

Ramin Ghahremanzadeh,^a Fatemeh Fereshtehnejad,^b Zahra Yasaei,^b
Tayebeh Amanpour,^b and Ayoob Bazgir^{b*}

^aNanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran

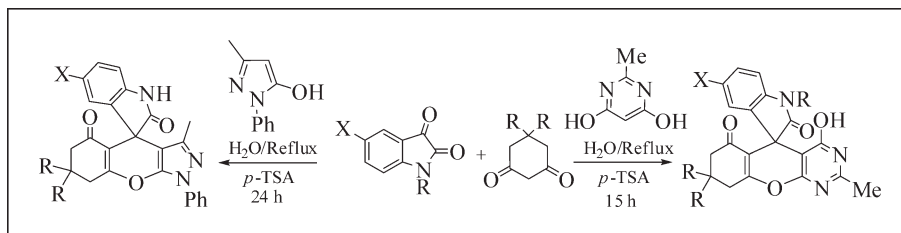
^bDepartment of Chemistry, Shahid Beheshti University, G.C. Tehran 1983963113, Iran

*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 laboratory 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].

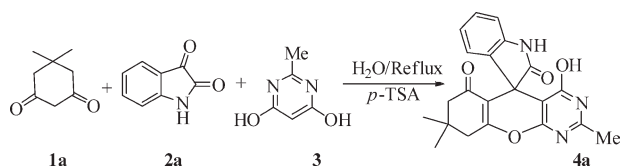
In continuation of our previous works for the synthesis of heterocyclic compounds [31–43], we performed the preparation of some new spirooxindole containing chromene ring fragments via three-component condensation reaction employing water as the reaction medium. Organic transformations in water without 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



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, ¹H NMR, and ¹³C 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).

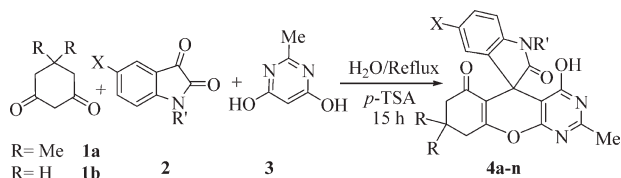
Table 1

Conditions effect on the reaction.^a

Entry	Conditions	Time (h)	Yield (%)
1	Water (80°C)	24	63
2	Water (reflux)	15	85
3	CH ₃ CN (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).

Scheme 2



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. ¹H NMR and ¹³C 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(7*H*)-dione (4a**).** Light Brown powder (85%); m.p 205°C (dec). IR (KBr): 3450, 2952, 1718, 1670, 1622, 1596 cm⁻¹. ¹H NMR (300 MHz, DMSO-*d*₆): δ = 0.97 (3H, s, CH₃), 1.03 (3H, s, CH₃), 2.05, 2.21 (2H, ABq, *J* = 15.9 Hz, CH₂), 2.25 (3H, s, CH₃), 2.57, 2.67 (2H, ABq, *J* = 18.4 Hz, CH₂), 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). ¹³C 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/z*

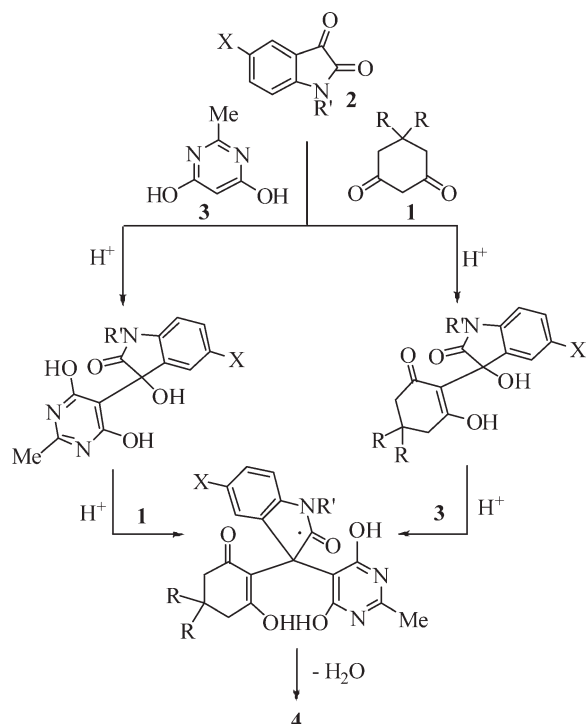
Table 2

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(7*H*)-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, CH₃), 1.03 (3H, s, CH₃), 2.07–2.22 (2H, m, CH₂), 2.26 (3H, s, CH₃), 2.60–2.73 (2H, m, CH₂), 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'-Benzoyl-4-hydroxy-2,8,8-trimethyl-8,9-dihydrospiro [chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2',6(7*H*)-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, CH₃), 0.99 (3H, s, CH₃), 1.05 (3H, s, CH₃), 2.09, 2.25 (2H, ABq, J = 16.0 Hz, CH₂),

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

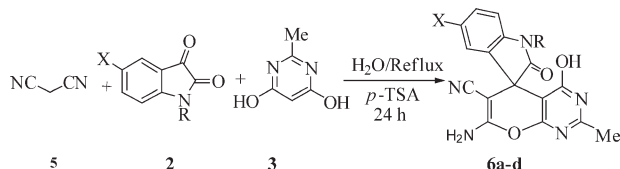
2.27 (3H, s, CH₂), 2.61, 2.71 (2H, ABq, J = 17.0 Hz, CH₂), 4.84, 4.94 (2H, ABq, J = 16.0 Hz, NCH₂), 6.53 (1H, d, J = 8.8 Hz, ArH), 6.82–6.87 (1H, m, ArH), 6.98 (1H, d, J = 8.4 Hz, ArH), 7.03–7.08 (1H, m, ArH), 7.25–7.34 (3H, m, ArH), 7.63–7.66 (2H, m, ArH), 12.64 (1H, s, OH). MS, m/z : 467 (M^+). Anal. 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(7*H*)-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, CH₃), 1.03 (3H, s, CH₃), 2.04, 2.18 (2H, ABq, J = 16.0 Hz, CH₂), 2.26 (3H, s, CH₃), 2.59, 2.67 (2H, ABq, J = 17.1 Hz, CH₂), 3.13 (3H, s, NCH₃), 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(7*H*)-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, CH₃), 1.02 (3H, s, CH₃), 2.12–2.15 (2H, m, CH₂), 2.27 (3H, s, CH₃), 2.63–2.69 (2H, m, CH₂), 3.24 (3H, s, NCH₃), 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(7*H*)-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, CH₃), 1.02 (3H, s, CH₃), 2.05–2.10 (2H, m, CH₂), 2.26 (3H, s, CH₃), 2.63 (2H, brs, CH₂), 3.12 (3H, s, NCH₃), 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

Scheme 4



Scheme 5

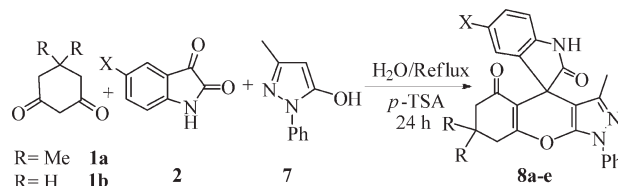


Table 4

Synthesis of spiro[chromenopyrazole-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 C₂₂H₂₀BrN₃O₄: 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, CH₃), 1.02 (3H, s, CH₃), 1.22 (3H, t, *J* = 6.9 Hz, CH₃), 2.09–2.15 (2H, m, CH₂), 2.60–2.74 (2H, m, CH₂), 3.80–3.82 (2H, m, NCH₂), 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). ¹³C 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 C₂₃H₂₂N₄O₆: 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, CH₂), 2.25 (5H, brs, CH₂, and CH₃), 2.71 (2H, brs, CH₂), 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). ¹³C 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 C₁₉H₁₄BrN₃O₄: 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 (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, CH₂), 2.27 (5H, brs, CH₂, and CH₃), 2.50 (2H, brs, CH₂), 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). ¹³C 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 C₁₉H₁₄N₄O₆: 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, CH₂), 2.19–2.25 (5H, m, CH₂, and CH₃), 2.72 (2H, brs, CH₂), 3.13 (3H, s, NCH₃), 6.82–6.95 (3H, m, ArH), 7.15–7.20 (1H, m, ArH), 12.43 (1H, s, OH). ¹³C 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 C₂₀H₁₇N₃O₄: 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, CH₃), 1.89–1.90 (2H, m, CH₂), 2.18–2.25 (5H, m, CH₂, and CH₃), 2.70–2.71 (2H, m, CH₂), 3.67–3.71 (2H, m, NCH₂), 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). ¹³C 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 C₂₁H₁₉N₃O₄: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.77; H, 5.00; N, 11.07.

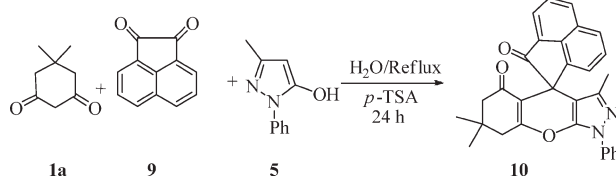
Due to very low solubility of the product **4l**, we can not report the ¹³C NMR data for this product.

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, CH₂), 2.27 (5H, brs, CH₃ and CH₂), 2.75 (2H, brs, CH₂), 4.87–4.96 (2H, m, NCH₂), 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 C₂₆H₁₉N₃O₄: 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, CH₂), 2.26 (3H, s, CH₃), 2.50 (2H, brs, CH₂), 3.12 (3H, s, NCH₃), 3.38 (2H, brs, CH₂), 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). ¹³C 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, 135.4, 145.1, 160.2, 160.4, 161.0, 167.6, 176.5, 195.8. MS, *m/z*: 441 (*M*⁺). Anal. Calcd. for C₂₀H₁₆BrN₃O₄: 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, CH₃), 1.22 (3H, t, *J* = 6.6 Hz, CH₃), 1.93 (2H, brs, CH₂), 2.23–2.26 (5H, m, CH₂, and CH₃), 2.75 (2H, brs, CH₂), 3.79–3.82 (2H, m, NCH₂), 7.20 (1H, d, *J* = 8.7 Hz, ArH), 7.95 (1H, s, ArH), 8.18 (1H, d, *J* = 8.7 Hz,

Scheme 6



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 $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_6$: 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} . ^1H 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 $\text{C}_{16}\text{H}_{11}\text{N}_5\text{O}_5$: 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} . ^1H 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 $\text{C}_{16}\text{H}_{10}\text{N}_6\text{O}_5$: 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} . ^1H 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 $\text{C}_{17}\text{H}_{12}\text{N}_6\text{O}_5$: 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} . ^1H 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 $\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_5$: 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} . ^1H NMR (300 MHz, DMSO- d_6): δ = 1.04 (6H, s, 2 CH_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 $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_3$: 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} . ^1H NMR (300 MHz, DMSO- d_6): δ = 1.04 (6H, s, 2 CH_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 $\text{C}_{26}\text{H}_{22}\text{N}_4\text{O}_5$: 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} . ^1H NMR (300 MHz, DMSO- d_6): δ = 1.05 (6H, s, 2 CH_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 ($\text{M}^+ + 2$), 503 (M^+). Anal. Calcd. for $\text{C}_{26}\text{H}_{22}\text{BrN}_3\text{O}_3$: 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} . ^1H 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 $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_3$: 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} . ^1H 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 $\text{C}_{24}\text{H}_{18}\text{N}_4\text{O}_5$: 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} . ^1H NMR (300 MHz, DMSO- d_6): δ = 1.02 (6H, s, 2 CH_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 $\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_3$: 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] Domling, 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.; Sonden-gam, 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. *Tetrahedron 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.