, 127.2, 125.0, 122.0, 120.8, 120.4, 119.8, 112.0, 111.4, 107.7, 107.1, 84.5, 55.6, 50.3, 33.0, 31.9, 29.3, 26.4. HRMS: calculated for $C_{27}H_{25}N_3O_2$ [M^+]: 423.1947, found 423.1943.

*4.2.19. 4-(2-Methoxyphenyl)-7,7-dimethyl-2-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{5, 2, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3291, 3066, 2954, 2195, 1630, 1374 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.49 (s, 1H, NH), 7.74 (s, 1H, ArH), 7.52 (d, 1H, J=8.0 Hz, ArH), 7.42 (d, 1H, J=8.0 Hz, ArH), 7.13–7.24 (m, 4H, ArH), 7.00 (d, 1H, J=8.0 Hz, ArH), 6.89 (s, 1H, J=7.2 Hz, ArH), 4.95 (s, 1H, CH), 3.83 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 1.99–2.59 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.3, 156.6, 151.0, 142.7, 136.4, 134.1, 131.2, 128.8, 127.9, 125.4, 122.1, 120.9, 120.4, 120.1, 120.0, 111.4, 110.5, 107.1, 106.7, 84.4, 55.6, 50.3, 39.6, 33.0, 32.8, 32.0, 29.4, 26.4. LC–MS: calculated for $C_{28}H_{28}N_3O_2$ [MH^+]: 438.2176, found 438.2176.

*4.2.20. 4-(2-Methoxyphenyl)-7,7-dimethyl-2-(4-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{5, 4, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3323, 3054, 2952, 2184, 1604, 1386 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.47 (s, 1H, NH), 9.60 (s, 1H, NH), 7.44 (s, 1H, ArH), 7.27 (d, 1H, J=8.0 Hz, ArH), 7.18 (t, 1H, J=7.6 Hz, ArH), 7.13 (d, 1H, J=7.2 Hz, ArH), 7.05 (t, 1H, J=7.2 Hz, ArH), 6.98 (d, 1H, J=8.0 Hz, ArH), 6.90 (t, 1H, J=7.6 Hz, ArH), 6.83 (s, 1H, ArH), 5.02 (s, 1H, CH), 3.79 (s, 3H, CH_3), 2.02–2.49 (m, 7H, CH_2+CH_3), 1.04 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.3, 156.4, 150.9, 144.5, 136.2, 134.0, 129.5, 128.8, 127.8, 126.8, 124.8, 122.1, 121.3, 120.5, 111.3, 109.9, 108.2, 106.8, 87.7, 55.6, 50.4, 32.2, 28.9, 27.0, 19.2. HRMS: calculated for $C_{28}H_{27}N_3O_2$ [M^+]: 437.2103, found 437.2102.

*4.2.21. 4-(2-Methoxyphenyl)-7,7-dimethyl-2-(7-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{5, 5, 1}).* Cream yellow solid; mp 206–208 °C. IR (KBr): ν 3415, 3272, 3060, 2956, 2194, 1627, 1385 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.65 (s, 1H, NH), 9.43 (s, 1H, NH), 7.66 (s, 1H, ArH), 7.14–7.24 (m, 3H, ArH), 6.87–7.00 (m, 4H, ArH), 4.96 (s, 1H, CH), 3.79 (s, 3H, CH_3), 1.99–2.59 (m, 7H, CH_2+CH_3), 1.06 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.4, 156.7, 151.1, 143.3, 135.5, 134.2, 128.9, 127.9, 127.0, 124.9, 122.5, 121.4, 121.0, 120.5, 120.1, 117.5, 111.4, 108.2, 107.1, 84.5, 55.6, 50.3, 33.0, 32.0, 29.5, 26.5, 16.8. HRMS: calculated for $C_{28}H_{27}N_3O_2$ [M^+]: 437.2103, found 437.2101.

*4.2.22. 2-(1H-Indol-3-yl)-7,7-dimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{6, 1, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3392, 3250, 3061, 2960, 2190, 1619, 1390 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.75 (s, 1H, NH), 9.57 (s, 1H, NH), 7.70 (s, 1H, ArH), 7.48 (d, 2H, J=8.0 Hz, ArH), 7.12–7.20 (m, 6H, ArH), 4.54 (s, 1H, CH), 2.02–2.60 (m, 7H, CH_2+CH_3), 1.05 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.6, 150.1, 143.4, 143.1, 136.0, 135.7, 129.0, 127.6, 127.2, 125.0, 122.1, 121.1, 120.0, 119.9, 112.2, 108.2, 107.5, 84.8, 50.3, 38.3, 32.0, 29.3, 26.5, 20.7. LC–MS: calculated for $C_{27}H_{26}N_3O$ [MH^+]: 408.2070, found 408.2076.

*4.2.23. 7,7-Dimethyl-2-(1-methyl-1H-indol-3-yl)-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{6, 2, 1}).* Cream yellow solid; mp 289–290 °C. IR (KBr): ν 3277, 3057, 2955, 2199, 1629, 1373 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.54 (s, 1H, NH), 7.80 (s, 1H, ArH), 7.54 (d, 1H, J=8.0 Hz, ArH), 7.49 (d, 1H, J=7.6 Hz, ArH), 7.26 (t, 1H, J=7.6 Hz, ArH), 7.12–7.20 (m, 5H, ArH), 4.54 (s, 1H, CH), 3.85 (s, 3H, CH_3), 2.02–2.59 (m, 7H, CH_2+CH_3), 1.05 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.6, 150.0, 143.4, 142.6, 136.5, 135.7, 131.4, 129.1, 127.1, 125.3, 122.2, 121.0, 120.3, 120.1, 110.6, 108.2, 106.5, 84.8, 50.2, 39.6, 38.3, 32.0, 29.3, 26.5, 20.7. HRMS: calculated for $C_{28}H_{27}N_3O$ [M^+]: 421.2154, found 421.2150.

*4.2.24. 7,7-Dimethyl-2-(7-methyl-1H-indol-3-yl)-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{6, 5, 1}).* Cream yellow solid; mp >300 °C. IR (KBr): ν 3273, 3059, 2948, 2198, 1630, 1385 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.72 (s, 1H, NH), 9.51 (s, 1H, NH), 7.73 (s, 1H, ArH), 7.30 (d, 1H, J=7.2 Hz, ArH), 7.19 (d, 2H, J=7.2 Hz, ArH), 7.13 (d, 2H, J=7.2 Hz, ArH), 7.00–7.04 (m, 2H, ArH), 4.54 (s, 1H, CH), 2.02–2.59 (m, 10H, CH_2+CH_3), 1.05 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.6, 150.1, 143.4, 143.2, 135.7, 135.6, 129.1, 127.2, 124.8, 122.6, 121.5, 121.1, 120.2, 117.5, 108.2, 107.9, 84.8, 50.3, 38.3, 32.0, 29.3, 26.5, 20.7, 16.8. HRMS: calculated for $C_{28}H_{27}N_3O$ [M^+]: 421.2154, found 421.2157.

*4.2.25. 2-(1H-Indol-3-yl)-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (compound **4**{7, 1, 1}).* Cream yellow solid; mp 298–300 °C. IR (KBr): ν 3273, 3065, 2958, 2189, 1617, 1385 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.74 (s, 1H, NH), 9.54 (s, 1H, NH), 7.77 (s, 1H, ArH), 7.49 (d, 2H, J=7.6 Hz, ArH), 7.19–7.24 (m, 3H, ArH), 7.13 (t, 1H, J=7.2 Hz, ArH), 6.91 (d, 2H, J=8.0 Hz, ArH), 4.54 (s, 1H, CH), 3.75 (s, 3H, CH_3), 2.04–2.60 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.5, 158.0, 149.8, 142.9, 138.5, 136.0, 128.2, 127.4, 125.0, 122.0, 121.0, 120.0, 119.8, 113.7, 112.1, 108.3, 107.5, 84.9, 54.9, 50.2, 39.6, 37.8, 31.9, 29.2, 26.5. HRMS: calculated for $C_{27}H_{25}N_3O_2$ [M^+]: 423.1947, found 423.1951.

*4.2.26. 4-(4-Methoxyphenyl)-7,7-dimethyl-2-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{7, 2, 1}).* Cream yellow solid; mp 254–255 °C. IR (KBr): ν 3260, 3073, 2953, 2197, 1607, 1376 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.53 (s, 1H, NH), 7.80 (s, 1H, ArH), 7.54 (d, 1H, J=8.0 Hz, ArH), 7.49 (d, 1H, J=8.0 Hz, ArH), 7.15–7.28 (m, 4H, ArH), 6.89 (d, 2H, J=7.6 Hz, ArH), 4.53 (s, 1H, CH), 3.86 (s, 3H, CH_3), 3.73 (s, 3H, CH_3),

2.03–2.59 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.6, 158.0, 149.9, 142.5, 138.5, 136.5, 131.4, 128.2, 125.3, 122.2, 121.1, 120.3, 120.1, 113.8, 110.6, 108.3, 106.5, 84.9, 55.0, 50.2, 39.6, 37.8, 32.0, 29.3, 26.5. HRMS: calculated for $C_{28}H_{27}N_3O_2$ [M^+]: 437.2103, found 437.2100.

*4.2.27. 4-(4-Methoxyphenyl)-7,7-dimethyl-2-(4-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{7, 4, 1}).* Cream yellow solid; mp 292–293 °C. IR (KBr): ν 3369, 3193, 3030, 2957, 2194, 1614, 1384 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.55 (s, 1H, NH), 9.72 (s, 1H, NH), 7.55 (s, 1H, ArH), 7.29 (d, 1H, J=8.0 Hz, ArH), 7.20 (d, 2H, J=8.0 Hz, ArH), 7.05–7.09 (m, 1H, ArH), 6.89 (d, 3H, J=8.0 Hz, ArH), 4.53 (s, 1H, CH), 3.74 (s, 3H, CH_3), 2.05–2.43 (m, 7H, CH_2+CH_3), 1.03 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.5, 158.1, 149.8, 144.2, 138.2, 136.3, 129.4, 128.3, 124.8, 122.2, 121.3, 120.7, 113.8, 109.9, 108.0, 88.0, 55.0, 50.3, 38.0, 32.3, 28.8, 27.0, 19.2. HRMS: calculated for $C_{28}H_{27}N_3O_2$ [M^+]: 437.2103, found 437.2105.

*4.2.28. 4-(4-Methoxyphenyl)-7,7-dimethyl-2-(7-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{7, 5, 1}).* Cream yellow solid; mp 282–283 °C. IR (KBr): ν 3281, 3061, 2948, 2189, 1611, 1386 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.73 (s, 1H, NH), 9.52 (s, 1H, NH), 7.74 (s, 1H, ArH), 7.22–7.31 (m, 3H, ArH), 6.90–7.02 (m, 4H, ArH), 4.53 (s, 1H, CH), 3.73 (s, 3H, CH_3), 2.03–2.59 (m, 7H, CH_2+CH_3), 1.06 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.6, 158.0, 149.9, 143.1, 138.6, 135.6, 128.3, 127.2, 124.8, 122.6, 121.5, 121.2, 120.2, 117.5, 113.8, 108.3, 108.0, 84.9, 55.0, 50.3, 37.9, 32.0, 29.3, 26.6, 16.8. HRMS: calculated for $C_{28}H_{27}N_3O_2$ [M^+]: 437.2103, found 437.2104.

*4.2.29. 2-(1H-Indol-3-yl)-7,7-dimethyl-4-(naphthalen-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{8, 1, 1}).* Cream yellow solid; mp 166–167 °C. IR (KBr): ν 3281, 3056, 2958, 2196, 1633, 1386 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.79 (s, 1H, NH), 9.68 (s, 1H, NH), 7.88–7.93 (m, 3H, ArH), 7.82 (s, 1H, ArH), 7.77 (s, 1H, ArH), 7.48–7.53 (m, 5H, ArH), 7.19 (t, J=7.6 Hz, 1H, ArH), 7.11 (t, 1H, J=7.2 Hz, ArH), 4.78 (s, 1H, CH), 2.03–2.65 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.7, 150.4, 143.4, 136.0, 132.9, 132.1, 128.4, 127.8, 127.7, 127.5, 126.2, 125.9, 125.7, 125.3, 125.0, 122.1, 121.0, 120.0, 119.8, 112.2, 107.9, 107.4, 84.4, 50.3, 32.0, 29.3, 26.5. HRMS: calculated for $C_{30}H_{25}N_3O$ [M^+]: 443.1998, found 443.1996.

*4.2.30. 7,7-Dimethyl-2-(1-methyl-1H-indol-3-yl)-4-(naphthalen-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{8, 2, 1}).* Cream yellow solid; mp 250–251 °C. IR (KBr): ν 3270, 3054, 2956, 2195, 1633, 1397 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.69 (s, 1H, NH), 7.86–7.93 (m, 4H, ArH), 7.76 (s, 1H, ArH), 7.48–7.56 (m, 5H, ArH), 7.26 (t, J=7.6 Hz, 1H, ArH), 7.15 (t, 1H, J=7.6 Hz, ArH), 4.78 (s, 1H, CH), 3.86 (s, 3H, CH_3), 2.03–2.64 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.7, 150.4, 143.4, 143.0, 136.5, 133.0, 132.1, 131.6, 128.4, 127.9, 127.5, 126.3, 125.9, 125.7, 125.3, 125.3, 125.0, 122.3, 121.0, 120.3, 120.1, 110.6, 107.9, 106.4, 84.4, 50.3, 32.9, 32.0, 29.3, 26.5. LC–MS: calculated for $C_{31}H_{28}N_3O$ [MH^+]: 458.2227, found 458.2235.

*4.2.31. 7,7-Dimethyl-2-(1-methyl-1H-indol-3-yl)-5-oxo-4-(thiophen-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**{9, 2, 1}).* Cream yellow solid; mp 260–261 °C. IR (KBr): ν 3265, 3067, 2954, 2187, 1626, 1367 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.82 (s, 1H, NH), 7.88 (s, 1H, ArH), 7.57 (t, 2H, J=8.0 Hz, ArH), 7.37 (t, 1H, J=8.0 Hz, ArH), 7.29 (t, 1H, J=7.6 Hz, ArH), 7.20 (t, 1H, J=6.8 Hz, ArH), 6.96 (t, 2H, J=4.4 Hz, ArH), 4.93 (s, 1H, CH), 3.88 (s, 1H, CH_3), 2.10–2.62 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 194.5, 150.2, 150.1, 143.3, 136.6, 131.7, 126.9, 125.3, 124.7, 123.3, 122.3, 120.4, 120.1, 110.6, 108.1, 106.3, 83.2, 50.1, 33.4, 32.9, 32.0, 29.4, 26.3. HRMS: calculated for $C_{25}H_{23}N_3OS$ [M^+]: 413.1562, found 413.1562.

*4.2.32. Methyl 5-cyano-4-(2,4-dichlorophenyl)-2-methyl-6-(1-methyl-1H-indol-3-yl)-1,4-dihydropyridine-3-carboxylate (**4**{3, 2, 2}).* Cream yellow solid; mp 225–226 °C. IR (KBr): ν 3275, 3089, 2947, 2199, 1702, 1385 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.49 (s, 1H, NH), 7.81 (s, 1H, ArH), 7.42–7.61 (m, 5H, ArH), 7.25 (s, 1H, ArH), 7.16 (s, 1H, ArH), 5.19 (s, 1H, CH), 3.85 (s, 1H, CH_3), 3.50 (s, 1H, CH_3), 2.41 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 166.6, 147.4, 143.4, 143.2, 136.5, 131.9, 131.5, 128.6, 128.2, 128.1, 125.3, 122.1, 120.1, 110.3, 106.1, 99.1, 82.0, 50.7, 38.0, 32.8, 18.2. HRMS: calculated for $C_{24}H_{19}Cl_2N_3O_2$ [M^+]: 451.0854, found 451.0851.

*4.2.33. 4-(4-Bromophenyl)-2-(1H-indol-3-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**5**{1, 1, 1}).* Khaki solid; mp >300 °C. IR (KBr): ν 3408, 3050, 2953, 2217, 1677 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.08 (s, 1H, NH), 8.56 (d, 1H, J=7.6 Hz, ArH), 8.50 (s, 1H, ArH), 7.66 (d, 2H, J=8.4 Hz, ArH), 7.54 (d, 1H, J=6.8 Hz, ArH), 7.21–7.29 (m, 4H, ArH), 3.22 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 1.09 (s, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 195.5, 165.9, 158.1, 154.5, 136.9, 136.5, 131.0, 129.9, 126.1, 122.9, 122.7, 121.7, 121.4, 120.7, 117.7, 112.3, 103.7, 52.7, 47.1, 32.0, 27.7. HRMS: calculated for $C_{26}H_{20}BrN_3O$ [M^+]: 469.0790, found 469.0789.

*4.2.34. Methyl 5-cyano-4-(2,4-dichlorophenyl)-2-methyl-6-(1-methyl-1H-indol-3-yl)nicotinate (**5**{3, 2, 2}).* Khaki solid; mp 194–196 °C. IR (KBr): ν 3207, 3008, 2203, 1704, 1372 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.49 (d, 1H, J=8.0 Hz, ArH), 8.41 (s, 1H, ArH), 7.90 (s, 1H, ArH), 7.61 (t, 2H, J=10.0 Hz, ArH), 7.50 (d, 1H, J=8.0 Hz, ArH), 7.25–7.35 (m, 2H, ArH), 3.94 (s, 1H, CH_3), 3.57 (s, 1H, CH_3), 2.74 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 166.0, 159.6, 156.2, 150.0, 137.1, 135.1, 133.5, 133.0, 131.5, 129.1, 127.8, 126.3, 123.5, 122.9, 122.4, 121.5, 117.0, 111.0, 110.6, 101.6, 52.6, 33.3, 24.0. HRMS: calculated for $C_{24}H_{17}Cl_2N_3O_2$ [M^+]: 449.0698, found 449.0701.

Acknowledgements

The work was partially supported by the National Natural Science Foundation of China (No. 20672079, 20910102041, 21042007), Natural Science Foundation of Jiangsu Province (No. BK 2006048), Nature Science Key Basic Research of Jiangsu Province for Higher Education (No. 10KJB 150016), the Specialized Research Fund for the Doctoral Program of Higher Education (No. 20060285001), and Key Project in Science and Technology Innovation Cultivation Program of Soochow University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.065.

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