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Efficient one-pot synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] dione via three-component reaction

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ABSTRACT

An efficient one-pot synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] dione derivatives via three-component reaction of 5-amino-3-methylpyrazole, isatin, and thioacid is described. This new protocol produces novel heptacyclic spirooxindole derivatives in good yields in comparison to conventional pentacyclic compounds. This method proceeds through a 3-(5-aminopyrazol-3-yl)-3-hydroxy-2-oxindoline intermediate (Baylis–Hillman type adduct), unlike 3-indolylimine (the intermediate like Shiff-Bases) as in conventional methods. The structure of one representative compound has been confirmed by X-ray diffraction analysis.

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1. Introduction

Multi-component reactions (MCRs) have been designed to produce elaborate biologically active compounds and have become an important area of research in organic, combinatorial, and medicinal chemistry.[1] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedure step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. Thus, they are perfectly amenable to automation for combinatorial synthesis.[2] In the past decade there have been tremendous development in three- and four-component reactions and great effort continue to be made to develop new MCRs.[3]

Heterocycles containing the 1,4-thiazepine moiety are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in a wide number of natural and synthetic biologically active agents.[4] Among them, aryl- and heteroaryl-fused derivatives of this heterocycle represent an important group of compounds with interesting pharmaceutical properties.[5,6] In particular, different alkyl derivatives of 3,4-dihydro-5-oxo-1,4-benzothiazepine were described as calcium channel antagonists,[5a] HIV-1 enzyme integrase[5b] and reverse transcriptase[5c] inhibitors, and antitumor agents.[5d] Several heteroannelated bioisosteric analogues of this core fragment were described as potent inhibitors of Herpes simplex virus type 1 (HSV-1) replication,[6a] compounds possessing H1 antihistamine activity,[6b] selective antagonists of 5-HT_{1A} and dopamine D_2 receptors,[6c] and vasoconstrictor agents.[6d] Numerous methods for the synthesis of fused 1,4-thiazepine derivatives in recent years have been reported with respect to their different structures.[7]

The spirooxindole moiety is a core structure in many complex natural products; such natural products often possess interesting biological activities.[8–10] This structure has also drawn the attention of medicinal chemists because of its potential as an important pharmacophore.[11] Various spiro ring systems have been reported in spirooxindole natural products, for example, communesin A and B, which were isolated from a *Penicillium* fungus growing on the marine alga *Enteromorpha intestinalis*.[12] Communesins A and B show cytotoxicity against P-388 lymphocytic leukemia cells with moderate to potent activity (ED_{50}=3.5 μg/mL and 0.45 μg/mL, respectively). Citrinadins A and B are recently isolated marine derived pentacyclic spiroindolinone alkaloids, they both exhibit important cytotoxic activities against various cancer cell lines with IC_{50}'s in the low micromolar range (Fig. 1).[13,14]

Thia-azaheterocycles have attracted considerable attention because of their wide biological and pharmacological activities.[15] Therefore, a number of methods have been reported for the preparation of spirooxindole derivatives involving the synthon thioacid.[16] However, all the above multi-component reactions involving isatin, 2-mercaptoacetic acid and aniline or heteroaniline afford spiro [indoline thiazolidines], which is obtained by reacting 2-mercaptoacetic acid with 3-indolylimines (the intermediate like Shiff-Bases formed by condensation of isatin and aniline) (Scheme 1a). In our previous work, we found 5-amino-3-methylpyrazoles **1** react with isatins **2** giving 3-(5-aminopyrazol-3-yl)-3-hydroxy-

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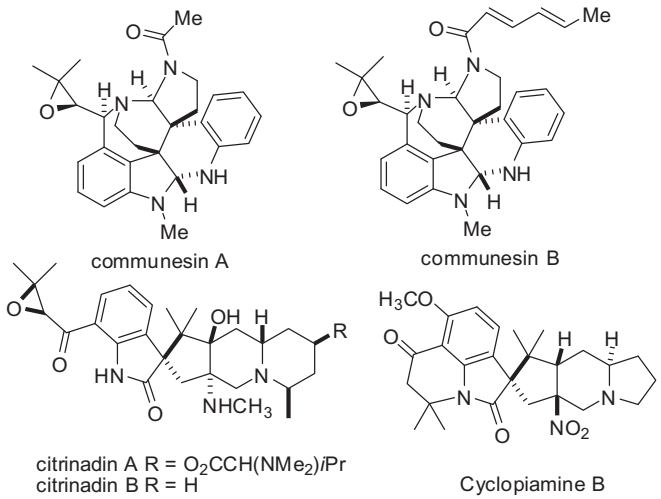
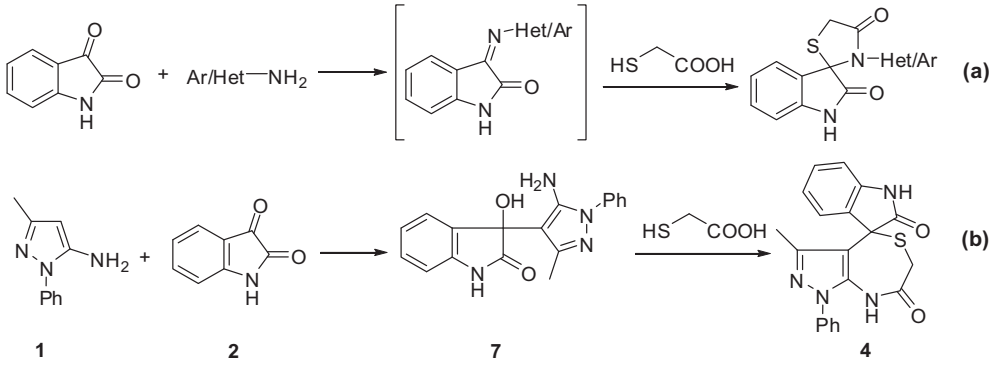


Fig. 1. Naturally occurring and biologically active spirocyclic oxindoles.

different Brønsted and Lewis acids (Table 1, entries 2–5). Lewis acids, such as CAN and $FeCl_3$ can catalyze this reaction with low yields (Table 1, entries 2 and 3). The use of Brønsted acid HCl led to moderate product formation (Table 1, entry 4). However, *p*-TSA was identified as the optimal catalyst with **4a** being isolated in 86% yield (Table 1, entry 5). Performing the reaction in the presence of *p*-TSA at room temperature led to low conversion of **4a** even with prolonged time (Table 1, entry 6). Subsequently, we further turned to testing the effect of solvents. AcOH, THF, DMF, EtOH or water showed no superiority to CH_3CN (Table 1, entries 7–11). Therefore, CH_3CN is the solvent of choice for this reaction.

The optimized reaction conditions were then tested for library construction with two 5-amino-3-methylpyrazoles **1**, seven isatins **2** and two thioacids **3**. A series of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine]dione derivatives **4** were obtained in good yields. The results are summarized in Table 2. The protocol was effective with isatins having either electron-withdrawing or electron-donating groups, and also with different position substituted isatins.

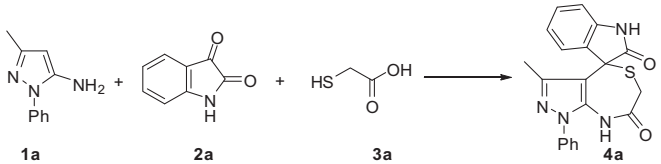


Scheme 1. Synthesis of spirooxindole derivatives involving the synthon thioacid.

2-oxindolines **7**,[17] we planned to synthesize novel heptacyclic spiro [indoline thiazepines] **4** by reacting **7** with thioacids **3** (Scheme 1b). Hence, in continuation of our earlier interest on the developments of new routes to spirooxindole derivatives,[18] we report herein for the first time a facile one-pot synthesis of spiro[indoline-3,4′- pyrazolo [3,4-*e*][1,4]thiazepine]dione derivatives catalyzed by *p*-TSA (*p*-toluenesulfonic acid).

2. Results and discussion

Initially, the three-component reaction of 5-amino-1-phenyl-3-methylpyrazole **1a**, isatin **2a**, and 2-mercaptoacetic acid **3a** as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Scheme 2). The effects of solvents and catalysts were evaluated for this model reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out without any catalysts only trace product was detected even after 24 h (Table 1, entry 1). To improve the yields, we examined this reaction using



Scheme 2. Model reaction.

Table 1
Optimization of reaction conditions

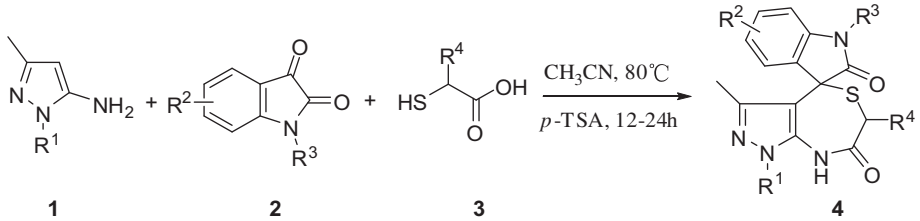
Entry	Solvent	Temperature (°C)	Catalyst	Time (h)	Isolated yield (%)
1	CH_3CN	80	—	24	Trace
2	CH_3CN	80	CAN (30%)	12	54
3	CH_3CN	80	$FeCl_3$ (30%)	12	39
4	CH_3CN	80	HCl (30%)	12	63
5	CH_3CN	80	*p*-TSA (30%)	12	86
6	CH_3CN	rt	*p*-TSA (30%)	24	<10
7	AcOH	95	*p*-TSA (30%)	12	72
8	THF	65	*p*-TSA (30%)	12	79
9	DMF	95	*p*-TSA (30%)	12	68
10	EtOH	80	*p*-TSA (30%)	12	76
11	Water	80	*p*-TSA (30%)	12	65

To further explore the potential of this protocol for synthesis of spiro-heterocyclic compounds, we investigated reaction involving acenaphthylene-1,2-dione **5** and obtained spiro[acenaphthylene-1,4′-pyrazolo[3,4-*e*][1,4]thiazepine]dione derivatives **6** (Fig. 2).

The structures of all products **4** and **6** were characterized by IR, ^1H NMR, ^{13}C NMR spectral data as well as HRMS analysis. The structure of **4p** was further confirmed by X-ray diffraction analysis. The molecular structure of **4p** is shown in Fig. 3.

Although the detailed mechanism of this reaction remains to be fully clarified, a plausible mechanism of this three-component reaction is presented in Scheme 3. The first step involves the formation of a Baylis–Hillman type adduct **7** by the nucleophilic addition of 5-amino-3-methylpyrazole **1** to isatin **2** as a key

Table 2
Synthesis of spirooxindole derivatives **4**



1 2 3 4

Entry	R^1	R^2	R^3	R^4	Products	Time (h)	Isolated yield (%)
1	Ph	H	H	H	**4a**	12	86
2	Ph	H	H	CH_3	**4b**	12	83
3	Ph	H	CH_3	H	**4c**	18	80
4	Ph	H	CH_3	CH_3	**4d**	12	85
5	Ph	5-CH_3	H	H	**4e**	12	83
6	Ph	5-CH_3	H	CH_3	**4f**	12	81
7	Ph	5-F	H	H	**4g**	12	85
8	Ph	5-F	H	CH_3	**4h**	12	89
9	Ph	5-Cl	H	CH_3	**4i**	24	74
10	Ph	5-Br	H	H	**4j**	24	75
11	Ph	6-Br	H	H	**4k**	24	78
12	Ph	6-Br	H	CH_3	**4l**	24	76
13	CH_3	H	H	H	**4m**	12	83
14	CH_3	H	H	CH_3	**4n**	12	83
15	CH_3	H	CH_3	CH_3	**4o**	12	85
16	CH_3	5-CH_3	H	H	**4p**	12	87
17	CH_3	5-CH_3	H	CH_3	**4q**	12	82
18	CH_3	5-F	H	CH_3	**4r**	18	80
19	CH_3	5-Br	H	H	**4s**	24	71
20	CH_3	6-Br	H	H	**4t**	24	79
21	CH_3	6-Br	H	CH_3	**4u**	24	75

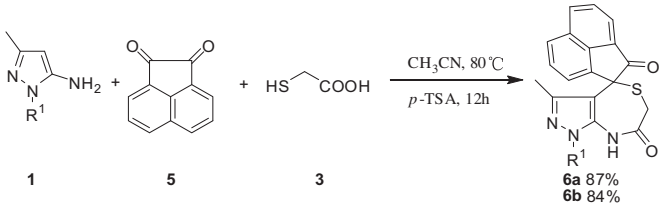


Fig. 2. Synthesis of spirocyclic acenaphthyleneones **6**.

intermediate, which might occur to afford **8**. Then, **8** is attacked via Michael addition of thioacid **3** to give the intermediate **9** followed by cycloaddition, dehydration to form the desired product **4**.

In order to prove the mechanism, when the reaction of 5-amino-1-phenyl-3-methylpyrazole **1a**, isatin **2a**, 2-mercaptoacetic acid **3a** carried out for 1 h, the intermediate 3-(5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-hydroxyindolin-2-one **7** was isolated and characterized by spectroscopic methods. We were pleased to find that the reaction of intermediate **7** with 2-mercaptoacetic acid **3a** in the presence of *p*-TSA under the same reaction conditions proceeded smoothly giving the desired product **4a** in a yield similar to that obtained in the one-pot reaction (Scheme 4).

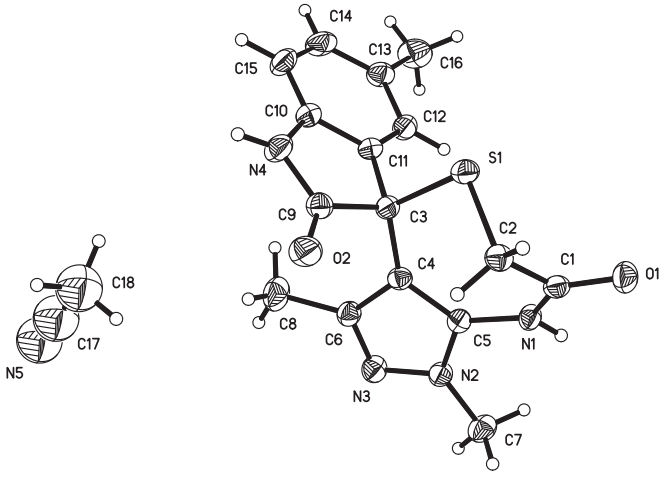


Fig. 3. The crystal structure of compound **4p**.

3. Conclusion

In summary, an efficient multi-component tandem reaction to give spiro[indoline thiazepines] has been developed. Unlike conventional pentacyclic spirooxindole products, this new procedure described in this paper is a very facile and practical method for the synthesis of novel heptacyclic spirooxindole derivatives. The one-pot operational simplicity and the high efficiency nature make this new heterocycle synthetic strategy highly attractive and promising for the access of compounds of potential biological interest.

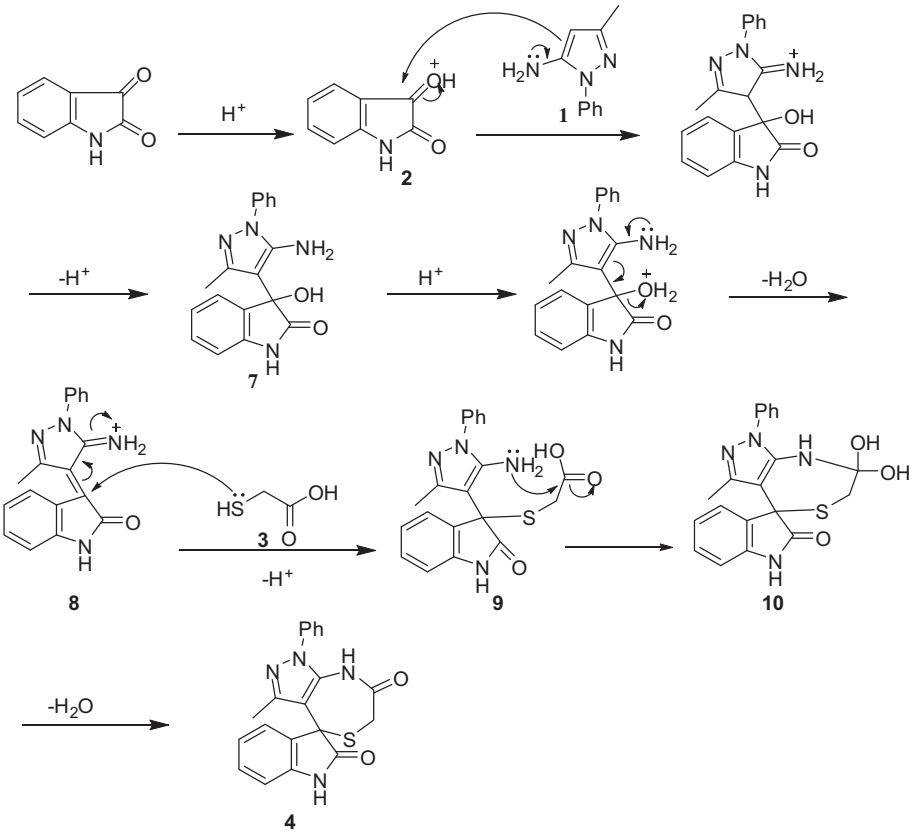
4. Experimental section

4.1. General

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer in KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were obtained from a solution in DMSO-d_6 with Me_4Si as internal standard using Varian Invoa-400 MHz or Invoa-300 MHz spectrometer. HRMS analyses were carried out using TOF-MS or GCT-TOF instrument.

4.2. General procedure for the synthesis of 4 and 6

A mixture of 5-amino-3-methylpyrazole (1 mmol), isatin or acenaphthylene-1,2-dione (1 mmol), thioacid (1 mmol), and *p*-TSA (30 mol %) in CH_3CN (5 mL) was stirred at 80 °C for 12–24 h. After



Scheme 3. Proposed mechanism for the synthesis of spirooxindole derivatives **4**.

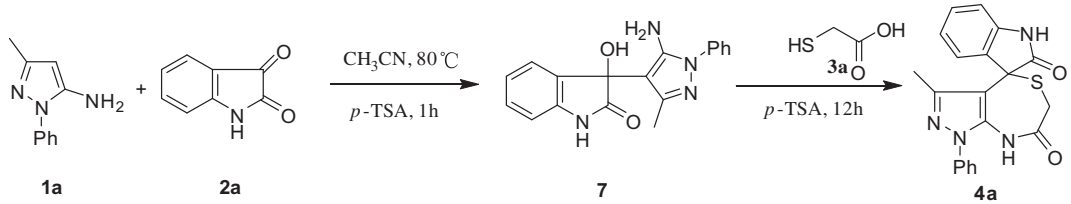
completion of the reaction confirmed by TLC (eluent acetone/petroleum ether, 1:2), the reaction mixture was cooled to room temperature. Then, the solvent was removed under vacuum. The solid was recrystallizated from CH_3CN and ethanol to afford the pure **4** or **6** as a white or yellow powder.

*4.2.1. 3′-Methyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′ (1′H)-dione (**4a**).* Mp: 256–257 °C. IR (KBr) ν: 3364, 3150, 1707, 1584, 1523, 1476, 1400, 1319, 1206, 1134, 757, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.46 (s, 3H, CH_3), 3.11 (d, J=15.0 Hz, 1H, CH_2), 4.54 (d, J=15.0 Hz, 1H, CH_2), 6.96–7.04 (m, 2H, ArH), 7.15 (d, J=7.2 Hz, 1H, ArH), 7.32 (t, J=7.8 Hz, 1H, ArH), 7.40 (t, J=6.9 Hz, 1H, ArH), 7.47–7.56 (m, 4H, ArH), 9.94 (s, 1H, NH), 10.89 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 30.8, 49.2, 106.5, 110.9, 123.4, 125.5, 125.6, 128.2, 129.0, 129.8, 130.7, 137.6, 139.0, 142.0, 147.2, 171.6, 178.5. HRMS [found: m/z 376.0993 (M^+), calcd for $C_{20}H_{16}N_4O_2S$: M, 376.0994].

*4.2.2. 3′,6′-Dimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4b**).* Mp: 270–271 °C. IR (KBr) ν: 3232, 2975, 2926, 2884, 1712, 1617, 1522, 1473, 1378, 1264, 1209, 1077, 917, 756, 692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.27 (d, J=7.2 Hz, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.73 (q, J=7.2 Hz, 1H, CH), 6.98–7.03 (m, 2H, ArH), 7.11 (d, J=7.6 Hz, 1H, ArH), 7.33 (t, J=7.6 Hz, 1H, ArH), 7.41 (t, J=7.2 Hz, 1H, ArH), 7.51 (t, J=7.6 Hz, 2H, ArH), 7.58 (d, J=7.6 Hz, 2H, ArH), 9.98 (s, 1H, NH), 10.89 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.6, 15.9, 35.8, 49.9, 107.0, 110.9, 123.4, 125.4, 125.6, 128.1, 128.5, 129.7, 130.7, 137.6, 139.0, 142.0, 147.0, 173.4, 178.7. HRMS (ESI): m/z calcd for $C_{21}H_{18}N_4O_2S$: 391.1223 $[M+H]^+$, found: 391.1205.

*4.2.3. 1,3′-Dimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4c**).* Mp: 243–244 °C. IR (KBr) ν: 3222, 3123, 2989, 2920, 1710, 1607, 1533, 1491, 1367, 1126, 1086, 932, 751, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.38 (s, 3H, CH_3), 3.15 (d, J=15.2 Hz, 1H, CH_2), 3.29 (s, 3H, CH_3), 4.58 (d, J=14.8 Hz, 1H, CH_2), 7.12 (t, J=7.2 Hz, 1H, ArH), 7.19–7.24 (m, 2H, ArH), 7.40–7.47 (m, 2H, ArH), 7.50–7.58 (m, 4H, ArH), 9.94 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 27.1, 31.0, 48.9, 106.4, 110.0, 124.1, 125.2, 125.6, 128.2, 128.3, 129.8, 130.8, 137.6, 139.0, 143.4, 147.1, 171.5, 176.8. HRMS (ESI): m/z calcd for $C_{21}H_{18}N_4O_2S$: 413.1043 $[M+Na]^+$, found: 413.1073.

*4.2.4. 1,3′,6′-Trimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4d**).* Mp: 280–281 °C. IR (KBr) ν: 3308, 1707, 1606, 1524, 1497, 1368, 1259, 1129, 1080, 934,



Scheme 4. Two-step synthesis of spirooxindole **4a**.

758, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.28 (d, J=7.2 Hz, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 4.75 (q, J=7.2 Hz, 1H, CH), 7.10 (t, J=7.2 Hz, 1H, ArH), 7.18 (t, J=8.0 Hz, 2H, ArH), 7.39–7.45 (m, 2H, ArH), 7.51 (t, J=7.6 Hz, 2H, ArH), 7.58 (d, J=8.0 Hz, 2H, ArH), 9.93 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 12.7, 15.9, 27.2, 36.0, 49.6, 107.0, 110.0, 124.1, 125.2, 125.6, 127.9, 128.1, 129.7, 130.8, 137.6, 139.0, 143.4, 146.8, 173.3, 177.1. HRMS (ESI): m/z calcd for $C_{22}H_{20}N_4O_2S$: 427.1208 $[M+Na]^+$, found: 427.1199.

*4.2.5. 3′,5-Dimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4e**).* Mp: 268–270 °C. IR (KBr) ν: 3219, 2916, 1715, 1621, 1490, 1398, 1345, 1196, 1107, 921, 811, 766, 692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.49 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.12 (d, J=14.8 Hz, 1H, CH_2), 4.55 (d, J=14.8 Hz, 1H, CH_2), 6.88 (d, J=8.0 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 7.13 (d, J=8.0 Hz, 1H, ArH), 7.42 (t, J=6.8 Hz, 1H, ArH), 7.50–7.57 (m, 4H, ArH), 9.92 (s, 1H, NH), 10.77 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 21.2, 30.9, 49.3, 106.6, 110.7, 125.6, 125.8, 128.2, 129.0, 129.8, 131.0, 132.5, 137.5, 139.0, 139.5, 147.3, 171.7, 178.5. HRMS (ESI): m/z calcd for $C_{21}H_{18}N_4O_2S$: 413.1043 $[M+Na]^+$, found: 413.1036.

*4.2.6. 3′,5,6′-Trimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4f**).* Mp: 193–194 °C. IR (KBr) ν: 3383, 3220, 2979, 2925, 1706, 1593, 1495, 1373, 1255, 1194, 1073, 912, 814, 765, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.26 (d, J=6.0 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.71–4.74 (m, 1H, CH), 6.87 (d, J=7.6 Hz, 1H, ArH), 6.93 (s, 1H, ArH), 7.11 (d, J=7.2 Hz, 1H, ArH), 7.41 (d, J=6.8 Hz, 1H, ArH), 7.49–7.58 (m, 4H, ArH), 9.96 (s, 1H, NH), 10.75 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 15.9, 21.1, 35.8, 50.0, 107.1, 110.7, 125.5, 125.7, 128.1, 128.6, 129.7, 131.0, 132.5, 137.6, 139.1, 139.6, 147.1, 173.4, 178.6. HRMS [found: m/z 404.1037 (M^+), calcd for $C_{22}H_{20}N_4O_2S$: M, 404.1037].

*4.2.7. 5-Fluoro-3′-methyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4g**).* Mp: 251–253 °C. IR (KBr) ν: 3381, 3155, 2921, 1708, 1587, 1486, 1402, 1289, 1178, 1126, 927, 859, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.50 (s, 3H, CH_3), 3.20 (d, J=14.8 Hz, 1H, CH_2), 4.51 (d, J=14.8 Hz, 1H, CH_2), 6.98–7.02 (m, 1H, ArH), 7.07–7.09 (m, 1H, ArH), 7.16–7.27 (m, 1H, ArH), 7.42 (t, J=6.8 Hz, 1H, ArH), 7.50–7.56 (m, 4H, ArH), 10.02 (s, 1H, NH), 10.97 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 30.8, 49.7, 106.0, 112.0, 112.1, 112.7, 113.1, 117.1, 117.4, 125.7, 128.2, 129.8, 130.8, 131.0, 137.7, 138.2, 139.0, 147.1, 157.4, 160.6, 171.4, 178.4. HRMS [found: m/z 394.0898 (M^+), calcd for $C_{20}H_{15}FN_4O_2S$: M, 394.0900].

*4.2.8. 5-Fluoro-3′,6′-dimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4] thiazepine]-2,7′(1′H)-dione (**4h**).* Mp: 281–282 °C. IR (KBr) ν: 3382, 3222, 3065, 2928, 2980, 1710, 1592, 1486, 1373, 1259, 1178, 1073, 913, 860, 765, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.28 (d, J=7.2 Hz, 3H, CH_3), 1.53 (s, 3H, CH_3), 4.74 (q, J=6.8 Hz, 1H, CH), 6.97–7.02 (m, 2H, ArH), 7.19 (t, J=8.8 Hz, 1H, ArH), 7.42 (t, J=7.2 Hz, 1H, ArH), 7.51 (t, J=7.6 Hz, 2H, ArH), 7.57 (d, J=7.6 Hz, 2H, ArH), 9.97 (s, 1H, NH), 10.91 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 15.9, 35.8, 50.2, 106.4, 112.0, 112.1, 112.7, 113.0, 117.2, 117.5, 125.6, 128.1, 129.7, 130.1, 130.2, 137.7, 138.2, 139.0, 146.9, 157.3, 160.5, 171.6, 178.4. HRMS [found: m/z 408.1056 (M^+), calcd for $C_{21}H_{17}FN_4O_2S$: M, 408.1056].

*4.2.9. 5-Chloro-3′,6′-dimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4] thiazepine]-2,7′(1′H)-dione (**4i**).* Mp: 270–272 °C. IR (KBr) ν: 3288, 3148, 2930, 1722, 1699, 1596, 1524, 1472, 1362, 1253, 1211, 1072, 912, 825, 767 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.29 (d, J=7.2 Hz, 3H, CH_3), 1.54 (s, 3H, CH_3), 4.71 (q, J=7.2 Hz, 1H, CH), 7.02 (d, J=8.4 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 7.20 (d, J=7.6 Hz, 1H, ArH), 7.38–7.44 (m, 2H, ArH), 7.52 (t, J=7.6 Hz, 2H, ArH), 7.58 (d, J=8.0 Hz, 2H, ArH), 9.91 (s, 1H, NH), 10.99 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 15.9, 35.9, 50.0, 106.4, 112.6, 125.2, 125.6, 127.2, 128.2, 129.7, 130.6, 130.7, 137.8, 139.0, 140.9, 146.9, 173.2, 178.3. HRMS (ESI): m/z calcd for $C_{21}H_{17}ClN_4O_2S$: 411.0677 $[M+H]^+$, found: 411.0663.

*4.2.10. 5-Bromo-3′-methyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4] thiazepine]-2,7′(1′H)-dione (**4j**).* Mp: 274–276 °C. IR (KBr) ν: 3129, 2926, 1722, 1681, 1610, 1532, 1468, 1401, 1206, 1162, 814, 766, 690 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.51 (s, 3H, CH_3), 3.22 (d, J=14.8 Hz, 1H, CH_2), 4.46 (d, J=14.8 Hz, 1H, CH_2), 6.98 (d, J=8.4 Hz, 1H, ArH), 7.31 (s, 1H, ArH), 7.43 (t, J=7.2 Hz, 1H, ArH), 7.50–7.58 (m, 5H, ArH), 9.98 (s, 1H, NH), 11.09 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 30.9, 49.5, 105.9, 113.1, 114.8, 125.7, 127.8, 128.3, 129.8, 131.8, 133.5, 137.7, 138.9, 141.2, 147.1, 171.4, 178.0. HRMS [found: m/z 456.0059 (M^+), calcd for $C_{20}H_{15}{}^{81}BrN_4O_2S$: M, 456.0079].

*4.2.11. 6-Bromo-3′-methyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4] thiazepine]-2,7′(1′H)-dione (**4k**).* Mp: 260–263 °C. IR (KBr) ν: 3165, 3124, 3040, 2923, 1709, 1601, 1448, 1405, 1314, 1210, 1133, 1056, 953, 764, 687 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.51 (s, 3H, CH_3), 3.16 (d, J=14.8 Hz, 1H, CH_2), 4.50 (d, J=14.8 Hz, 1H, CH_2), 7.13 (d, J=8.0 Hz, 1H, ArH), 7.16 (s, 1H, ArH), 7.22 (d, J=8.0 Hz, 1H, ArH), 7.42 (t, J=7.2 Hz, 1H, ArH), 7.50–7.57 (m, 4H, ArH), 9.93 (s, 1H, NH), 11.03 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 12.7, 30.8, 49.0, 105.9, 113.8, 123.3, 125.6, 125.7, 126.1, 127.2, 128.4, 129.7, 137.7, 138.9, 143.5, 147.1, 171.4, 178.2. HRMS (ESI): m/z calcd for $C_{20}H_{15}BrN_4O_2S$: 476.9991 $[M+Na]^+$, found: 377.0011.

*4.2.12. 6-Bromo-3′,6′-dimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4] thiazepine]-2,7′(1′H)-dione (**4l**).* Mp: 280–282 °C. IR (KBr) ν: 3385, 3230, 3058, 2928, 1726, 1679, 1606, 1479, 1445, 1373, 1258, 1195, 1060, 946, 910, 767, 684 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.28 (d, J=7.2 Hz, 3H, CH_3), 1.53 (s, 3H, CH_3), 4.70 (q, J=7.2 Hz, 1H, CH), 7.06 (d, J=8.0 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 7.20 (d, J=7.6 Hz, 1H, ArH), 7.41 (t, J=7.2 Hz, 1H, ArH), 7.51 (t, J=7.6 Hz, 2H, ArH), 7.58 (d, J=7.6 Hz, 2H, ArH), 9.94 (s, 1H, NH), 10.99 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7, 15.9, 35.9, 49.7, 106.4, 113.8, 123.3, 125.6, 126.2, 127.3, 127.9, 128.7, 129.7, 137.7, 139.0, 143.6, 146.9, 173.3, 178.4. HRMS (ESI): m/z calcd for $C_{21}H_{17}BrN_4O_2S$: 491.0148 $[M+Na]^+$, found: 491.0141.

*4.2.13. 1′,3′-Dimethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4m**).* Mp: 252–254 °C. IR (KBr) ν: 3338, 3164, 3063, 2974, 2889, 2825, 1683, 1578, 1473, 1369, 1319, 1226, 1173, 1092, 1048, 889, 741, 673 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.35 (s, 3H, CH_3), 3.08 (d, J=14.8 Hz, 1H, CH_2), 3.66 (s, 3H, CH_3), 4.37 (d, J=14.8 Hz, 1H, CH_2), 6.95–7.01 (m, 2H, ArH), 7.11 (d, J=7.2 Hz, 1H, ArH), 7.30 (t, J=7.6 Hz, 1H, ArH), 10.18 (s, 1H, NH), 10.85 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.4, 30.4, 36.3, 49.1, 104.9, 110.8, 123.2, 125.3, 129.1, 130.5, 137.7, 142.0, 144.7, 171.8, 178.6. HRMS [found: m/z 314.0835 (M^+), calcd for $C_{15}H_{14}N_4O_2S$: M, 314.0837].

*4.2.14. 1′,3′,6′-Trimethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4n**).* Mp: 181–183 °C. IR (KBr) ν: 3217, 3160, 2937, 2817, 1704, 1536, 1472, 1377, 1225, 1174, 1070, 998, 747, 672 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.24 (d, J=6.8 Hz, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.53 (q, J=7.2 Hz, 1H, CH), 6.94–7.00 (m, 2H, ArH), 7.05 (d, J=7.2 Hz, 1H, ArH), 7.29 (t, J=7.6 Hz, 1H, ArH), 10.11 (s, 1H, NH), 10.75 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.4, 15.9, 35.4, 36.2, 49.8, 105.4, 110.8, 123.3, 125.3, 128.7, 130.5, 137.7, 142.0, 144.5, 173.6, 178.7.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}N_4O_2S$: 329.1067 $[M+H]^+$, found: 329.1081.

*4.2.15. 1,1′,3′,6′-Tetramethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′ (1′H)-dione (**4o**).* Mp: 276–278 °C. IR (KBr) *ν*: 3237, 3175, 3067, 2980, 2943, 1698, 1611, 1570, 1471, 1367, 1347, 1273, 1127, 1085, 924, 754, 690 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.25 (d, *J*=7.2 Hz, 3H, CH_3), 1.28 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.55 (q, *J*=7.2 Hz, 1H, CH), 7.04–7.12 (m, 2H, ArH), 7.15 (d, *J*=7.6 Hz, 1H, ArH), 7.40 (t, *J*=7.6 Hz, 1H, ArH), 10.13 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.4, 15.9, 27.1, 35.6, 36.2, 49.5, 105.4, 109.9, 124.0, 125.1, 128.0, 130.7, 137.7, 143.4, 144.4, 173.5, 177.2. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}N_4O_2S$: 343.1223 $[M+H]^+$, found: 343.1231.

*4.2.16. 1′,3′,5-Trimethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4p**).* Mp: 260–262 °C. IR (KBr) *ν*: 3296, 2989, 2939, 1710, 1572, 1528, 1491, 1378, 1300, 1233, 1127, 996, 870, 813, 676 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.36 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.06 (d, *J*=14.8 Hz, 1H, CH_2), 3.66 (s, 3H, CH_3), 4.37 (d, *J*=15.2 Hz, 1H, CH_2), 6.84 (d, *J*=8.0 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 7.09 (d, *J*=8.0 Hz, 1H, ArH), 10.12 (s, 1H, NH), 10.68 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.5, 21.1, 30.5, 36.3, 49.1, 105.1, 110.6, 125.7, 129.1, 130.8, 132.4, 137.7, 139.5, 144.8, 171.9, 178.7. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}N_4O_2S$: 351.0886 $[M+Na]^+$, found: 351.0892.

*4.2.17. 1′,3′,5,6′-Tetramethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′ (1′H)-dione (**4q**).* Mp: 260–261 °C. IR (KBr) *ν*: 3195, 2973, 2929, 1702, 1625, 1573, 1538, 1492, 1373, 1236, 1067, 815, 764, 704 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.23 (d, *J*=7.2 Hz, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 4.51 (q, *J*=7.2 Hz, 1H, CH), 6.84 (d, *J*=8.0 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 7.08 (d, *J*=8.0 Hz, 1H, ArH), 10.16 (s, 1H, NH), 10.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 11.8, 15.3, 20.5, 34.8, 35.6, 49.4, 105.0, 110.0, 125.1, 128.1, 130.2, 131.8, 137.1, 138.9, 144.0, 173.1, 178.2. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}N_4O_2S$: 343.1223 $[M+H]^+$, found: 343.1238.

*4.2.18. 5-Fluoro-1′,3′,6′-trimethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4r**).* Mp: 300-202 °C. IR (KBr) *ν*: 3267, 3118, 3069, 2988, 2934, 2862, 1697, 1571, 1485, 1374, 1258, 1185, 1065, 1002, 811, 680 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.25 (d, *J*=7.2 Hz, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.53 (q, *J*=7.2 Hz, 1H, CH), 6.92 (d, *J*=6.8 Hz, 1H, ArH), 6.95–6.98 (m, 1H, ArH), 7.14 (t, *J*=8.8 Hz, 1H, ArH), 10.15 (s, 1H, NH), 10.81 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.4, 15.9, 35.4, 36.3, 50.1, 104.9, 111.8, 111.9, 112.6, 112.9, 117.0, 117.3, 130.3, 130.4, 137.8, 138.2, 144.5, 157.3, 160.5, 173.5, 178.7. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}FN_4O_2S$: 347.0973 $[M+H]^+$, found: 347.0986.

*4.2.19. 5-Bromo-1′,3′-dimethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4s**).* Mp: 220–222 °C. IR (KBr) *ν*: 3248, 1709, 1575, 1472, 1403, 1312, 1221, 1169, 1131, 1057, 865, 816, 709 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.39 (s, 3H, CH_3), 3.14 (d, *J*=14.8 Hz, 1H, CH_2), 3.67 (s, 3H, CH_3), 4.30 (d, *J*=14.8 Hz, 1H, CH_2), 6.94 (d, *J*=8.4 Hz, 1H, ArH), 7.24 (d, *J*=2.0 Hz, 1H, ArH), 7.48–7.50 (m, 1H, ArH), 10.15 (s, 1H, NH), 10.98 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 12.3, 30.3, 36.2, 49.0, 104.1, 112.7, 114.5, 127.6, 131.5, 133.1, 137.7, 141.0, 144.4, 171.4, 178.0. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}BrN_4O_2S$: 393.0015 $[M+H]^+$, found: 393.0026.

*4.2.20. 6-Bromo-1′,3′-dimethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4t**).* Mp: 296–298 °C. IR (KBr) *ν*: 3228, 3162, 3045, 2925, 1708, 1677, 1608, 1574, 1480, 1447, 1371, 1315, 1223, 1056, 993, 860, 806, 684 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.39 (s, 3H, CH_3), 3.11 (d, *J*=15.2 Hz, 1H, CH_2), 3.67 (s, 3H, CH_3), 4.33 (d, *J*=14.8 Hz, 1H, CH_2), 7.07 (d, *J*=8.0 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.18 (d, *J*=7.6 Hz, 1H, ArH), 10.15 (s, 1H, NH), 10.97 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.5, 30.4, 36.4, 48.9, 104.3, 113.7, 123.1, 126.0, 127.1, 128.5, 137.8, 143.5, 144.6, 171.6, 178.4. HRMS [found: *m*/*z* 391.9945 (M^+), calcd for $C_{15}H_{13}N_4O_2S^{79}Br$: M, 391.9943].

*4.2.21. 6-Bromo-1′,3′,6′-trimethyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**4u**).* Mp: 208–210 °C. IR (KBr) *ν*: 3236, 2933, 2813, 1712, 1610, 1577, 1480, 1450, 1374, 1314, 1273, 1237, 1173, 1059, 991, 929, 805, 682 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.24 (d, *J*=7.2 Hz, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.49 (q, *J*=6.8 Hz, 1H, CH), 7.00 (d, *J*=7.6 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.17 (d, *J*=8.0 Hz, 1H, ArH), 10.14 (s, 1H, NH), 10.94 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.5, 15.9, 35.4, 36.3, 49.6, 104.8, 113.7, 123.1, 126.0, 127.1, 128.0, 137.8, 143.6, 144.4, 173.5, 178.5. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}BrN_4O_2S$: 428.9991 $[M+Na]^+$, found: 428.9988.

*4.2.22. 3′-Methyl-1′-phenyl-6′,8′-dihydro-2H-spiro[acenaphthylene-1,4′-pyrazolo[3,4-e][1,4] thiazepine]-2,7′(1′H)-dione (**6a**).* Mp: 258–260 °C. IR (KBr) *ν*: 3229, 3110, 2990, 2915, 1683, 1582, 1410, 1252, 1144, 997, 932, 862, 778, 696 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.14 (s, 3H, CH_3), 3.20 (d, *J*=14.8 Hz, 1H, CH_2), 4.48 (d, *J*=14.4 Hz, 1H, CH_2), 7.43 (t, *J*=6.8 Hz, 1H, ArH), 7.52–7.62 (m, 5H, ArH), 7.75 (t, *J*=7.2 Hz, 1H, ArH), 7.94 (t, *J*=7.6 Hz, 1H, ArH), 8.10 (d, *J*=7.6 Hz, 1H, ArH), 8.18 (d, *J*=6.4 Hz, 1H, ArH), 8.40 (d, *J*=8.0 Hz, 1H, ArH), 10.04 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 13.2, 32.0, 53.9, 106.9, 123.0, 125.1, 125.6, 126.8, 128.2, 129.8, 129.9, 130.0, 130.3, 130.7, 133.4, 137.8, 137.9, 139.0, 139.8, 147.3, 171.3, 198.8. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{17}N_3O_2S$: 434.0934 $[M+Na]^+$, found: 434.0934.

*4.2.23. 1′,3′-Dimethyl-6′,8′-dihydro-2H-spiro[acenaphthylene-1,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (**6b**).* Mp: 268–270 °C. IR (KBr) *ν*: 3239, 3177, 3055, 2945, 1678, 1572, 1450, 1367, 1256, 1450, 1367, 1256, 1144, 1000, 894, 782, 676 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.03 (s, 3H, CH_3), 3.15 (d, *J*=14.8 Hz, 1H, CH_2), 3.72 (s, 3H, CH_3), 4.27 (d, *J*=14.4 Hz, 1H, CH_2), 7.50 (d, *J*=5.6 Hz, 1H, ArH), 7.72 (t, *J*=6.8 Hz, 1H, ArH), 7.93 (d, *J*=6.8 Hz, 1H, ArH), 8.07 (d, *J*=7.6 Hz, 1H, ArH), 8.13 (d, *J*=6.0 Hz, 1H, ArH), 8.37 (d, *J*=7.6 Hz, 1H, ArH), 10.24 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 13.0, 31.6, 36.4, 53.8, 105.2, 122.9, 124.9, 126.7, 129.9, 130.0, 130.1, 130.6, 133.3, 136.0, 139.7, 144.9, 171.5, 199.1. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{15}N_3O_2S$: 372.0777 $[M+Na]^+$, found: 372.0782.

4.3. Procedure for preparation of intermediate 7

A mixture of 5-amino-1-phenyl-3-methylpyrazole **1a** (2 mmol), isatin **2a** (2 mmol), 2-mercaptoacetic acid **3a** (2 mmol), and *p*-TSA (30 mol %) in CH_3CN (5 mL) was stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature. Then, the precipitated product was filtered, dried, and washed by 10 mL hot ethanol to afford the pure **7** as a white powder.

*4.3.1. 3-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-hydroxyindolin-2-one (**7**).* Mp: 235–236 °C. IR (KBr) *ν*: 3439, 3361, 3135, 3073, 2832, 1713, 1619, 1516, 1386, 1187, 1115, 1049, 934, 747, 692 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.42 (s, 3H, CH_3), 5.28 (s, 2H, NH_2), 6.61 (s, 1H, OH), 6.84 (d, *J*=7.8 Hz, 1H, ArH), 6.97 (t, *J*=7.5 Hz, 1H, ArH), 7.21–7.30 (m, 3H, ArH), 7.45 (t, *J*=7.5 Hz, 2H, ArH), 7.55 (d, *J*=7.5 Hz, 2H, ArH), 10.35 (s, 1H, NH). HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}N_4O_2$: 321.1346 $[M+H]^+$, found: 321.1347.

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References and notes

1. (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499; (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111; (c) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415–2437; (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
2. Terrett, N. K. *Combinatorial Chemistry*; Oxford University: New York, NY, 1998.
3. (a) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427–4429; (b) List, B.; Castello, C. *Synlett* **2001**, 1687–1689; (c) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans, D. H. *Org. Lett.* **2002**, *4*, 423–425; (d) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147–3150; (e) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309–3311; (f) Cheng, J. F.; Chen, M.; Arrhenius, T.; Nadzen, A. *Tetrahedron Lett.* **2002**, *43*, 6293–6295; (g) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485–6488; (h) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435–438; (i) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205–1208.
4. (a) Skiles, J. W.; Suh, J. T.; Williams, B. E.; Menard, P. R.; Barton, J. N.; Love, B.; Jones, H.; Neiss, E. S.; Schwab, A.; Mann, W. S. *J. Med. Chem.* **1986**, *29*, 784–796; (b) Crescenza, A.; Botta, M.; Corelli, F.; Santini, A.; Tafi, A. *J. Org. Chem.* **1999**, *64*, 3019–3025; (c) Umemiya, H.; Fukasawa, H.; Ebisawa, M.; Eyrolles, L.; Kawachi, E.; Eisenmann, G.; Gronemeyer, H.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *J. Med. Chem.* **1997**, *40*, 4222–4234; (d) Venkatesan, A. M.; Gu, Y.; Dos Santos, O.; Abe, T.; Agarwal, A.; Yang, Y.; Petersen, P. J.; Weiss, W. J.; Mansour, T. S.; Nukaga, M.; Hujer, A. M.; Bonomo, R. A.; Knox, J. R. *J. Med. Chem.* **2004**, *47*, 6556–6568.
5. (a) Malli, R.; Frieden, M.; Trenker, M.; Graier, W. F. *J. Biol. Chem.* **2005**, *280*, 12114–12122; (b) Neamati, N.; Turpin, J. A.; Winslow, H. E.; Christensen, J. L.; Williamson, K.; Orr, A.; Rice, W. G.; Pommier, Y.; Garofalo, A.; Brizzi, A.; Campiani, G. *J. Med. Chem.* **1999**, *42*, 3334–3341; (c) Maruenda, H.; Johnson, F. *J. Med. Chem.* **1995**, *38*, 2145–2151; (d) Garofalo, A.; Campiani, G.; Fiorini, I.; Nacci, V. *Farmaco* **1993**, *48*, 275–283.
6. (a) Boulware, S. L.; Bronstein, J. C.; Nordby, E. C.; Weber, P. C. *Antiviral Res.* **2001**, *51*, 111–125; (b) Cale, A. D.; Gero, T. W.; Walker, K. R.; Lo, Y. S.; Welstead, W. J.; Jaques, L. W.; Johnson, A. F.; Leonard, C. A.; Nolan, J. C.; Johnson, D. N. *J. Med. Chem.* **1989**, *32*, 2178–2199; (c) Nakao, T.; Tanaka, H.; Yamato, H.; Akagi, T.; Takehara, S. U.S. Patent 5,141,930, 1991; *Chem. Abstr.* **1992**, *116*, 194290b; (d) Schlosser, K. M.; Krasutsky, A. P.; Hamilton, H. W.; Reed, J. E.; Sexton, K. *Org. Lett.* **2004**, *6*, 819–821.
7. (a) Uskoković, M.; Grethe; Iacobelli, J.; Wenner, W. *J. Org. Chem.* **1965**, *30*, 3111–3114; (b) Swett, L. R.; Ratajczyk, J. D.; Nordeen, C. W.; Aynilian, G. H. *J. Heterocycl. Chem.* **1975**, *12*, 1137–1142; (c) Joshi, K. C.; Pathak, V. N.; Garg, U. *J. Heterocycl. Chem.* **1980**, *17*, 789–791; (d) Joshi, K. C.; Dubey, K.; Dandia, A. *Heterocycles* **1981**, *16*, 71–76; (e) Yang, X. J.; Buzon, L.; Hamanaka, E.; Liu, K. K.-C. *Tetrahedron: Asymmetry* **2000**, *11*, 4447–4450; (f) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091–2092; (g) Miki, T.; Kori, M.; Fujishima, A.; Mabuchi, H.; Tozawa, R.; Nakamura, M.; Sugiyama, Y.; Yukimasa, H. *Bioorg. Med. Chem.* **2002**, *10*, 385–400; (h) Pei, Y. Z.; Lilly, M. J.; Owen, D. J.; D'Souza, L. J.; Tang, X. Q.; Yu, J. H.; Nazarbaghi, R.; Hunter, A.; Anderson, C. M.; Glasco, S.; Ede, N. J.; James, I. W.; Maitra, U.; Chandrasekaran, S.; Moos, W. H.; Ghosh, S. S. *J. Org. Chem* **2003**, *68*, 92–103; (i) Elmaati, T. M. A.; El-Taweel, F. M. *J. Chin. Chem. Soc.* **2003**, *59*, 413–418 (Taipei, Taiwan); (j) Angibaud, P.; Bourdrez, X.; Devine, A.; End, D. W.; Freyne, E.; Ligny, Y.; Muller, P.; Mannens, G.; Pilatte, I.; Poncelet, V.; Skrzat, S.; Smets, G.; Van Dun, J.; Van Remoortere, P.; Venet, M.; Wouters, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1543–1547; (k) Neo, A. G.; Marcos, C. F.; Marcaccinib, S.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 7977–7979; (l) Ilyn, A. P.; Loseva, M. V.; Vvedensky, V. Y.; Putsykina, E. B.; Tkachenko, S. E.; Kravchenko, D. V.; Khvat, A. V.; Krasavin, M. Y.; Ivachtchenko, A. V. *J. Org. Chem.* **2006**, *71*, 2811–2819; (m) Sarabia, F.; Chammaa, S.; García-Castro, M.; Mártín-Galvez, F. *Chem. Commun.* **2009**, 5763–5765; (n) Tu, S. J.; Cao, X. D.; Hao, W. J.; Zhang, X. H.; Yan, S.; Wu, S. S.; Han, Z. G.; Shi, F. *Org. Biomol. Chem.* **2009**, *7*, 557–563.
8. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219.
9. Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758.
10. Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025.
11. (a) Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J. C.; Hudak, V. A.; Marella, M. A.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudt, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *J. Med. Chem.* **2008**, *51*, 1861–1873; (b) Teno, N.; Masuya, K.; Ehara, T.; Kosaka, T.; Miyake, T.; Irie, O.; Hitomi, Y.; Matsuura, N.; Umemura, I.; Iwasaki, G.; Fukaya, H.; Toriyama, K.; Uchiyama, N.; Nonomura, K.; Sugiyama, I.; Kometani, M. *J. Med. Chem.* **2008**, *51*, 5459–5462.
12. Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355–2358.
13. Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087–3089.
14. Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430–9435.
15. (a) Reifschneider, W.; Bisabari-Ershadi, B.; Dripps, J. E.; Bonron, J. B. U.S. Patent 5,075,293, 1991; *Chem. Abstr.* **1991**, *116*, 129249f; (b) Rovnyak, G. C.; Narayanan, V. L.; Haugwitz, R. D. U.S. Patent 4,053,613, 1975; *Chem. Abstr.* **1978**, *88*, 22892; (c) Ali, S.; Alam, M. *Arch. Pharmacal Res.* **1994**, *17*, 131–133.
16. (a) Rajopadhye, M.; Popp, F. D. *J. Heterocycl. Chem.* **1984**, *21*, 289–291; (b) Rajopadhye, M.; Popp, F. D. *J. Heterocycl. Chem.* **1985**, *22*, 93–96; (c) Popp, F. D.; Rajopadhye, M.; Brown, D. S.; Waddington, D.; Uff, B. C. *J. Heterocycl. Chem.* **1987**, *24*, 261–265; (d) Rajopadhye, M.; Popp, F. D. *J. Heterocycl. Chem.* **1987**, *24*, 1637–1642; (e) Azizian, J.; Morady, A. V.; Jadidi, K.; Mehrdad, M.; Sarrafi, Y. *Synth. Commun.* **2000**, *30*, 537–542; (f) Jain, S. C.; Sinha, J.; Bhagat, S.; Errington, W.; Olsen, C. E. *Synth. Commun.* **2003**, *33*, 563–577; (g) Dandia, A.; Singh, R.; Arya, K. *Org. Prep. Proced. Int.* **2003**, *35*, 401–408; (h) Dandia, A.; Arya, K.; Sati, M.; Gautam, S. *Tetrahedron* **2004**, *60*, 5253–5258; (i) Jain, M.; Khanna, P.; Saxena, A.; Bhagat, S.; Olsen, C. E.; Jain, S. C. *Synth. Commun.* **2006**, *36*, 1863–1872; (j) Mashelkar, U. C.; Rane, D. M.; Kenny, R. S. *J. Heterocycl. Chem.* **2008**, *45*, 865–872; (k) Pandey, M.; Raghuvanshi, D. S.; Singh, K. N. *J. Heterocycl. Chem.* **2009**, *46*, 49–53.
17. Chen, H.; Shi, D. Q. *J. Comb. Chem.* **2010**, *12*, 571–576.
18. (a) Li, Y. L.; Chen, H.; Shi, C. L.; Shi, D. Q.; Ji, S. J. *J. Comb. Chem.* **2010**, *12*, 231–237; (b) Liu, H.; Dou, G. L.; Shi, D. Q. *J. Comb. Chem.* **2010**, *12*, 292–294; (c) Liu, H.; Dou, G. L.; Shi, D. Q. *J. Comb. Chem.* **2010**, *12*, 633–637.