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One-pot three-component synthesis of functionalized spirooxindoles in gluconic acid aqueous solution

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ABSTRACT

A general, efficient, and green method for one-pot synthesis of functionalized spirooxindoles through three-component condensation reaction of isatins, cyclohexane-1,3-diones, and barbituric acids is described employing gluconic acid aqueous solution (GAAS) as a novel reaction medium and catalyst. The reaction medium could be recycled and reused several times without significant loss of its efficiency.

1. Introduction

With ever-increasing environmental consciousness in chemical research and industry, there has been a growing interest in the development of efficient, practical, and environmentally friendly synthetic methods. In this regard, to address the problem of pollution of traditional volatile organic solvents (VOCs) used in many synthetic organic processes, tremendous efforts have been devoted toward sustainable reaction media. Although a variety of unconventional solvents, such as water,[1] ionic liquids,[2] fluorous media,[3] supercritical fluids,[4] and polyethylene glycol[5] have been extensively studied and fascinating results have been reported, the use of these solvents is still subject to strict limitations, such as the instability of reactive reagents or substrates in water, high prices and lack of data about the toxicity and bio-compatibility for ionic liquids, the demand of sophisticated equipment for supercritical fluids. Therefore, the search of new reaction media is thus gaining prominence. Meanwhile, multicomponent reactions (MCRs) offer significant advantages over conventional linear-type synthesis, such as high atom economy and bond-forming efficiency, reducing labor time, energy input and waste.[6] The combination of multicomponent reactions and benign reaction media has become a promising frontier field of research, which enables simultaneous growth of both MCRs and green solvents toward ideal organic synthesis.[7]

Recently, the use of bio-based materials as alternatives to conventional organic solvents has grabbed considerable interest among synthetic community. Many naturally available products, such as glycerol,[8] ethyl lactate,[9] γ-valerolactone,[10] 2-methyl-tetrahydrofuran,[11] carbohydrates-based low melting mixtures[12] have been proposed as safer, sustainable, renewable, and biodegradable solvents for catalysis and organic chemistry. However, the number of bio-based solvents is still limited at this stage. More recently, Gu et al. introduced gluconic acid aqueous solution (GAAS, 50 wt %) as a promoting medium and catalyst for organic transformations.[13] Gluconic acid is an organic compound with molecular formula $C_6H_{12}O_7$ and it is abundantly available in plants, fruits, and other foodstuffs, such as rice, meat, dairy products, wine, honey, and vinegar. In particular, the low toxicity of gluconic acid also allows its use in the formulation of food, pharmaceutical and hygienic products. It is normally available as an aqueous solution of gluconic acid, which is composed of equilibrium between the free acid and the two lactones. GAAS is a noncorrosive, nonvolatile, stable, inexpensive industrial product and largely available in the market. It is a weakly acidic aqueous solution and can promote some organic reactions that need the assistance of a week acid. Thus, such media may constitute alternative solvents for the development of sustainable chemistry.

It is well known that spirooxindole system is important core structure of many natural and synthetic molecules with a wide range of utilities in medicinal chemistry. Spirooxindoles, especially

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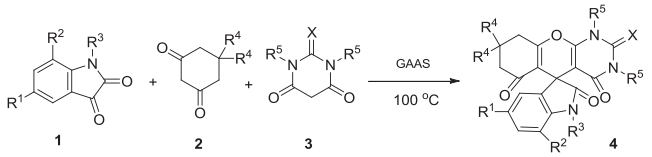
those spiroannulated with heterocycles at the 3-position, have shown good biological activities.[14] Owing to their important, there is a need to augment a simple and novel method to generate structurally varied spirooxindoles with a variety of substituents.

As part of an ongoing program geared toward the design and development of novel and environmental benign synthetic methodologies,[15] we report herein a straightforward one-pot three-component method for the synthesis of functionalized spirooxindoles by multiple covalent bond. To the best of our knowledge, this is the first report for the synthesis of spirooxindole-pyrimidines using GAAS an efficient and reusable promoting medium and catalyst (Scheme 1).

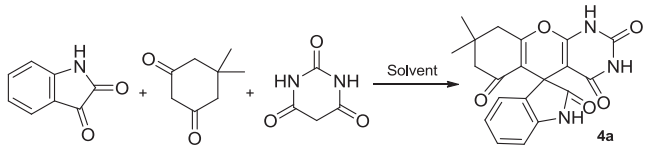


Scheme 1. Synthesis of functionalized spirooxindole in GAAS.

2. Results and discussion

Initially, we conducted the model reaction of isatin, 5,5-dimethylcyclohexane-1,3-dione and barbituric acid in different solvents under catalyst-free conditions and the results are listed in Table 1. Only a trace amount of products were detected in acetonitrile, dimethyl sulfoxide, tetrahydrofuran, ethanol, polyethylene glycol 400, or in neat conditions (Table 1, entries 1–6). When the reaction was performed in deep eutectic solvents (DES),[16] such as choline chloride-urea, the desired product was obtained in 12% yield (entry 7). Low melting sugar-urea-salt mixtures also moderately promoted the reaction, and gave the product in 35–51% yields (entries 8–12). The reaction conducted in glycerol also occurred to give the corresponding product in 56% isolated yields (entry 13). It has previously been reported in the literature that this three-component reaction was usually carried out in the presence of acid catalysts, such as *p*-toluenesulfonic acid,[17] alum,[18] magnetic nanoparticle supported dodecyl benzenesulfonic acid,[19] and montmorillonite K-10[20] in water or ionic liquid media. This prompted us to investigate acidic solvent to improve the reaction. Acetic acid was examined and displayed less efficiency (entry 14). When the reaction proceeded in low melting mixtures, such as citric acid-dimethylurea (DMU) and L-(+)-tartaric acid-choline chloride, slightly improved yields were obtained (entries 15 and 16). To our great delight, the yield of **4a** was enhanced to 95% when GAAS was used as the solvent (entry 18). Further tests with lowering of the reaction temperature (entries 19–20), inferior results in terms of reaction time and yield were observed.

Table 1
Reaction of isatin, 5,5-dimethylcyclohexane-1,3-dione and barbituric acid in different solvents[a]



Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	No	100	10	Trace
2	CH_3CN	Reflux	10	Trace
3	DMSO	Reflux	10	Trace
4	THF	Reflux	10	Trace
5	EtOH	Reflux	10	Trace
6	PEG 400	100	10	Trace
7	Choline chloride–urea (55:45)	100	10	12
8	Maltose–DMU–NH_4Cl (50:40:10)	100	10	39
9	D-(−)-Fructose–DMU (70:30)	100	10	36
10	L-(+)-Tartaric acid–DMU (30:70)	100	10	51
11	Lactose–DMU–NH_4Cl (50:40:10)	100	10	35
12	Mannose–DMU–NH_4Cl (50:40:10)	100	10	41
13	Glycerol	100	10	56
14	Acetic acid	100	10	15
15	Citric acid–DMU (40:60)	100	10	58
16	L-(+)-Tartaric acid–choline chloride (50:50)	100	10	78
17	H_2O	Reflux	10	38
18	GAAS	100	1	95
19	GAAS	60	5	21
20	GAAS	80	5	48

[a] Reaction condition: 5,5-dimethyl-cyclohexane-dione (1 mmol), barbituric (1 mmol), isatin (1 mmol), solvent (3 ml).

This interesting finding promised a bright prospect and made us start to investigate the substrate scope and generality of this three-component reaction and the results are summarized in Table 2. Various isatins bearing electron-donating and electron-withdrawing substituents underwent the reaction with 5,5-dimethylcyclohexane-1,3-dione and barbituric acid to afford the desired spirooxindole-pyrimidines (**4**) in high yields (Table 2, entries 1–10). This system was tolerant to a number of functional groups. Generally, isatins possessing electron-withdrawing showed better reactivity and needed shorter reaction time than those with electron-donating groups. Furthermore, the nitrogen protected isatin substrates were also consistent with the optimized conditions (entries 11–15). In addition, 7-substituted isatin reacted smoothly to give the corresponding product **4f** in 94% yield (entry 6). To our disappointment, when the more sterically substrate, such as 4-bromoistain was subjected to the reaction system, no reaction was observed.

Additionally, the substrate scope of cyclic 1,3-dicarbobonyl compounds was further investigated. When cyclohexane-1,3-dione was subjected to the reaction system, similar results were observed. Other cyclic 1,3-dicarbobonyl compounds, such as cyclopentane-1,3-dione and 2*H*-indene-1,3-dione, were used under the same conditions, however, TLC and ^1H NMR spectra of the reaction mixture showed a combination of starting materials and numerous by-products and the yield of the desired product was very poor. Different barbituric acids, such as 1,3-dimethylbarbituric acid and thiobarbituric acid were also tested. As revealed in Table 2, these barbituric acids also worked well and furnished the desired products in high yields.

Compounds **4** are stable solids and their structures were established by IR, ^1H NMR and ^{13}C NMR spectra, and elemental analysis. The structure of **4ak** was further confirmed by X-ray diffraction analysis (Fig. 1).[21]

Although the detailed mechanism of this three-component reaction remains to be fully clarified, the condensation of isatin, 5,5-dimethylcyclohexane-1,3-dione, and barbituric acid, which rationalizes the formation of product **4a**, could be explained by the reaction sequence via two plausible pathways (Scheme 2). Isatin may react with 5,5-dimethylcyclohexane-1,3-dione to afford the aldol adduct **I**, which may be subsequently attacked by barbituric acid to furnish intermediate **II**. Alternatively, the reaction may be initiated by aldol reaction of isatin with barbituric acid to give **III**, followed by nucleophilic attack of 5,5-dimethylcyclohexane-1,3-dione, to provide intermediate **II**. Finally, the hydroxyl group of intermediate **II** attacks the adjacent carbonyl group, followed by dehydration, to produce the expected product **4a**. Only a trace amount of self-condensation product **5** was detected. Although by-product **6** seems to be a reasonable candidate, it was not observed in the reaction.

In addition, we investigated the reusability of GAAS using the model reaction of isatin and 5-dimethylcyclohexane-1,3-dione

Table 2
One-pot synthesis of functionalized spirooxindoles

Entry	R^1	R^2	R^3	R^4	R^5	X	Product	Time (min)	Yield[a] (%)	Mp (°C)
1	H	H	H	Me	H	O	**4a**	60	95	>300[17]
2	OMe	H	H	Me	H	O	**4b**	180	81	>300
3	OCF_3	H	H	Me	H	O	**4c**	30	93	267–269
4	Me	H	H	Me	H	O	**4d**	120	85	293–294 (290)[17]
5	F	H	H	Me	H	O	**4e**	30	94	>300[19]
6	H	F	H	Me	H	O	**4f**	40	90	>300
7	Cl	H	H	Me	H	O	**4g**	45	93	>300[19]
8	Br	H	H	Me	H	O	**4h**	50	93	>300[18]
9	I	H	H	Me	H	O	**4i**	60	92	>300[19]
10	NO_2	H	H	Me	H	O	**4j**	20	96	293–295 (292)[18]
11	H	H	Me	Me	H	O	**4k**	60	90	>300[18]
12	H	H	Et	Me	H	O	**4l**	60	91	254–256 (253–255)[18]
13	H	H	$CH_2CH_2CH_2CH_3$	Me	H	O	**4m**	120	90	211–212
14	H	H	Bz	Me	H	O	**4n**	60	92	259–260 (258–259)[18]
15	H	H	$CH_2CH{=}CH_2$	Me	H	O	**4o**	120	90	>300
16	H	H	H	Me	Me	O	**4p**	70	90	>300[17]
17	OMe	H	H	Me	Me	O	**4q**	180	82	>300
18	OCF_3	H	H	Me	Me	O	**4r**	25	93	281–282
19	Me	H	H	Me	Me	O	**4s**	140	83	>300[19]
20	F	H	H	Me	Me	O	**4t**	70	90	>300[19]
21	Cl	H	H	Me	Me	O	**4u**	50	92	>300[19]
22	Br	H	H	Me	Me	O	**4v**	55	91	>300[19]
23	NO_2	H	H	Me	Me	O	**4w**	50	90	>300 (298)[17]
24	H	H	$CH_2CH_2CH_2CH_3$	Me	Me	O	**4x**	110	92	187–188
25	H	H	Bz	Me	Me	O	**4y**	130	90	209–210
26	H	H	$CH_2CH{=}CH_2$	Me	Me	O	**4z**	120	90	232–233
27	H	H	H	H	H	O	**4aa**	70	83	>300[19]
28	Me	H	H	H	H	O	**4ab**	150	85	>300[19]
29	F	H	H	H	H	O	**4ac**	40	90	>300[18]
30	Cl	H	H	H	H	O	**4ad**	45	91	>300[19]
31	Br	H	H	H	H	O	**4ae**	45	92	245–247 (242–245)[18]
32	NO_2	H	H	H	H	O	**4af**	30	93	282–284 (280–281)[18]
33	H	H	Me	H	H	O	**4ag**	70	89	>300[18]
34	H	H	H	H	Me	O	**4ah**	60	90	>300[19]
35	Me	H	H	H	Me	O	**4ai**	120	85	>300[19]
36	F	H	H	H	Me	O	**4aj**	40	89	>300[19]
37	Cl	H	H	H	Me	O	**4ak**	45	93	>300[19]
38	Br	H	H	H	Me	O	**4al**	50	92	290–291 (2888–289)[19]
39	NO_2	H	H	H	Me	O	**4am**	35	94	>300[17]
40	H	H	Me	H	Me	O	**4an**	60	88	293–295 (292–293)[19]
41	OMe	H	H	Me	H	S	**4ao**	200	82	>300
42	OCF_3	H	H	Me	H	S	**4ap**	25	93	>300
43	Me	H	H	Me	H	S	**4aq**	180	84	>300[19]
44	F	H	H	Me	H	S	**4ar**	75	85	>300[19]
45	Cl	H	H	Me	H	S	**4as**	70	89	>300[19]
46	Br	H	H	Me	H	S	**4at**	35	92	285 (282–283)[19]
47	NO_2	H	H	Me	H	S	**4au**	50	90	>300[17]
48	H	H	Me	Me	H	S	**4av**	80	91	>300[19]
49	H	H	H	H	H	S	**4aw**	80	93	>300[19]
50	Me	H	H	H	H	S	**4ax**	170	93	>300[19]
51	F	H	H	H	H	S	**4ay**	60	92	>300[19]
52	Cl	H	H	H	H	S	**4az**	50	93	>300[19]
53	Br	H	H	H	H	S	**4ba**	50	91	>300[19]
54	H	H	Me	H	H	S	**4bb**	60	89	>300[19]
55	H	H	$CH_2CH_2CH_2CH_3$	H	H	S	**4bc**	100	91	201–202
56	H	H	Bz	H	H	S	**4bd**	140	90	223–235

[a] Isolated yield.

with barbituric acid. After the reaction was completed, the reaction mixture was cooled to room temperature, the product was isolated by simple filtration. The recovered gluconic acid aqueous solution could be reused three additional times in subsequent reactions without significant loss of its activity.

3. Conclusion

In conclusion, we have developed a novel, high efficient, green, and sustainable protocol for synthesis of functionalized spirooxindoles through one-pot, three-component condensation reaction of isatins, cyclohexane-1,3-diones, and barbituric acids using gluconic acid aqueous solution as an inexpensive, biodegradable, commercially available and reusable promoting medium without the addition of any additive or organic co-solvent. The notable advantages of this methodology are operational simplicity, wide substrate scope, excellent functional group tolerance, environmentally benign, inexpensive reaction medium, short reaction time, high yield of products, and easy-handing. Further investigations on the applications of gluconic acid aqueous solution on other catalytically synthetic reactions are under progress in our group.

4. Experimental

4.1. General information

All solvents and chemicals were obtained commercially and were used as received without further purification. Melting points

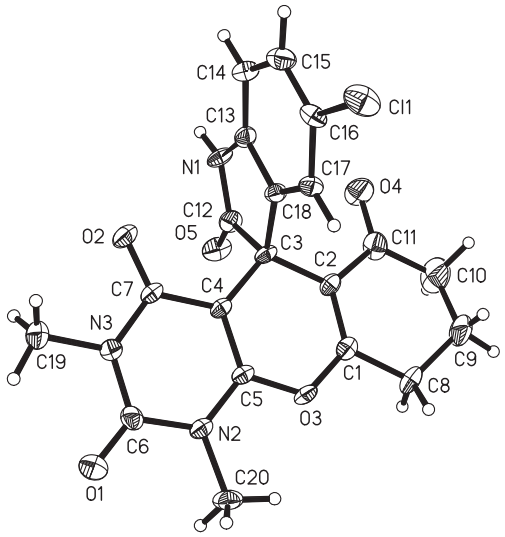
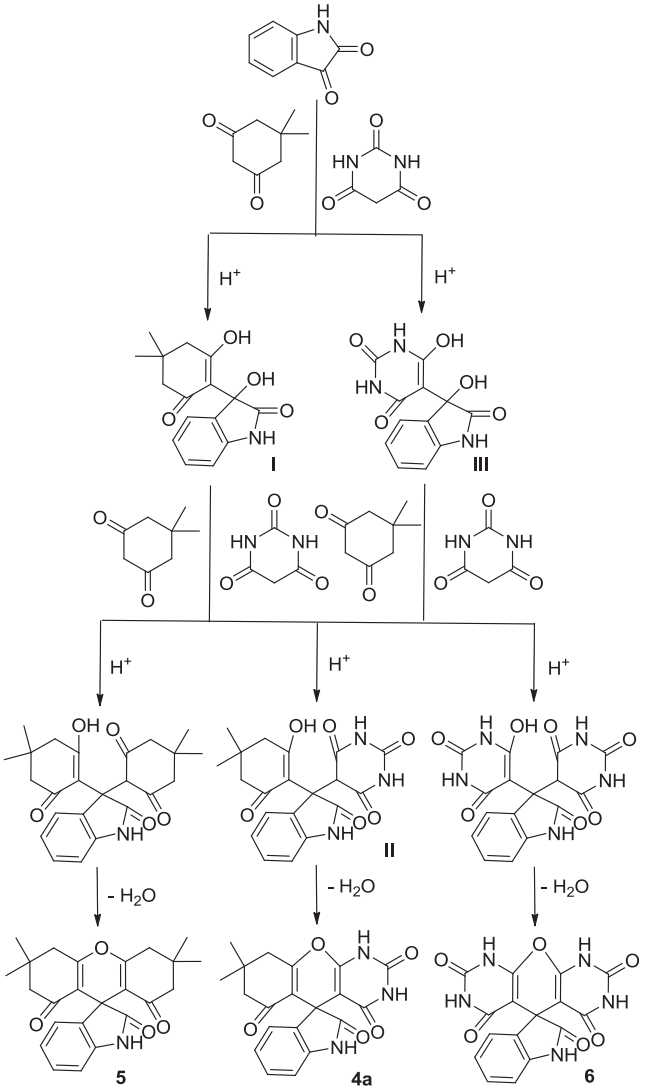


Fig. 1. Crystal structure of compound **4ak**.



Scheme 2. Plausible reaction mechanism.

were determined on an X-4 digital melting point apparatus without correction. IR spectra were taken as KBr discs using a Bruker-TENSOR 27 spectrometer instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-500 spectrometer at 500 MHz and 125 MHz, respectively, using DMSO-d_6 as the solvent and TMS as an internal standard. Elemental analyses were determined on a Vario EL III CHNOS elemental analyzer.

4.2. Typical procedure for the synthesis of functionalized spirooxindoles 4a

A mixture of isatin (0.15 g, 1 mmol), 5,5-dimethylcyclohexanedione (0.14 g, 1 mmol), barbituric (0.13 g, 1 mmol) in gluconic acid aqueous solution (3 ml) was stirred at 100 °C. The reaction progress was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water. The crude product was crystallized from ethanol to give **4a**.

4.3. Characterization data

*4.3.1. 5′-Methoxy-8,8-dimethyl-8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4b**).* White crystals, mp>300 °C; IR (KBr): 3340, 2960, 1685, 1624, 1538, 1521, 1482, 1436, 1363, 1332, 1307, 1209, 1151, 1026, 873, 794, 696 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.97 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.07 and 2.18 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.54 and 2.63 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.60 (s, 3H, OCH_3), 6.61–6.64 (m, 3H, Ar*H*), 10.18 (s, 1H, N*H*), 10.99 (s, 1H, N*H*) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.2, 28.2, 32.2, 46.0, 50.9, 55.8, 89.5, 109.1, 110.8, 112.6, 113.5, 135.3, 137.7, 149.6, 153.6, 155.0, 161.9, 163.7, 178.2, 195.4 ppm; Anal. Calcd for $C_{21}H_{19}N_3O_6$: C, 61.61; H, 4.68; N, 10.26. Found: C, 61.45; H, 4.80; N, 10.08.

*4.3.2. 8,8-Dimethyl-5′-(trifluoromethoxy)-8,9-dihydrospiro-[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4c**).* White crystals, mp 267–269 °C; IR (KBr): 3310, 2966, 1627, 1533, 1489, 1421, 1363, 1332, 1240, 1176, 1165, 1074, 1003, 885, 771 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.07 and 2.23 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.54 and 2.77 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 6.77 (d, J=8.5 Hz), 7.09 (d, J=8.5 Hz, 1H, Ar*H*), 7.16 (s, 1H, Ar*H*), 10.58 (s, 1H, N*H*), 11.06 (s, 1H, N*H*), 12.25 (s, 1H, N*H*) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 26.7, 28.3, 32.2, 45.9, 50.7, 88.9, 109.3, 113.0, 117.5, 119.6, 121.4, 121.6, 135.6, 143.2, 143.5, 149.5, 153.8, 162.0, 164.1, 178.4, 195.6 ppm; Anal. Calcd for $C_{21}H_{16}F_3N_3O_6$: C, 54.43; H, 3.48; N, 9.07. Found: C, 54.24; H, 3.66; N, 9.25.

*4.3.3. 7′-Fluoro-8,8-dimethyl-8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4f**).* Light yellow solid, mp>300 °C; IR (KBr): 3340, 2958, 2821, 1685, 1624, 1521, 1490, 1471, 1419, 1307, 1236, 1195, 1178, 1155, 1089, 1001, 852, 734 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.94 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.06 and 2.18 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.54 and 2.63 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 6.77–6.81 (m, 1H, Ar*H*), 6.84 (d, J=7.5 Hz, 1H, Ar*H*), 6.98 (d, J=9.0 Hz, 1H, Ar*H*), 10.85 (s, 1H, N*H*), 11.05 (s, 1H, N*H*) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.2, 28.1, 32.2, 45.8, 50.7, 89.2, 113.2, 115.6 (d, $^2J_{CF}$=17.4 Hz), 119.4, 122.1 (d, $^3J_{CF}$=5.4 Hz), 131.2, 131.3, 136.8 (d, $^4J_{CF}$=3.8 Hz), 145.4, 147.3, 149.5, 153.6, 163.1 (d, $^1J_{CF}$=249.6 Hz), 178.1, 195.6 ppm; Anal. Calcd for $C_{20}H_{16}FN_3O_5$: C, 60.45; H, 4.06; N, 10.57. Found: C, 60.61; H, 3.89; N, 10.38.

*4.3.4. 1′-Butyl-8,8-dimethyl-8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4m**).* White crystals, mp 211–212 °C; IR (KBr): 3414, 2954, 1627, 1521, 1480, 1465, 1425, 1361, 1338, 1230, 1168, 1083, 923, 754 cm^{-1}; ^{1}H NMR (DMSO-

d_6, 500 MHz) δ: 0.91 (t, J=7.5 Hz, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.43 (sext, J=7.5 Hz, 2H, CH_2), 1.63 (quin, J=7.5 Hz, 2H, CH_2), 2.05 and 2.19 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.56 and 2.67 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.56–3.67 (m, 2H, CH_2), 6.85 (t, J=7.5 Hz, 1H, ArH), 6.90 (d, J=7.5 Hz, 1H, ArH), 7.03 (d, J=7.5 Hz, 1H, ArH), 7.16 (t, J=7.5 Hz, 1H, ArH), 11.01 (s, 1H, NH), 12.22 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ:14.4, 20.2, 27.1, 28.2, 29.3, 32.2, 45.0, 50.7, 89.5, 107.9, 113.5, 121.7, 123.2, 128.5, 133.3, 145.3, 149.5, 153.6, 161.9, 163.8, 176.5, 195.3 ppm; Anal. Calcd for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65. Found: C, 65.99; H, 5.98; N, 9.56.

*4.3.5. 1′-Allyl-8,8-dimethyl-8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4o**).* White crystals, mp>300 °C; IR (KBr): 3414, 2928, 1568, 1525, 1504, 1435, 1263, 1186, 1166, 1136, 1097, 1082, 993, 871, 758 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.98 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.07 and 2.21 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.56 and 2.69 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 4.23–4.34 (m, 2H, N–CH_2), 5.17 (dd, J=10.5, 1.5 Hz, 1H, =CH_2), 5.61 (dd, J=17.0, 1.5 Hz, 1H, =CH_2), 5.87–5.94 (m, 1H, =CH), 6.79 (d, J=7.5 Hz, 1H, ArH), 6.88 (t, J=7.5 Hz, 1H, ArH), 7.07 (d, J=7.5 Hz, 1H, ArH), 7.16 (t, J=7.5 Hz, 1H, ArH), 11.06 (s, 1H, NH), 12.28 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.1, 28.2, 32.3, 42.9, 45.1, 50.7, 55.4, 89.4, 108.6, 113.5, 117.2, 122.0, 123.2, 128.4, 132.8, 133.1, 144.9, 149.5, 153.6, 161.9, 163.9, 176.6, 195.4 ppm; Anal. Calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.05; N, 10.02. Found: C, 66.05; H, 4.90; N, 9.83.

*4.3.6. 5′-Methoxy-1,3,8,8-tetramethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4q**).* White crystals, mp>300 °C; IR (KBr): 3356, 2956, 1627, 1458, 1371, 1354, 1316, 1298, 1265, 1215, 1184, 1165, 1084, 1031, 785 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.00 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.12 and 2.21 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.65 and 2.73 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.03 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 6.63–6.68 (m, 3H, ArH), 10.22 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.2, 28.09, 28.1, 29.7, 32.2, 46.8, 51.0, 55.7, 89.9, 109.1, 111.1, 112.5, 113.5, 135.2, 137.8, 150.1, 152.4, 155.0, 159.9, 163.5, 178.2, 195.4 ppm; Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 63.15; H, 5.30; N, 9.61. Found: C, 59.96; H, 5.12; N, 9.80.

*4.3.7. 1,3,8,8-Tetramethyl-5′-(trifluoromethoxy)-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4r**).* White crystals, mp 281–282 °C; IR (KBr): 3227, 2962, 1423, 1082, 1057, 1039, 989, 966, 831, 680 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.98 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.10 and 2.26 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.64 and 2.78 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.04 (s, 3H, N–CH_3), 3.41 (s, 3H, N–CH_3), 6.79 (d, J=8.5 Hz), 7.09 (d, J=8.5 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 10.61 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 26.6, 28.1, 28.3, 29.7, 32.2, 46.6, 50.8, 89.3, 109.4, 113.1, 117.5, 119.6, 121.6, 135.4, 143.2, 143.6, 150.0, 152.6, 160.0, 163.9, 178.3, 195.5 ppm; Anal. Calcd for $C_{23}H_{20}F_3N_3O_6$: C, 56.21; H, 4.10; N, 8.55. Found: C, 56.03; H, 3.92; N, 8.71.

*4.3.8. 1′-Butyl-1,3,8,8-tetramethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4x**).* White crystals, mp 187–188 °C; IR (KBr): 3423, 2960, 1626, 1313, 1211, 1180, 1155, 1139, 1091, 1049, 1031, 958, 893, 752 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.94 (t, J=7.5 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.45 (sext, J=7.5 Hz, 2H, CH_2), 1.67 (quin, J=7.5 Hz, 2H, CH_2), 2.08 and 2.22 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.67 and 2.76 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.01 (s, 3H, N–CH_3), 3.42 (s, 3H, N–CH_3), 3.58–3.70 (m, 2H, CH_2), 6.86 (t, J=7.5 Hz, 1H, ArH), 6.92 (d, J=7.5 Hz, 1H, ArH), 7.03 (d, J=7.5 Hz, 1H, ArH), 7.18 (t, J=7.5 Hz, 1H, ArH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 14.3, 20.2, 27.2, 28.2, 29.3, 29.8, 32.2, 45.8, 50.8, 89.8, 107.9, 113.5, 121.8, 123.4, 128.7, 133.1, 145.2, 150.0, 152.5, 159.9, 163.6, 176.6, 195.4 ppm; Anal. Calcd for $C_{26}H_{29}N_3O_5$: C, 67.37; H, 6.31; N, 9.07. Found: C, 67.18; H, 6.50; N, 8.91.

*4.3.9. 1′-Benzyl-1,3,8,8-tetramethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4y**).* White crystals, mp 209–210 °C; IR (KBr): 3032, 2955, 1654, 1629, 1608, 1489, 1458, 1371, 1356, 1317, 1273, 1230, 1178, 1101, 964, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.01 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.15 and 2.28 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.70 and 2.80 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.05 (s, 3H, N–CH_3), 3.43 (s, 3H, N–CH_3), 4.85 and 4.97 (AB system, J_{AB}=16.0 Hz, 2H, PhCH_2), 6.55 (d, J=7.5 Hz, 1H, ArH), 6.87 (t, J=7.5 Hz, 1H, ArH), 7.06–7.10 (m, 2H, ArH), 7.28 (t, J=7.5 Hz, 1H, ArH), 7.35 (t, J=7.5 Hz, 2H, ArH), 7.64 (d, J=7.5 Hz, 2H, ArH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.2, 28.2, 29.8, 32.3, 44.7, 45.9, 50.8, 89.9, 108.7, 113.4, 122.2, 123.5, 127.4, 127.7, 128.6, 128.8, 133.0, 137.2, 145.0, 150.0, 152.5, 160.0, 163.9, 177.2, 195.6 ppm; Anal. Calcd for $C_{29}H_{27}N_3O_5$: C, C, 70.01; H, 5.47; N, 8.45. Found: C, 69.82; H, 5.66; N, 8.23.

*4.3.10. 1′-Allyl-1,3,8,8-tetramethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone (**4z**).* White crystals, mp 232–233 °C; IR (KBr): 2958, 2872, 1541, 1425, 1286, 1278, 1259, 1230, 1134, 1099, 1049, 1028, 1003, 925, 761 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.12 and 2.23 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.68 and 2.77 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.02 (s, 3H, N–CH_3), 3.42 (s, 3H, N–CH_3), 4.26–4.37 (m, 2H, N–CH_2), 5.21 (dd, J=10.0, 2.0 Hz, 1H, =CH_2), 5.63 (dd, J=17.5, 2.0 Hz, 1H, =CH_2), 5.90–5.97 (m, 1H, =CH), 6.81 (d, J=7.5 Hz, 1H, ArH), 6.88 (t, J=7.5 Hz, 1H, ArH), 7.07 (d, J=7.5 Hz, 1H, ArH), 7.17 (t, J=7.5 Hz, 1H, ArH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.2, 28.2, 29.8, 32.3, 43.0, 45.8, 50.8, 89.8, 108.6, 113.5, 117.5, 122.0, 123.3, 128.6, 132.9, 133.0, 144.9, 150.0, 152.5, 160.0, 163.7, 176.6, 195.4 ppm; Anal. Calcd for $C_{25}H_{25}N_3O_5$: C, 67.10; H, 5.63; N, 9.39. Found: C, 66.92; H, 5.48; N, 9.21.

*4.3.11. 5′-Methoxy-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,4,6(1H,7H)-trione (**4ao**).* White crystals, mp>300 °C; IR (KBr): 3357, 2928, 1670, 1610, 1490, 1334, 1303, 1203, 1190, 1176, 1203, 1157, 1105, 1037, 956, 786 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.97 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.07 and 2.18 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.53 and 2.63 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.59 (s, 3H, OCH_3), 6.59 (d, J=8.5 Hz, 1H, ArH), 6.63 (dd, J=8.5, 2.0 Hz, 1H, ArH), 6.71 (d, J=2.0 Hz, 1H, ArH), 10.22 (s, 1H, NH), 12.37 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.2, 28.1, 32.2, 46.0, 49.1, 50.8, 55.8, 94.2, 109.2, 111.0, 112.9, 113.3, 134.7, 137.8, 152.9, 155.1, 159.6, 163.6, 174.0, 177.6, 195.3 ppm; Anal. Calcd for $C_{21}H_{19}N_3O_5S$: C, 59.28; H, 4.50; N, 9.88. Found: C, 59.10; H, 4.68; N, 10.06.

*4.3.12. 8,8-Dimethyl-2-thioxo-5′-(trifluoromethoxy)-2,3,8,9-tetrahydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,4,6(1H,7H)-trione (**4ap**).* White crystals, mp>300 °C; IR (KBr): 3360, 2960, 1624, 1489, 1456, 1396, 1363, 1136, 1093, 1068, 1043, 831, 686 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.07 and 2.23 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.54 and 2.70 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 6.79 (d, J=8.5 Hz), 7.09 (d, J=8.5 Hz, 1H, ArH), 7.25 (s, 1H, ArH), 10.63 (s, 1H, NH), 12.44 (s, 1H, NH), 12.25 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 26.7, 28.3, 32.2, 45.9, 50.7, 93.6, 109.4, 112.8, 117.8, 121.6, 135.0, 143.3, 143.5, 153.3, 159.7, 164.2, 174.1, 177.9, 199.5 ppm; Anal. Calcd for $C_{21}H_{16}F_3N_3O_5S$: C, 52.61; H, 3.36; N, 8.76. Found: C, 52.80; H, 3.55; N, 8.60.

*4.3.13. 1′-Butyl-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,4,6(1H,7H)-trione (**4bc**).* White crystals, mp 201–202 °C; IR (KBr): 2958, 2872, 1662,

1610, 1554, 1491, 1465, 1452, 1406, 1363, 1340, 1309, 1203, 1165, 1039 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ: 0.92 (t, J=7.5 Hz, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.43 (sext, J=7.5 Hz, 2H, CH_2), 1.64 (quin, J=7.5 Hz, 2H, CH_2), 2.07 and 2.21 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.57 and 2.69 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 3.60–3.65 (m, 2H, CH_2), 6.87 (t, J=7.5 Hz, 1H, ArH), 6.92 (d, J=7.5 Hz, 1H, ArH), 7.10 (d, J=7.5 Hz, 1H, ArH), 7.19 (t, J=7.5 Hz, 1H, ArH), 12.38 (s, 1H, NH), 13.74 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 14.3, 20.2, 27.1, 28.2, 29.3, 32.2, 45.0, 50.7, 94.1, 108.0, 113.3, 121.8, 123.5, 128.7, 132.7, 145.3, 153.0, 159.5, 163.8, 174.1, 176.0, 195.3 ppm; Anal. Calcd for $C_{24}H_{25}N_3O_4S$: C, 63.84; H, 5.58; N, 9.31. Found: C, 64.01; H, 5.76; N, 9.12.

*4.3.14. 1′-Benzyl-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,4,6(1H,7H)-trione (**4bd**).* White crystals, mp 223–225 °C; IR (KBr): 3444, 2926, 1610, 1556, 1489, 1465, 1456, 1361, 1311, 1203, 1163, 1074, 1041, 1010, 923, 750 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ: 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.13 and 2.26 (AB system, J_{AB}=16.0 Hz, 2H, CH_2), 2.60 and 2.72 (AB system, J_{AB}=17.5 Hz, 2H, CH_2), 4.89 (s, 2H, CH_2), 6.55 (d, J=7.5 Hz, 1H, ArH), 6.88 (t, J=7.5 Hz, 1H, ArH), 7.09 (t, J=7.5 Hz, 1H, ArH), 7.16 (d, J=7.5 Hz, 1H, ArH), 7.27 (t, J=7.5 Hz, 1H, ArH), 7.33 (t, J=7.5 Hz, 2H, ArH), 7.61 (d, J=7.5 Hz, 2H, ArH), 12.50 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.1, 28.2, 32.3, 44.6, 45.2, 50.7, 94.1, 108.7, 113.3, 122.4, 123.5, 127.6, 128.8, 132.6, 137.1, 145.0, 153.2, 159.8, 164.1, 174.1, 176.8, 195.6 ppm; Anal. Calcd for $C_{27}H_{23}N_3O_4S$: C, 66.79; H, 4.77; N, 8.65. Found: C, 66.96; H, 4.59; N, 8.83.

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21. Crystallographic data for the structure of 4ak reported in this paper have been deposited at Cambridge Crystallographic Data Centre with CCDC 863099. Copy of this information may be obtained free of charge via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi? (e-mail: deposit@ccdc.cam.ac.uk).