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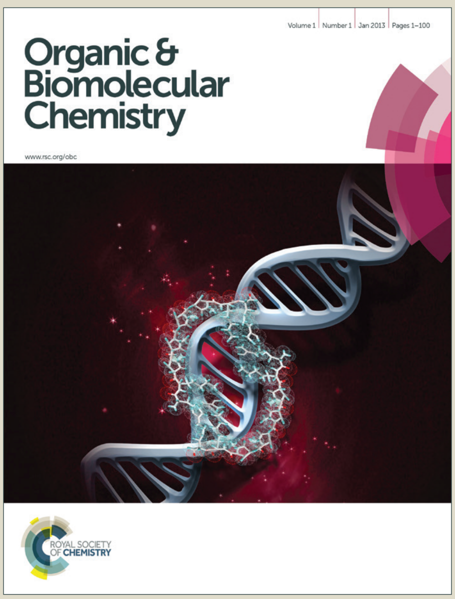

Journal Name

ARTICLE

One-pot synthesis of spiropyrroloquinoline-isoindolinone and their aza-analogs via Ugi-4CR/ metal-free intramolecular bis-annulation process†

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This presentation discloses a one-pot synthesis of a series of spiropyrroloquinoline isoindolinone and spiropyrroloquinoline aza-isoindolinone scaffolds. The reaction proceeds by combination of an Ugi four-component reaction (4CR) and two intramolecular cyclizations under metal-free conditions. The proof of the structures relies on analytical investigation and X-ray crystallography.

Introduction

Multicomponent reactions (MCRs) have extensively been used as powerful synthetic strategies for the construction of biological interesting compounds. The isocyanide-based multicomponent reactions (IMCRs) have emerged particularly as efficient tools in this area based on their high efficiency, rich diversity, and easy operation.[1] Recently, there have been efforts on the synthesis of more complex structures with the tandem Ugi/post-Ugi reactions.[2]

The spirocyclic nitrogen-containing heterocycles like spiroisoindoline, spiroisoindolinone and spirooxindole are present in many pharmaceuticals and biolologically active natural compounds (Fig. 1a).[3] Isoindolinones can be regarded as valuable building blocks in view of the presence of this core structure in many natural and pharmaceutical compounds[4] like Lennoxamine,[4a] Taliscanine,[4b] as well as Zopiclone[4c] and Pazinaclone[4d] (Fig. 1b). In addition, isoindolinone and their analogs show a wide spectrum of considerable biological activities[5] such as antiviral,[5a] anti HIV-1,[5b] antihypertensive,[5c] antileukemic,[5d] and anesthetic.[5e] Therefore, a variety of synthetic methods have been developed for the generation of isoindolinones including Diels-Alder[5d,6] and Wittig reactions,[7] electrophilic[8] and radical cyclization,[9] lithiation approaches,[10] based-mediated procedures,[11] metal-catalyzed processes[12] (Ru,[12a,b] Rh,[12c,d] Re,[12e] Cu,[12f,g] Co,[12h] Ni,[12i,j] Pt[12k] and Pd[12l,m]), as well as tandem aldol(Henry)/heterocyclization reactions of suitable carbon nucleophiles with 2-formylbenzonitriles using chemical[13] or electrochemical[14] methods.

Nonetheless, limited methodologies for construction of spiroisoindolinones have been reported.[15] In this context, palladium-catalyzed heterocyclization of 2-iodobenzoyl chloride with ketimines,[15a] silver-catalyzed spirolactonization of 3-(2-propynyl)isoindoline-1-one-3-carboxylic acids,[15b] oxidative cleavage of 3a,8a-dihydroxyindeno[2,1-*d*]imidazole-2,8-dione using lead(IV) acetate,[15c] Rh(III)-catalyzed C-H activation of *N*-benzoylsulfonamide with cyclic olefins,[15d] or C–H activation reaction of cyclic diazo compound with *O*-pivaloyl benzhydroxamic acids,[15e] and a domino dehydration/condensation/cyclization reaction of cyclic enaminones with 3-hydroxy-3-ethoxycarbonylisoindolin-1-one derivatives using (±)-CSA as a Brønsted acid catalyst.[15f] However, one has to use either expensive transition metal catalysts or multistep procedures in these methods. Therefore, alternative catalyst-free protocols using mild conditions, low cost, and simple operation are desirable.

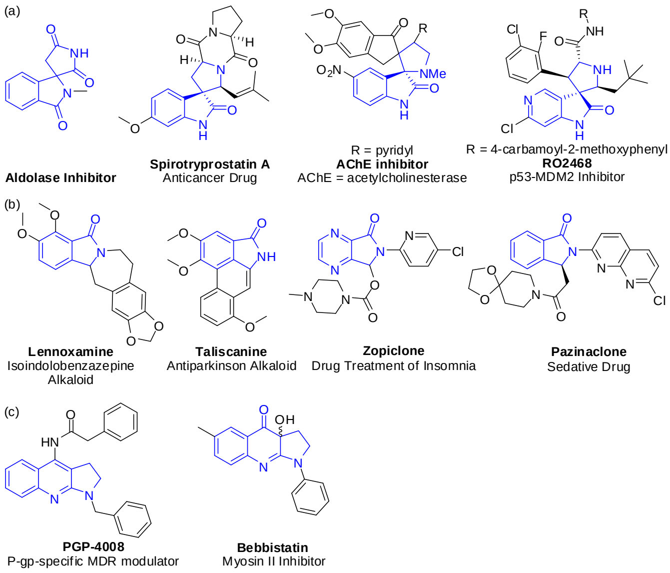

Fig. 1 Example of pharmaceuticals and bioactive natural compounds contain spiroisoindolinone, spirooxindoles, pyrrolo[2,3-*b*]quinoline and isoindolinone fragments.

On the other hand, pyrroloquinoline core is widely present in various biological active natural products and pharmaceutics[16] such as Ammosamide B,[16a] Mycenarubin A,[16b] Marinoquinoline A-F,[16c] Martinelline and Martinellic acid.[16d] Particularly significant are PGP-4008[16e] and blebbistatin[16f] which contain pyrrolo[2,3-*b*]quinoline scaffolds (Fig. 1c). Most synthetic approaches toward pyrrolo[2,3-

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† Electronic Supplementary Information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR, MS and IR of all the compounds, and crystallographic data for **8a** and **10j** (CIF). See DOI: 10.1039/x0xx00000x

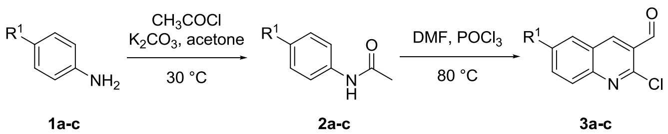
b]quinolines involved multiplestep synthetic methods and harsh conditions,[17] or metal-catalyzed processes.[18] For example, Yum has reported a palladium-catalyzed heteroannulation of 2-amino-3-iodoquinoline derivatives with 1-trimethylsilyl internal alkynes to access pyrrolo[2,3-*b*]quinolones in 2003.[18a] Moreover, a Pauson-Khand-type reaction of *N*-[2-(2-alkyn-1- yl)phenyl]carbodiimides has been described for the synthesis of pyrrolo[2,3-*b*]quinolines using Rh(I) catalyst by Saito in 2010[18b] and Cu-catalyzed heteroannulation of 1,2-haloaldehydes with alkylisocyanoacetates has been also developed for the synthesis of pyrrolo[2,3-*b*]quinolones by Nagarajan in 2015.[18c] Consequently, development of milder and metal-free routes for the preparation of pyrrolo[2,3-*b*]quinolines is still highly desirable.

Inspired by the known properties of isoindolinone derivatives along with the documented biological activities of pyrrolo[2,3-*b*]quinolones, we undertook a study of the synthesis of heterocyclic scaffolds containing both motifs into one molecule in a spiro manner. In continuation of our investigation in searching for new heterocyclic scaffolds via Ugi reactions,[19] in addition to some drawbacks in some of the reported methods for these compounds, we disclose a sequential Ugi/post-Ugi intramolecular bis-annulation approach for the synthesis of spiropyrroloquinoline-isoindolinone and their aza-analogs. Similar C–C cyclizations were found in literature in which the Ugi product prepared with electron-deficient aldehydes readily cyclizied to 3-oxoisoindoline scaffolds under basic condition.[20]On the other hand, N-C cyclization were expected to be carried out easily using Buchwald-Hartwig protocols.[21]

Results and discussion

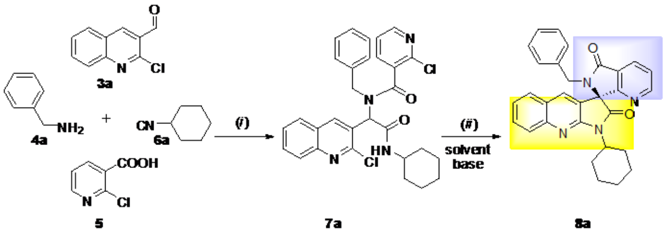
Initially, 2-chloroquinoline-3-carbaldehydes **3a-c** were prepared using the previously reported procedure (Scheme 1).[22] To probe the proposed strategy, the Ugi product **7a**, obtained via the reaction of electron-deficient 2-chloroquinoline-3-carbaldehyde (**3a**), benzylamine (**4a**), 2-chloronicotinic acid (**5**) and cyclohexyl isocyanide (**6a**) (Table 1), was characterized and served for our early exploration to study the effect of various bases and solvents for the next step. To our surprise, spiro compound **8a** was identified as the sole product when the solution of **7a** in toluene containing two equivalents of cesium carbonate was heated at reflux for 24 h (entry 1, Table 1). Further efforts to increase the yield by varying the reaction time, solvent or temperature were found to be successful (Table 1). The best conditions were concluded to be Cs_2CO_3 and DMF at 120 °C (entry 15, Table 1).

This new method was then applied to a domino reaction of aldehydes **3a-c**, amines **4a-e**, 2-chloronicotinic acid **5** and isocyanides **6a-c** in MeOH and then in DMF under the optimized conditions, to afford the bis-annulated products **8a-o** in moderate to high yields (Table 2).



Scheme 1 Preparation of 2-Chloroquinoline-3-Carbaldehydes **3a-c**.

Table 1 Optimization of reaction conditions[a]



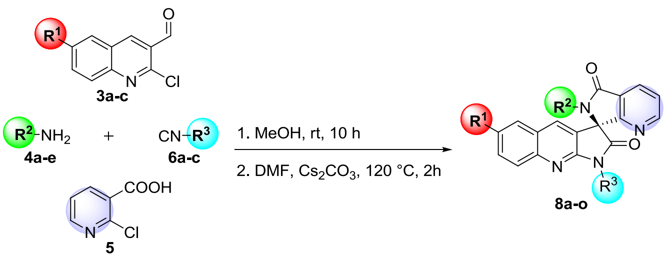
Entry	Solvent	Base	T (°C)	Time (h)	Yield[b]
1	Toluene	Cs_2CO_3	reflux	24	23%
2	Dioxane	Cs_2CO_3	reflux	24	21%
3	MeOH	Cs_2CO_3	reflux	24	NR
4	DCE	Cs_2CO_3	reflux	24	NR
5	MeCN	Cs_2CO_3	reflux	24	NR
6	Toluene	K_2CO_3	reflux	24	trace
7	Dioxane	K_2CO_3	reflux	24	trace
8	MeOH	K_2CO_3	reflux	24	NR
9	DCE	K_2CO_3	reflux	24	NR
10	MeCN	K_2CO_3	reflux	24	NR
11	DMF	NEt_3	120	24	NR
12	DMF	NaOMe	120	10	75%
13	DMF	KO*t*Bu	120	2	81%
14	DMF	K_2CO_3	120	3	88%
15	DMF	Cs_2CO_3	120	2	93%

[a] Reacction conditions: (*i*) **3a** (1 mmol), **4a** (1 mmol), **5** (1 mmol), **6a** (1 mmol) in MeOH (5 ml) at rt for 10 h. (*ii*) all reactions were carried out with **7a** (1mmol), base (2 equiv), and 3 mL of solvent. [b] Isolated yields, NR = No reaction.

To explore the generality and the substrate scope of the developed condensation, we replaced **5** with 2-bromobenzoic acid **9**. The corresponding products **10a-l** were obtained in excellent yields (Table 3). Compounds **8a-o** and **10a-l** were characterized by elemental analysis, MS, IR, and ^{1}H and ^{13}C NMR spectroscopy. Unambiguous evidence for the proposed structures of **8a** and **10j** was finally obtained by single crystal X-ray-diffraction analysis (Fig. 2 and Fig. 3).

As indicated in Tables 1 and 2, whereas products **8j**, **8k** and **10i** were obtained in moderate yields using aromatic amines, utilization of aliphatic amines afforded the corresponding products in rather higher yields (Tables 2 and 3). Such behavior is expected perhaps due to the the rather lower elctrophilicity of the in situ generated imines from aromatic amines. Ready cyclization of sterically hindered amides such as 2,4,4-trimethylpentyl amides to the corresponding products indicated that the reaction is not sensitive to steric hindrance around the amide (entries 2, 5, 8, 13, 15, Table 2) and (entries 2, 4, 8, 11, Table 3). On the other hand, although unsubstituted aldehyde or substituted with modest electron-donating methyl group produced the products in satisfactory yields, those bearing stronger electron-donating methoxy group afforded product **8f** (Table 2) and **10f** (Table 3) in 61% and 65% yields, repectively. This behavior is in accord with the S_NAr reaction

Table 2 Synthesis of spiropyrroloquinoline aza-isoindolinones[a]



Entry	R^1	R^2	R^3	Product	Yield[b]
1	H	Bn	Cy	**8a**	91%
2	H	Bn	*t*BuCH$_2$CMe$_2$	**8b**	87%
3	H	Bn	*t*Bu	**8c**	90%
4	Me	Bn	Cy	**8d**	89%
5	Me	Bn	*t*BuCH$_2$CMe$_2$	**8e**	85%
6	OMe	Bn	Cy	**8f**	61%
7	H	4-MeBn	Cy	**8g**	93%
8	H	4-MeBn	*t*BuCH$_2$CMe$_2$	**8h**	89%
9	H	4-MeBn	*t*Bu	**8i**	91%
10	Me	4-MePh	Cy	**8j**	71%
11	H	3,4-diMePh	*t*BuCH$_2$CMe$_2$	**8k**	77%
12	H	Tryptamine[c]	Cy	**8l**	92%
13	H	Tryptamine[c]	*t*BuCH$_2$CMe$_2$	**8m**	89%
14	Me	Tryptamine[c]	Cy	**8n**	91%
15	Me	Tryptamine[c]	*t*BuCH$_2$CMe$_2$	**8o**	88%

[a]Reacction conditions: 2-chloroquinoline-3-carbaldehyde (1 mmol), amine (1 mmol), acid (1 mmol), and isocyanide (1 mmol) in MeOH (5 mL) at rt for 10 h, followed by treatment with DMF (3 ml) and Cs_2CO_3 (2 equiv for all amines except for tryptamine (3 equiv)) at 120 °C for 2 h. [b] Isolated yields. [c] R^2NH_2.

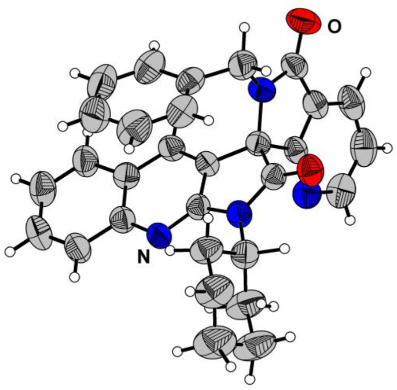
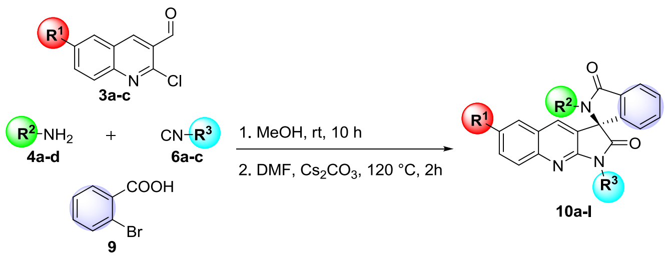


Fig. 2 ORTEP diagram of spiro compound **8a** (CCDC 1010288).

in which the presence of methoxy group makes the 2-chloroquinoline a weaker electrophile. Due to obtaining even lower product yields with aldehyde **3c** in other experiments that were carried out, we decided not to employ it anymore even though the diversity of aldehyde precursor was limited to two elements.

Table 3 Synthesis of spiropyrroloquinoline-isoindolinones[a]



Entry	R^1	R^2	R^3	Product	Yield[b]
1	H	Bn	Cy	**10a**	91%
2	H	Bn	*t*BuCH$_2$CMe$_2$	**10b**	89%
3	Me	Bn	Cy	**10c**	90%
4	Me	Bn	*t*BuCH$_2$CMe$_2$	**10d**	87%
5	Me	Bn	*t*Bu	**10e**	90%
6	OMe	Bn	Cy	**10f**	65%
7	Me	4-MeBn	Cy	**10g**	86%
8	Me	4-MeBn	*t*BuCH$_2$CMe$_2$	**10h**	88%
9	H	4-MePh	Cy	**10i**	73%
10	H	Tryptamine[c]	Cy	**10j**	90%
11	H	Tryptamine[c]	*t*BuCH$_2$CMe$_2$	**10k**	88%
12	H	Tryptamine[c]	*t*Bu	**10l**	87%

[a] Reaction conditions: See Table 2. [b] Isolated yields. [c] R^2NH_2.

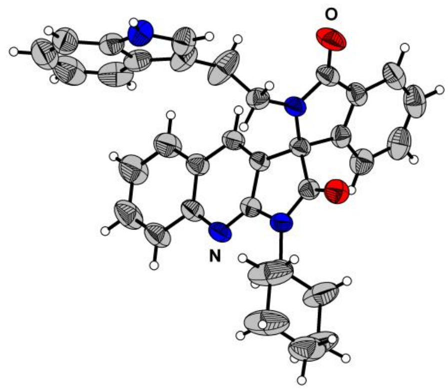
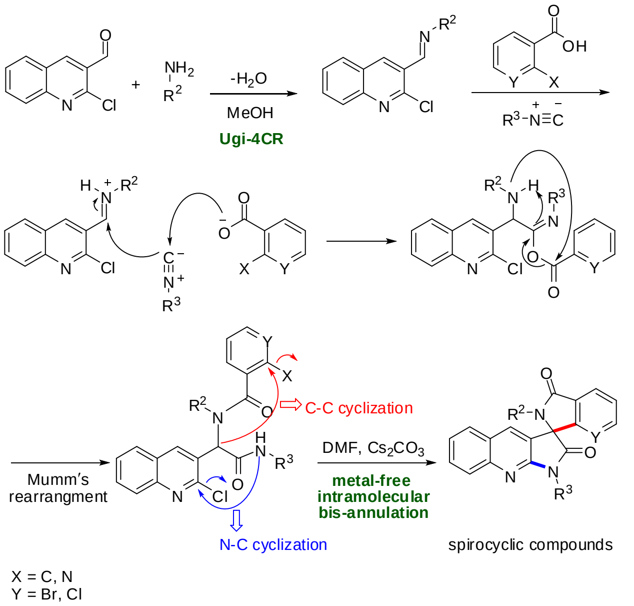


Fig. 3 ORTEP diagram of spiro compound **10j** (CCDC 1053522).

It has been postulated that the ugi reaction involved a sequence of imine formation, protonation of the imine by acid thus strongly increasing the electrophilicity of the C=N bond, α-addition of the electrophilic iminium cation, the nucleophilic carboxylate anion attack to isocyanide and finally intramolecular acyl-transfer (Mumm's rearrangement) (Scheme 2). The generated α-acylaminoamides were subsequently bis-annulated under basic condition, affording the desired spyrocyclic products .

Conclusions

In summary, we have developed a method for the synthesis of highly functionalized spirocyclic scaffolds by modification of Ugi-4CR followed by two consecutive post condensation intramolecular C–C and N-C cyclizations, respectively. These reactions are particularly interesting in terms of molecular diversity, simplicity, and atom economy along with using readily available starting materials. A novel route to a variety of spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione and spiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-diones was disclosed. These reactions were designed to initially generate in situ



Scheme 2 Suggested mechanism for the formation of spirocyclic products.

a Ugi product containing four active centers in order to accomplish two bis-annulation post-Ugi processes. These new structures broaden the scaffolds that are accessible through Ugi/post-Ugi reactions and many of them may represent interesting pharmacophores.

Experimental

General information

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer, in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 300 (^{1}H) and 75 MHz (^{13}C) using DMSO-d_6 as solvent. Mass spectra of the products were obtained with an HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for synthesis of compound 8a-o and 10a-l

To a stirring solution of aldehyde (1 mmol) in MeOH (5 ml) were added amine (1 mmol), acid (1 mmol), and isocyanide (1 mmol), and the reaction mixture was stirred at rt for 10 h. After completion of this step as indicated by TLC, the solvent was removed under reduced pressure, then DMF (3 ml) and Cs_2CO_3 (2 equiv for all amines except for tryptamine (3 equiv)) were added to the residue. The reaction mixture was heated at 120 °C for 2 h. The progress of the reaction was monitored by TLC. On completion, the reaction mixture was cooled to rt, and then H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 ml). The combined organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 5:1, *n*-hexane/ EtOAc for all compounds except 3:1, *n*-hexane/ EtOAc for **8l-o** and **10j-l**) to afford the desired products.

6'-Benzyl-1-cyclohexylspiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8a). White crystal (431 mg, 91%); mp 187-189 °C; IR (KBr) ν_{max} 1713 cm^{-1}; R_f (20% EtOAc/hexane) 0.23; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13-2.35 (m, 10H), 4.30-4.38 (m, 1H), 4.56 (s, 2H), 7.04 (s, 5H), 7.41 (t, J = 7.4 Hz, 1H), 7.59-7.71 (m, 3H), 7.86 (s, 1H), 7.90 (d, J = 8.3 Hz, 1H), 8.37 (d, J = 7.1 Hz, 1H), 8.65 (d, J = 3.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.8, 25.3 (2C), 28.2, 28.4, 44.0, 52.1, 70.5, 118.9, 124.8, 125.0 (2C), 125.4, 127.4 (2C), 128.1 (2C), 128.4 (2C), 128.6, 130.6, 132.6, 133.7, 135.5, 146.8, 153.8, 155.6, 163.3, 166.9, 170.7 ppm; *m/z* (EI, 70 eV) 474 (13, M^+) 392 (39), 301 (100), 287 (11), 258 (5), 230 (9), 91 (40%); Anal. Calcd for $C_{30}H_{26}N_4O_2$: C, 75.93; H, 5.52, N, 11.81. Found: C, 75.91; H, 5.39; N, 11.80%.

6'-Benzyl-1-(2,4,4-trimethylpentan-2-yl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8b). White crystal (439 mg, 87%); mp 150-152 °C; IR (KBr) ν_{max} 1706 cm^{-1}; R_f (20% EtOAc/hexane) 0.30; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9H), 1.70 and 1.76 (2s, 6H), 2.04 (d, J = 14.4 Hz, 1H), 2.46 (d, J = 14.4 Hz, 1H), 4.55 (s, 2H), 7.08 (s, 5H), 7.39 (br t, J = 6.5 Hz, 1H), 7.60-7.66 (m, 3H), 7.80 (s, 1H), 7.87 (br d, J = 7.8 Hz, 1H), 8.36 (br d, J = 7.0 Hz, 1H), 8.62 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.1, 29.5, 31.0, 31.3, 43.9, 49.3, 63.2, 71.1, 118.8, 124.76 (2C), 124.84, 125.1, 127.2, 127.8 (3C), 128.0 (2C), 128.3, 130.5, 132.3, 133.2, 135.9, 146.6, 153.5, 157.9, 163.7, 167.1, 171.8 ppm; *m/z* (EI, 70 eV) 505 (28, M^++1) 393 (72), 301 (100), 287 (10), 258 (5), 230 (9), 91 (43%); Anal. Calcd for $C_{32}H_{32}N_4O_2$: C, 76.16; H, 6.39, N, 11.10. Found: C, 76.17; H, 6.42; N, 11.11%.

6'-Benzyl-1-*tert*-butylspiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8c). White crystal (403 mg, 90%); mp 158-160 °C; IR (KBr) ν_{max} 1731, 1694 cm^{-1}; R_f (20% EtOAc/hexane) 0.25; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (s, 9H), 4.42 (d, J = 15.3 Hz, 1H), 4.72 (d, J = 15.3 Hz, 1H), 7.05-7.08 (m, 5H), 7.41 (t, J = 7.4 Hz, 1H), 7.59-7.71 (m, 3H), 7.86-7.88 (m, 2H), 8.35 (dd, J = 7.6, 1.3 Hz, 1H), 8.64 (dd, J = 4.8, 1.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.1, 43.8, 59.4, 70.8, 118.9, 124.8, 124.8, 124.9, 125.1, 127.4, 127.8, 128.0 (2C), 128.3, 128.5 (2C), 130.4, 132.4, 133.0, 135.5, 146.6, 153.6, 157.4, 163.7, 166.9, 171.2 ppm; *m/z* (EI, 70 eV) 448 (9, M^+) 392 (51), 301 (100), 287 (10), 258 (8), 230 (20), 91 (74%); Anal. Calcd for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.39, N, 12.49. Found: C, 75.01; H, 5.40; N, 12.53%.

6'-Benzyl-1-cyclohexyl-6-methylspiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8d). White crystal (434 mg, 89%); mp 218-220 °C; IR (KBr) ν_{max} 1733, 1706 cm^{-1}; R_f (20% EtOAc/hexane) 0.25; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26-2.31 (m, 10H), 2.39 (s, 3H), 4.26-4.34 (m, 1H), 4.50 (d, J = 15.3 Hz, 1H), 4.60 (d, J = 15.3 Hz, 1H), 7.03-7.08 (m, 5H), 7.41 (s, 1H), 7.51 (dd, J =

8.6, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.6, 4.9 Hz, 1H), 7.78-7.80 (m, 2H), 8.35 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 24.9, 25.3 (2C), 28.2, 28.4, 44.0, 52.1, 70.6, 118.9, 124.8, 125.0, 125.3, 127.2, 127.4, 127.5, 128.1 (2C), 128.4 (2C), 132.45, 132.53, 133.1, 134.3, 135.4, 145.2, 153.7, 155.0, 163.4, 167.0, 170.7 ppm; *m/z* (EI, 70 eV) 488 (25, M$^+$), 406 (76), 391 (20), 315 (100), 301 (18), 272 (9), 244 (15), 91 (72%); Anal. Calcd for $C_{31}H_{28}N_4O_2$: C, 76.21; H, 5.78, N, 11.47. Found: C, 76.20; H, 5.81; N, 11.56%.

6'-Benzyl-6-methyl-1-(2,4,4-trimethylpentan-2-yl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8e). White crystal (440 mg, 85%); mp 128-130 °C; IR (KBr) ν_{max} 1701 cm^{-1}; R$_f$ (20% EtOAc/hexane) 0.34; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (s, 9H), 1.67 and 1.72 (2s, 6H), 2.02 (d, *J* = 14.8 Hz, 1H), 2.36 (s, 3H), 2.43 (d, *J* = 14.8 Hz, 1H), 4.50 (s, 2H), 7.04-7.13 (m, 5H), 7.37 (s, 1H), 7.50 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.60 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.71 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 8.33 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.61 (dd, *J* = 4.8, 1.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 29.2, 29.5, 31.1, 31.3, 43.9, 49.4, 63.1, 71.2, 118.8, 124.8 (2C), 124.9, 127.2, 127.3, 127.6, 127.8 (2C), 128.0 (2C), 132.3, 132.4, 132.6, 134.5, 135.9, 145.1, 153.5, 157.4, 163.8, 167.2, 171.7 ppm; *m/z* (EI, 70 eV) 518 (1, M$^+$), 407 (77), 315 (100), 301 (13), 272 (8), 244 (14), 91 (46%); Anal. Calcd for $C_{33}H_{34}N_4O_2$: C, 76.42; H, 6.61, N, 10.80. Found: C, 76.57; H, 6.71; N, 10.97%.

6'-Benzyl-1-cyclohexyl-6-methoxyspiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8f). White crystal (307 mg, 61%); mp 221-223 °C; IR (KBr) ν_{max} 1729, 1706 cm^{-1}; R$_f$ (20% EtOAc/hexane) 0.21; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13-2.27 (m, 10H), 3.78 (s, 3H), 4.24-4.32 (m, 1H), 4.50 (d, *J* = 15.2 Hz, 1H), 4.60 (d, *J* = 15.2 Hz, 1H), 7.03-7.09 (m, 6H), 7.35 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.62 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.74 (s, 1H), 7.81 (d, *J* = 9.1 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.64 (d, *J* = 4.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.8, 25.3 (2C), 28.2, 28.4, 44.0, 52.1, 55.4, 70.6, 107.7, 119.2, 121.6, 124.7, 125.0, 126.2, 127.4, 128.0 (2C), 128.4 (2C), 128.7, 132.5, 132.6, 135.4, 142.1, 153.7, 153.9, 156.1, 163.4, 166.9, 170.4 ppm; *m/z* (EI, 70 eV) 504 (28, M$^+$), 422 (27), 331 (100), 317 (8), 288 (6), 91 (31%); Anal. Calcd for $C_{31}H_{28}N_4O_3$: C, 73.79; H, 5.59, N, 11.10. Found: C, 73.74; H, 5.56; N, 11.08%.

1-Cyclohexyl-6'-(4-methylbenzyl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8g). White crystal (454 mg, 93%); mp 190-192 °C; IR (KBr) ν_{max} 1732, 1707 cm^{-1}; R$_f$ (20% EtOAc/hexane) 0.25; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.14-1.82 (m, 8H), 1.95 (s, 3H), 2.14-2.32 (m, 2H), 4.27-4.35 (m, 1H), 4.47 (d, *J* = 15.0 Hz, 1H), 4.59 (d, *J* = 15.0 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.57-7.63 (m, 2H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.76 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 8.34 (d, *J* = 7.7 Hz, 1H), 8.62 (d, *J* = 4.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.3, 24.8, 25.3, 25.4 (2C), 28.2, 28.4, 43.7, 52.1, 70.4, 118.9, 124.8, 124.9, 125.0, 125.3, 127.4, 128.5 (3C), 128.6 (2C), 130.4, 132.1, 132.5, 133.4, 136.8, 146.6, 153.7, 155.5, 163.3, 166.7, 170.7 ppm; *m/z* (EI, 70 eV) 488 (4, M$^+$), 406 (16), 369 (19), 301 (100), 287 (23), 230 (11), 213 (7), 105 (63%); Anal. Calcd for $C_{31}H_{28}N_4O_2$: C, 76.21; H, 5.78, N, 11.47. Found: C, 76.22; H, 5.81; N, 11.49%.

6'-(4-Methylbenzyl)-1-(2,4,4-trimethylpentan-2-yl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8h). White crystal (462 mg, 89%); mp 175-177 °C; IR (KBr) ν_{max} 1738, 1704 cm^{-1}; R$_f$ (20% EtOAc/hexane) 0.28; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 9H), 1.73 and 1.78 (2s, 6H), 2.00-2.05 [4H, consisting s, 3H (2.02) and d, *J* = 14.6 Hz, 1H (2.03)], 2.49 (d, *J* = 14.6 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 2H), 6.92 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.56-7.67 (m, 4H), 7.86 (d, *J* = 8.3 Hz, 1H), 8.61 (d, *J* = 7.1 Hz, 1H), 8.62 (d, *J* = 4.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.4, 29.1, 29.5, 31.1, 31.3, 43.6, 49.4, 63.2, 71.0, 118.9, 124.76 (2C), 124.84, 125.0, 127.7, 127.9 (2C), 128.2, 128.5 (2C), 130.3, 132.3, 132.8, 133.0, 136.5, 146.5, 153.5, 157.8, 163.6, 167.0, 171.8 ppm; *m/z* (EI, 70 eV) 520 (20, M$^+$+2), 406 (60), 301 (100), 287 (22), 230 (9), 105 (54%); Anal. Calcd for $C_{33}H_{34}N_4O_2$: C, 76.42; H, 6.61, N, 10.80. Found: C, 76.41; H, 6.60; N, 10.77%.

1-*tert*-Butyl-6'-(4-methylbenzyl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8i). White crystal (420 mg, 91%); mp 179-181 °C; IR (KBr) ν_{max} 1733, 1706 cm^{-1}; R$_f$ (20% EtOAc/hexane) 0.26; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70 (s, 9H), 1.99 (s, 3H), 4.49 (d, *J* = 15.0 Hz, 1H), 4.57 (d, *J* = 15.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.59-7.63 (m, 2H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.75 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 8.34 (d, *J* = 7.4 Hz, 1H), 8.63 (d, *J* = 4.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.4, 28.1, 43.6, 59.3, 70.7, 119.0, 124.76, 124.82, 124.9, 125.0, 127.8, 128.2, 128.57 (2C), 128.60 (2C), 130.3, 132.2, 132.4, 132.8, 136.8, 146.4, 153.6, 157.3, 163.6, 166.8, 171.2 ppm; *m/z* (EI, 70 eV) 462 (6, M$^+$), 406 (39), 343 (11), 301 (100), 287 (20), 230 (17), 105 (81%); Anal. Calcd for $C_{29}H_{26}N_4O_2$: C, 75.30; H, 5.67, N, 12.11. Found: C, 75.31; H, 5.62; N, 11.98%.

1-Cyclohexyl-6-methyl-6'-*p*-tolylspiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8j). White crystal (346 mg, 71%); mp 242-245 °C; IR (KBr) ν_{max} 1720 cm^{-1}; R$_f$ (20% EtOAc/hexane) 0.23; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15-1.82 (m, 8H), 2.14 (s, 3H), 2.24-2.40 [5H, consisting s, 3H (2.36) and m, 2H], 4.38-4.46 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.50-7.52 (m, 2H), 7.68 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 8.25 (s, 1H), 8.41 (d, *J* = 7.6 Hz, 1H), 8.72 (d, *J* = 4.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.4, 20.7, 24.8, 25.3 (2C), 28.3 (2C), 52.2, 72.5, 119.6, 125.0, 125.2, 125.4, 126.4 (2C), 127.3, 127.6, 129.8 (2C), 132.6, 132.7, 132.9, 133.3, 134.7, 137.4, 145.2, 154.1, 155.0, 162.8, 166.3, 171.6 ppm; *m/z* (EI, 70 eV) 488 (80, M$^+$), 406 (100), 377 (17), 363 (13), 349 (7), 334 (24), 316 (5), 301 (6), 272 (19), 244 (18), 55 (17%); Anal. Calcd for $C_{31}H_{28}N_4O_2$: C, 76.21; H, 5.78, N, 11.47. Found: C, 76.12; H, 5.85; N, 11.36%.

6'-(3,4-Dimethylphenyl)-1-(2,4,4-trimethylpentan-2-yl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8k). White crystal (398 mg, 77%); mp 116-118 °C; IR (KBr) ν_{max} 1727, 1712 cm^{-1}; R$_f$ (20% EtOAc/hexane) 0.27; ^{1}H NMR (300 MHz, DMSO-d_6) δ .77 (s, 9H), 1.73 (s, 3H), 1.87 (s, 3H), 2.07 (s, 6H), 2.16 (d, *J* = 14.9 Hz, 1H), 2.34 (d, *J* = 14.9 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.02-7.04 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.63-7.70 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 8.32 (s, 1H), 8.37 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.69 (dd, *J* = 4.8, 1.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.8, 19.3, 29.5, 29.8, 30.8, 31.1, 49.3, 63.1, 73.1, 119.8, 124.86, 124.91, 125.1, 125.3, 125.4, 127.8, 128.4, 128.5, 130.0, 130.6, 132.65, 132.69, 133.0, 136.5, 137.1, 146.6, 153.9, 158.0, 163.2, 166.4, 172.4 ppm; *m/z* (EI, 70 eV) 519 (8, M$^+$+1), 406 (100), 363 (12), 349 (6), 334 (10), 258 (9), 230 (8), 57 (32%); Anal. Calcd for $C_{33}H_{34}N_4O_2$: C, 76.42; H, 6.61, N, 10.80. Found: C, 76.38; H, 6.52; N, 10.77%.

6'-(2-(1*H*-Indol-3-yl)ethyl)-1-cyclohexylspiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8l). White crystal (485 mg, 92%); mp 232-235 °C; IR (KBr) ν_{max} 3332, 1727, 1695 cm^{-1}; R$_f$ (33% EtOAc/hexane) 0.21; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13-2.45 (m, 10H), 2.90 (t, *J* = 8.0 Hz, 2H), 3.43-3.53 (m, 1H), 3.57-3.67 (m, 1H), 4.49-4.57 (m, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.92-6.99 (m, 2H), 7.11 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.63 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.72-7.76 (m, 2H), 7.98 (d, *J* = 8.7 Hz, 1H), 8.06 (s, 1H), 8.34 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.67 (dd, *J*

= 4.8, 1.3 Hz, 1H), 10.78 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.1, 24.8, 25.3 (2C), 28.4, 28.5, 41.8, 52.4, 71.0, 110.3, 111.5, 117.3, 118.1, 119.3, 120.9, 122.9, 125.1, 125.2, 125.3, 125.5, 126.6, 127.5, 128.8, 130.9, 132.3, 133.7, 136.1, 147.1, 153.6, 155.9, 163.1, 166.9, 171.7 ppm; *m/z* (EI, 70 eV) 527 (9, M$^+$), 385 (28), 369 (8), 303 (11), 287 (45), 143 (100), 130 (87), 55 (24%); Anal. Calcd for $C_{33}H_{29}N_5O_2$: C, 75.12; H, 5.54, N, 13.27. Found: C, 75.16; H, 5.47; N, 13.22%.

6'-(2-(1*H*-Indol-3-yl)ethyl)-1-(2,4,4-trimethylpentan-2-yl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8m). Yellowish crystal (496 mg, 89%); mp 182-184 °C; IR (KBr) v_{max} 3322, 1725, 1693 cm^{-1}; R_f (33% EtOAc/hexane) 0.26; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (s, 9H), 1.86 and 1.92 (2s, 6H), 2.27 (d, *J* = 15.0 Hz, 1H), 2.44 (d, *J* = 15.0 Hz, 1H), 2.90-3.05 (m, 2H), 3.43-3.61 (m, 2H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 7.07 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.61 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.70-7.74 (m, 2H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.99 (s, 1H), 8.32 (d, *J* = 7.4 Hz, 1H), 8.65 (d, *J* = 4.2 Hz, 1H), 10.79 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.2, 29.6, 29.9, 31.0, 31.4, 42.0, 49.3, 63.4, 71.7, 110.4, 111.5, 117.5, 118.1, 119.5, 120.9, 122.7, 124.9 (2C), 125.1, 125.4, 126.7, 127.9, 128.5, 130.7, 132.2, 132.9, 136.1, 146.8, 153.5, 158.1, 163.4, 167.1, 172.7 ppm; *m/z* (EI, 70 eV) 557 (20, M$^+$), 445 (11), 415 (6), 315 (16), 303 (51), 287 (54), 143 (100), 130 (70), 57 (66%); Anal. Calcd for $C_{35}H_{35}N_5O_2$: C, 75.38; H, 6.33, N, 12.56. Found: C, 75.43; H, 6.36; N, 12.60%.

6'-(2-(1*H*-Indol-3-yl)ethyl)-1-cyclohexyl-6-methylspiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8n). Yellowish crystal (492 mg, 91%); mp 227-229 °C; IR (KBr) v_{max} 3351, 1726, 1693 cm^{-1}; R_f (33% EtOAc/hexane) 0.23; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13-1.80 (m, 8H), 2.38-2.45 [5H, consisting s, 3H (2.38) and m, 2H], 2.91 (t, *J* = 8.0 Hz, 2H), 3.46-3.65 (m, 2H), 4.48-4.56 (m, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.93-6.98 (m, 2H), 7.12 (s, *J* = 1.1 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.63 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.90 (s, 1H), 8.34 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.67 (dd, *J* = 4.9, 1.2 Hz, 1H), 10.81 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 24.1, 24.9, 25.3 (2C), 28.5, 28.6, 41.7, 52.3, 71.1, 110.3, 111.5, 117.3, 118.2, 119.2, 120.9, 122.9, 125.0, 125.2, 125.5, 126.6, 127.3, 127.7, 132.3, 132.7, 133.2, 134.6, 136.1, 145.4, 153.6, 155.3, 163.1, 167.0, 171.7 ppm; *m/z* (EI, 70 eV) 541 (6, M$^+$), 412 (2), 399 (26), 383 (5), 316 (13), 301 (29), 143 (100), 130 (93), 55 (29%); Anal. Calcd for $C_{34}H_{31}N_5O_2$: C, 75.39; H, 5.77, N, 12.93. Found: C, 75.48; H, 5.78; N, 12.89%.

6'-(2-(1*H*-Indol-3-yl)ethyl)-6-methyl-1-(2,4,4-trimethylpentan-2-yl)spiro[pyrrolo[2,3-*b*]quinoline-3,7'-pyrrolo[3,4-*b*]pyridine]-2,5'(1*H*,6'*H*)-dione (8o). White crystal (503 mg, 88%); mp 208-210 °C; IR (KBr) v_{max} 3298, 1728, 1686 cm^{-1}; R_f (33% EtOAc/hexane) 0.28; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (s, 9H), 1.85 and 1.91 (2s, 6H), 2.56 (d, *J* = 15.0 Hz, 1H), 2.38 (s, 3H), 2.43 (d, *J* = 15.0 Hz, 1H), 2.90-3.04 (m, 2H), 3.43-3.48 (m, 1H), 3.54-3.64 (m, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.93-7.00 (m, 2H), 7.06 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.59-7.63 (m, 1H), 7.83-7.84 (m, 2H), 8.31 (d, *J* = 7.7 Hz, 1H), 8.64 (d, *J* = 4.8 Hz, 1H), 10.80 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 24.2, 29.6, 29.9, 31.0, 31.4, 41.9, 49.3, 63.3, 71.8, 110.4, 111.4, 117.5, 118.1, 119.4, 120.9, 122.7, 124.87, 124.94, 125.1, 126.6, 127.4, 127.6, 132.2, 132.3, 132.5, 134.7, 136.1, 145.2, 153.5, 157.5, 163.4, 167.1, 172.6 ppm; *m/z* (EI, 70 eV) 572 (27, M$^+$+1), 459 (23), 429 (9), 317 (68), 301 (57), 143 (100), 130 (55), 57 (45%); Anal. Calcd for $C_{36}H_{37}N_5O_2$: C, 75.63; H, 6.52, N, 12.25. Found: C, 75.67; H, 6.56; N, 12.34%.

2-Benzyl-1'-cyclohexylspiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10a). White crystal (430 mg, 91%); mp 198-200 °C; IR (KBr) v_{max} 1728, 1696 cm^{-1}; R_f (20% EtOAc/hexane) 0.34; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13-2.89 (m, 10H), 4.30-4.40 (m, 1H), 4.42 (d, *J* = 15.3 Hz, 1H), 4.54 (d, *J* = 15.0 Hz, 1H), 6.99 (s, 5H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.59-7.71 (m, 3H), 7.75 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.9, 25.3 (2C), 28.1, 28.4, 44.0, 52.1, 69.4, 119.9, 121.5, 123.7, 124.9, 125.5, 127.3, 127.4, 128.0 (2C), 128.3 (2C), 128.6, 129.8, 130.6, 130.8, 133.1, 133.5, 135.7, 143.9, 146.8, 155.2, 168.4, 171.6 ppm; *m/z* (EI, 70 eV) 473 (3, M$^+$), 391 (19), 300 (100), 286 (31), 257 (5), 229 (14), 91 (95%); Anal. Calcd for $C_{31}H_{27}N_3O_2$: C, 78.62; H, 5.75, N, 8.87. Found: C, 78.69; H, 5.75; N, 8.92%.

2-Benzyl-1'-(2,4,4-trimethylpentan-2-yl)spiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10b). White crystal (448 mg, 89%); mp 179-181 °C; IR (KBr) v_{max} 1721, 1639 cm^{-1}; R_f (20% EtOAc/hexane) 0.41; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9H), 1.75 (s, 6H), 2.04 (d, *J* = 14.8 Hz, 1H), 2.49 (d, *J* = 14.8 Hz, 1H), 3.32 (d, *J* = 15.8 Hz, 1H), 4.58 (d, *J* = 15.8 Hz, 1H), 7.03 (s, 6H), 7.38 (t, *J* = 7.4 Hz, 1H), 2.52-6.70 [5H, consisting m, 4H and s, 1H (7.67)], 7.86 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.1, 29.5, 31.0, 31.4, 43.9, 49.2, 63.2, 70.0, 119.7, 121.3, 123.7, 124.9, 125.1, 127.1, 127.6 (2C), 127.8, 127.9 (2C), 128.3, 129.7, 130.5, 130.9, 133.0, 133.3, 136.2, 144.1, 146.6, 157.5, 168.5, 172.8 ppm; *m/z* (EI, 70 eV) 504 (12, M$^+$+1), 391 (76), 300 (100), 286 (15), 257 (3), 229 (8), 91 (56%); Anal. Calcd for $C_{33}H_{33}N_3O_2$: C, 78.70; H, 6.60, N, 8.34. Found: C, 78.74; H, 6.72; N, 8.38%.

2-Benzyl-1'-cyclohexyl-6'-methylspiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10c). White crystal (438 mg, 90%); mp 258-260 °C; IR (KBr) v_{max} 1734, 1698 cm^{-1}; R_f (20% EtOAc/hexane) 0.34; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13-2.67 (m, 10H), 2.38 (s, 3H), 4.27-4.35 (m, 1H), 4.46 (AB-q, *J* = 15.4 Hz, 2H), 6.69-7.05 (m, 5H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.50-7.64 [4H, consisting m, 3H and s, 1H (7.64)], 7.78 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 24.9, 25.3 (2C), 28.1, 28.4, 44.0, 52.0, 69.5, 119.9, 121.4, 123.6, 125.5, 127.2, 127.3, 127.6, 128.0 (2C), 128.3 (2C), 129.7, 130.8, 132.4, 132.9, 133.1, 134.2, 135.7, 144.0, 145.2, 154.6, 168.5, 171.5 ppm; *m/z* (EI, 70 eV) 487 (4, M$^+$), 473 (47), 405 (9), 391 (100), 349 (25), 334 (20), 314 (51), 300 (20), 286 (9), 271 (6), 257 (17), 243 (10), 229 (48), 91 (91%); Anal. Calcd for $C_{32}H_{29}N_3O_2$: C, 78.82; H, 5.99, N, 8.62. Found: C, 78.83; H, 6.10; N, 8.75%.

2-Benzyl-6'-methyl-1'-(2,4,4-trimethylpentan-2-yl)spiro[isoindoline-1,3'-pyrrolo[2,3-b]quinoline]-2',3(1'*H*)-dione (10d). White crystal (451 mg, 87%); mp 175-177 °C; IR (KBr) v_{max} 1720, 1694 cm^{-1}; R_f (20% EtOAc/hexane) 0.41; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (s, 9H), 1.73 (s, 6H), 2.03 (d, *J* = 14.8 Hz, 1H), 2.35 (s, 3H), 2.45 (d, *J* = 14.8 Hz, 1H), 4.33 (d, *J* = 15.9 Hz, 1H), 4.53 (d, *J* = 15.9 Hz, 1H), 6.96-7.08 (m, 6H), 7.34 (s, 1H), 7.48-7.63 [4H, consisting m, 3H and s, 1H (7.56)], 7.76 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 29.1, 29.5, 30.9, 31.3, 43.9, 49.2, 63.1, 70.1, 119.6, 121.2, 123.6, 124.8, 127.1, 127.2, 127.6 (3C), 127.9 (2C), 129.7, 131.0, 132.4, 132.6, 132.9, 134.5, 136.2, 144.2, 145.1, 156.9, 168.6, 172.7 ppm; *m/z* (EI, 70 eV) 518 (31, M$^+$+1), 405 (100), 314 (91), 300 (29), 271 (5), 243 (9), 91 (91%); Anal. Calcd for $C_{34}H_{35}N_3O_2$: C, 78.89; H, 6.81, N, 8.12. Found: C, 78.90; H, 6.77; N, 8.10%.

2-Benzyl-1'-*tert*-butyl-6'-methylspiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10e). White crystal (415 mg, 90%); mp 192-194 °C; IR (KBr) v_{max} 1730, 1694 cm^{-1}; R_f (20% EtOAc/hexane) 0.36; ^1H NMR (300 MHz, DMSO-d_6) δ 1.68 (s, 9H), 2.37 (s, 3H), 4.37 (d, J = 15.3 Hz, 1H), 4.57 (d, J = 15.3 Hz, 1H), 6.96-7.04 (m, 6H), 7.36 (s, 1H), 7.48-7.91 [4H, consisting m, 3H and s, 1H (7.56)], 7.77 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 28.1, 43.9, 59.2, 69.8, 119.9, 121.2, 123.6, 124.9, 127.3 (2C), 127.6, 128.0 (2C), 128.4 (2C), 129.6, 130.8, 132.2, 132.3, 133.0, 134.4, 135.7, 144.4, 145.0, 156.4, 168.5, 172.1 ppm; m/z (EI, 70 eV) 461 (5, M^+), 404 (43), 314 (79), 300 (19), 243 (9), 91 (100%); Anal. Calcd for $C_{30}H_{27}N_3O_2$: C, 78.07; H, 5.90, N, 9.10. Found: C, 78.09; H, 5.91; N, 9.06%.

2-Benzyl-1'-cyclohexyl-6'-methoxyspiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10f). White crystal (327 mg, 65%); mp 243-245 °C; IR (KBr) v_{max} 1731, 1695 cm^{-1}; R_f (20% EtOAc/hexane) 0.30; ^1H NMR (300 MHz, DMSO-d_6) δ 1.13-2.28 (m, 10H), 3.77 (s, 3H), 4.26-4.34 (m, 1H), 4.47 (AB-q, J = 15.3 Hz, 2H), 6.96-7.06 (m, 7H), 7.33 (dd, J = 9.1, 2.8 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.56 (s, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.81 (d, J = 9.1 Hz, 1H), 7.92 (d, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.9, 25.3 (2C), 28.1, 28.3, 44.0, 51.9, 55.4, 69.5, 107.7, 120.1, 121.4, 121.6, 123.6, 126.4, 127.3, 128.0 (2C), 128.3 (2C), 128.7, 129.7, 130.7, 132.4, 133.0, 135.7, 142.1, 144.0, 153.5, 156.1, 168.4, 171.3 ppm; m/z (EI, 70 eV) 503 (19, M^+), 420 (9), 398 (13), 330 (100), 316 (19), 301 (11), 286 (6), 143 (29), 91 (88%); Anal. Calcd for $C_{32}H_{29}N_3O_3$: C, 76.32; H, 5.80, N, 8.34. Found: C, 76.33; H, 5.77; N, 8.34%.

1'-Cyclohexyl-6'-methyl-2-(4-methylbenzyl)spiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10g). White crystal (431 mg, 86%); mp 220-222 °C; IR (KBr) v_{max} 1735, 1670 cm^{-1}; R_f (20% EtOAc/hexane) 0.29; ^1H NMR (300 MHz, DMSO-d_6) δ 1.14-1.83 (m, 8H), 1.93 (s, 3H), 2.12-2.29 (m, 2H), 2.38 (s, 3H), 4.28-4.33 [2H, consisting d, J = 15.0 Hz, 1H (2.30) and m, 1H], 4.56 (d, J = 15.0 Hz, 1H), 6.72 (d, J = 7.9 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 7.32 (s, 1H), 7.42 (s, 1H), 7.47-7.52 (m, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.2, 20.7, 24.9, 25.3 (2C), 28.1, 28.4, 43.7, 52.0, 69.3, 119.8, 121.3, 123.6, 125.4, 127.2, 127.5, 128.3 (2C), 128.5 (2C), 129.6, 130.8, 132.2, 132.5, 132.6, 132.9, 134.1, 136.7, 143.9, 145.0, 154.5, 168.2, 171.5 ppm; m/z (EI, 70 eV) 501 (7, M^+), 419 (12), 382 (83), 314 (100), 300 (62), 243 (12), 105 (81), 55 (35%); Anal. Calcd for $C_{33}H_{31}N_3O_2$: C, 79.01; H, 6.23, N, 8.38. Found: C, 78.98; H, 6.25; N, 8.45%.

6'-Methyl-2-(4-methylbenzyl)-1'-(2,4,4-trimethylpentan-2-yl)spiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10h). White crystal (467 mg, 88%); mp 163-165 °C; IR (KBr) v_{max} 1728, 1709 cm^{-1}; R_f (20% EtOAc/hexane) 0.36; ^1H NMR (300 MHz, DMSO-d_6) δ .92 (s, 9H), 1.76 and 1.99 (2s, 6H), 2.00-2.06 (singlet overlapped with a doublet, 4H), 2.36 (s, 3H), 2.49 (d, J = 14.3 Hz, 1H), 6.77 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 7.4 Hz, 1H), 7.27 (s, 1H), 7.38 (s, 1H), 7.47-7.62 (m, 3H), 7.75 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.3, 20.7, 29.1, 29.5, 31.0, 31.3, 43.6, 49.3, 63.2, 70.0, 119.6, 121.2, 123.6, 124.8, 127.2, 127.5, 127.6 (2C), 128.5 (2C), 129.6, 131.0, 132.2, 132.5, 132.9, 133.3, 134.4, 136.3, 144.0, 144.9, 156.7, 168.4, 172.7 ppm; m/z (EI, 70 eV) 533 (6, M^++2), 419 (69), 314 (100), 300 (31), 243 (8), 105 (65), 57 (42%); Anal. Calcd for $C_{35}H_{37}N_3O_2$: C, 79.06; H, 7.01, N, 7.90. Found: C, 79.05; H, 7.05; N, 7.90%.

1'-Cyclohexyl-2-*p*-tolylspiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10i). White crystal (345 mg, 73%); mp 241-243 °C; IR (KBr) v_{max} 1719 cm^{-1}; R_f (20% EtOAc/hexane) 0.45; ^1H NMR (300 MHz, DMSO-d_6) δ 1.17-1.84 (m, 8H), 2.15 (s, 3H), 2.21-2.38 (m, 2H), 4.39-4.47 (m, 1H), 4.09 (s, 4H), 7.30 (d, J = 7.1 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.60-7.72 (m, 3H), 7.79 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 6.8 Hz, 1H), 8.27 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.4, 24.8, 25.3 (2C), 28.1, 28.2, 52.1, 71.2, 120.8, 121.8, 123.9, 125.2, 125.6, 126.3 (2C), 127.5, 128.7, 129.7 (2C), 129.9, 130.8, 130.9, 133.0, 133.4, 133.5, 137.1, 143.3, 146.8, 155.3, 167.7, 172.4 ppm; m/z (EI, 70 eV) 473 (80, M^+), 391 (100), 362 (21), 349 (28), 334 (19), 319 (17), 300 (8), 286 (9), 257 (17), 244 (9), 229 (37), 174 (21), 91 (39%); Anal. Calcd for $C_{31}H_{27}N_3O_2$: C, 78.62; H, 5.75, N, 8.87. Found: C, 78.63; H, 5.79; N, 8.97%.

2-(2-(1*H*-Indol-3-yl)ethyl)-1'-cyclohexylspiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10j). White crystal (473 mg, 90%); mp 187-189 °C; IR (KBr) v_{max} 3333, 1728, 1689 cm^{-1}; R_f (33% EtOAc/hexane) 0.28; ^1H NMR (300 MHz, DMSO-d_6) δ 1.38-2.44 (m, 10H), 2.86 (t, J = 8.4 Hz, 2H), 3.39-3.58 (m, 2H), 4.51-4.59 (m, 1H), 6.69 (t, J = 7.4 Hz, 1H), 6.92-6.96 (m, 2H), 7.09 (s, 1H), 7.24 (m, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.54-7.64 (m, 2H), 7.75 (m, 2H), 7.91 (d, J = 7.2 Hz, 1H), 7.99-8.01 (m, 2H), 10.77 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.0, 24.9, 25.3 (2C), 28.3, 28.5, 41.7, 52.3, 69.8, 110.4, 111.4, 117.3, 118.1, 120.3, 120.9, 121.6, 122.8, 123.4, 125.1, 125.7, 126.6, 127.5, 128.8, 129.7, 130.8, 131.3, 132.9, 133.4, 136.1, 143.6, 147.1, 155.6, 168.4, 172.6 ppm; m/z (EI, 70 eV) 526 (27, M^+), 443 (2), 396 (6), 384 (24), 368 (23), 300 (13), 286 (66), 143 (100), 130 (76), 55 (24%); Anal. Calcd for $C_{34}H_{30}N_4O_2$: C, 77.54; H, 5.74, N, 10.64. Found: C, 77.63; H, 5.70; N, 10.71%.

2-(2-(1*H*-Indol-3-yl)ethyl)-1'-(2,4,4-trimethylpentan-2-yl)spiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10k). White crystal (490 mg, 88%); mp 201-202 °C; IR (KBr) v_{max} 3242, 1733, 1658 cm^{-1}; R_f (20% EtOAc/hexane) 0.33; ^1H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 9H), 1.84 and 1.96 (2s, 6H), 2.36 (AB-q, J = 14.9 Hz, 2H), 2.88-3.07 (m, 2H), 3.37-3.45 (m, 1H), 3.54-3.64 (m, 1H), 6.72 (t, J = 7.4 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.03-7.11 (m, 3H), 7.27 (d, J = 8.1 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.52-7.62 (m, 2H), 7.67-7.72 (m, 2H), 7.92-7.97 (m, 3H), 10.80 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.2, 29.6, 29.9, 30.9, 31.4, 42.1, 49.3, 63.3, 70.6, 110.6, 111.4, 117.6, 118.1, 120.4, 120.9, 121.2, 122.6, 123.5, 125.1, 125.3, 126.7, 127.9, 128.5, 129.7, 130.6, 131.4, 132.8, 132.9, 136.2, 143.9, 146.9, 157.7, 168.6, 173.6 ppm; m/z (EI, 70 eV) 557 (23, M^++1), 443 (6), 414 (3), 314 (20), 302 (27), 286 (61), 143 (100), 130 (41), 57 (51%); Anal. Calcd for $C_{36}H_{36}N_4O_2$: C, 77.67; H, 6.52, N, 10.06. Found: C, 77.63; H, 6.57; N, 10.15%.

2-(2-(1*H*-Indol-3-yl)ethyl)-1'-*tert*-butylspiro[isoindoline-1,3'-pyrrolo[2,3-*b*]quinoline]-2',3(1'*H*)-dione (10l). White crystal (435 mg, 87%); mp 185-187 °C; IR (KBr) v_{max} 3261, 1725, 1690 cm^{-1}; R_f (33% EtOAc/hexane) 0.31; ^1H NMR (300 MHz, DMSO-d_6) δ 1.87 (s, 9H), 2.87-2.96 (m, 2H), 3.46 (t, J = 8.1 Hz, 2H), 6.68 (t, J = 7.4 Hz, 1H), 6.88-6.96 (m, 2H), 7.10 (s, 1H), 7.24 (m, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.54-7.63 (m, 2H), 7.71-7.76 (m, 2H), 7.89 (d, J = 6.9 Hz, 1H), 7.94-7.97 (m, 2H), 10.77 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.1, 28.4, 41.8, 59.6, 70.3, 110.5, 111.4, 117.3, 118.1, 120.5, 120.9, 121.4, 122.9, 123.4, 125.1, 125.3, 126.6, 127.9, 128.5, 129.7, 130.6, 131.2, 132.8, 132.9, 136.1, 143.8, 146.8, 157.4, 168.5, 173.3 ppm; m/z (EI, 70 eV) 500 (17, M^+), 443 (2), 314 (13), 301 (27), 286 (64), 143 (100), 130 (58), 57 (49%); Anal. Calcd for $C_{32}H_{28}N_4O_2$: C, 76.78; H, 5.64, N, 11.19. Found: C, 76.80; H, 5.65; N, 11.19%.

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Table of contents

Graphical abstract

One-pot synthesis of spiropyrroloquinoline-isoindolinone and their aza-analogs via Ugi-4CR/ metal-free intramolecular bis-annulation process†

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