Efficient Catalyst-Free One-Pot Three-Component Synthesis of Novel Spirooxindole Derivatives, and Their Cytotoxic Activities

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Abstract: A simple and efficient one-pot approach for assembling novel spiro[indolepyranopyrrole] derivatives was developed and used to prepare a series of biologically important compounds. The reaction was easily performed with high efficiency under very simple and mild conditions without any catalysts and it gave good yields, avoiding time-consuming costly synthesis and laborious workup and purification of products. The cytotoxic activities of these new spiro[indolepyranopyrrole] derivatives were evaluated in vitro. Most of the tested compounds exhibited significant cytotoxicities to Raji cell lines.

Key words: polycyclic compounds, heterocyclic compounds, spiro compounds, multicomponent reactions, cytotoxins

The development of highly efficient chemical reaction sequences is a major challenge in modern drug discovery. Recently developed multicomponent reactions offer a wide range of possibilities for the efficient construction of highly complex molecules by single procedural steps.[1,2] Furthermore, convenient methods for constructing molecules containing two or more separate biologically interesting scaffolds fused in various sequences are of great value to both organic and medical chemists.[3]

Spirocyclic moieties are present in many natural products.[4] Because of their highly constrained nature, spiro compounds have attracted considerable interest from medicinal chemists.[5] Spirooxindole heterocycles, in which a simple heterocycle is linked to an indole ring through a spiro atom in the 3-position, have been reported to show an increased spectrum of biological activities,[6–8] and these compounds might be capable of being synthesized by multicomponent methods.[9] The spirooxindole system is a core structure in many pharmacological agents and natural alkaloids, for example, spirotryprostatin B, pteropodine, and isopteropodine.[10] Therefore, heterocyclic spiroindoles are attractive targets in terms of both organic synthesis and the construction of drug candidates.[11] Moreover, it is well known that derivatives of tetramic acid (2,4-pyrrolidinedione) are important in medicinal chemistry, as they display antineoplastic, antiviral, HIV-1 protease-inhibiting, insecticidal, and antibacterial properties.[12]

Compounds containing the pyran structural motif exhibit a wide range of biological activities, such as diuretic, analgesic, myorelaxant,[13] antitumor,[14] and anti-HIV activities.[15] There have been many reports[16] on syntheses of spiroindoline derivatives containing 4*H*-pyran moieties by means of multicomponent reactions. Several synthetic spiro heterocyclic compounds containing both indole and pyran moieties possess anticonvulsant, analgesic, herbicidal, and antimicrobial activities.[17] Because of the importance of such compounds, we became interested in developing an efficient method for the synthesis of spiroindoline derivatives containing a 4*H*-pyran-fused pyrrolidinone substructure by means of a three-component condensation reaction, to provide novel structurally and biologically interesting compounds for drug-discovery research.

Efficient, practical, and environmentally friendly synthesis methods can reduce amounts of toxic wastes and by-products arising from chemical processes. Catalyst-free reactions have received particular attention in recent years.[18,19] However, there are few reports[20] on syntheses of spirooxindole derivatives under catalyst-free conditions. In connection with our studies on the development of multicomponent reactions, we report an efficient approach to a novel spiro[indolepyranopyrrole] derivatives of chemical and, potentially, biological importance. The compounds were prepared by the reaction of a tetramic acid, an isatin, and malononitrile as starting materials in ethanol. The main difference between our method and other previously reported methods is the absence in our method of any organic or metallic catalyst, as generally used in previous syntheses of analogues of the spiroindoline compounds.

Conventional methods for the three-component condensation of isatin with an active methylene component and a 1,3-dicarbonyl compound involve the use of a catalyst in an organic or aqueous medium, microwave heating, the use of an electro-generated base, or water-mediated surfactant catalysis. However, despite their merits, most of the reported methods have drawbacks such as the use of poisonous organic additives or the need for expensive catalysts. Therefore, in developing practical methods for one-pot three-component condensations, environmental and economic impacts of the reactions must be among the foremost considerations.

Because some the three-component condensation of isatins with other active components can be carried out in aqueous media, we initially attempted a one-pot reaction

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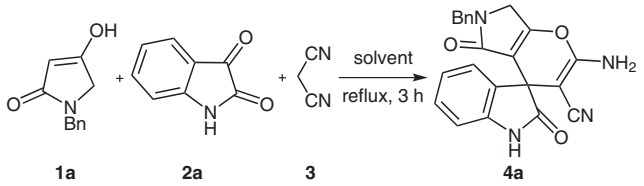
of *N*-benzyltetramic acid (**1a**), isatin (**2a**), and malononitrile (**3**) in water under catalyst-free conditions as a model system. Unfortunately, the three-component reaction in the absence of a catalyst did not occur favorably in water, even at the reflux, and product **4a** was obtained in less than 30% yield after six hours. We then focused our attention on the use of some common organic solvents. The reactions were carried out in various solvents at various temperatures in the absence of any catalyst or additive. The results obtained are listed in Table 1.

Table 1 Optimization of Conditions for the Model Reaction



1a **2a** **3** **4a**

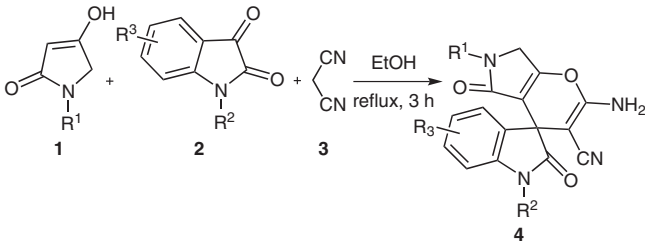
Entry[a]	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	H_2O	100	6	<30
2	THF	66	3	56
3	DCE	84	3	50
4	MeCN	82	3	60
5	toluene	110	3	60
6	$CHCl_3$	61	3	55
7	MeOH	65	3	76
8	80% EtOH–H_2O	79	3	75
9	95% EtOH–H_2O	78	3	80
10	EtOH	78	3	94
11	EtOH	78	6	94
12	EtOH	60	3	85
13	EtOH	30	3	75
14	neat	80	3	30

[a] Reaction conditions: isatin (**1a**; 1 mmol), malononitrile (**3a**; 1 mmol), *N*-benzyltetramic acid (**2a**; 1 mmol), reflux.
[b] Isolated yield.

Reactions in organic solvents all gave better yields than that obtained in water (Table 1, entries 1–10). The yields of the reactions in protonated organic solvents (entries 7–10) were markedly higher than those in nonprotonated solvents (entries 2–6). Ethanol was the best solvent for the reaction, and the presence of water in ethanol was disadvantageous to the reaction (entries 8–10). Prolonging the reaction time from three to six hours did not improve the yield (entry 11). The results for reactions in ethanol at various temperatures indicated that higher temperatures significantly favored the reaction. More importantly, all the starting materials were soluble in ethanol, whereas the spirooxindole products were all insoluble in this solvent, greatly simplifying the reaction procedure and the workup in both large- and small-scale syntheses. Therefore, the optimal conditions that we identified for the catalyst-free three-component reaction have practical advantages and are environmentally friendly.

By using the optimized reaction conditions, we prepared a series of spirooxindole derivatives in good yields through the one-pot, catalyst-free approach (Table 2). In particular, we assessed the method as a means of constructing a product library by using various substituted isatins, including isatins substituted with electron-withdrawing or electron-donating groups, together with various tetramic acid derivatives and malononitrile as starting materials. The results obtained indicated that the method

Table 2 Synthesis of Spirooxindole Derivatives **4**

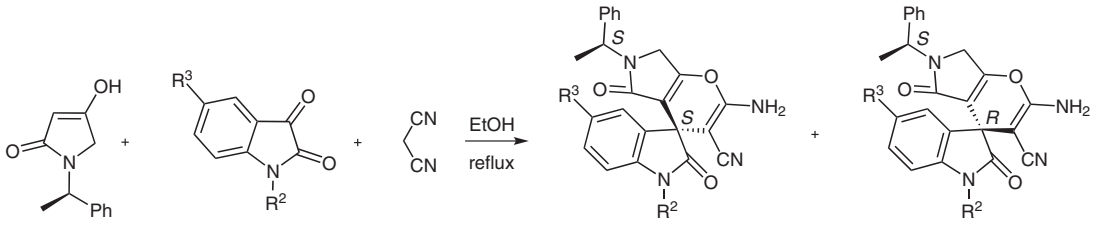


1 **2** **3** **4**

Entry[a]	R^1	R^2	R^3	Product	Yield (%)
1	Bn	H	H	**4a**	94
2	Bn	Me	H	**4b**	93
3	Bn	Et	H	**4c**	92
4	Bn	Bu	H	**4d**	90
5	Bn	Bn	H	**4e**	90
6	Bn	H	4-Cl	**4f**	91
7	Bn	H	4-Br	**4g**	92
8	Bn	H	5-Me	**4h**	92
9	Bn	H	5-F	**4i**	90
10	Bn	H	5-Cl	**4j**	91
11	Bn	H	5-Br	**4k**	91
12	Bn	H	5-NO_2	**4l**	93
13	Bn	H	6- Cl	**4m**	92
14	Bn	H	6- Br	**4n**	90
15	Bn	H	5,7-Br_2	**4o**	90
16	Bn	H	7-F_3C	**4p**	91
17	Ph	H	H	**4q**	91
18	Ph	H	5-O_2N	**4r**	91
19[b]	Bn	H	H	**4a**	90

[a] The general reaction was carried out on a 1.0-mmol scale for all the three reactants.
[b] Carried out on a 10-mmol scale for all the three reactants.

Table 3 Synthesis of Chiral Spirooxindole Derivatives



Product	R^2	R^3	Yield (%)	Config.	dr[a]	$[\alpha]_D^{20}$
4s	H	H	91	*S*,*S* *S*,*R*	1:1	+171.8 +122.3
4t	Me	H	90	*S*,*S* *S*,*R*	1:1	+176.4 +206.7
4u	H	Me	90	*S*,*S* *S*,*R*	1:1	+148.6 +90.2

[a] By ^{1}H NMR spectroscopy of the crude product.

should be applicable to syntheses of libraries of compounds with a high degree of diversity. The structures of all the products **4** were unambiguously characterized by means of IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and by electrospray-ionization high-resolution mass spectrometry.

To check the applicability of our method on a larger scale, we examined the reaction on a 10-mmol scale, and we observed a similar behavior (Table 2, entry 19). This method should, therefore, find extensive use in the fields of combinatorial chemistry and drug discovery.

Generally, the spirooxindole derivatives formed by the three-component one-pot reaction always possess a stereogenic quaternary carbon center. There have been some reports on asymmetric syntheses of spirooxindole derivatives.[21] Our successful development of the three-component reaction for the synthesis of spirooxindole derivatives enabled us to develop a strategy for preparing the two diastereoisomers of the spirooxindole derivatives. Because (1*R*)- and (1*S*)-(1-phenylethyl)amine are widely used in separating diastereoisomers,[22] we prepared 1-[(1*S*)-1-phenylethyl]pyrrolidine-2,4-dione to permit direct chromatographic separation of the two diastereoisomeric spirooxindole derivatives. As expected, the two diastereoisomers (*R*,*S* and *S*,*S*) of the spirooxindole derivatives were efficiently separated (Table 3).

To verify the absolute configuration of the spirooxindole derivatives, one of the two isomers of product **4u** was obtained as a single crystal and selected as a representative compound for X-ray crystallographic characterization; this confirmed that the compound was the *S*,*S*-diastereoisomer (Figure 1). With this isomer as a reference compound, two pairs of other spirooxindole derivatives, **4s** and **4t**, were also separated and characterized. The diastereoisomeric ratio (dr) was determined by ^{1}H NMR spectroscopy of the crude samples of **4s**, **4t**, and **4u**.

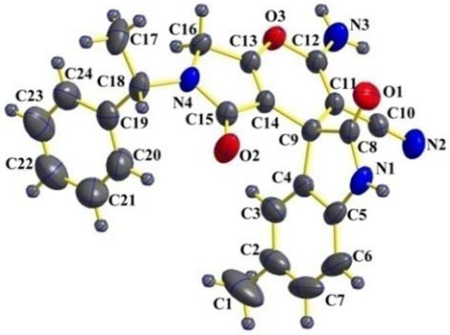
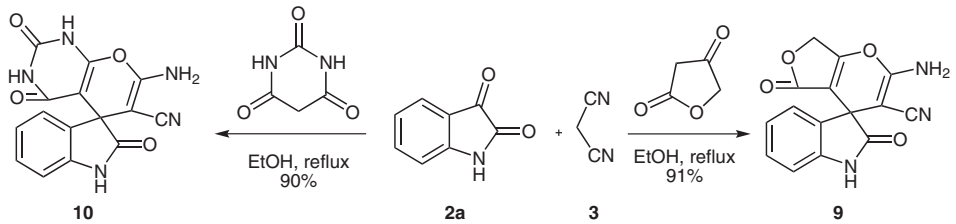
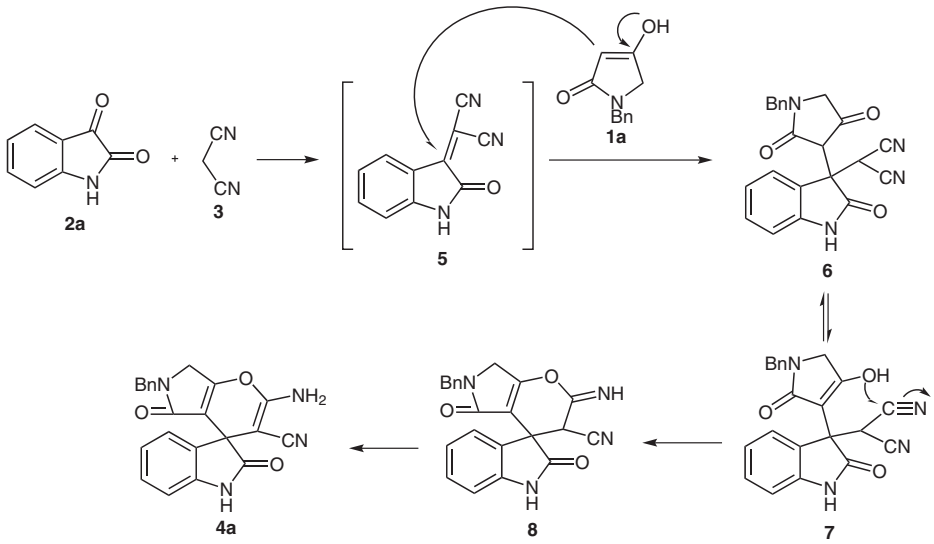


Figure 1 The molecular structure of spirooxindole (*S*,*S*)-**4u**

As expected, the catalyst-free one-pot three-component reaction method was also shown to be applicable to other



Scheme 1 Extended application of the catalyst-free reaction conditions



Scheme 2 Plausible mechanism for the reaction of isatin, malononitrile, and *N*-benzyltetramic acid

1,3-dicarbonyl compounds. When the tetramic acid **1** was replaced with tetronic acid or barbituric acid, the desired spirooxindole products **9** and **10**, respectively, were obtained in good yields under the same reaction condition (Scheme 1).

A proposed mechanism for the formation of the spirooxindole derivatives **4** is summarized in Scheme 2. The catalyst-free three-component reaction represents a typical cascade reaction in which isatin (**2a**) first condenses with malononitrile (**3**) to afford the derivative **5** by a Knoevenagel condensation. Nucleophilic attack by the active tetramic acid **1a** on the electron-deficient C=C double bond then occurs to give intermediate **6** in equilibrium with its enol form **7**. This leads to intramolecular nucleophilic attack by the enol oxygen atom on the cyano group to give the spirooxindole imine **8**, which then tautomerizes to the expected product **4a**.

To survey the bioactivities of this class of novel compounds, all the spirooxindole derivatives **4**, **9**, and **10** were subjected in vitro cytotoxicity tests with the Raji cell line, with cisplatin as a positive control. The IC_{50} values for growth inhibition of the Raji cell line in the presence of **4a**–**u**, **9**, and **10** are listed in Table 4. Several interesting structure–activity relationships were identified by analyses of the IC_{50} values of these compounds.

In general, most of the tested compounds exhibited obvious cytotoxicity to Raji cell lines. Among the compounds tested, **4n** (R^1 = Bn; R^2 = H; R^3 = 6-Br) showed the most potent cytotoxicity, with an IC_{50} value of 17.56 μM, which was almost equal to that of cisplatin under the same conditions. Replacement of the *N*-hydrogen atom by various alkyl group did not affect the cytotoxicity markedly, indicating that this is an unimportant subunit (**4a** vs **4b**–**e**). Note that when R^1 was changed from benzyl group to an α-phenylethyl group, the cytotoxicity of the spirooxindole derivatives to the Raji cell line decreased markedly (**4a** vs

Table 4 Cytotoxic Activities of Compounds **4a**–**u**, **9**, and **10** to the Raji Cell Line In Vitro

Compound	IC_{50}[a] (μM)	Compound	IC_{50}[a] (μM)	Compound	IC_{50}[a] (μM)
4a	23.87	**4j**	33.34	(*S*,*S*)-**4s**	62.21
4b	24.68	**4k**	28.25	(*S*,*R*)-**4s**	62.30
4c	25.88	**4l**	84.97	(*S*,*S*)-**4t**	70.66
4d	28.18	**4m**	25.43	(*S*,*R*)-**4t**	70.87
4e	25.68	**4n**	17.56	(*S*,*S*)-**4u**	65.45
4f	74.81	**4o**	61.89	(*S*,*R*)-**4u**	65.69
4g	39.22	**4p**	25.01	**9**	35.29
4h	32.83	**4q**	32.21	**10**	42.68
4i	30.74	**4r**	87.67	cisplatin	17.32

[a] Assayed by exposure for 48 h.

4s; **4b** vs **4t**). The electronic characters of various substituents as well as their position on the benzene ring had a marked effect on the cytotoxicity of the corresponding products to the Raji cell line. Although strongly electron-withdrawing groups, such as nitro, produced a marked decrease in the bioactivity (**4r**, R^3 = 5-NO_2; R^1 = Ph; IC_{50} = 87.67 μM; **4l**, 5-NO_2; R^1 = Bn; IC_{50} = 84.97 μM), the 7-trifluoromethyl-substituted spirooxindole derivative showed a contrary result (**4p**, IC_{50} = 25.01 μM). The cytotoxicities of halo-substituted compounds were markedly dependent on the position of the halo group on the benzene ring. Generally, the trends in cytotoxicity followed the sequence 6-X > 5-X > 4-X (X = Br, Cl; i.e. **4n** > **4k** > **4g**; **4m** > **4j** > **4f**). In addition, the bromo derivatives all showed much higher cytotoxicities than the corresponding chloro derivatives. Furthermore, compounds **9** and **10**, which have different heterocycles fused to the spiro pyran ring, did not show noteworthy cytotoxicities, suggesting that the tetramic acid subunit might also be beneficial to cytotoxicity. Spirooxindole derivatives **4** with moderate to strong cytotoxicities might become promising antitumor drug candidates after further structural modifications and biological investigations.

In summary, we have developed an efficient, catalyst-free, and convenient method for the preparation of spirooxindoles derivatives in ethanol as a solvent. To the best of our knowledge, this is the first example of a multicomponent reaction for the synthesis of spiroindoline derivatives containing a 4*H*-pyran-fused pyrrolidinone subunit. The present green synthesis shows attractive characteristics, such as one-pot conditions, short reaction times, easy workup and purification, and reduced waste production, without needing any catalyst or additive. The in vitro cytotoxicities of these new spirooxindoles derivatives were investigated. Most of the tested compounds exhibited moderate to strong cytotoxicities to Raji cell lines. Further research and drug development on derivatives for cytotoxicity testing are ongoing in our laboratory, and the results will be reported in due course.

All reagents were obtained from commercial suppliers and used without further purification. Commercial-grade solvents were dried and purified by standard procedures. All the reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 NMR spectrometer with TMS as an internal reference. Melting points were determined on a Beijing Keyi XT5 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Thermo Nicolet (IR 200) spectrometer. High-resolution mass spectra were recorded on a Waters Micromass Q-Tof Micro instrument operated in the ESI mode. The optical rotations were measured by using a PerkinElmer model 343 polarimeter at 20 °C.

Spirooxindole Derivatives 4a–r; General Procedure

A mixture of tetramic acid **1a** (1 mmol), isatin **2** (1 mmol), and malononitrile (**3**; 1 mmol) in EtOH (2 mL) was stirred at reflux for 3 h. When the reaction was complete (TLC), the mixture was cooled to r.t. The precipitated product was collected by filtration and washed successively with H_2O and cold EtOH.

2′-Amino-6′-benzyl-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4a)

White powder; yield: 0.361 g (94%); mp 224–226 °C.

IR (KBr): 3423, 3246, 3138, 2198, 1710, 1680, 1656, 1599, 1367, 704 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.20 (s, 2 H, CH_2), 4.38 (d, *J* = 15.6 Hz, 1 H, CH_2), 4.44 (d, *J* = 15.6 Hz, 1 H, CH_2), 6.85 (d, *J* = 7.6 Hz, 1 H, ArH), 6.97 (t, *J* = 7.2 Hz, 1 H, ArH), 7.13 (m, 3 H, ArH), 7.24 (m, 2 H, ArH), 7.32 (t, *J* = 7.2 Hz, 2 H, ArH), 7.44 (s, 2 H, NH_2), 10.58 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.72, 165.98, 161.28, 160.77, 142.00, 137.38, 132.16, 128.90, 128.59, 127.41, 127.25, 124.33, 122.07, 117.68, 109.56, 106.57, 56.61, 47.39, 46.62, 44.54.

MS (ESI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}N_4O_3$: 385.1; found: 385.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}N_4O_3$: 385.1295; found: 385.1294.

2′-Amino-6′-benzyl-1-methyl-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4b)

White powder; yield: 0.370 g (93%); mp 241–242 °C.

IR (KBr): 3433, 3268, 3121, 2196, 1711, 1683, 1633, 1594, 1362, 705 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.17 (s, 3 H, CH_3), 4.22 (s, 2 H, CH_2), 4.37 (d, *J* = 15.2 Hz, 1 H, CH_2), 4.43 (d, *J* = 15.2 Hz, 1 H, CH_2), 7.07 (m, 2 H, ArH), 7.15 (m, 2 H, ArH), 7.21 (m, 1 H, ArH), 7.26 (m, 1 H, ArH), 7.33 (m, 3 H, ArH), 7.49 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.13, 165.85, 161.38, 160.91, 143.39, 137.33, 131.34, 129.12, 128.59, 127.41, 127.27, 124.03, 122.85, 117.54, 108.55, 106.43, 56.19, 47.46, 46.27, 44.52, 26.45.

MS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1; found: 398.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1452; found: 399.1452.

2′-Amino-6′-benzyl-1-ethyl-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4c)

White powder; yield: 0.379 g (92%); mp 248–250 °C.

IR (KBr): 3433, 3268, 3121, 2196, 1711, 1683, 1633, 1594, 1362, 705 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.16 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 3.75 (m, 2 H, CH_2CH_3), 4.21 (s, 2 H, CH_2), 4.40 (s, 2 H, CH_2), 7.04 (m, 1 H, ArH), 7.12 (m, 3 H, ArH), 7.20 (m, 1 H, ArH), 7.26 (m, 1 H, ArH), 7.32 (m, 3 H, ArH), 7.47 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.70, 165.88, 161.39, 160.81, 142.36, 137.37, 131.67, 129.07, 128.58, 127.39, 127.24, 124.23, 122.60, 117.41, 108.64, 106.46, 56.40, 47.47, 46.13, 44.53, 34.49, 12.31.

MS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.2; found: 412.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.1608; found: 413.1593.

2′-Amino-6′-benzyl-1-butyl-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4d)

White powder; yield: 0.396 g (90%); mp 225–22 °C.

IR (KBr): 3436, 3271, 3123, 2197, 1710, 1685, 1635, 1594, 1363, 757 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.89 (t, *J* = 7.6 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.38 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.61 (m, 2 H, $CH_2CH_2CH_2CH_3$), 3.70 (m, 2 H, $CH_2CH_2CH_2CH_3$), 4.20 (s, 2 H, CH_2), 4.40 (s, 2 H, CH_2), 7.04 (t, *J* = 7.2 Hz, 1 H, ArH), 7.08 (d, *J* = 7.6 Hz, 1 H, ArH), 7.13 (d, *J* = 7.2 Hz, 2 H, ArH) 7.19 (d, *J* = 7.2 Hz, 1 H, ArH), 7.25 (m, 1 H, ArH), 7.32 (m, 3 H, ArH), 7.47 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.05, 165.86, 161.40, 160.85, 142.86, 137.37, 131.53, 129.05, 128.58, 127.40, 127.25,

124.18, 122.56, 117.50, 108.71, 106.48, 56.48, 47.43, 46.20, 44.54, 39.39, 29.00, 19.25, 13.67.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_4O_3$: 441.2; found: 441.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_4O_3$: 441.1921; found: 441.1925.

2′-Amino-1,6′-dibenzyl-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4e)
White powder; yield: 0.427 g (90%); mp 203–206 °C.

IR (KBr): 3299, 3236, 3195, 2197, 1712, 1640, 1611, 1588, 1360, 750 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.25 (s, 2 H, CH_2), 4.44 (s, 2 H, CH_2), 4.94 (d, *J* = 16.0 Hz, 1 H, CH_2), 4.99 (d, *J* = 16.0 Hz, 1 H, CH_2), 6.78 (d, *J* = 7.6 Hz, 1 H, ArH), 7.04 (t, *J* = 7.6 Hz, 1 H, ArH), 7.16 (d, *J* = 7.2 Hz, 2 H, ArH), 7.28 (m, 8 H, ArH), 7.44 (d, *J* = 7.2 Hz, 2 H, ArH), 7.54 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.46, 165.95, 161.60, 160.94, 142.43, 137.35, 135.67, 131.44, 128.98, 128.60, 128.39, 127.40, 127.27, 127.18, 126.90, 124.27, 122.90, 117.70, 109.24, 106.37, 56.37, 47.50, 46.37, 44.58, 43.16.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{23}N_4O_3$: 475.2; found: 475.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{23}N_4O_3$: 475.1765; found: 475.1767.

2′-Amino-6′-benzyl-4-chloro-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4f)
White powder; yield: 0.381 g (91%); mp 286–288 °C.

IR (KBr): 3348, 3300, 3154, 2192, 1713, 1682, 1650, 1595, 1368, 706 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.20 (d, *J* = 19.2 Hz, 1 H, CH_2), 4.26 (d, *J* = 19.2 Hz, 1 H, CH_2), 4.42 (d, *J* = 15.6 Hz, 1 H, CH_2), 4.46 (d, *J* = 15.6 Hz, 1 H, CH_2), 6.86 (d, *J* = 7.6 Hz, 1 H, ArH), 6.99 (d, *J* = 8.4 Hz, 1 H, ArH), 7.12 (d, *J* = 7.2 Hz, 2 H, ArH), 7.26 (m, 2 H, ArH), 7.33 (m, 2 H, ArH), 7.54 (s, 2 H, NH_2), 10.85 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.83, 165.93, 162.12, 161.57, 143.88, 137.33, 130.83, 130.08, 128.60, 127.26, 127.19, 126.86, 122.55, 117.38, 108.79, 104.73, 54.08, 47.33, 47.00, 44.47.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_4O_3$: 419.1; found: 418.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_4O_3$: 419.0905; found: 419.0919.

2′-Amino-6′-benzyl-4-bromo-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4g)
White powder; yield: 0.424 g (92%); mp 294–296 °C.

IR (KBr): 3350, 3298, 3154, 2191, 1712, 1680, 1649, 1590, 1367, 705 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.16 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.26 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.41 (d, *J* = 15.6 Hz, 1 H, CH_2), 4.48 (d, *J* = 15.6 Hz, 1 H, CH_2), 6.89 (d, *J* = 7.6 Hz, 1 H, ArH), 7.13 (m, 3 H, ArH), 7.20 (t, *J* = 8.0 Hz, 1 H, ArH), 7.26 (t, *J* = 7.2 Hz, 1 H, ArH), 7.33 (m, 2 H, ArH), 7.55 (s, 2 H, NH_2), 10.85 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.84, 165.90, 162.29, 161.66, 144.12, 137.32, 131.04, 128.60, 128.29, 127.25, 127.15, 125.60, 118.98, 117.39, 109.24, 104.60, 54.08, 48.19, 47.30, 44.42.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}BrN_4O_3$: 463.0; found: 463.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}BrN_4O_3$: 463.0400; found: 463.0401

2′-Amino-6′-benzyl-5-methyl-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4h)
White powder; yield: 0.367 g (92%); mp 232–234 °C.

IR (KBr): 3347, 3290, 3151, 2194, 1710, 1683, 1650, 1594, 1364, 703 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.24 (s, 3 H, CH_3), 4.17 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.23 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.46 (d, *J* = 15.6 Hz, 1 H, CH_2), 4.36 (d, *J* = 15.6 Hz, 1 H, CH_2), 6.73 (d, *J* = 8.0 Hz, 1 H, ArH), 6.94 (s, 1 H, ArH), 7.02 (d, *J* = 8.0 Hz, 1 H, ArH), 7.15 (d, *J* = 7.2 Hz, 2 H, ArH), 7.26 (t, *J* = 7.2 Hz, 1 H, ArH), 7.33 (t, *J* = 7.2 Hz, 2 H, ArH), 7.40 (s, 2 H, NH_2), 10.46 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.66, 166.03, 161.21, 160.72, 139.55, 137.38, 132.27, 130.92, 129.18, 128.58, 127.47, 127.27, 124.81, 117.72, 109.30, 106.69, 56.81, 47.39, 46.65, 44.58, 20.59.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1; found: 398.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1452; found: 399.1455.

2′-Amino-6′-benzyl-5-fluoro-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4i)
White powder; yield: 0.377 g (94%); mp 267–270 °C.

IR (KBr): 3346, 3294, 3148, 2193, 1727, 1681, 1651, 1593, 1369, 692 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.16 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.23 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.39 (d, *J* = 15.6 Hz, 1 H, CH_2), 4.43 (d, *J* = 15.6 Hz, 1 H, CH_2), 6.84 (m, 1 H, ArH), 7.06 (m, 1 H, ArH), 7.15 (m, 3 H, ArH), 7.26 (m, 1 H, ArH), 7.33 (m, 2 H, ArH), 7.52 (s, 2 H, NH_2), 10.62 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.78, 165.95, 161.56, 160.86, 158.36 (d, $^1J_{FC}$ = 235.9 Hz), 138.19 (d, $^4J_{FC}$ = 1.5 Hz), 137.35, 133.84 (d, $^3J_{FC}$ = 7.6 Hz), 128.59, 127.42, 127.26, 117.58, 115.28 (d, $^2J_{FC}$ = 23.1 Hz), 112.23 (d, $^2J_{FC}$ = 24.5 Hz), 110.32 (d, $^3J_{FC}$ = 7.8 Hz), 106.04, 56.13, 47.47, 47.10, 44.55.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}FN_4O_3$: 403.1; found: 402.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}FN_4O_3$: 403.1201; found: 403.1206.

2′-Amino-6′-benzyl-5-chloro-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4j)
White powder; yield: 0.388 g (93%); mp 278–280 °C.

IR (KBr): 3353, 3298, 3142, 2192, 1711, 1680, 1650, 1590, 1365, 707 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.17 (d, *J* = 19.2 Hz, 1 H, CH_2), 4.22 (d, *J* = 19.2 Hz, 1 H, CH_2), 4.38 (d, *J* = 15.6 Hz, 1 H, CH_2), 4.46 (d, *J* = 15.6 Hz, 1 H, CH_2), 6.87 (d, *J* = 8.4 Hz, 1 H, ArH), 7.16 (d, *J* = 7.2 Hz, 2 H, ArH), 7.28 (m, 3 H, ArH), 7.33 (t, *J* = 7.2 Hz, 2 H, ArH) 7.52 (s, 2 H, NH_2), 10.72 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.52, 165.97, 161.67, 160.90, 140.93, 137.34, 134.17, 128.88, 128.58, 127.46, 127.27, 126.08, 124.62, 117.58, 111.01, 105.87, 55.95, 47.54, 46.85, 44.59.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_4O_3$: 419.1; found: 418.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_4O_3$: 419.0905; found: 419.0912.

2′-Amino-6′-benzyl-5-bromo-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4k)
White powder; yield: 0.424 g (92%); mp 274–276 °C.

IR (KBr): 3357, 3299, 3149, 2193, 1711, 1680, 1649, 1590, 1363, 699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.17 (d, J = 19.2 Hz, 1 H, CH_2), 4.22 (d, J = 19.2 Hz, 1 H, CH_2), 4.38 (d, J = 15.6 Hz, 1 H, CH_2), 4.47 (d, J = 15.6 Hz, 1 H, CH_2), 6.82 (d, J = 8.0 Hz, 1 H, ArH), 7.16 (d, J = 6.8 Hz, 2 H, ArH), 7.26 (t, J = 7.2 Hz, 1 H, ArH), 7.33 (t, J = 7.2 Hz, 2 H, ArH), 7.41 (m, 2 H, ArH), 7.52 (s, 2 H, NH_2), 10.72 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.39, 165.99, 161.69, 160.90, 141.35, 137.34, 134.55, 131.72, 128.58, 127.47, 127.30, 127.27, 117.59, 113.77, 111.54, 105.86, 55.95, 47.55, 46.79, 44.60.

MS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}BrN_4O_3$: 463.0; found: 463.7.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}BrN_4O_3$: 463.0400; found: 463.0402.

2′-Amino-6′-benzyl-5-nitro-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4l)
Yellow powder; yield: 0.386 g (90%); mp 254–256 °C.

IR (KBr): 3364, 3307, 3183, 2191, 1735, 1715, 1675, 1650, 1588, 1370, 690 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.21 (d, J = 19.2 Hz, 1 H, CH_2), 4.26 (d, J = 19.2 Hz, 1 H, CH_2), 4.38 (d, J = 15.2 Hz, 1 H, CH_2), 4.44 (d, J = 15.2 Hz, 1 H, CH_2), 7.09 (d, J = 8.4 Hz, 1 H, ArH), 7.15 (d, J = 6.8 Hz, 2 H, ArH), 7.25 (t, J = 6.8 Hz, 1 H, ArH), 7.32 (t, J = 7.2 Hz, 2 H, ArH), 8.17 (s, 1 H, ArH), 8.22 (d, J = 8.4 Hz, 1 H, ArH), 7.64 (s, 2 H, NH_2), 11.34 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.36, 165.93, 162.15, 161.15, 148.44, 142.74, 137.26, 133.15, 128.58, 127.44, 127.28, 126.43, 120.35, 117.47, 109.91, 105.25, 55.11, 47.71, 46.72, 44.59.

MS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}N_5O_5$: 430.1; found: 429.8.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}N_5O_5$: 430.1146; found: 430.1147.

2′-Amino-6′-benzyl-6-chloro-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4m)
White powder; yield: 0.385 g (92%); mp 289–291 °C.

IR (KBr): 3353, 3298, 3170, 2195, 1712, 1680, 1650, 1590, 1362, 704 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.19 (d, J = 18.8 Hz, 1 H, CH_2), 4.25 (d, J = 18.8 Hz, 1 H, CH_2), 4.40 (d, J = 16.0 Hz, 1 H, CH_2), 4.48 (d, J = 16.0 Hz, 1 H, CH_2), 6.89 (d, J = 8.4 Hz, 1 H, ArH), 7.18 (t, J = 7.2 Hz, 2 H, ArH), 7.30 (m, 3 H, ArH), 7.36 (t, J = 7.2 Hz, 2 H, ArH) 7.54 (s, 2 H, NH_2), 10.74 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.53, 165.98, 161.68, 160.90, 140.94, 137.34, 134.18, 128.89, 128.59, 127.47, 127.28, 126.09 124.63, 117.79, 111.02, 105.88, 55.96, 47.55, 46.86, 44.60.

MS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}ClN_4O_3$: 419.1; found: 418.9.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}ClN_4O_3$: 419.0905; found: 419.0907.

2′-Amino-6′-benzyl-6-bromo-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4n)
White powder; yield: 0.416 g (90%); mp 290–291 °C.

IR (KBr): 3435, 3186, 3141, 2195, 1710, 1672, 1635, 1598, 1368, 704 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.21 (s, 2 H, CH_2), 4.41 (s, 2 H, CH_2), 7.01 (s, 1 H, ArH), 7.14 (m, 4 H, ArH), 7.28 (m, 3 H, ArH), 7.52 (s, 2 H, NH_2), 10.75 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.36, 165.93, 162.15, 161.15, 148.45, 142.74, 137.26, 133.15, 128.58, 127.44, 127.28, 126.43, 120.36, 117.47, 109.91, 105.25, 55.12, 47.71, 46.72, 44.59.

MS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}BrN_4O_3$: 463.0; found: 463.3.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{16}BrN_4O_3$: 463.0400; found: 463.0405.

2′-Amino-6′-benzyl-5,7-dibromo-2,5′-dioxo-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4o)
White powder; yield: 0.491 g (91%); mp 296–297 °C.

IR (KBr): 3373, 3292, 3156, 2195, 1735, 1712, 1680, 1640, 1589, 1367, 703 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.20 (s, 2 H, CH_2), 4.38 (d, J = 15.2 Hz, 1 H, CH_2), 4.48 (d, J = 15.2 Hz, 1 H, CH_2), 7.17 (d, J = 7.2 Hz, 2 H, ArH), 7.28 (t, J = 7.2 Hz, 1 H, ArH), 7.34 (m, 2 H, ArH), 7.48 (m, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.49 (s, 2 H, NH_2), 11.17 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.50, 165.90, 161.85, 160.90, 141.00, 137.16, 135.47, 133.75, 128.62, 127.48, 127.36, 126.69, 117.49, 114.40, 105.47, 102.78, 55.48, 47.88, 47.63, 44.60.

MS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{15}Br_2N_4O_3$: 541.0; found: 540.6.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{15}Br_2N_4O_3$: 540.9505; found: 540.9512.

2′-Amino-6′-benzyl-2,5′-dioxo-7-(trifluoromethyl)-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4p)
White powder; yield: 0.416 g (92%); mp 242–244 °C.

IR (KBr): 3438, 3294, 3184, 2198, 1731, 1714, 1681, 1630, 1369, 704 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.21 (d, J = 19.2 Hz, 1 H, CH_2), 4.26 (d, J = 19.2 Hz, 1 H, CH_2), 4.38 (d, J = 15.2 Hz, 1 H, CH_2), 4.44 (d, J = 15.2 Hz, 1 H, CH_2), 7.14 (d, J = 7.2 Hz, 2 H, ArH), 7.18 (d, J = 7.6 Hz, 1 H, ArH), 7.26 (m, 1 H, ArH), 7.33 (m, 2 H, ArH), 7.48 (d, J = 7.2 Hz, 1 H, ArH), 7.53 (d, J = 8.0 Hz, 1 H, ArH), 7.58 (s, 2 H, NH_2), 11.09 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.30, 165.80, 161.75, 161.02, 139.42, 137.30, 133.90, 128.59, 128.54, 127.44, 127.28, 125.58, 122.32, 117.40, 110.77, 110.44, 105.87, 55.72, 47.54, 45.87, 44.57.

MS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{16}F_3N_4O_3$: 453.1; found: 452.9.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{16}F_3N_4O_3$: 453.1169; found: 453.1175.

2′-Amino-2,5′-dioxo-6′-phenyl-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4q)
White powder; yield: 0.337 g (92%); mp 202–205 °C.

IR (KBr): 3429, 3290, 3203, 2197, 1737, 1710, 1632, 1594, 1362, 753 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.81 (d, J = 18.0 Hz, 1 H, CH_2), 4.89 (d, J = 18.0 Hz, 1 H, CH_2), 6.87 (d, J = 7.6 Hz, 1 H, ArH), 6.98 (t, J = 7.6 Hz, 1 H, ArH), 7.07 (t, J = 7.2 Hz, 1 H, ArH), 7.17 (d, J = 7.2 Hz, 1 H, ArH), 7.23 (t, J = 7.6 Hz, 1 H, ArH), 7.32 (m, 2 H, ArH), 7.59 (s, 1 H, ArH), 7.61 (s, 1 H, ArH), 7.57 (s, 2 H, NH_2), 10.65 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.60, 164.95, 161.55, 160.64, 141.99, 138.62, 131.87, 129.02, 128.85, 124.39, 123.41, 122.12, 118.21, 117.51, 109.62, 107.21, 56.68, 47.75, 46.48.

MS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{15}N_4O_3$: 371.1; found: 371.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{15}N_4O_3$: 371.1139; found: 371.1142.

2′-Amino-5-nitro-2,5′-dioxo-6′-phenyl-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (4r)
White powder; yield: 0.382 g (92%); mp 222–225 °C.

IR (KBr): 3360, 3303, 3198, 2193, 1735, 1711, 1675, 1640, 1589, 1370, 703 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.78 (d, *J* = 18.4 Hz, 1 H, CH_2), 4.92 (d, *J* = 18.4 Hz, 1 H, CH_2), 7.12 (m, 2 H, ArH), 7.32 (m, 2 H, ArH), 7.61 (d, *J* = 8.4 Hz, 2 H, ArH), 8.21 (m, 2 H, ArH), 7.77 (s, 2 H, NH_2), 11.42 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.20, 164.94, 162.35, 161.01, 148.45, 142.74, 138.56, 132.87, 128.87, 126.49, 123.53, 120.45, 118.16, 117.33, 109.94, 105.97, 55.26, 48.10, 46.57.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}N_5O_5$: 416.1; found: 415.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}N_5O_5$: 416.0989; found: 416.0990.

(*S*,*S*)- and (*S*,*R*)-Spirooxindole Diastereomers 4s–u; General Procedure

A mixture of *N*-[(1*S*)-1-phenylethyl]tetramic acid **1b** (1 mmol), isatin **2** (1 mmol), and malononitrile (**3**; 1 mmol), in EtOH (2 mL) was stirred at the reflux for 3 h. When the reaction was complete (TLC), the mixture was cooled to r.t. The precipitate was collected by filtration and washed successively with H_2O and cold EtOH to afford a mixture of the two diastereomers, which was then separated by column chromatography [silica gel, $CHCl_3$–MeOH (15:1)] to give the pure (*S*,*S*)-**4** and (*S*,*R*)-**4**.

(3*S*)-2′-Amino-2,5′-dioxo-6′-[(1*S*)-1-phenylethyl]-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (*S*,*S*-4s)
White powder; yield: 0.187 g (47%); mp 228–229 °C; R_f = 0.65 ($CHCl_3$–MeOH, 15:1); $[\alpha]_D^{20}$ +171.8 (*c* 0.100, MeOH).

IR (KBr): 3422, 3245, 3141, 2199, 1712, 1676, 1651, 1599, 1366, 748 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.47 (d, *J* = 7.2 Hz, 3 H, CH_3), 4.01 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.36 (d, *J* = 18.8 Hz, 1 H, CH_2), 5.09 (q, *J* = 7.2 Hz, 1 H, CH), 6.84 (d, *J* = 7.6 Hz, 1 H, ArH), 6.97 (t, *J* = 7.6 Hz, 1 H, ArH), 7.11 (d, *J* = 7.2 Hz, 1 H, ArH), 7.21 (m, 3 H, ArH), 7.26 (m, 1 H, ArH), 7.33 (t, *J* = 7.2 Hz, 2 H, ArH), 7.45 (s, 2 H, NH_2), 10.54 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.68, 165.51, 161.32, 160.78, 141.99, 141.61, 132.09, 128.87, 128.49, 127.18, 126.41, 124.32, 122.03, 117.68, 109.55, 106.70, 56.53, 48.70, 46.57, 44.18, 18.23.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1; found: 398.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1452; found: 399.1453.

(3*R*)-2′-Amino-2,5′-dioxo-6′-[(1*S*)-1-phenylethyl]-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (*S*,*R*-4s)
White powder; yield: 0.175 g (44%); mp 227–228 °C; R_f = 0.55 ($CHCl_3$–MeOH, 15:1); $[\alpha]_D^{20}$ +122.3 (*c* 0.100, MeOH).

IR (KBr): 3423, 3240, 3143, 2197, 1711, 1673, 1649, 1595, 1366, 705 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.48 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.98 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.39 (d, *J* = 18.8 Hz, 1 H, CH_2), 5.11 (q, *J* = 7.2 Hz, 1 H, CH), 6.83 (d, *J* = 7.6 Hz, 1 H, ArH), 6.94 (t, *J* = 7.6 Hz, 1 H, ArH), 7.10 (d, *J* = 7.2 Hz, 1 H, ArH), 7.19 (m, 3 H, ArH), 7.23 (m, 1 H, ArH), 7.31 (t, *J* = 7.2 Hz, 2 H, ArH), 7.45 (s, 2 H, NH_2), 10.59 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.73, 165.58, 161.44, 160.76, 141.96, 141.56, 132.24, 128.85, 128.49, 127.14, 126.41, 124.25, 122.09, 117.70, 109.52, 106.67, 56.65, 48.82, 46.58, 44.31, 18.48.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1; found: 398.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O_3$: 399.1452; found: 399.1452.

(3*S*)-2′-Amino-1-methyl-2,5′-dioxo-6′-[(1*S*)-1-phenylethyl]-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (*S*,*S*-4t)
White powder; yield: 0.189 g (46%); mp 239–241 °C; R_f = 0.80 ($CHCl_3$–MeOH, 15:1); $[\alpha]_D^{20}$ +176.4 (*c* 0.100, MeOH).

IR (KBr): 3430, 3246, 3141, 2196, 1710, 1676, 1650, 1599, 1363, 705 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.47 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.16 (s, 3 H, CH_3), 4.04 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.39 (d, *J* = 18.8 Hz, 1 H, CH_2), 5.09 (q, *J* = 7.2 Hz, 1 H, CH), 7.07 (m, 2 H, ArH), 7.20 (m, 3 H, ArH), 7.27 (m, 1 H, ArH), 7.34 (m, 3 H, ArH), 7.51 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.12, 165.38, 161.45, 160.92, 143.39, 141.66, 131.34, 129.10, 128.53, 127.19, 126.39, 124.02, 122.82, 117.56, 108.53, 106.58, 56.23, 48.78, 46.24, 44.32, 26.47, 18.37.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.2; found: 413.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.1608; found: 413.1611.

(3*R*)-2′-Amino-1-methyl-2,5′-dioxo-6′-[(1*S*)-1-phenylethyl]-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (*S*,*R*-4t)
White powder; yield: 0.182 g (44%); mp 238–239 °C; R_f = 0.70 ($CHCl_3$–MeOH, 15:1); $[\alpha]_D^{20}$ +206.7 (*c* 0.100, MeOH).

IR (KBr): 3432, 3244, 3139, 2197, 1710, 1680, 1650, 1596, 1365, 703 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.47 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.16 (s, 3 H, CH_3), 4.00 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.40 (d, *J* = 18.8 Hz, 1 H, CH_2), 5.10 (q, *J* = 7.2 Hz, 1 H, CH), 7.05 (m, 2 H, ArH), 7.19 (m, 3 H, ArH), 7.24 (m, 1 H, ArH), 7.31 (m, 3 H, ArH), 7.50 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.14, 165.44, 161.52, 160.94, 143.40, 141.52, 131.41, 129.07, 128.49, 127.15, 126.42, 123.95, 122.85, 117.59, 108.50, 106.57, 56.22, 48.83, 46.26, 44.34, 26.42, 18.44.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.2; found: 413.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.1608; found: 413.1614.

(3*S*)-2′-Amino-5-methyl-2,5′-dioxo-6′-[(1*S*)-1-phenylethyl]-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (*S*,*S*-4u)
White powder; yield: 0.194 g (47%); mp 235–237 °C; R_f = 0.60 ($CHCl_3$–MeOH, 15:1); $[\alpha]_D^{20}$ +148.6 (*c* 0.100, MeOH).

IR (KBr): 3347, 3288, 3141, 2195, 1710, 1680, 1643, 1594, 1364, 704 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.48 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 4.00 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.36 (d, *J* = 18.8 Hz, 1 H, CH_2), 5.11 (q, *J* = 6.8 Hz, 1 H, CH), 6.72 (d, *J* = 7.6 Hz, 1 H, ArH), 6.92 (s, 1 H, ArH), 7.02 (d, *J* = 7.6 Hz, 1 H, ArH), 7.20 (d, *J* = 7.6 Hz, 2 H, ArH), 7.26 (d, *J* = 6.8 Hz, 1 H, ArH), 7.33 (t, *J* = 7.2 Hz, 2 H, ArH), 7.42 (s, 2 H, NH_2), 10.42 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.62, 165.55, 161.25, 160.73, 141.65, 139.56, 132.20, 130.86, 129.16, 128.49, 127.18, 126.40, 124.79, 117.73, 109.31, 106.81, 56.74, 48.68, 46.61, 44.16, 20.60, 18.25.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.2; found: 412.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.1608; found: 413.1610.

(3*R*)-2′-Amino-5-methyl-2,5′-dioxo-6′-[(1*S*)-1-phenylethyl]-1,2,6′,7′-tetrahydro-5′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrrole]-3′-carbonitrile (*S*,*R*-4u)
White powder; yield: 0.177 g (43%); mp 230–231 °C; R_f = 0.50 ($CHCl_3$–MeOH, 15:1); $[\alpha]_D^{20}$ +90.2 (*c* 0.100, MeOH).

IR (KBr): 3345, 3288, 3140, 2195, 1711, 1681, 1646, 1594, 1365, 705 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.48 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.22 (s, 3 H, CH_3), 3.98 (d, *J* = 18.8 Hz, 1 H, CH_2), 4.39 (d, *J* = 18.8 Hz, 1 H, CH_2), 5.12 (q, *J* = 6.8 Hz, 1 H, CH), 6.71 (d, *J* = 8.0 Hz, 1 H, ArH), 6.91 (s, 1 H, ArH), 6.99 (d, *J* = 7.6 Hz, 1 H, ArH), 7.19 (d, *J* = 7.2 Hz, 2 H, ArH), 7.25 (d, *J* = 7.2 Hz, 1 H, ArH), 7.31 (t, *J* = 7.6 Hz, 2 H, ArH), 7.40 (s, 2 H, NH_2), 10.45 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.65, 165.65, 161.39, 160.70, 141.55, 139.51, 132.36, 130.90, 129.15, 128.48, 127.17, 126.50, 124.75, 117.74, 109.24, 106.79, 56.83, 48.93, 46.61, 44.33, 20.57, 18.51.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.2; found: 412.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_4O_3$: 413.1608; found: 413.1612.

2-Amino-2′,5-dioxo-1′,2′,5,7-tetrahydrospiro[furo[3,4-*b*]pyran-4,3′-indole]-3-carbonitrile (9)
White powder; yield: 0.269 g (92%); mp 234–236 °C.

IR (KBr): 3339, 3246, 3170, 2198, 1747, 1700, 1597, 1378, 1030, 918 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.09 (d, *J* = 20.8 Hz, 1 H, CH_2), 5.21 (d, *J* = 20.8 Hz, 1 H, CH_2), 6.87 (s, 1 H, ArH), 7.00 (m, 1 H, ArH), 7.22 (m, 2 H, ArH), 7.66 (s, 2 H, NH_2), 10.67 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.04, 169.28, 167.99, 160.45, 141.87, 130.98, 129.37, 124.60, 122.30, 117.24, 109.78, 101.46, 65.97, 56.41, 46.09.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{10}N_3O_4$: 296.1; found: 296.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{10}N_3O_4$: 296.0666; found: 296.0674.

7′-Amino-2,2′,4′-trioxo-1,1′,2,2′,3′,4′-hexahydrospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (10)
White powder; yield: 0.298 g (92%); mp 268–269 °C.

IR (KBr): 3354, 3305, 3143, 2830, 2204, 1723, 1674, 1535, 1340, 755 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.78 (d, *J* = 8.0 Hz, 1 H, ArH), 6.91 (t, *J* = 8.0 Hz, 1 H, ArH), 7.12–7.18 (m, 2 H), 7.36 (s, 2 H, NH_2), 10.47 (s, 1 H, NH), 11.11 (s, 1 H, NH), 12.28 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.60, 161.37, 158.21, 153.29, 149.19, 142.07, 133.46, 128.37, 123.71, 121.72, 116.88, 109.22, 86.77, 57.79, 46.60.

MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{10}N_5O_4$: 324.1; found: 324.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{10}N_5O_4$: 324.0727; found: 324.0725.

In Vitro Cytotoxicity Assay
Human B lymphoma Raji cell line was obtained from the China Center for Type Culture Collection, Wuhan, China. The cells were cultured in RPMI-1640 medium with 10% fetal bovine serum, 100 U/mL of penicillin, and 100 mg/mL of streptomycin under a 5% CO_2 humidified atmosphere at 37 °C. Cell cytotoxicity was assayed by the MTT method. Briefly, cells were seeded in 96-well tissue-culture plates and incubated with the test compound (0–50 mmol/mL) for 48 h at 37 °C under 5% CO_2. Following this treatment, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; 0.5 mg/mL) was added. After an additional 4 h of incubation, the assay was terminated by removal of the supernatant. DMSO (200 μL) was then added to each well to dissolve the formazan product, and the optical density of each well was measured at 570 nm with a PowerWaveX microplate scanning spectrophotometer (BioTek Instruments). The percentage inhibition of cell growth by each compound at various concentrations was then calculated.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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