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New four-component reactions in water: a convergent approach to the metal-free synthesis of spiro[indoline/acenaphthylene-3,4′-pyrazolo[3,4-*b*]pyridine derivatives

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ABSTRACT

New four-component domino reactions are described that allow the one-pot synthesis of spiro[indoline/acenaphthylene-3,4′-pyrazolo[3,4-*b*]pyridine derivatives from the reaction of phenylhydrazine, 3-aminocrotononitrile, isatin/acenaphthylene-1,2-dione, and cyclic 1,3-dicarbonyl compounds, including cyclohexane-1,3-diones, barbituric acid, and 2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione, in the presence of (±)-camphor-10-sulfonic acid (CSA). These processes take place in water and involve the generation of two rings and five new bonds (two C–C, two C–N and one C=N) in a single synthetic operation, with expedient work-up and diminished waste generation due to the absence of extraction and purification steps.

1. Introduction

Multicomponent domino reactions (MDRs), particularly those performed in aqueous media, have become an increasingly useful tool for the synthesis of chemically and biologically important compounds because of their convergence, atom economy, and other suitable characteristics from the point of view of green chemistry.[1–3] These reactions, which involve at least three different simple substrates, are powerful for the expedient building up of molecular complexity and diversity[4] through the facile formation of several new covalent bonds in a one-pot transformation, quite closely approaching the concept of an ideal synthesis, and are particularly well adapted for combinatorial synthesis.[5] The search for alternative reaction media to replace volatile, flammable, and often toxic solvents commonly employed in organic synthesis is also a priority area for the development of green chemical processes. From both environmental and economic points of view, water has emerged as the medium of choice to perform organic reactions, as it is the most environmentally acceptable, safest, and most abundant solvent.[6] In addition, water generally enables facile work-up protocols, as most organic compounds, being lipophilic, are readily segregated from aqueous media. In addition, many organic reactions, that take place 'on water', i.e., with the reactants initially emulsionated in water, exhibit important rate enhancements.[7] Finally, water as a reaction medium enables novel solvation and assembly processes conferring unique selectivity and reactivity.[6e] For these reasons, the development of synthetically useful reactions that take place in water is of considerable topical interest.

Pyrazoles constitute an interesting family of heterocycles due to their application as pharmaceuticals[8] and in the agrochemical industry as herbicides and insecticides.[9] Pyrazoles also provide privileged scaffolds in lead identification/drug discovery programmes[10] and have provided therapeutically useful compounds in fields, such as cyclooxygenase **2** inhibitors (e.g., SC-558, tepoxalin, and celecoxib)[11,12] and cannabinoid-1 inverse agonists, which are very promising for reducing obesity (e.g., rimonabant).[13] Fused pyrazoles, and pyrazolopyridines in particular, also display a variety of interesting pharmacological properties,[14] besides finding applications as fluorescence standards and luminophores in organic light emitting diodes,[15] and therefore their synthesis has been an attractive research topic in recent years[16,17] Moreover, pyrazolo[3,4-*b*]quinoline derivatives also display relevant bioactivities.[18] Other important structural fragments present in our final products include the pyridopyrimidine motif, a well known pharmacophore in drug design which is associated with a wide range of biological activities,[19] and spiro-oxindole substructures, present in many alkaloids (e.g., spirotryprostatin B, alantrypinone, and citrinadin A), which have received much attention from the synthetic

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community,[20] prompted by their interesting structures and biological properties (Fig. 1).[21]

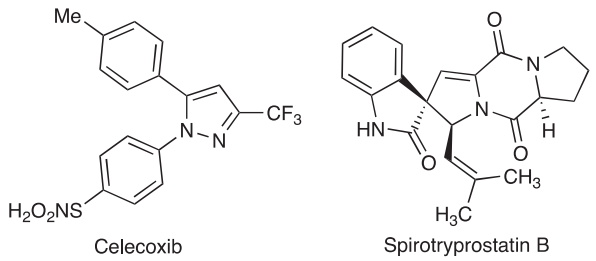
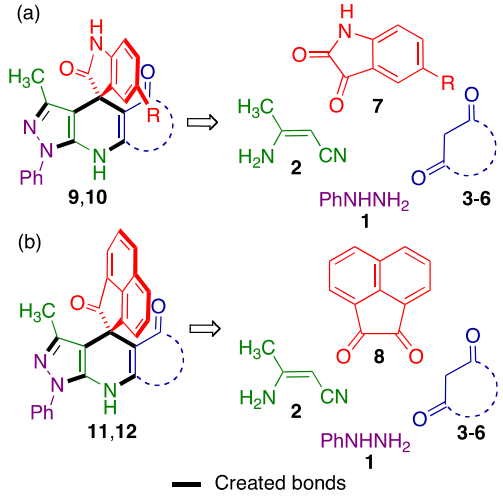


Fig. 1. Structures of representative pyrazole drug and spiro-oxindole alkaloid.

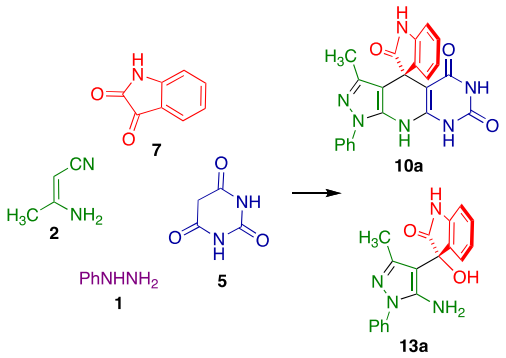
In this context, we describe in this paper the one-pot, four-component, domino reactions of phenylhydrazine **1**, 3-aminocrotononitrile **2**, cyclic 1,3-diketones **3**–**6**, and substituted isatins **7** or acenaphthylene-1,2-diones **8** in water for the construction of spiro-heterocycles **9**–**12** (Scheme 1), comprising spiro-oxindole, pyrazole, pyrazolopyridine, pyridopyrimidine, pyrazolopyrido-pyrimidine, and pyrazoloquinoline substructures. This work bears some relationship with a recently reported CAN-catalyzed three-component reaction between 5-aminopyrazoles, isatins, and cyclic 1,3-diketones,[16a] but some crucial differences exist, namely the higher yields and broader scope of our method, its four-component nature, which makes it more efficient, and the absence of any metal-containing catalyst, which renders our method more environmentally benign. The study reported here constitutes a part of our ongoing research program, aimed at evolving new methodologies by systematic use of tandem/domino multi-component reactions for the construction of novel heterocycles[22] and/or unearthing new lead molecules with antimycobacterial activities.[23]



Scheme 1. Disconnections explored in the present work.

2. Results and discussion

We started our investigation by examining the four-component reaction of phenylhydrazine, 3-aminocrotononitrile, isatin, and barbituric acid in the presence of 1 equiv of *p*-toluenesulfonic acid (*p*-TSA) under reflux for 10 h, which afforded compound **10a** in 80% yield (Scheme 2 and Table 1, entry 1). Interestingly, when (±)-camphor-10-sulfonic acid (CSA) was used instead, 0.5 equiv of acid were sufficient for the reaction to achieve completion in 2 h, affording an enhanced yield of 92% (Table 1, entry 2). It is pertinent to note that CSA, a mild, inexpensive, readily available Brønsted acid, has recently emerged as a powerful catalyst for organic transformations in aqueous medium.[24] As the selection of an appropriate reaction medium is of crucial importance for the success of reactions under conventional heating conditions, the four-component reaction was examined in polar, non-protic solvents like *N*,*N*-dimethylformamide and acetonitrile (entries 3 and 4), and other protic solvents including ethanol (entry 5) and ethylene glycol (entry 6). From the data listed in Table 1, water emerge as the solvent of choice, furnishing the highest yield of the product. Furthermore, when the reaction was performed in water in the presence of CSA, the product could be obtained in high purity by simple filtration. Other catalysts were also assayed, with the previously mentioned CAN and sulfamic acid giving relatively sluggish reactions (entries 7 and 8). In the presence of other catalysts, the model four-component reaction failed to give **10a** and thus, in the presence of citric acid, $SnCl_4.6H_2O$, $YbCl_3$, $Yb(OTf)_3$, $BiCl_3$, and $InCl_3$ the reaction instead afforded exclusively 3-(5-amino-3-methyl-1-phenyl-1*H*-4-pyrazolyl)-3-hydroxy-2-indolinone **13a**, presumably an intermediate of the four-component process, in 75–95% yields (entries 9–14). From the above experiments, it follows that: (i) The CSA/water pair is the ideal catalyst-solvent combination for the expedient four-component synthesis of **10a** in high yield and (ii) the product selectivity of the reaction can be tuned by employing appropriate catalysts.



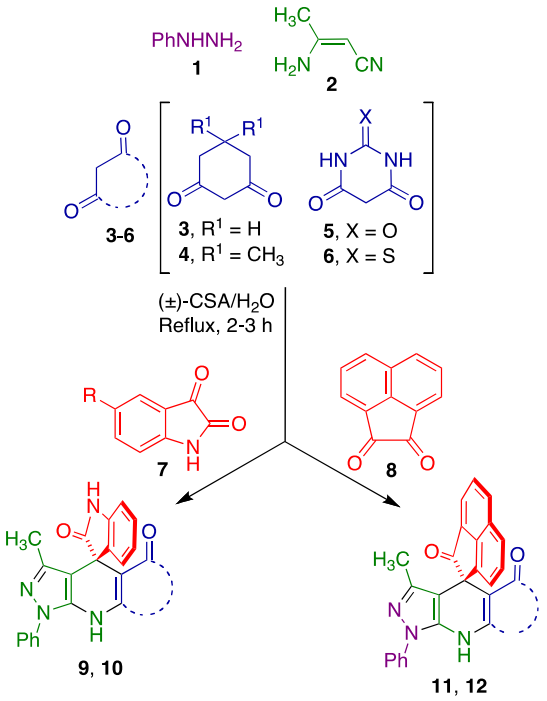
Scheme 2. Model reaction for optimization studies.

Table 1
Solvent and acids screen for the synthesis of **10a**

Entry	Solvent	Acid (mol%)	Time (h)	Yield of **10a** (%)	Yield of **13a** (%)
1	Water	*p*-TSA (100)	10	80	0
2	Water	CSA (50)	2	92	0
3	DMF	CSA (50)	8	35	0
4	CH_3CN	CSA (50)	10	40	0
5	EtOH	CSA (50)	8	55	0
6	Ethylene/glycol	CSA (50)	8	65	0
7	Water	CAN (10)	7	75	0
8	Water	Sulfamic acid (100)	7	68	0
9	Water	Citric acid	0.5	0	82
10	Water	$SnCl_4.6H_2O$	1	0	76
11	Water	$YbCl_3$	0.25	0	90
12	Water	$Yb(OTf)_3$	0.10	0	75
13	Water	$BiCl_3$	0.25	0	80
14	Water	$InCl_3$	0.10	0	95

After determining the optimal conditions, the scope of the reaction was examined in more detail. As shown in Scheme 3, the four-component reactions of phenylhydrazine **1**, 3-aminocrotononitrile **2**, substituted isatins **7** (R=H, Cl, and NO_2) or acenaphthylene-1,2-dione **8** and cyclic 1,3-diketones, viz. cyclohexane-1,3-dione **3**, dimedone **4**, barbituric acid **5**, and thiobarbituric acid **6** were carried out in water in the presence of CSA

under heating at 100 °C for 2–3 h, and these conditions afforded excellent yields of spiro-heterocycles **9**–**12** (Fig. 2).



Scheme 3. Camphorsulfonic acid-promoted, four-component synthesis of spirocyclic compounds **9**–**12** in aqueous solution.

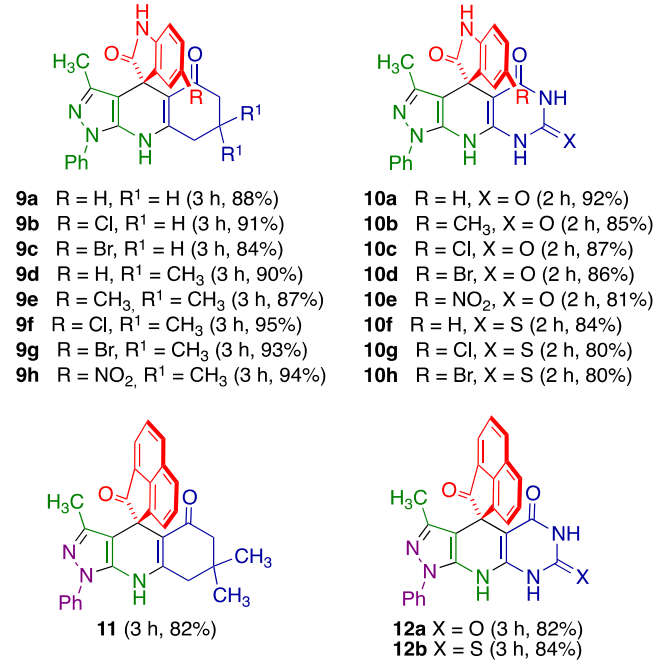


Fig. 2. Scope and yields of the synthesis of spirocycles **9**–**12**.

The structure of the spiro-heterocycles **9**–**12** is in full agreement with elemental analyses, HRMS and ^{1}H, ^{13}C, and 2D NMR spectroscopic data, as illustrated below for a representative example (compound **9d**). In the ^{1}H NMR spectrum of **9d**, hydrogens of the two methyl groups the cyclohexenone part appeared as singlets at 0.98 and 1.01 ppm, which showed HMBCs with C-8′ at 41.1 ppm, C-7′ at 32.3 ppm and C-6′ at 48.9 ppm (Fig. 3). The 6′-CH_2 hydrogens

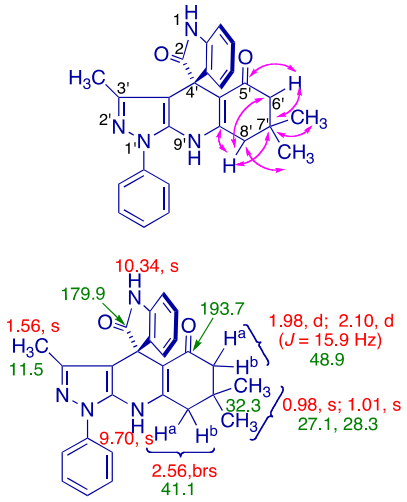
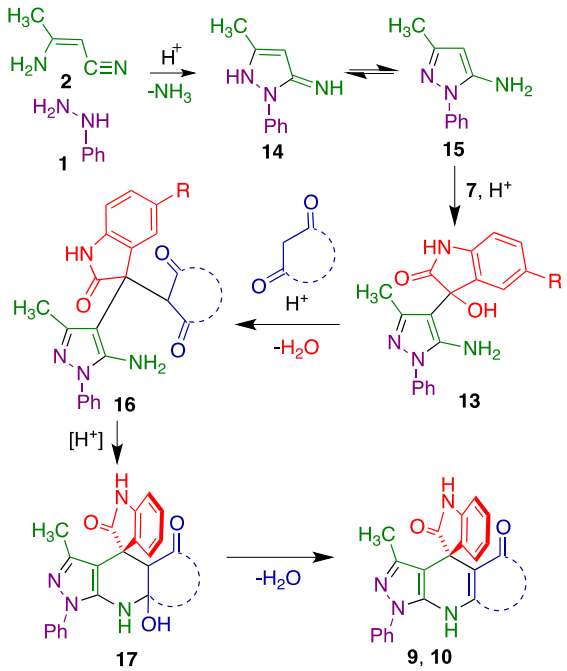


Fig. 3. Selected HMBCs and chemical shifts of **9d**.

appeared as doublets at 1.98 and 2.10 ppm (J=15.9 Hz), which showed HMBCs with C-8′ at 41.1 and C-5′ at 195.7 ppm. The 8′-CH_2 hydrogens appearing as broad singlet at 2.56 ppm, with negligible coupling, showed HMBCs with C-7′ at 32.3 ppm, C-6′ at 48.9 ppm, C-9′a at 153.4 ppm and C-5′a at 108.1 ppm. The fact that these two hydrogens have coupling connection is established by a clear H,H-COSY correlation. The two singlets at 9.70 and 10.34 ppm are due to the NH groups in pyrazolopyridine and oxindol, respectively. The NMR spectroscopic data of the known compounds, **9a**, **9d**, **9e**, and **9g** reported in the present work agree well with those reported earlier.[16a]

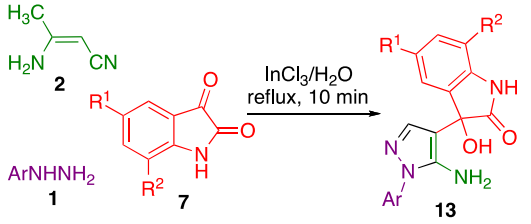
A plausible mechanism for the formation of the spiro-heterocycles is proposed in Scheme 4. The domino sequence of reactions is, presumably triggered by the formation of 5-amino-3-methyl-1-phenylpyrazole **15** from the acid-catalyzed reaction of phenylhydrazine with 3-aminocrotononitrile. Intermediate **15**, upon reaction with isatin **7**, affords intermediate **13**, which has been isolated as the sole reaction product in some of the reactions carried out during the optimization studies. This compound, upon



Scheme 4. Mechanism proposed to explain the formation of compounds **9** and **10**.

reaction with the starting cyclic 1,3-diketones under acidic conditions presumably furnishes intermediate **16**, which subsequently undergoes annulation leading to the final spiro-heterocycles via intermediate **17**. The involvement of aminopyrazole **15** in this reaction is supported by the fact that when phenylhydrazine (1 mmol), 3-aminocrotononitrile (1 mmol), CSA (0.5 mmol), and water (10 ml) are refluxed for 10 min at 100 °C, **15** is formed in 98% yield.[25] Furthermore, the reaction of **15** with barbituric acid and isatin **7** (R=H) in the presence of CSA under reflux conditions for 2 h afforded the corresponding spiro-product **10a** in near quantitative (96%) yield. The intermediacy of **13** in the domino reactions is also evident from (i) the isolation of 3-(5-amino-3-methyl-1-phenyl-1*H*-4-pyrazolyl)-3-hydroxy-2-indolinone **13a**[16a] in 90% yield in the reaction of phenylhydrazine (1 mmol), 3-aminocrotononitrile (1 mmol), isatin, and barbituric acid (1 mmol) in the presence of CSA in water for 1 h at room temperature and (ii) the fact that the subsequent reaction of **13a** with dimedone in the presence of CSA at reflux conditions for 3h afforded the corresponding spirocyclic product **9d** in 90% yield. The greater efficacy of CSA (pK_a −1.2) compared with *p*-toluenesulfonic acid (pK_a 0.7) is explicable on the basis of higher acidity of the former.[26]

Finally, due to the importance of both pyrazole and oxindole systems, we decided to take the opportunity of the isolation of compound **13a** as the sole reaction product in some of the reactions carried out during optimization work to establish a new, three-component method for the synthesis of 3-(4-pyrazolyl)oxindoles and chose for this purpose $InCl_3$ (0.10 equiv) as the catalyst. The results obtained in the reaction between arylhydrazines, 3-aminocrotonitrile and isatins in water at 100 °C for 10 min are summarized in Scheme 5 and Table 2, where it can be appreciated that these conditions led to an excellent yield of 5-aminopyrazole derivatives **13**.



Scheme 5. Three-component reaction for the synthesis of 3-hydroxy-3-(3-pyrazolyl) oxindoles **13**.

Table 2
Yields of 3-(5-amino-3-methyl-1-aryl-1*H*-4-pyrazolyl)-3-hydroxyoxindoles **13**

Compd	Ar	R^1	R^2	Yield (%)
13a	C_6H_5	H	H	96[a]
13b	C_6H_5	Cl	H	94
13c	C_6H_5	Br	H	90
13d	C_6H_5	NO_2	H	95
13e	C_6H_5	CH_3	CH_3	86
13f	4-FC_6H_4	CH_3	H	88
13g	4-FC_6H_4	Cl	H	90
13h	4-FC_6H_4	Br	H	91
13i	4-FC_6H_4	CH_3	CH_3	82

[a] This compound was described in Ref. 29.

3. Conclusions

In conclusion, we describe new four-component domino reactions for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridines containing up to five rings in good to excellent yields from the reactions of phenylhydrazine, 3-aminocrotononitrile, isatin/acenaphthylene-1,2-dione, and cyclic 1,3-dicarbonyl compounds in the presence of CSA in aqueous medium. This protocol is endowed with prominent advantages such as convergence, short reaction time, excellent yields, easy operation, and broad scope of applicability. Furthermore, it can be considered as environmentally friendly, since it does not require the use of metal-containing catalysts, uses water as the reaction medium and purification is done by simple filtration, avoiding the use of organic solvents at any point of the experimental procedure. Our study also demonstrates that the product selectivity of the reactions can be controlled by judicious choice of the catalyst, leading to the development of a three-component synthesis of 3-(5-amino-4-pyrazolyl)oxindoles. Further synthetic applications of this methodology and screening of the novel heterocyclic ring systems thus generated for biological activities are in progress in our laboratory.

4. Experimental section

4.1. General

Melting points were measured in open capillary tubes and are uncorrected. The ^1H NMR, ^{13}C NMR, H,H-COSY, C,H-COSY, and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and DMSO-d_6 as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. HRMS measurements were performed by the CAI de Espectrometria de Mass, Universidad Complutense, using an FTMS Bruker APEX QIV instrument.

4.2. General procedure for synthesis of spiro[indoline/acenaphthylene-3,4′-pyrazolo[3,4-*b*]pyridines (9–12)

A mixture of phenylhydrazine (1 mmol), 3-aminocrotononitrile (1 mmol), and CSA (0.5 mmol) in water (10 ml) was added to isatin (1 mmol) and a suitable cyclic 1,3-dicarbonyl compound (1 mmol) and the reaction mixture was heated under reflux at 100 °C for 2–3 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature, the precipitate filtered off, and washed with methanol to obtain the pure spiro-heterocycles **9**–**12** as yellow solids. Spectroscopic data for all these compounds are given below.

*4.2.1. (±)-3′-Methyl-1′-phenyl-6′,7′,8′,9′-tetrahydrospiro-[indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9a**).* Isolated as a yellow solid, yield: 88%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^1H NMR (300 MHz, DMSO-d_6) δ_H 1.56 (s, 3H, CH_3), 1.86 (s, 2H, CH_2), 2.15 (s, 2H, CH_2), 2.69 (s, 2H, CH_2), 6.80–6.87 (m, 3H, Ar–H), 7.41–7.52 (m, 6H, Ar–H), 9.77 (s, 1H, NH), 10.37 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.4, 21.1, 27.7, 37.1, 48.9, 101.7, 108.6, 109.3, 121.6, 123.4, 123.6, 127.4, 129.6, 136.6, 137.1, 137.9, 141.8, 145.1, 155.1, 179.8, 193.8. Anal. Calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13%. Found: C, 72.65; H, 5.17; N, 14.18%.

*4.2.2. (±)-5-Chloro-3′-methyl-1′-phenyl-6′,7′,8′,9′-tetra-hydrospiro [indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9b**).* Isolated as a yellow solid, yield: 91%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^1H NMR (300 MHz, DMSO-d_6) δ_H 1.56 (s, 3H, CH_3), 1.86 (s, 2H, CH_2), 2.15 (s, 2H, CH_2), 2.69 (s, 2H, CH_2), 6.80–6.87 (m, 3H, Ar–H), 7.41–7.52 (m, 6H, Ar–H), 9.77 (s, 1H, NH), 10.37 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.4, 21.1, 27.7, 37.1, 48.9, 101.7, 108.6, 109.3, 121.6, 123.4, 123.6, 127.4, 129.6, 136.6, 137.1, 137.9, 141.8, 145.1, 155.1, 179.8, 193.8. Anal. Calcd for $C_{24}H_{19}ClN_4O_2$: C, 66.90; H, 4.44; N, 13.00%. Found: C, 66.98; H, 4.38; N, 12.92%.

*4.2.3. (±)-5-Bromo-3′-methyl-1′-phenyl-6′,7′,8′,9′-tetra-hydrospiro [indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9c**).* Isolated as a yellow solid, yield: 84%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.59 (s, 3H, CH_3), 1.87 (s, 2H, CH_2), 2.18–2.28 (m, 2H, CH_2), 2.69 (s, 2H, CH_2), 6.80–7.12 (m, 2H, Ar–H), 7.30–7.52 (m, 6H, Ar–H), 9.86 (s, 1H, NH), 10.52 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.5, 21.1, 27.7, 37.0, 49.2, 100.9, 108.7, 110.6, 113.2, 123.8, 125.6, 126.1, 127.5, 129.5, 130.1, 136.7, 137.8, 139.4, 141.2, 144.9, 155.6, 179.4, 193.9. Anal. Calcd for $C_{24}H_{19}BrN_4O_2$: C, 60.64; H, 4.03; N, 11.79%. Found: C, 60.71; H, 4.08; N, 11.71%.

*4.2.4. (±)-3′,7′,7′-Trimethyl-1′-phenyl-6′,7′,8′,9′-tetrahydro-spiro[indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9d**).* Isolated as a yellow solid, yield: 90%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 0.98 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.56 (s, CH_3), 1.98 (d, 1H, J=15.9 Hz, H-6′a), 2.10 (d, 1H, J=15.9 Hz, H-6′b), 2.56 (br s, 2H, 8′CH_2), 6.80–6.85 (m, 4H, Ar–H), 7.40–7.53 (m, 5H, Ar–H), 9.70 (s, 1H, NH), 10.34 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.5, 27.1, 28.3, 32.3, 38.7, 41.1, 48.9, 101.8, 108.1, 108.8, 121.7, 123.3, 123.6, 127.5, 129.7, 136.9, 137.1, 141.8, 145.2, 153.4, 179.9, 193.7. HRMS (ESI) m/z calcd for $C_{26}H_{24}N_4O_2$ $[M-1]^+$: 423.1899 found: 423.1847. Anal. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20%. Found: C, 73.66; H, 5.64; N, 13.15%.

*4.2.5. (±)-3′,5,7′,7′-Tetramethyl-1′-phenyl-6′,7′,8′,9′-tetrahydro-spiro[indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9e**).* Isolated as a yellow solid, yield: 87%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.01 (s, 6H, 2CH_3), 1.58 (s, 3H, CH_3), 2.02 (d, 1H, J=15.9 Hz, H-6′a), 2.07–2.29 (m, 2H, H-6′b, H-8′a), 2.58 (s, 1H, H-8′b), 6.68–6.90 (m, 3H, Ar–H), 7.41–7.52 (m, 5H, Ar–H), 9.69 (s, 1H, NH), 10.25 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.50, 20.8, 27.3, 28.1, 32.3, 48.9, 50.6, 101.8, 108.5, 123.5, 123.8, 127.3, 127.7, 129.6, 130.2, 136.7, 137.2, 137.9, 139.4, 145.2, 153.2, 179.7, 193.5. Anal. Calcd for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78%. Found: C, 73.88; H, 5.92; N, 12.83%.

*4.2.6. (±)-5-Chloro-3′,7′,7′-trimethyl-1′-phenyl-6′,7′,8′,9′-tetrahydrospiro[indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9f**).* Isolated as a yellow solid, yield: 95%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 0.99 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.01–2.13 (m, 2H, H-6′a, H-6′b), 2.49 (m, 1H, H-8′a), 2.58 (s, 1H, H-8′b), 6.82–7.17 (m, 3H, Ar–H), 7.42–7.52 (m, 5H, Ar–H), 9.80 (s, 1H, NH), 10.51 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.5, 27.3, 27.9, 32.2, 49.1, 50.4, 100.9, 107.4, 110.1, 123.3, 123.7, 125.5, 127.3, 127.4, 129.5, 136.8, 137.8, 139.0, 140.8, 144.9, 153.6, 179.4, 193.6. Anal. Calcd for $C_{26}H_{23}ClN_4O_2$: C, 68.04; H, 5.05; N, 12.21%. Found: C, 67.97; H, 5.12; N, 12.15%.

*4.2.7. (±)-5-Bromo-3′,7′,7′-trimethyl-1′-phenyl-6′,7′,8′,9′-tetrahydrospiro[indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9g**).* Isolated as a yellow solid, yield: 93%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.00 (s, 6H, 2CH_3), 1.59 (s, CH_3), 2.01 (s, 2H, 6′CH_2), 2.58 (s, 2H, 8′CH_2), 6.79 (d, 1H, J=8.1 Hz, Ar–H), 6.99 (s, 1H, Ar–H), 7.29 (d, 1H, J=7.8 Hz, Ar–H), 7.43–7.52 (m, 5H, Ar–H), 9.80 (s, 1H, NH), 10.52 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.5, 27.4, 27.9, 32.2, 40.9, 49.0, 50.4, 100.9, 107.4, 110.6, 113.2, 123.7, 125.9, 127.4, 129.5, 130.1, 136.8, 137.8, 139.4, 141.2, 144.9, 153.6, 179.3, 193.6. Anal. Calcd for $C_{26}H_{23}BrN_4O_2$: C, 62.03; H, 4.61; N, 11.13%. Found: C, 61.96; H, 4.54; N, 11.19%.

*4.2.8. (±)-3′,7′,7′-Trimethyl-5-nitro-1′-phenyl-6′,7′,8′,9′-tetrahydrospiro[indoline-3,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**9h**).* Isolated as a yellow solid, yield: 94%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.00 (s, 6H, 2CH_3), 1.59 (s, CH_3), 2.08 (br s, 2H, 6′CH_2), 2.61 (br s, 2H, 8′CH_2), 7.04 (dd, 1H, J=9.0, 3.0 Hz, Ar–H), 7.43–7.55 (m, 5H, Ar–H), 7.22 (d, 1H, J=2.1 Hz, Ar–H), 8.14 (dd, 1H, J=8.7, 2.4 Hz, Ar–H), 9.93 (s, 1H, NH), 11.14 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.5, 27.4, 27.7, 32.3, 40.9, 48.9, 50.2, 100.2, 107.0, 108.9, 118.5, 123.9, 125.2, 127.6, 129.5, 137.0, 137.7, 137.8, 142.3, 144.8, 148.5, 154.1, 180.2, 193.8. Anal. Calcd for $C_{26}H_{23}N_5O_4$: C, 66.51; H, 4.94; N, 14.92%. Found: C, 66.44; H, 4.87; N, 14.99%.

*4.2.9. (±)-3′-Methyl-1′-phenylspiro[indoline-3,4′-pyrazolo [4′,3′:5,6] pyrido[2,3-d]pyrimidine]-2,5′,7′(6′H,8′H,9′H)-trione (**10a**).* Isolated as a yellow solid, yield: 92%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.57 (s, 3H, CH_3), 6.85 (d, 1H, J=7.8 Hz, Ar–H), 6.90 (d, 1H, J=7.5 Hz, Ar–H), 6.97 (d, 1H, J=7.2 Hz, Ar–H), 7.15 (t, 1H, J=7.5 Hz, Ar–H), 7.41–7.62 (m, 5H, Ar–H), 9.32 (s, 1H, NH), 10.21 (s, 1H, NH), 10.50 (s, 1H, NH), 10.77 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.4, 47.8, 87.3, 100.4, 108.9, 121.8, 122.7, 123.8, 127.5, 127.9, 129.9, 135.8, 136.0, 137.7, 142.0, 145.2, 146.7, 149.7, 162.2, 178.9. Anal. Calcd for $C_{22}H_{16}N_6O_3$: C, 64.07; H, 3.91; N, 20.38%. Found: C, 63.99; H, 3.86; N, 20.44%.

*4.2.10. (±)-3′,5-Dimethyl-1′-phenylspiro[indoline-3,4′-pyrazolo [4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′,7′(6′H,8′H,9′H)-trione (**10b**).* Isolated as a yellow solid, yield: 85%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.59 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 6.44 (s, 1H, NH), 7.02 (d, 1H, J=8.1 Hz, Ar–H), 7.13 (d, 1H, J=8.1 Hz, Ar–H), 7.34–7.45 (m, 3H, Ar–H), 7.60 (d, 1H, J=9.0 Hz, Ar–H), 7.97 (t, 1H, J=8.4 Hz, Ar–H), 9.58 (s, 1H, NH), 10.75 (s, 1H, NH), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.5, 20.1, 49.9, 82.6, 111.6, 117.1, 119.9, 121.1, 124.5, 126.9, 127.8, 129.7, 130.0, 130.2, 131.0, 132.4, 146.1, 149.3, 149.9, 162.0, 178.4. Anal. Calcd for $C_{23}H_{18}N_6O_3$: C, 64.78; H, 4.25; N, 19.71%. Found: C, 64.72; H, 4.32; N, 19.65%.

*4.2.11. (±)-5-Chloro-3′-methyl-1′-phenylspiro[indoline-3,4′-pyrazolo [4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′,7′(6′H,8′H,9′H)-trione (**10c**).* Isolated as a yellow solid, yield: 87%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.59 (s, 3H, CH_3), 6.86 (dd, 1H, J=6.0, 2.1 Hz, Ar–H), 7.08 (d, 1H, J=6.0 Hz, Ar–H), 7.18–7.22 (m, 1H, Ar–H), 7.44–7.59 (m, 5H, Ar–H), 9.33 (s, 1H, NH), 10.18 (s, 1H, NH), 10.63 (s, 1H, NH), 10.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.4, 48.0, 86.7, 99.7, 110.3, 122.8, 124.0, 125.7, 127.6, 127.8, 129.9, 136.1, 137.6, 137.8, 140.9, 145.0, 146.8, 149.6, 162.6, 178.7. HRMS (ESI) m/z calcd for $C_{22}H_{15}ClN_6O_3$ $[M-1]^+$: 445.0894; found: 445.0810. Anal. Calcd for $C_{22}H_{15}ClN_6O_3$: C, 59.13; H, 3.38; N, 18.81%. Found: C, 59.19; H, 3.31; N, 18.73%.

*4.2.12. (±)-5-Bromo-3′-methyl-1′-phenylspiro[indoline-3,4′-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′,7′(6′H,8′H, 9′H)-trione (**10d**).* Isolated as a yellow solid, yield: 86%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.60 (s, 3H, CH_3), 6.82 (d, 1H, J=8.1 Hz, Ar–H), 7.19 (s, 1H, Ar–H), 7.34 (dd, 1H, J=8.4, 1.5 Hz, Ar–H), 7.42–7.47 (m, 1H, Ar–H), 7.57–7.59 (m, 4H, Ar–H), 9.34 (s, 1H, NH), 10.18 (s, 1H, NH), 10.65 (s, 1H, NH), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.4, 48.0, 86.7, 99.7, 110.9, 113.5, 122.8, 126.7, 127.6, 129.9, 130.6, 136.1, 137.6, 138.2, 141.3, 145.0, 146.8, 149.6, 162.2, 178.6. Anal. Calcd for $C_{22}H_{15}BrN_6O_3$: C, 53.78; H, 3.08; N, 17.11%. Found: C, 53.71; H, 3.13; N, 17.19%.

*4.2.13. (±)-3′-Methyl-5-nitro-1′-phenylspiro[indoline-3,4′-pyrazolo [4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′,7′(6′H,8′H,9′H)-trione (**10e**).* Isolated as a yellow solid, yield: 81%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.59 (s, 3H, CH_3), 6.20 (d, 1H, J=8.4 Hz, Ar–H), 6.66 (d, 1H, J=8.7 Hz, Ar–H), 6.94 (t, 2H, J=8.1 Hz, Ar–H), 7.02–7.10 (m, 3H,

Ar–H), 7.19 (dd, 1H, *J*=6.3, 2.4 Hz, Ar–H), 9.47 (s, 1H, NH), 10.05 (s, 1H, NH), 10.11 (s, 1H, NH), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.5, 49.2, 82.8, 109.0, 110.9, 111.4, 120.1, 124.2, 125.5, 126.9, 129.0, 130.5, 130.9, 134.5, 142.1, 146.7, 148.5, 148.7, 161.4, 178.5. Anal. Calcd for $C_{22}H_{15}N_7O_5$: C, 57.77; H, 3.31; N, 21.44%. Found: C, 57.85; H, 3.37; N, 21.38%.

*4.2.14. (±)-3′-Methyl-1′-phenyl-7′-thioxo-spiro[indoline-3,4′-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′(6′H,8′H,9′H)-dione (**10f**).* Isolated as a yellow solid, yield: 84%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.53 (s, 3H, CH_3), 6.82 (d, 1H, *J*=7.8 Hz, Ar–H), 6.87 (d, 1H, *J*=7.5 Hz, Ar–H), 6.98 (d, 1H, *J*=7.2 Hz, Ar–H), 7.13 (t, 1H, *J*=7.5 Hz, Ar–H), 7.40–7.54 (m, 5H, Ar–H), 9.29 (s, 1H, NH), 10.52 (s, 1H, NH), 11.90 (s, 1H, NH), 12.05 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.3, 48.7, 91.4, 100.1, 109.0, 121.9, 122.5, 124.0, 127.5, 128.1, 129.9, 135.3, 135.4, 137.5, 141.9, 145.2, 146.0, 159.6, 173.6, 178.4. Anal. Calcd for $C_{22}H_{16}N_6O_2S$: C, 61.67; H, 3.76; N, 19.61%. Found: C, 61.60; H, 3.85; N, 19.55%.

*4.2.15. (±)-5-Chloro-3′-methyl-1′-phenyl-7′-thioxo-spiro-[indoline-3,4′-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′(6′H,8′H,9′H)-dion (**10g**).* Isolated as a yellow solid, yield: 80%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.59 (s, 3H, CH_3), 6.86 (d, 1H, *J*=8.1 Hz, Ar–H), 6.87 (d, 1H, *J*=2.1 Hz, Ar–H), 7.22 (dd, 1H, *J*=6.0, 2.1 Hz, Ar–H), 7.42–7.47 (m, 1H, Ar–H), 7.57–7.59 (m, 4H, Ar–H), 9.35 (s, 1H, NH), 10.71 (s, 1H, NH), 11.91 (s, 1H, NH), 12.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.4, 48.1, 90.8, 99.4, 110.5, 122.6, 124.2, 125.9, 127.7, 128.0, 129.9, 135.5, 137.3, 137.5, 140.9, 145.1, 146.2, 159.7, 173.6, 178.2. HRMS (ESI) *m*/*z* calcd for $C_{22}H_{15}ClN_6O_2S$ $[M-1]^+$: 461.0666; found: 461.0571. Anal. Calcd for $C_{22}H_{15}ClN_6O_2S$: C, 57.08; H, 3.27; N, 18.15%. Found: C, 57.15; H, 3,22; N, 18.23%.

*4.2.16. (±)-5-Bromo-3′-methyl-1′-phenyl-7′-thioxo-spiro-[indoline-3,4′-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′(6′H,8′H,9′H)-dione (**10h**).* Isolated as a yellow solid, yield: 80%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.67 (s, 3H, CH_3), 6.83 (d, 1H, *J*=8.4 Hz, Ar–H), 7.26 (s, 1H, Ar–H), 7.36 (dd, 1H, *J*=8.4, 1.5 Hz, Ar–H), 7.43–7.45 (m, 1H, Ar–H), 7.58–7.65 (m, 4H, Ar–H), 9.35 (s, 1H, NH), 10.72 (s, 1H, NH), 11.90 (s, 1H, NH), 12.05 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.4, 48.0, 90.8, 99.5, 111.0, 113.7, 122.7, 126.9, 127.7, 129.9, 130.9, 135.6, 137.4, 137.7, 141.3, 145.1, 146.2, 159.7, 173.6, 178.1. Anal. Calcd for $C_{22}H_{15}ClN_6O_2S$: C, 52.08; H, 2.98; N, 16.56%. Found: C, 52.01; H, 3.04; N, 16.50%.

*4.2.17. (±)-3′,7′,7′-Trimethyl-1′-phenyl-6′,7′,8′,9′-tetra-hydro-2H-spiro[acenaphthylene-1,4′-pyrazolo[3,4-b]quinoline]-2,5′(1′H)-dione (**11**).* Isolated as a yellow solid, yield: 82%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.94 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.94 (d, 1H, *J*=16.2 Hz, H-6a), 2.05 (d, 1H, *J*=16.2 Hz, H-6b), 2.63 (br s, 2H, 8–CH_2), 7.24 (d, 1H, *J*=6.6 Hz, Ar–H), 7.41–7.43 (m, 1H, Ar–H), 7.52–7.62 (m, 5H, Ar–H), 7.82 (d, 1H, *J*=7.2 Hz, Ar–H), 7.87 (d, 1H, *J*=8.7 Hz, Ar–H), 8.08 (d, 1H, *J*=6.9 Hz, Ar–H), 8.23 (d, 1H, *J*=8.1 Hz, Ar–H), 9.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.2, 27.2, 28.3, 32.4, 41.0, 50.1, 53.7, 103.1, 109.6, 120.0, 120.9, 121.5, 123.9, 127.6, 128.6, 129.2, 129.5, 129.7, 131.0, 134.0, 136.9, 137.9, 139.9, 145.1, 145.9, 153.8, 193.9, 205.0. Anal. Calcd for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14%. Found: C, 78.47; H, 5.55; N, 9.08%.

*4.2.18. (±)-3′-Methyl-1′-phenyl-spiro[acenaphthylene-3,4′-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′,7′(6′H,8′H,9′H)-trione (**12a**).* Isolated as a yellow solid, yield: 82%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.93 (s, 3H, CH_3), 7.35 (d, 1H, *J*=6.9 Hz, Ar–H), 7.43–7.45 (m, 1H, Ar–H), 7.57–7.66 (m, 4H, Ar–H), 7.85 (d, 1H, *J*=6.9 Hz, Ar–H), 7.92 (d, 1H, *J*=8.4 Hz, Ar–H), 7.99 (d, 1H, *J*=6.9 Hz, Ar–H), 8.27 (d, 1H, *J*=8.1 Hz, Ar–H), 9.42 (s, 1H, NH), 10.29 (s, 1H, NH), 10.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.3, 52.8, 88.7, 101.8, 120.7, 121.6, 123.0, 124.5, 127.8, 128.9, 129.4, 129.8, 130.2, 131.8, 133.3, 136.3, 137.9, 140.8, 144.8, 145.3, 147.1, 150.0, 162.9, 204.9. HRMS (ESI) *m*/*z* calcd for $C_{26}H_{17}N_5O_3$ $[M-1]^+$: 446.1331; found: 446.1272. Anal. Calcd for $C_{26}H_{17}N_5O_3$: C, 69.79; H, 3.83; N, 15.65%. Found: C, 69.71; H, 3.88; N, 15.59%.

*4.2.19. (±)-3′-Methyl-1′-phenyl-7′-thioxo-spiro[acenaph-thylene-3,4′-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′(6′H,8′H,9′H)-dione (**12b**).* Isolated as a yellow solid, yield: 84%, mp >300 °C (recrystallization from EtOH/DMF mixture); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.99 (s, 3H, CH_3), 7.39–7.47 (m, 2H, Ar–H), 7.58–7.67 (m, 5H, Ar–H), 7.85 (t, 1H, *J*=7.2 Hz, Ar–H), 7.94 (d, 1H, *J*=8.4 Hz, Ar–H), 8.01 (d, 1H, *J*=6.9 Hz, Ar–H), 8.29 (d, 1H, *J*=8.1 Hz, Ar–H), 9.42 (s, 1H, NH), 11.82 (s, 1H, NH), 12.19 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 11.5, 52.0, 92.0, 100.7, 120.3, 121.1, 122.1, 123.9, 127.2, 128.2, 128.7, 129.0, 129.5, 131.2, 132.3, 135.0, 137.0, 140.1, 143.5, 144.6, 145.8, 159.5, 173.2, 203.7. Anal. Calcd for $C_{26}H_{17}N_5O_2S$: C, 67.37; H, 3.70; N, 15.11%. Found: C, 67.43; H, 3.62; N, 15.19%.

4.3. General procedure for synthesis of 3-(5-amino-3-methyl-1-phenyl-1*H*-4-pyrazolyl)-3-hydroxy-2-indolinone (13)

A mixture of phenylhydrazine (1 mmol), 3-aminocrotononitrile (1 mmol), and $InCl_3$ (0.1 mmol) in water (10 ml) was added to isatin (1 mmol) and the reaction mixture heated under reflux at 100 °C for 10 min. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature; the precipitate was filtered off and washed with methanol to obtain pure **13** as a colorless solid. Spectroscopic data for all the compounds are given below.

*4.3.1. 3-(5-Amino-3-methyl-1-phenyl-1H-4-pyrazolyl)-3-hydroxy-2-indolinone (**13a**)*[16a]. Isolated as a colorless solid, yield: 96%, mp 236 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.43 (s, 3H, CH_3), 5.28 (s, 2H, NH_2), 6.63 (s, 1H, OH), 6.84 (d, *J*=7.8 Hz, 1H, Ar–H), 6.97 (t, *J*=7.5 Hz, 1H, Ar–H), 7.20–7.28 (m, 3H, Ar–H), 7.44 (t, *J*=7.5 Hz, 2H, Ar–H), 7.54 (d, *J*=7.5 Hz, 2H, Ar–H), 10.35 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.8, 74.6, 99.7, 109.9, 122.1, 122.8, 125.1, 126.2, 129.2, 129.6, 132.9, 139.0, 141.7, 144.8, 146.3, 178.3. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{16}N_4O_2$ $[M-1]^+$: 319.1273; found: 319.1200. Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49%. Found: C, 67.42; H, 4.97; N, 17.45%.

*4.3.2. 3-(5-Amino-3-methyl-1-phenyl-1H-4-pyrazolyl)-5-chloro-3-hydroxy-2-indolinone (**13b**).* Isolated as a colorless solid, yield: 94%, mp 243 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.45 (s, 3H, CH_3), 5.31 (s, 2H, NH_2), 6.80 (s, 1H, OH), 6.87 (t, 2H, *J*=7.2 Hz, Ar–H), 7.28–7.32 (m, 2H, Ar–H), 7.44–7.48 (m, 2H, Ar–H), 7.52–7.57 (m, 2H, Ar–H), 10.53 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.7, 74.5, 99.0, 111.3, 122.8, 124.8, 125.9, 126.1, 129.1, 129.2, 134.9, 138.9, 140.4, 144.3, 146.2, 177.7. Anal. Calcd for $C_{18}H_{15}ClN_4O_2$: C, 60.94; H, 4.26; N, 15.79%. Found: C, 60.87; H, 4.20; N, 15.72%.

*4.3.3. 3-(5-Amino-3-methyl-1-phenyl-1H-4-pyrazolyl)-5-bromo-3-hydroxy-2-indolinone (**13c**).* Isolated as a colorless solid, yield: 90%, mp 254 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.48 (s, 3H, CH_3), 5.30 (s, 2H, NH_2), 6.79 (s, 1H, OH), 6.83 (t, 2H, *J*=8.1 Hz), 7.29 (t, 2H, *J*=8.1 Hz, Ar–H), 7.38–7.48 (m, 3H, Ar–H), 7.55 (d, 1H, *J*=7.8 Hz), 10.53 (s, 1H, NH); ^{13}C NMR (DMSO-d_6 75 MHz) δ 12.7, 74.5, 99.0, 111.9, 113.5, 122.8, 126.1, 127.5, 129.0, 132.0, 135.2, 138.8, 140.8, 144.3, 146.2, 177.6. Anal. Calcd for $C_{18}H_{15}BrN_4O_2$: C, 54.15; H, 3.79; N, 14.03%. Found: C, 54.09; H, 3.71; N, 13.96%.

*4.3.4. 3-(5-Amino-3-methyl-1-phenyl-1H-4-pyrazolyl)-3-hydroxy-5-nitro-2-indolinone (**13d**).* Isolated as a colorless solid, yield: 95%, mp 268 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.47 (s, 3H, CH_3), 5.37 (s, 2H, NH_2), 7.00 (s, 1H, OH), 7.08 (t, 2H, J=8.7 Hz), 7.30 (t, 2H, J=8.7 Hz, Ar–H), 7.46–7.56 (m, 2H, Ar–H), 8.06 (s, 1H, Ar–H), 8.23 (d, 1H, J=7.5 Hz), 10.35 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.8, 74.0, 98.2, 110.2, 120.1, 122.9, 126.2, 126.7, 129.1, 133.8, 138.7, 142.4, 144.1, 146.4, 147.9, 178.3. Anal. Calcd for $C_{18}H_{15}N_5O_4$: C, 54.15; H, 3.79; N, 14.03%. Found: C, 59.18; H, 4.14; N, 19.17%.

*4.3.5. 3-(5-Amino-3-methyl-1-phenyl-1H-4-pyrazolyl)-3-hydroxy-5,7-dimethyl-2-indolinone (**13e**).* Isolated as a colorless solid, yield: 86%, mp 216 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.45 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 5.25 (s, 2H, NH_2), 6.52 (s, 1H, OH), 6.87–6.90 (m, 1H, Ar–H), 7.27 (t, 2H, J=7.5 Hz, Ar–H), 7.45 (t, 2H, J=7.5 Hz, Ar–H), 7.53 (s, 1H, Ar–H), 7.57 (s, 1H, Ar–H), 10.30 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.6, 16.1, 20.4, 74.8, 99.9, 118.6, 122.6, 122.7, 125.8, 128.9, 130.6, 130.8, 132.5, 137.6, 139.0, 144.7, 145.8, 178.4. Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08%. Found: C, 68.86; H, 5.72; N, 16.02%.

*4.3.6. 3-[5-Amino-1-(4-fluorophenyl)-3-methyl-1H-4-pyrazolyl]-3-hydroxy-5-methyl-2-indolinone (**13f**).* Isolated as a colorless solid, yield: 88%, mp 222 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.44 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 5.26 (s, 2H, NH_2), 6.58 (s, 1H, OH), 6.74 (d, 2H, J=7.5 Hz, Ar–H), 7.03–7.08 (m, 1H, Ar–H), 7.26–7.35 (m, 3H, Ar–H), 7.55–7.59 (m, 1H, Ar–H), 10.30 (s, 1H, NH); ^{13}C NMR (DMSO-d_6 75 MHz) δ 12.6, 20.6, 74.6, 99.8, 109.5, 115.6, 115.9, 124.9, 125.0, 125.5, 129.6, 130.8, 132.8, 139.1, 144.7, 146.1, 178.1. Anal. Calcd for $C_{19}H_{17}FN_4O_2$: C, 64.76; H, 4.86; N, 15.90%. Found: C, 64.71; H, 4.79; N, 15.84%.

*4.3.7. 3-[5-Amino-1-(4-fluorophenyl)-3-methyl-1H-4-pyrazolyl]-5-chloro-3-hydroxy-2-indolinone (**13g**).* Isolated as a colorless solid, yield: 90%, mp 235 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.48 (s, 3H, CH_3), 5.30 (s, 2H, NH_2), 6.80 (s, 1H, OH), 6.87 (d, 1H, J=8.1 Hz, Ar–H), 7.26–7.32 (m, 4H, Ar–H), 7.54–7.59 (m, 2H, Ar–H), 10.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.6, 74.4, 99.1, 111.3, 115.5, 115.8, 124.7, 125.0, 125.1, 125.9, 129.1, 134.8, 140.4, 144.3, 146.2, 177.6. Anal. Calcd for $C_{18}H_{14}ClFN_4O_2$: C, 57.99; H, 3.79; N, 15.03%. Found: C, 57.91; H, 3.73; N, 14.98%.

*4.3.8. 3-[5-Amino-1-(4-fluorophenyl)-3-methyl-1H-4-pyrazolyl]-5-bromo-3-hydroxy-2-indolinone (**13h**).* Isolated as a colorless solid, yield: 91%, mp 249 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.40 (s, 3H, CH_3), 5.30 (s, 2H, NH_2), 6.79 (s, 1H, OH), 6.82 (d, 2H, J=8.1 Hz, Ar–H), 7.26 (d, 2H, J=8.1 Hz, Ar–H), 7.38 (d, 1H, J=1.8 Hz, Ar–H), 7.42 (dd, 1H, J=8.4, 2.1 Hz, Ar–H), 7.54–7.59 (m, 1H, Ar–H), 10.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.6, 74.4, 99.1, 111.9, 113.5, 115.6, 115.9, 125.0, 125.1, 127.5, 132.0, 135.2, 140.8, 144.2, 146.3, 177.5. Anal. Calcd for $C_{18}H_{14}BrFN_4O_2$: C, 51.82; H, 3.38; N, 13.43%. Found: C, 51.76; H, 3.31; N, 13.39%.

*4.3.9. 3-[5-Amino-1-(4-fluorophenyl)-3-methyl-1H-4-pyrazolyl]-3-hydroxy-5,7-dimethyl-2-indolinone (**13i**).* Isolated as a colorless solid, yield: 82%, mp 229 °C (recrystallized from EtOH/AcOEt); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.45 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 5.26 (s, 2H, NH_2), 6.53 (s, 1H, OH), 6.87 (s, 1H, Ar–H), 6.91 (s, 1H, Ar–H), 7.46 (d, 2H, J=7.8 Hz, Ar–H), 7.56 (d, 2H, J=7.8 Hz, Ar–H), 10.33 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 12.7, 16.2, 20.5, 74.8, 99.9, 118.7, 122.6, 122.8, 125.9, 129.0, 130.6, 130.9, 132.6, 137.6, 139.0, 144.7, 145.9, 178.5. Anal. Calcd for $C_{20}H_{19}FN_4O_2$: C, 65.56; H, 5.23; N, 15.29%. Found: C, 65.50; H, 5.16; N, 15.22%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.03.020. These data include MOL files and InChiKeys of the most important compounds described in this article.

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