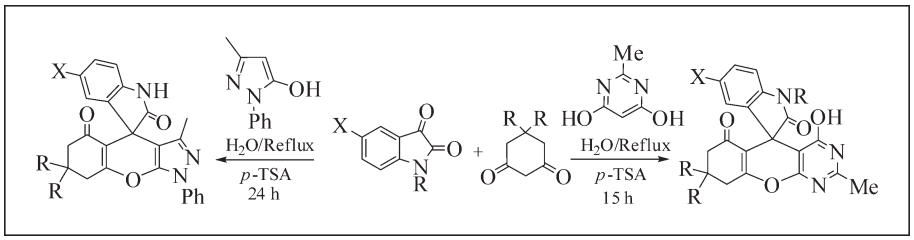
One-Pot and Three-Component Synthesis of Spiro[chromeno[2,3-*d*] pyrimidine-5,3′-indoline]-diones and Spiro[chromeno[2,3-*c*] pyrazole-4,3′-indoline]-diones

Ramin Ghahremanzadeh,[a] Fatemeh Fereshtehnejad,[b] Zahra Yasaei,[b] Tayebeh Amanpour,[b] and Ayoob Bazgir[b]*

[a]Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran
[b]Department of Chemistry, Shahid Beheshti University, G.C. Tehran 1983963113, Iran
*E-mail: a_bazgir@sbu.ac.ir

Received November 23, 2009
DOI 10.1002/jhet.399
Published online 21 June 2010 in Wiley InterScience (www.interscience.wiley.com).



A novel, clean, one-pot and three-component synthesis of new spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones and spiro[chromeno[2,3-*c*]pyrazole-4,3′-indoline]-2′,5(6*H*)-diones via cyclocondensation reaction of isatins, 1,3-cyclohexadiones, and 2-methylpyrimidine-4,6-diol or 3-methyl-1-phenyl-1*H*-pyrazol-5-ol, in aqueous media is reported.

J. Heterocyclic Chem., **47**, 967 (2010).

INTRODUCTION

Multi-step reactions usually produce significant amount of waste, principally due to a series of isolation procedures which often involves toxic, hazardous, and expensive solvents after each step. Thus, multi-component reactions (MCRs) constitute an efficient synthetic strategy for the rapid and effective libratory organic transformations. Because, products are prepared in a one-pot and the diversity can be obtained directly by changing the reacting components [1,2]. On the other hand, polyfunctionalized heterocycles play considerable roles in the drug discovery process, and analysis of drugs shows that most of them are polyfunctionalized heterocycles [3]. Therefore, research on the multi-component synthesis of polyfunctionalized heterocyclic compounds is an interesting challenge.

Pyrimidine and its derivatives are important heterocyclic compounds with wide applications in medicinal chemistry, as antibacterial, antiviral, and antitumor agents [4]. A number of heterocycles fused with pyrimidines are known for their varied biological activities [5–8]. Similarly, chromene derivatives are an important group of compounds, widely exist in plants, including edible vegetables and fruits [9]. Synthetic analogues were developed over the years, some of them displaying remarkable effects as pharmaceuticals [10–13], including antifungal [12,14] and antimicrobial activity [15–17].

The indole skeleton is common in many natural products and medicinal agents [18]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindolines can highly enhance biological activity [19–21]. The spirooxindole nucleus occurs in several natural alkaloids and pharmacologically active substances displaying a broad range of biological activity [22–25]. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles [26–30].

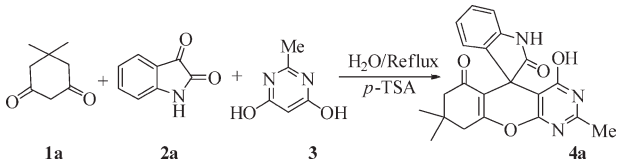
In continuation of our previous works for the synthesis of heterocyclic compounds [31–43], we performed the preparation of some new spirooxindole containing chromene ring fragments via three-component condensation reaction employing water as the reaction medium. Organic transformations in water without using toxic organic solvents are one of the current focuses today especially in our environmentally conscious society.

RESULTS AND DISCUSSION

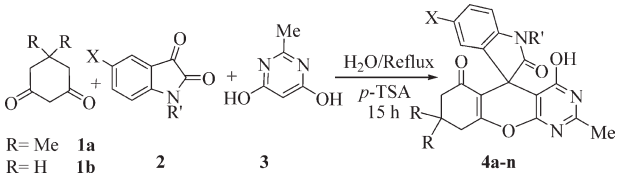
First, we carried out the three-component reaction of dimedone 1a, isatin **2a**, and 2-methylpyrimidine-4,6-diol **3** as a model reaction in different solvents in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive catalyst (Scheme 1). It was found that refluxing water was a best condition for the reaction and the desired product obtained in good yield after 15 h (Table 1).

Encouraged by this result, we extended the reaction of cyclic 1,3-dicarbonyls 1a,b and 2-methylpyrimidine-4,6-diol 3 with a range of isatins 2 under similar

Scheme 1



Scheme 2



conditions (Water/*p*-TSA) for 15 h, furnishing the respective 4-hydroxy-2-methyl-8,9-dihydrospiro[chromeno [2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones **4a–n** in good yields (Scheme 2, Table 2).

The results were good in terms of yields and product purity in the presence of *p*-TSA, while without *p*-TSA the yields of products were very low (<30%) even after 48 h.

To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of 8,9-dihydrospiro [chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones.

Compounds **4a–n** are stable solids whose structures were established by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analysis. We have not established an exact mechanism for the formation of spiro [chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-dione 4, however, a reasonable possibility is shown in Scheme 3.

To further explore the potential of this protocol for spiro-heterocyclic synthesis, we investigated reaction of malononitrile 5 instead of 1,3-cyclohexadione 1 and obtained spiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitriles 6a–d selectively, in good yields for 24 h (Scheme 4, Table 3).

To further expand the scope of the reaction, we replaced 2-methylpyrimidine-4,6-diol **3** with 3-methyl-1-phenyl-1*H*-pyrazol-5-ol **7** and desired spiro[chromeno[2,3-*c*]pyrazole-4,3′-indoline]-2′,5(6*H*)-diones **8** was selectively synthesized in good yields for 24 h (Scheme 5, Table 4).

Finally, when we extended this reaction to acenaphthylene-1,2-dione **9**, product of 3′,7′,7′-trimethyl-1′-phenyl-7′,8′-dihydro-1′*H*,2*H*-spiro[acenaphthylene-1,4′-chromeno[2,3-*c*]pyrazole]-2,5′(6′*H*)-dione **10** was generated in 70% yield after 24 h (Scheme 6).

Table 1

Conditions effect on the reaction.[a]

Entry	Conditions	Time (h)	Yield (%)
1	Water (80°C)	24	63
2	Water (reflux)	15	85
3	CH_3CN (reflux)	24	60
4	EtOH (reflux)	24	67
5	DMF (100°C)	24	60

[a] Dimedone (1 mmol), 2-methylpyrimidine-4,6-diol (1 mmol), isatin (1 mmol), and *p*-TSA (0.05 g).

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using a Shimadzu IR-470 apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of 4-hydroxy-2-methyl-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones (4a–n). A mixture of dimedone or 1,3-cyclohexadione (1 mmol), 2-methylpyrimidine-4,6-diol (1 mmol), isatins (1 mmol), and *p*-TSA (0.05 g) in refluxing water (5 mL) was stirred for 15 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with water (10 mL) and recrystallized by EtOH to afford the pure product **4**.

4-Hydroxy-2,8,8-trimethyl-8,9-dihydrospiro[chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4a). Light Brown powder (85%); m.p 205°C (dec). IR (KBr): 3450, 2952, 1718, 1670, 1622, 1596 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.97 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.05, 2.21 (2H, ABq, J = 15.9 Hz, CH_2), 2.25 (3H, s CH_3), 2.57, 2.67 (2H, ABq, J = 18.4 Hz, CH_2), 6.70–6.78 (2H, m, ArH), 6.85–6.87 (1H, m, ArH), 7.05–7.10 (1H, m, ArH), 10.37 (1H, s, NH), 12.49 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.2, 27.1, 28.3, 32.2, 46.6, 50.9, 100.6, 108.9, 112.8, 121.2, 123.2, 128.3, 133.9, 144.3, 159.8, 160.5, 161.1, 164.9, 178.1, 195.4. MS, *m*/

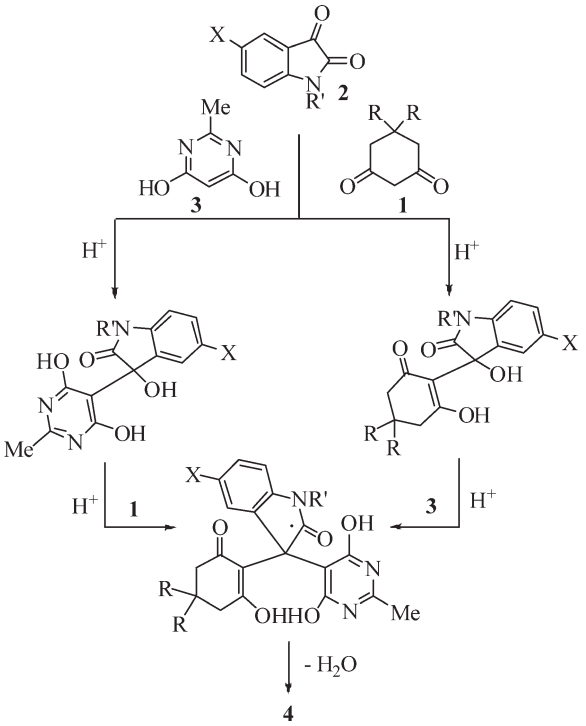
Table 2

Synthesis of spirochromenopyrimidine-indolines **4a–n**.

Product **4**	R	R'	X	Yield (%)[a]
a	Me	H	H	85
b	Me	H	NO_2	89
c	Me	$PhCH_2$	H	75
d	Me	Me	H	80
e	Me	Me	NO_2	84
f	Me	Me	Br	80
g	Me	Et	NO_2	82
h	H	H	Br	76
i	H	H	NO_2	80
j	H	Me	H	77
k	H	Et	H	75
l	H	$PhCH_2$	H	74
m	H	Me	Br	75
n	H	Et	NO_2	77

[a] Isolated yields.

Scheme 3



z: 377 (M^+). Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.88; H, 5.01; N, 11.06.

4-Hydroxy-2,8,8-trimethyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4b). Light Brown powder (89%); m.p 245°C (dec). IR (KBr): 3445, 2957, 1737, 1680, 1627, 1600 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.00 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.07–2.22 (2H, m, CH_2), 2.26 (3H, s, CH_3), 2.60–2.73 (2H, m, CH_2), 6.62–6.96 (1H, m, ArH), 7.87 (1H, m ArH), 8.11 (1H, d, J = 8.5 Hz, ArH), 11.17 (1H, s, NH), 12.60 (1H,s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 27.5, 27.7, 32.3, 46.6, 50.6, 99.5, 108.8, 111.8, 119.0, 126.1, 134.8, 142.2, 151.0, 160.4, 160.7, 161.3, 165.0, 166.1, 178.8, 196.0. MS, m/z: 422 (M^+). Anal. Calcd. for $C_{21}H_{18}N_4O_6$: C, 59.71; H, 4.30; N, 13.26. Found: C, 59.65; H, 4.35; N, 13.19.

Due to very low solubility of the product **4c**, we can not report the ^{13}C NMR data for this product.

1′-Bnzoyl-4-hydroxy-2,8,8-trimethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4c). Light Brown powder (74%); mp 125–135°C (dec). IR (KBr): 3452, 2957, 1730, 1673, 1608 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1. 21 (3H, t, J = 6.7 Hz, CH_3), 0.99 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.09, 2.25 (2H, ABq, J = 16.0 Hz, CH_2), 2.27 (3H, s, CH_2), 2.61, 2.71 (2H, ABq, J = 17.0 Hz, CH_2), 4.84, 4.94 (2H, ABq, J = 16.0 Hz, NCH_2), 6.53 (1H, d, J = 8.8 Hz, ArH), 6.82–6.87 (1H, m, ArH), 6.98 (1H, d, J = 8.4 Hz, ArH), 7.03–7.08 (1H, m, ArH), 7.25–7.34 (3H, m, ArH), 7.63–7.66 (2H, m, ArH), 12.64 (1H, s, OH). MS, m/z: 467 (M^+). Anal. Calcd. for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.88; H, 5.44; N, 8.91.

4-Hydroxy-1′,2,8,8-tetramethyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4d). Light Brown powder (80%); m.p 218°C (dec). IR (KBr): 3527, 2952, 1694, 1671, 1596 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0. 98 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.04, 2.18 (2H, ABq, J = 16.0 Hz, CH_2), 2.26 (3H, s, CH_3), 2.59, 2.67 (2H, ABq, J = 17.1 Hz, CH_2), 3.13 (3H, s, NCH_3), 6.82–6.94 (3H, m, ArH), 7.16–7.21 (1H, m,ArH), 12.44 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 26.9, 27.2, 28.3, 32.2, 46.1, 50.8, 100.4, 107.8, 112.6, 122.0, 123.0, 128.6, 133.0, 145.7, 159.9, 160.5, 160.9, 165.1, 176.8, 195.4, 195.6. MS, m/z: 391 (M^+). Anal. Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.47; H, 5.36; N, 10.69.

4-Hydroxy-1′,2,8,8-tetramethyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4e). Light Brown powder (84%); m.p 207°C (dec). IR (KBr): 3548, 2967, 1740, 1686, 1609 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0. 99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.12–2.15 (2H, m, CH_2), 2.27 (3H, s, CH_3), 2.63–2.69 (2H, m, CH_2), 3.24 (3H, s, NCH_3), 7.19 (1H, d, J = 8.7 Hz, ArH), 7.92 (1H, s, ArH), 8.19 (1H, d, J = 8.7 Hz, ArH), 12.57 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.4, 27.3, 27.7, 27.8, 32.2, 32.3, 46.0, 50.5, 99.3, 107.9, 111.7, 118.6, 126.2, 133.9, 142.7, 151.8, 160.6, 160.8, 161.2, 166.3, 177.7, 196.0. MS, m/z: 436 (M^+). Anal. Calcd. for $C_{22}H_{20}N_4O_6$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.61; H, 4.66; N, 12.89.

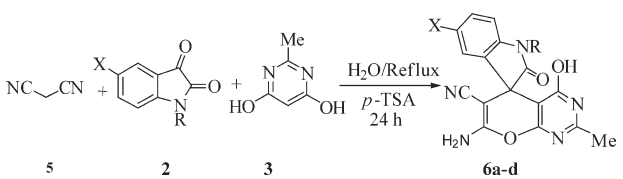
5′-Bromo-4-hydroxy-1′,2,8,8-tetramethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4f). Light Brown powder (80%); m.p 230°C (dec). IR (KBr): 3517, 2952, 1703, 1677, 1653, 1607 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0. 99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.05–2.10 (2H, m, CH_2), 2.26 (3H, s, CH_3), 2.63 (2H, brs, CH_2), 3.12 (3H, s, NCH_3), 6.90 (1H,d, J = 8.4 Hz, ArH), 7.16 (1H, s, ArH), 7.37 (1H, d, J = 8.6 Hz, ArH), 12.50 (1H, s, OH). ^{13}C

Table 3

Synthesis of spiro[indoline-pyranopyrimidine]-carbonitriles **6a–d**.

Product **6**	R	X	Yield (%)
a	H	H	80
b	H	NO_2	82
c	Me	NO_2	65
d	Et	NO_2	63

Scheme 4



Scheme 5

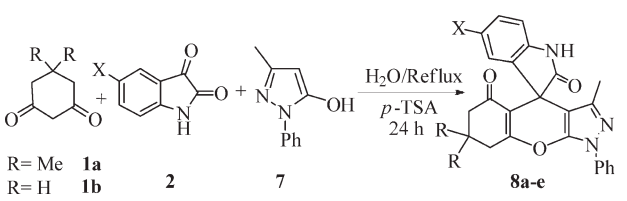


Table 4

Synthesis of spiro[chromenopyazole-indoline]-diones **8a–e**.

Product **8**	R	R'	X	Yield (%)
a	Me	H	H	80
b	Me	H	NO_2	75
c	Me	H	Br	81
d	H	H	H	73
e	H	H	NO_2	70

NMR (75 MHz, DMSO-d_6): δ = 21.3, 27.0, 27.7, 27.8, 32.2, 46.2, 50.7, 99.8, 109.7, 112.1, 113.7, 126.0, 131.2, 135.3, 145.2, 160.2, 160.6, 161.3, 165.7, 176.5, 195.7, 195.8. MS, *m*/*z*: 471 (M^+), 469 (M^+). Anal. Calcd. for $C_{22}H_{20}BrN_3O_4$: C, 56.18; H, 4.29; N, 8.93. Found: C, 56.23; H, 4.23; N, 8.85.

1′-Ethyl-4-hydroxy-2,8,8-trimethyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4g). Light Brown powder (82%); m.p 240°C (dec). IR (KBr): 3530, 2952, 1735, 1680, 1608 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0. 99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.22 (3H, t, *J* = 6.9 Hz, CH_3), 2.09–2.15 (2H, m, CH_2), 2.60–2.74 (2H, m, CH_2), 3.80–3.82 (2H, m, NCH_2), 7.21 (1H, d, *J* = 8.7 Hz, ArH), 7.91 (1H, s, ArH), 8.18 (1H, d, *J* = 8.4 Hz, ArH), 12.57 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.1, 21.4, 27.7, 32.2, 32.3, 35.3, 50.5, 50.6, 99.4, 107.8, 111.7, 118.7, 126.2, 134.1, 142.5, 151.0, 160.5, 160.8, 161.2, 165.2, 166.2, 177.1, 195.9. MS, *m*/*z*: 450 (M^+). Anal. Calcd. for $C_{23}H_{22}N_4O_6$: C, 61.33; H, 4.92; N, 12.44. Found: C, 61.39; H, 4.97; N, 12.38.

5′-Bromo-4-hydroxy-2-methyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4h). Light Brown powder (74%); m.p 240°C (dec). IR (KBr): 3404, 2957, 1748, 1704, 1647, 1615 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1. 92 (2H, brs, CH_2), 2.25 (5H, brs, CH_2, and CH_3), 2.71 (2H, brs, CH_2), 6.68 (1H, d, *J* = 8.1 Hz, ArH), 7.11 (1H, s, ArH), 7.25 (1H, d, *J* = 8.1 Hz, ArH), 10.55 (1H, s, NH), 12.53 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.1, 21.3, 27.6, 37.2, 46.9, 100.1, 110.7, 112.9, 113.3, 125.9, 126.2, 131.0, 136.4, 143.7, 160.4, 160.1, 167.3, 177.9, 195.8. MS, *m*/*z*: 427 (M^+). Anal. Calcd. for $C_{19}H_{14}BrN_3O_4$: C, 53.29; H, 3.30; N, 9.81. Found: C, 53.23; H, 3.36; N, 9.88.

4-Hydroxy-2-methyl-5′-nitro-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4i). Light Brown powder n(80%); m.p 250°C (dec). IR (KBr): 2450, 3203, 1717, 1682, 1627 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.93 (2H, brs, CH_2), 2.27 (5H, brs, CH_2, and CH_3), 2.50 (2H, brs, CH_2), 6.93 (1H,d, *J* = 8.7 Hz, ArH), 7.89 (1H, s, ArH), 8.10 (1H,d, *J* = 8.6 Hz, ArH), 11.18 (1H, s, NH), 12.58 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.1, 21.3, 27.6, 37.0, 46.7, 99.6, 108.8, 112.8, 119.2, 126.1, 134.9, 142.2, 150.9, 160.4, 160.6, 161.2, 168.0, 178.9, 196.1. MS, *m*/*z*: 394 (M^+). Anal. Calcd. for $C_{19}H_{14}N_4O_6$: C, 57.87; H, 3.58; N, 14.21. Found: C, 57.92; H, 3.53; N, 14.15.

4-Hydroxy-1′,2-dimethyl-8,9-dihydrospiro[chromeno[2,3-d] pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4j). Light Brown powder (76%); m.p 246°C (dec). IR (KBr): 3450, 2936, 1693, 1647, 1607 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1. 91 (2H, brs, CH_2), 2.19–2.25 (5H, m, CH_2, and CH_3), 2.72 (2H, brs, CH_2), 3.13 (3H, s, NCH_3), 6.82–6.95 (3H, m, ArH), 7.15–7.20 (1H, m, ArH), 12.43 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.2, 21.3, 26.8, 27.5, 37.2, 46.1, 100.4, 107.7, 113.7, 122.0, 123.1, 128.5, 133.1, 145.6, 159.8, 160.3, 160.9, 167.0, 176.9, 195.6. MS, *m*/*z*: 363 (M^+). Anal. Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56. Found: C, 66.17; H, 4.68; N, 11.62.

1′-Ethyl-4-hydroxy-2-methyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4k). Light Brown powder (72%); m.p 235°C (dec). IR (KBr): 3435, 2931, 1683, 1599 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1. 21 (3H, t, *J* = 6.7 Hz, CH_3), 1.89–1.90 (2H, m, CH_2), 2.18–2.25 (5H, m, CH_2, and CH_3), 2.70–2.71 (2H, m, CH_2), 3.67–3.71 (2H, m, NCH_2), 6.80–6.85 (1H, m, ArH), 6.90–6.92 (2H, m, ArH), 7.14–7.19 (1H, m, ArH), 12.43 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.1, 20.2, 21.3, 27.5, 34.7, 37.2, 46.3, 100.5, 107.6, 113.8, 121.7, 123.3, 128.5, 133.3, 144.7, 159.8, 160.3, 160.9, 166.9, 176.1, 195.5. MS, *m*/*z*: 377 (M^+). Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.77; H, 5.00; N, 11.07.

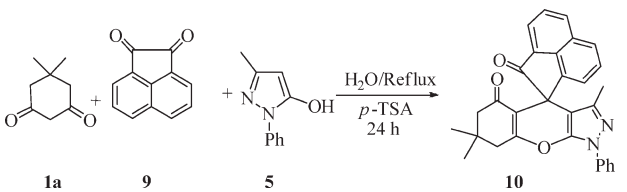
Due to very low solubility of the product **4l**, we can not report the ^{13}C NMR data for this product.

1′-Benzoyl-4-hydroxy-2-methyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4l). Light Brown powder (75%); m.p 129°C (dec). IR (KBr): 3440, 2921, 1734, 1671, 1609 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.93 (2H, brs, CH_2), 2.27 (5H, brs, CH_3 and CH_2), 2.75 (2H, brs, CH_2), 4.87–4.96 (2H, m, NCH_2), 6.52 (1H, d, *J* = 7.1 Hz, ArH), 6.83 (1H, m, H—Ar), 6.97 (1H, m, ArH), 7.03–7.10 (1H, m, Ar H), 7.31–7.33 (3H, m, ArH), 7.56–7.64 (2H, m, ArH), 12.62 (1H, s, OH). MS, *m*/*z*: 439 (M^+). Anal. Calcd. for $C_{26}H_{19}N_3O_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 71.00; H, 4.87; N, 9.48.

5′-Bromo-4-hydroxy-1′,2-dimethyl-8,9-dihydro spiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4m). Light Brown powder (75%); m.p 232°C (dec). IR (KBr): 3471, 2926,1702, 1688, 1599 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.91–1.93 (2H, m, CH_2), 2.26 (3H, s, CH_3), 2.50 (2H, brs, CH_2), 3.12 (3H, s, NCH_3), 3.38 (2H, brs, CH_2), 6.89 (1H, d, *J* = 7.5 Hz, ArH), 7.20 (1H, s, ArH), 7.36 (1H, d, *J* = 8.4 Hz, ArH), 12.48 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.1, 21.4, 26.9, 27.6, 46.3, 100.0, 109.6, 113.1, 113.7, 126.1, 131.1,m 135.4, 145.1, 160.2, 160.4, 161.0, 167.6, 176.5, 195.8. MS, *m*/*z*: 441 (M^+). Anal. Calcd. for $C_{20}H_{16}BrN_3O_4$: C, 54.31; H, 3.65; N, 9.50. Found: C, 54.26; H, 3.61; N, 9.56.

1′-Ethyl-4-hydroxy-2-methyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4n). Light Brown powder (77%); m.p 228°C (dec). IR (KBr): 3527, 2936, 1704, 1683, 1605 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.97 (3H, s, CH_3), 1.22 (3H, t, *J* = 6.6 Hz, CH_3), 1.93 (2H, brs, CH_2), 2.23–2.26 (5H, m, CH_2, and CH_3), 2.75 (2H, brs, CH_2), 3.79–3.82 (2H, m, NCH_2), 7.20 (1H, d, *J* = 8.7 Hz, ArH), 7.95 (1H, s, ArH), 8.18 (1H, d, *J* = 8.7 Hz,

Scheme 6



1a **9** **5** **10**

ArH), 12.56 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.1, 20.1, 21.4, 27.6, 35.3, 36.9, 46.2, 99.4, 107.7, 112.7, 119.0, 126.1, 134.2, 142.5, 151.0, 160.5, 161.2, 168.2, 177.1, 196.1. MS, *m*/*z*: 422 (M^+). Anal. Calcd. for $C_{21}H_{18}N_4O_6$: C, 59.71; H, 4.30; N, 13.26. Found: C, 59.77; H, 4.36; N, 13.20.

7′-Amino-4′-hydroxy-2′-methyl-2-oxospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6a). Cream powder (80%); m.p 287°C (dec). IR (KBr): 3378, 3306, 3142, 2207, 1716, 1676 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.27 (3H, s, CH_3), 6.78–7.18 (4H, m, ArH), 7.31 (2H, s, NH_2), 10.49 (1H, s, NH), 12.61 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.4, 47.9, 57.1, 98.3, 109.7, 117.9, 122.2, 124.0, 128.8, 134.0, 142.6, 160.0, 160.3, 160.8, 161.0, 177.9. MS, *m*/*z*: 321 (M^+). Anal. Calcd. for $C_{16}H_{11}N_5O_3$: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.76; H, 3.41; N, 21.86.

7′-Amino-4′-hydroxy-2′-methyl-5-nitro-2-oxospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6b). Cream powder (82%); m.p 270°C (dec). IR (KBr): 3471, 3363, 3193, 2202, 1704, 1658 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (3H, s, CH_3), 7.02 (1H, d, *J* = 8.8 Hz, ArH), 7.50 (2H, s, NH_2), 8.04 (1H, s, ArH), 8.16 (1H, d, *J* = 8.6 Hz, ArH), 11.24 (1H, s, NH), 12.68 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.5, 48.1, 55.4, 97.2, 109.9, 117.7, 120.0, 126.4, 134.9, 142.9, 149.1, 160.4, 160.8, 161.1, 161.2, 178.7. MS, *m*/*z*: 366 (M^+). Anal. Calcd. for $C_{16}H_{10}N_6O_5$: C, 52.46; H, 2.75; N, 22.94. Found: C, 52.50; H, 2.80; N, 22.88.

7′-Amino-4′-hydroxy-1,2′-dimethyl-5-nitro-2-oxospiro [indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6c). powder (65%); m.p 180°C (dec). IR (KBr): 3429, 3322, 2202, 1730, 1667 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.29 (3H, s, CH_3), 3.25 (3H, s, CH_3), 7.30 (1H, d, *J* = 9.0 Hz, ArH), 7.57 (2H, s, NH_2), 8.11 (1H, s, ArH), 8.27 (1H, d, *J* = 8.9 Hz, ArH), 12.66 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.5, 27.3, 47.7, 55.1, 97.1, 108.9, 117.6, 119.6, 126.4, 134.2, 143.4, 150.1, 160.6, 160.9, 161.0, 161.1, 177.3. MS, *m*/*z*: 380 (M^+). Anal. Calcd. for $C_{17}H_{12}N_6O_5$: C, 53.69; H, 3.18; N, 22.10. Found: C, 53.64; H, 3.22; N, 22.18.

7′-Amino-1-ethyl-4′-hydroxy-2′-methyl-5-nitro-2-oxospiro [indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6d). Cream powder (63%); m.p 233°C (dec). IR (KBr): 3481, 3325, 2197, 1755, 1668, 1647 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (3H, t, *J* = 8.4 Hz, CH_3), 2.22 (3H, s, CH_3), 3.74 (2H, m, CH_2), 7.10 (1H, d, *J* = 8.9 Hz, ArH), 8.14 (1H, d, *J* = 8.9 Hz, ArH), 8.14 (1H, s, ArH), 12.16 (3H, bs, NH_2 and OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.9, 18.0, 34.9, 39.07, 48.5, 95.3, 107.5, 118.4, 125.3, 135.3, 141.8, 150.6, 158.2, 161.4, 171.8, 178.6. MS, *m*/*z*: 394 (M^+). Anal. Calcd. for $C_{18}H_{14}N_6O_5$: C, 54.82; H, 3.58; N, 21.31. Found: C, 54.86; H, 3.63; N, 21.36.

3,7,7-Trimethyl-1-phenyl-7,8-dihydro-1H-spiro [chromeno [2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8a). Cream powder (80%); m.p 243°C (dec). IR (KBr): 3142, 2880, 1703, 1591 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.04 (6H, s, $2CH_3$), 1.61 (3H, s, CH_3), 2.19 (2H, bs, CH_2), 2.78 (2H, bs, CH_2), 6.87–7.73 (9H, m, ArH), 10.64 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.2, 27.5, 27.9, 32.5, 41.1, 47.2, 50.8, 99.1, 109.6, 112.3, 120.8, 122.3, 123.7, 127.1, 128.6, 129.9, 134.6, 137.7, 142.5, 144.9, 145.2, 166.4, 178.1, 196.1. MS, m/z : 397 (M^+). Anal. Calcd. for $C_{26}H_{23}N_3O_3$: C, 73.39; H, 5.45; N, 9.88. Found: C, 73.35; H, 5.40; N, 9.82.

Due to very low solubility of the product **8b**, we can not report the ^{13}C NMR data for this product.

3,7,7-Trimethyl-5′-nitro-1-phenyl-7,8-dihydro-1H-spiro [chromeno[2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8b). Cream powder (75%); m.p 315°C (dec). IR (KBr): 3424, 2957, 1749, 1649 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.04 (6H, s, $2CH_3$), 1.61 (3H, s, CH_3), 2.21 (2H, bs, CH_2), 2.78 (2H, bs, CH_2), 7.08–8.15 (8H, m, ArH), 11.38 (1H, s, NH). MS, *m*/*z*: 470 (M^+). Anal. Calcd. for $C_{26}H_{22}N_4O_5$: C, 66.37; H, 4.71; N, 11.91. Found: C, 66.42; H, 4.75; N, 11.97.

3,7,7-Trimethyl-5′-bromo-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8c). Cream powder (81%); m.p 244°C (dec). IR (KBr): 3441, 2955, 1734, 1646 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.05 (6H, s, $2CH_3$), 1.64 (3H, s, CH_3), 2.22 (2H, bs, CH_2), 2.77 (2H, bs, CH_2), 6.84–7.53 (8H, m, ArH), 10.79 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.2, 27.6, 27.8, 32.6, 41.2, 47.3, 50.6, 99.4, 109.5, 113.9, 120.9, 122.3, 123.6, 127.2, 128.5, 129.9, 131.4, 137.6, 141.9, 144.7, 145.3, 166.4, 178.3, 196.3. MS, *m*/*z*: 505 (M^++2), 503 (M^+). Anal. Calcd. for $C_{26}H_{22}BrN_3O_3$: C, 61.91; H, 4.40; N, 8.33. Found: C, 61.95; H, 4.35; N, 8.40.

3-Methyl-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8d). Light brown powder (73%); m.p 312°C (dec). IR (KBr): 3193, 3085, 1730, 1634 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.60 (3H, s, CH_3), 1.97 (2H, bs, CH_2), 2.29 (2H, bs, CH_2), 2.85 (2H, bs, CH_2), 6.86–7.74 (9H, m, ArH), 10.64 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.2, 20.5, 28.0, 37.2, 47.3, 99.1, 109.5, 113.3, 120.9, 122.2, 123.8, 127.1, 128.6, 129.9, 134.8, 137.7, 142.5, 144.9, 145.0, 168.3, 178.2, 196.2. MS, *m*/*z*: 397 (M^+). Anal. Calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.49; H, 4.85; N, 10.62.

Due to very low solubility of the products **8e** and **10**, we can not report the ^{13}C NMR data for these products.

3-Methyl-5′-nitro-1-phenyl-7,8-dihydro-1H-spiro [chromeno [2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8e). Cream powder (70%); m.p 310°C (dec). IR (KBr): 3290, 2952, 1750, 1640 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.63 (3H, s, CH_3), 2.14 (2H, m, CH_2), 2.46 (2H, m, CH_2), 2.91 (2H, m, CH_2), 7.02–8.54 (8H, m, ArH), 10.73 (1H, s, NH). MS, *m*/*z*: 442 (M^+). Anal. Calcd. for $C_{24}H_{18}N_4O_5$: C, 65.15; H, 4.10; N, 12.66. Found: C, 65.19; H, 4.06; N, 12.60.

3′,7′,7′-Trimethyl-1′-phenyl-7′,8′-dihydro-1′H,2H-spiro [acenaphthylene-1,4′-chromeno[2,3-c]pyrazole]-2,5′(6′H)-dione (10). Cream powder (70%); m.p 188°C (dec). IR (KBr): 3162, 3055, 1704, 1643 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.02 (6H, s, $2CH_3$), 1.22 (3H, s, CH_3), 2.10 (2H, bs, CH_2), 2.80 (2H, bs, CH_2), 7.31–8.26 (1H, m, ArH). MS, m/z: 460 (M^+). Anal. Calcd. for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08. Found: C, 78.19; H, 5.29; N, 6.15.

REFERENCES AND NOTES

[1] Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[2] Ugi, I.; Domling, A. Endeavour 1994, 18, 115.

[3] Dömling, A. Chem Rev 2006, 106, 17.

[4] Fellahi, Y.; Dubois, P.; Agafonov, V.; Moussa, F.; Ombetta-Goka, J. E.; Guenzet, J.; Frangin, Y. Bull Soc Chim Fr 1996, 133, 869.

[5] Sharma, P.; Rane, N.; Gurram, V. K. Bioorg Med Chem Lett 2004, 14, 4185.

[6] Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. F. Adv Heterocycl Chem 1984, 41, 319.

[7] Suzuki, N. Chem Pharm Bull 1980, 28, 761.

[8] Parakash, L.; Shaihla, M.; Mital, R. L. Pharmazie 1989, 44, 490.

[9] Curini, M.; Cravotto, G.; Epifano, F.; Giannone, G. Curr Med Chem 2006, 13, 199.

[10] Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K. H. Med Res Rev 2003, 23, 322.

[11] Khan, K. M.; Saify, Z. S.; Khan, M. Z.; Choudhary, M. I.; Perveen, S.; Chohan, Z. H.; Supuran, C. T.; Atta-Ur-Rahman, Z. U. J Enzyme Inhib Med Chem 2004, 19, 373.

[12] Abd El-Aziz, A. S.; El-Agrody, A. M.; Bedair, A. H.; Corkery, T. C.; Ata, A. Heterocycles 2004, 63, 1793.

[13] Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Curr Med Chem 2005, 12, 887.

[14] Tangmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. Tetrahedron Lett 2006, 43, 3067.

[15] Kitamura, R. O. S.; Romoff, P.; Young, M. C. M.; Kato, M. J.; Lago, J. H. G. Phytochemistry 2006, 67, 2398.

[16] Iqbal, M. C. M.; Jayasinghe, U. L. B.; Herath, H. M. T. B.; Wijesekara, K. B.; Fujimoto, Y. Phytoparasitica 2004, 32, 119.

[17] Kraus, G. A.; Kim, I. J Org Chem 2003, 68, 4517.

[18] Sundberg, R. J. The Chemistry of Indoles; Academic Press: New York, 1996.

[19] Joshi, K. C.; Chand, P. Pharmazie 1982, 37, 1.

[20] Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273.

[21] Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, S. M. Bioorg Med Chem 2006, 12, 2488.

[22] Kang, T. H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur J Pharmacol 2002, 444, 39.

[23] Ma, J.; Hecht, S. M. Chem Commun 2004, 1190.

[24] Usui, T.; Kondoh, M.; Cui, C. B.; Mayumi, T.; Osada, H. Biochem J 1998, 333, 543.

[25] Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. Farmaco 2002, 57, 715.

[26] Zhu, S. L.; Jia, S. J.; Zhang, Y. Tetrahedron 2007, 63, 9365.

[27] Kumar, R. S.; Perumal, S. Tetrahedron Lett 2007, 48, 7164.

[28] Redkin, R. G.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. Tetrahedron 2007, 63, 11444.

[29] Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Ghazanfarpour-Darjani, M. Tetrahedron 2007, 63, 9423.

[30] Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. Tetrahedron 2007, 63, 2057.

[31] Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. Tetrahedron Lett 2007, 48, 8790.

[32] Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 2375.

[33] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. J Heterocycl Chem 2007, 44, 1009.

[34] Dabiri, M.; Azimi, S. C.; Arvin-Nezhad, H.; Bazgir, A. Heterocycles 2008, 75, 87.

[35] Dabiri, M.; Delbari, A. S.; Bazgir, A. Synlett 2007, 821.

[36] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2007, 63, 1770.

[37] Dabiri, M.; Delbari, A. S.; Bazgir, A. Heterocycles 2007, 71, 543.

[38] Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. Terahedron Lett 2008, 49, 5165.

[39] Ghahremanzadeh, R.; Imani Shakibaei, G.; Bazgir, A. Synlett 2008, 1129.

[40] Dabiri, M.; Azimi, S. C.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 7307.

[41] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. J Comb Chem 2009, 11, 341.

[42] Ghahremanzadeh, R.; Sayyafi, M.; Ahadi, S.; Bazgir, A. J Comb Chem 2009, 11, 393.

[43] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. Tetrahedron 2009, 65, 2005.