Synthesis of Monospiro-2-amino-4*H*-pyran Derivatives Catalyzed by Propane-1-sulfonic Acid-Modified Magnetic Hydroxyapatite Nanoparticles

by **Leili Jalili-Baleh**, **Narges Mohammadi**, **Mehdi Khoobi**, **Leila Ma'mani**, **Alireza Foroumadi**, and **Abbas Shafiee***

Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, 14176, Iran
(phone: +98-21-66406757; fax +98-21-66461178; e-mail: ashafiee@ams.ac.ir)

Various monospiro-2-amino-4*H*-pyran derivatives have been synthesized in high yields (*via* three-component coupling of ninhydrin or different isatins with malononitrile and 1,3-dicarbonyl compounds) in the presence of catalytic amount of propane-1-sulfonic acid-modified magnetic hydroxyapatite nanoparticles in H_2O. Due to easy magnetic removal of nanocatalyst and applying of H_2O as solvent, this protocol enhanced product purity, and promised economic as well as environmental benefits, exemplifying a waste-free chemistry. More importantly, the catalyst could be easily recycled for more than five times without loss of activity.

Introduction. – Introduction of new protocols for easy access to more complex products is one of the main goals of the recent research in organic synthesis. Organic chemists have been attempting to meet this goal *via* the development of multi-component reactions (MCR) [1].

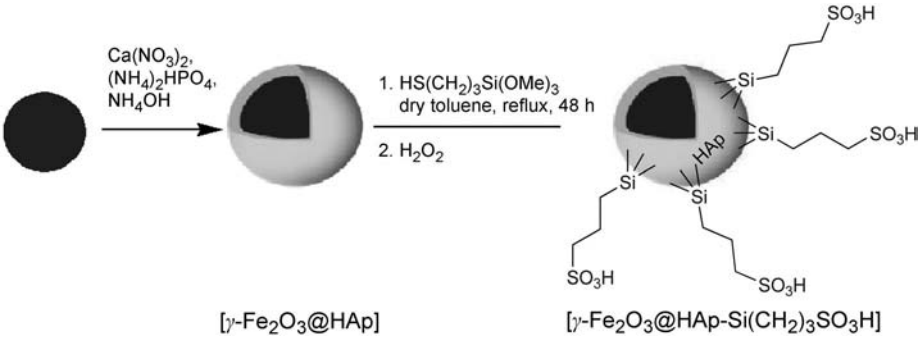
Recently, many synthetic methodologies have been developed for constructing spirooxindoles, whereby most of them were based on multicomponent condensation reactions [2–19]. Although each of these methods has its merit, they display at least one limitation, such as low yield, complicated workup, requiring large amounts of organic solvents, and using unrecoverable catalysts. *Zhao et al.* prepared spirooxindoles without any catalyst at 60° [20]. However, this protocol was limited in some cases, specifically for the synthesis of diverse spiro-4*H*-pyrans from ninhydrins or isatins as substrate. Therefore, introduction of a simple and efficient catalyst, overcoming the above mentioned drawbacks, would be an interesting challenge.

Results and Discussion. – Herein, in continuation of our previous works, using magnetic nanocatalysts and the usefulness of hydroxyapatite coated γ-Fe_2O_3 [γ-Fe_2O_3@HAp] [20–22], we report a clean, simple, and efficient one-pot synthesis of biologically interesting monospiro-2-amino-4*H*-pyran derivatives applying a magnetic catalytic system based on organic–inorganic hybrid nanocatalyst.

For this purpose, propane-1-sulfonic acid-functionalized magnetic core-shell catalyst (denoted as [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$]) was synthesized according to the procedure depicted in *Scheme 1*. The coprecipitation approach in basic aqueous solution, followed by thermal treatment, led to the formation of [γ-Fe_2O_3@HAp]. These nanoparticles were reacted with (trimethoxy)(3-sulfanylpropyl)silane to pro-

duce an organic–inorganic hybrid. Then, this hybrid was reacted with H_2O_2 to furnish [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$]. The nanoparticles were fully characterized by transition electron microscopy (TEM), scanning electron microscopy (SEM), thermogravimetric analysis (TGA), X-ray diffraction (XRD), *Fourier*-transform IR (FT-IR), and back titration.

Scheme 1. *Synthesis of Magnetic Nanocatalyst*



To test the catalytic activity of the catalyst [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$], the three-component reaction of isatin (**1**), malononitrile (**2**), and dimedone (**3**) in the presence of 2 mol-% of [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$] at 30° in H_2O was selected. *Table 1* displays the efficiency of [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$] as catalyst in this transformation. On search for optimal conditions, we examined the condensation of malononitrile, different isatins (=1*H*-indole-2,3-dione; such as *N*-benzylisatin-1-acetamide, 5-[(pyrrolidin-1-yl)sulfonyl)]isatin, and benzo[*h*]chromen-2-one) with various 1,3-dicarbonyl compounds in the presence of catalytic amount of [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$] (2 mol-%) in aqueous medium. As compiled in *Table 2*, the reactions proceed smoothly, and corresponding spirooxindoles could be obtained in high yields. The atom numberings of the target compounds are depicted in the cases of **4a**, **4g**, **4i**, and **4m** in *Table 2*.

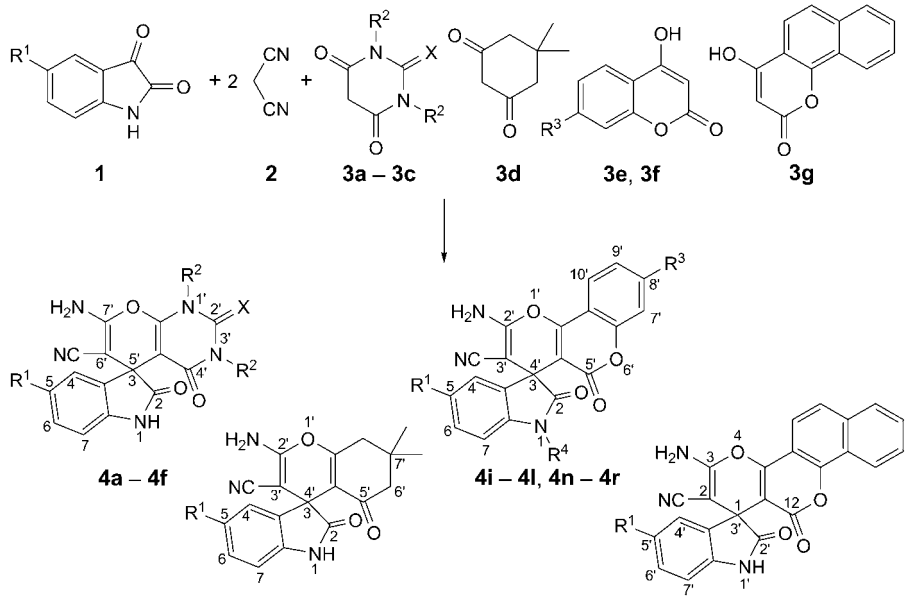
After optimization of the protocol for the synthesis of spirooxindoles, to expand this approach particularly regarding a library construction, this methodology was evaluated for the three-component reactions of ninhydrin (**5**), malononitrile, and 1,3-dicarbonyl compounds for the preparation of corresponding spiro compounds under the same conditions. The results of the latter reaction were also excellent (*Table 3*). The atom

Table 1. *Efficiency of the Catalyst in the Synthesis of Compound* **4s**[a])

Entry	Catalyst	Yield [%]
1	No catalyst	No reaction
2	Fe_3O_4	No reaction
3	[γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$]	95%

[a]) Reaction conditions: H_2O, 30°, 20 min.

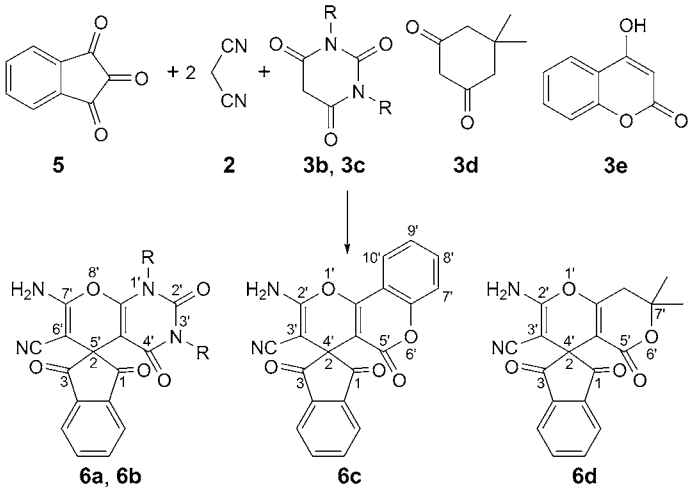
Table 2. *Synthesis of Spirooxindoles from Isatins catalyzed by [γ-Fe_2O_3@HAp-$Si(CH_2)_3SO_3H$] in H_2O*



R^1	R^2	X	R^3	R^4	**3**	**4**	Yield [%][a])	M.p. [°]	
								Observed	Reported
H	H	S		H	**3a**	**4a**	78	240–242	238–242 [20]
Br	H	S		H	**3a**	**4b**	80	249–251	246–248 [23]
H	H	O		H	**3b**	**4c**	90	291–293	290–292 [24]
Br	H	O		H	**3b**	**4d**	75	225–227	220–222 [23]
H	Me	O		H	**3c**	**4e**	80	225–228	231 [25]
Br	Me	O		H	**3c**	**4f**	75	250–252	[b])
H				H	**3d**	**4g**	75	>300	305–307 [17]
Br				H	**3d**	**4h**	75	>300	305–307 [17]
H			H	H	**3e**	**4i**	73	291–293	292–294 [12]
Br			H	H	**3e**	**4j**	80	>300	>300 [12]
H			OH	H	**3f**	**4k**	80	>300	[b])
Br			OH	H	**3f**	**4l**	80	>300	[b])
Br				H	**3g**	**4m**	75	>300	[b])
py[c])			H	H	**3e**	**4n**	75	>300	[b])
mo[d])			H	H	**3e**	**4o**	90	273–275	[b])
H			H	$PhCH_2NHCOCH_2$	**3e**	**4p**	70	275–278	[b])
mo			OH	H	**3f**	**4q**	90	268–270	[b])
py			OH	H	**3f**	**4r**	82	>300	[b])
mo				H	**3d**	**4s**	95	>300	[b])
py				H	**3d**	**4t**	90	>300	[b])

[a]) Yields of isolated spiro compounds. [b]) New compounds. [c]) py = (Pyrrolidin-1-yl)sulfonyl. [d]) mo = (Morpholin-4-yl)sulfonyl.

Table 3. *Synthesis of Spiro Compounds from Ninhydrin Catalyzed by [γ-Fe_2O_3@HAp-$Si(CH_2)_3SO_3H$] in H_2O*



R	3	6	Yield [%][a])	m.p. [°]	
				Observed	Reported
H	**3b**	**6a**	85	> 300	> 300 [26]
Me	**3c**	**6b**	90	290 – 292	> 300 [26]
	3e	**6c**	90	250 – 252	246 [18]
	3d	**6d**	90	> 300	> 300 [26]

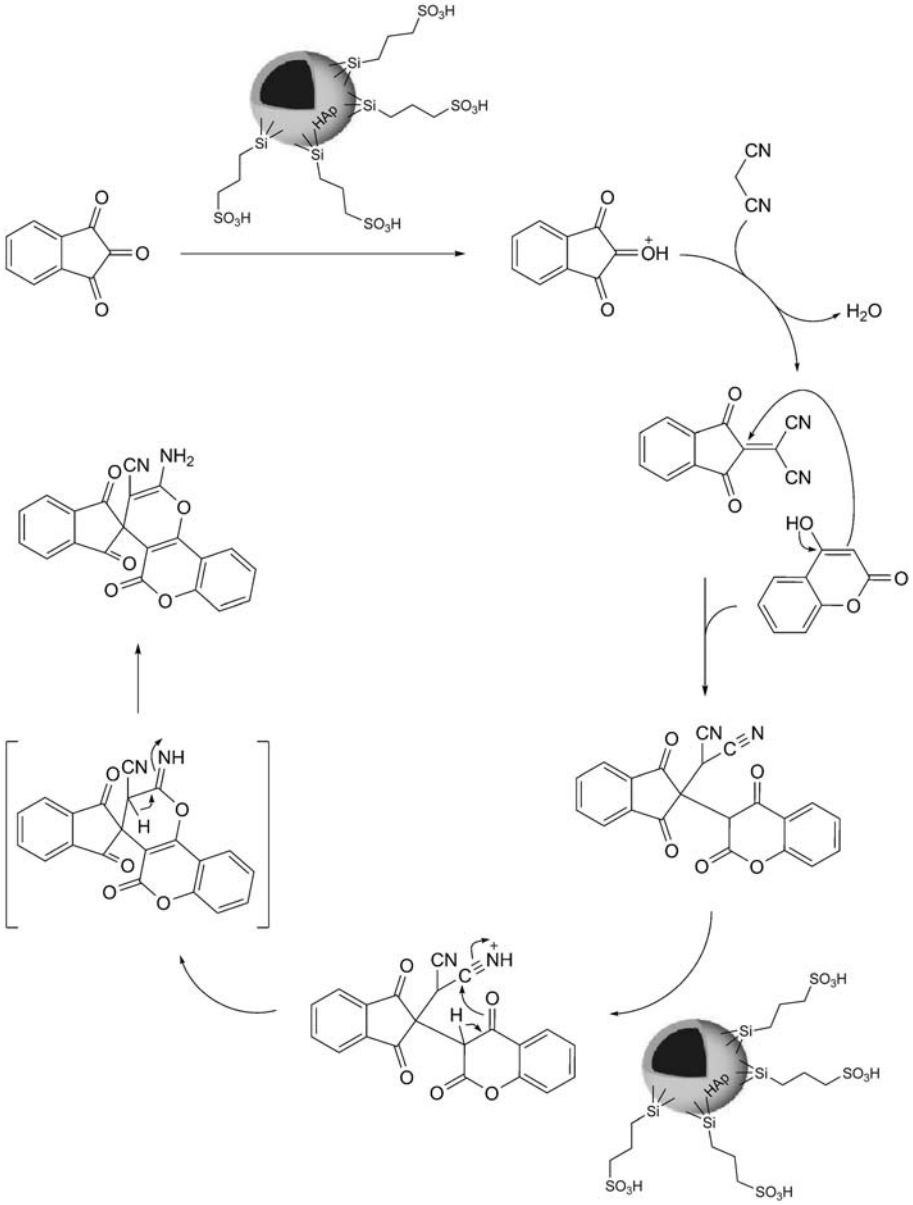
[a]) Yields of isolated spiro compounds.

numberings of the target compounds are depicted in the cases of **6a**, **6c**, and **6d** in *Table 3*.

In addition, the possibility of the magnetic recycling of the catalyst was examined. For this purpose, the synthesis of compound **4s** was selected. At the end of the reaction, the catalyst was easily separated by attaching an external magnet onto the reaction vessel and decantation of the reaction solution. The remaining catalyst was washed with Et_2O, dried under vacuum, and reused in subsequent runs. For example, this reaction afforded the corresponding spiro product **4s** in yields of *ca.* 95, 94, 94, 93, and 92% in five consecutive runs, which clearly evidenced the practical recyclability of this catalyst. The proposed mechanism for the synthesis of spiro compound catalyzed by [γ-Fe_2O_3@HAp-$Si(CH_2)_3SO_3H$] is outlined in *Scheme 2*.

In conclusion, we have demonstrated that the robust and magnetically recoverable propane-1-sulfonic acid-supported HAp nanoparticles catalyzed three-component couplings of different isatins or ninhydrin, malononitrile, and 1,3-dicarbonyl compounds. A diverse range of monospiro-2-amino-4*H*-pyran derivatives were obtained in acceptable yields under mild conditions in H_2O. The separation and reusing of the magnetic nanocatalyst were very simple, clean, and effective. Furthermore, propane-1-

Scheme 2. *Possible Mechanism for Synthesis of Spiro-2-amino-4*H*-pyran Derivatives Catalyzed by [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$]*



sulfonic acid supported onto magnetic nanoHAp as solid catalyst is an inexpensive, nontoxic, and reusable catalyst, rendering this process convenient, economical, and environmentally benign.

Experimental Part

General. M.p.: *Kofler* hot stage apparatus; uncorrected. IR Spectra: *Shimadzu 470* spectrophotometer; in KBr. ^{1}H- and ^{13}C-NMR spectra: in (D_6)DMSO or $CDCl_3$, on *Brucker FT-500* or *Varian 400*, and TMS as internal standard. Elemental analyses: *Elementar Analysensystem GmbH VarioEL* CHNS mode.

Synthesis of Propane-1-sulfonic Acid Attached to Magnetic Hydroxyapatite Nanoparticles. A sample of magnetic hydroxyapatite (3 g) was pre-activated by heating under vacuum for 48 h at 120°, suspended in dry toluene containing 5.3 g of (trimethoxy)(3-sulfanylpropyl)silane, followed by heating at reflux for 6 h, and the solid was separated, washed with dry toluene, and dried in air. The solid was oxidized with 35% H_2O_2 (threefold) by stirring at 60° for 24 h. The product was separated by an external magnet, washed with EtOH, and dried under vacuum for 24 h at 50° to give the solid-surface-bound propane-1-sulfonic acid.

*Synthesis of Monospiro-2-amino-4*H*-pyran Derivatives: General Procedure.* A mixture of a 1,3-dicarbonyl compound (1 mmol), malononitrile (1.2 mmol), magnetic catalyst (0.021 g, 2 mol-%), and H_2O (5 ml) was stirred for a few min. To this mixture, isatin or ninhydrin (1 mmol) was added. The mixture was stirred at 30° for 20 min. The progress of the reaction was monitored by TLC, and visible color change from orange to gray was observed. After completion of the reaction, the mixture was diluted with acetone, and the catalyst was separated with an external magnet and washed with acetone. The combined org. layers were concentrated in vacuum, and the resulting residue was recrystallized from EtOH or acetone.

*7′-Amino-1,1′,2,2′,3′,4′-hexahydro-2,4′-dioxo-2′-thioxospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**4a**). IR: 3382, 3294 (NH_2), 3249 (NH), 2200 (CN), 1693 (C=O). ^{1}H-NMR (400 MHz): 7.86 (br. *s*, NH_2); 8.04–8.08 (*m*, 4 H of indole); 12.70 (br. *s*, NH).

*7′-Amino-5-bromo-1,1′,2,2′,3′,4′-hexahydro-2,4′-dioxo-2′-thioxospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**4b**). IR: 3430, 3314 (NH_2), 3167 (NH), 2199 (CN), 1711 (C=O), 1671 (C=O). ^{1}H-NMR (400 MHz): 6.75 (*d*, *J* = 7.8, H–C(7)); 7.33 (*d*, *J* = 7.8, H–C(6)); 7.50 (br. *s*, NH_2, H–C(4)); 10.69 (br. *s*, NH); 12.52 (br. *s*, NH).

*7′-Amino-1,1′,2,2′,3′,4′-hexahydro-2,2′,4′-trioxospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**4c**). IR: 3404, 3336 (NH_2), 3063 (NH), 2198 (CN), 1736 (C=O), 1672 (C=O). ^{1}H-NMR (400 MHz): 6.80–7.14 (*m*, 4 H of indole); 7.36 (br. *s*, 2 NH_2); 10.35 (br. *s*, NH); 11.2 (br. *s*, NH); 12.25 (br. *s*, NH).

*7′-Amino-5-bromo-1,1′,2,2′,3′,4′-hexahydro-2,2′,4′-trioxospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**4d**). IR: 3475, 3369 (NH_2), 3178 (NH), 2204 (CN), 1705 (C=O), 1665 (C=O), 1688 (C=O). ^{1}H-NMR (400 MHz): 6.74 (*d*, *J* = 8.0, H–C(7)); 7.32 (*d*, *J* = 8.0, H–C(6)); 7.40–7.48 (*m*, NH_2, H–C(4)); 10.61 (br. *s*, NH); 11.15 (br. *s*, NH).

*7′-Amino-1,1′,2,2′,3′,4′-hexahydro-1′,3′-dimethyl-2,2′,4′-trioxospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**4e**). IR: 3412, 3302 (NH_2), 3183 (NH), 2202 (CN), 1731 (C=O), 1682 (C=O). ^{1}H-NMR (400 MHz): 3.02 (*s*, MeN); 3.10 (*s*, MeN); 6.80 (*d*, *J* = 7.8, H–C(7)); 6.91 (*d*, *J* = 7.8, H–C(5)); 7.12–7.16 (*m*, H–C(6), H–C(8)); 7.57 (br. *s*, NH_2); 10.51 (br. *s*, NH).

*7′-Amino-5-bromo-1,1′,2,2′,3′,4′-hexahydro-1′,3′-dimethyl-2,2′,4′-trioxospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**4f**). IR: 3453, 3394 (NH_2), 3252 (NH), 2200 (CN), 1682 (C=O), 1721 (C=O). ^{1}H-NMR (400 MHz): 3.04 (*s*, MeN); 3.09 (*s*, MeN); 6.78 (*d*, *J* = 8.0, H–C(7)); 7.35 (*d*, *J* = 8.0, H–C(6)); 7.39 (*s*, H–C(4)); 7.65 (br. *s*, NH_2); 10.65 (br. *s*, NH).

2-Amino-1′,2′,5,6,7,8-hexahydro-7,7-dimethyl-2′,5-dioxospiro[chromene-4,3′-indole]-3-carbonitrile (**4g**). IR: 3401, 3285 (NH_2), 3133 (NH), 2190 (CN), 1722 (C=O), 1668 (C=O). ^{1}H-NMR (500 MHz): 1.03 (*s*, 2 Me); 2.15 (*s*, 2 CH_2); 2.58 (*s*, CH_2CO); 6.75–7.22 (*m*, NH_2, 4 H of indole); 10.42 (br. *s*, NH).

2-Amino-5′-bromo-1′,2′,5,6,7,8-hexahydro-7,7-dimethyl-2′,5-dioxospiro[chromene-4,3′-indole]-3-carbonitrile (**4h**). IR: 3401, 3285 (NH_2), 3133 (NH), 2190 (CN), 1721 (C=O), 1661 (C=O). ^{1}H-NMR (500 MHz): 1.03 (*s*, 2 Me); 2.15 (*s*, 2 CH_2); 2.58 (*s*, CH_2CO); 6.76 (*d*, *J* = 8.0, H–C(7) of indole); 7.20 (*s*, H–C(4) of indole); 7.25–7.37 (*m*, H–C(6) of indole, NH_2); 10.5 (br. *s*, NH).

*2′-Amino-1,2-dihydro-2,5′-dioxo-5′*H*-spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4i**). IR: 3359, 3299 (NH_2), 3202 (NH), 2205 (CN), 1714 (C=O), 1673 (C=O). ^{1}H-NMR (500 MHz): 6.86

(*d*, *J* = 7.0, H–C(7) of indole); 6.93 (*t*, *J* = 7.0, H–C(5)); 7.17 – 7.25 (*m*, H–C(4), H–C(6)); 7.49 (*d*, *J* = 7.8, H–C(7′)); 7.54 (*t*, *J* = 7.8, H–C(9′)); 7.67 (br. *s*, NH_2); 7.77 (*t*, *J* = 7.8, H–C(8′)); 7.95 (*d*, *J* = 7.8, H–C(10′)); 10.68 (br. *s*, NH).

*2′-Amino-5-bromo-1,2-dihydro-2,5′-dioxo-5′*H-*spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4j**). IR: 3325, 3246 (NH_2), 3205 (NH), 2200 (CN), 1711 (C=O), 1670 (C=O). ^{1}H-NMR (500 MHz): 6.82 (*d*, *J* = 7.4, H–C(7) of indole); 7.38 (*d*, *J* = 7.4, H–C(7′) of chromene); 7.48 – 7.59 (*m*, H–C(4), H–C(6), H–C(9′)); 7.71 – 7.83 (*m*, H–C(8′), NH_2); 7.93 (*d*, *J* = 7.4, H–C(10′)); 10.82 (br. *s*, NH).

*2′-Amino-1,2-dihydro-8′-hydroxy-2,5′-dioxo-5′*H-*spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4k**). IR: 3459 (OH), 3314, 3260 (NH_2), 3176 (NH), 2197 (CN), 1703 (C=O), 1668 (C=O). ^{1}H-NMR (500 MHz): 6.77 (*s*, H–C(7′)); 6.84 (*d*, *J* = 7.5, H–C(9′)); 6.87 – 7.00 (*m*, H–C(5), H–C(7)); 7.10 – 7.27 (*m*, H–C(10′), H–C(6)); 7.58 (br. *s*, NH_2); 7.75 (*d*, *J* = 7.5, H–C(4)); 10.62 (br. *s*, NH); 10.90 (br. *s*, OH). ^{13}C-NMR (125 MHz): 47.3; 95.4; 97.6; 102.2; 104.1; 109.4; 113.8; 117.06; 121.9; 123.8; 124.0; 128.7; 133.2; 142.1; 154.0; 155.5; 158.4; 158.7; 162.5; 177.3. Anal. calc. for $C_{20}H_{11}N_3O_5$ (373.32): C 64.35, H 2.97, N 11.26; found C 64.55, H 2.72, N 11.01.

*2′-Amino-5-bromo-1,2-dihydro-8′-hydroxy-2,5′-dioxo-5′*H-*spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4l**). IR: 3468 (OH), 3365, 3220 (NH_2), 3146 (NH), 2193 (CN), 1703 (C=O), 1613 (C=O). ^{1}H-NMR (500 MHz): 6.78 (*s*, H–C(7′)); 6.81 (*d*, *J* = 8.0, H–C(9′)); 6.95 (*d*, *J* = 8.0, H–C(10′)); 7.38 (*d*, *J* = 7.5, H–C(7)); 7.49 (*s*, H–C(4)); 7.70 (br. *s*, NH_2), 7.75 (*d*, *J* = 7.5, H–C(6)); 10.77 (*s*, NH); 10.94 (*s*, OH). ^{13}C-NMR (125 MHz): 47.6; 95.4; 97.0; 102.3; 104.3; 111.3; 113.7; 113.8; 117.0; 124.2; 127.0; 131.5; 135.6; 142.2; 154.1; 155.8; 158.6; 158.9; 162.6; 177.1. Anal. calc. for $C_{20}H_{10}BrN_3O_5$ (452.21): C 53.12, H 2.23, N 9.29; found C 53.31, H 2.51, N 9.52.

*3-Amino-5′-bromo-1′,2′-dihydro-2′,12-dioxo-12*H-*spiro[benzo[*h*]pyrano[3,2-*c*]chromene-1,3′-indole]-2-carbonitrile* (**4m**). IR: 3401, 3275 (NH_2), 3206 (NH), 2203 (CN), 1731 (C=O), 1701 (C=O), 1672 (C=O). ^{1}H-NMR (500 MHz): 6.84 (*d*, *J* = 7.8, H–C(7′)); 7.40 (*d*, *J* = 7.8, H–C(6′)); 7.55 (*s*, H–C(4′)); 7.71 – 7.78 (*m*, NH_2, H–C(8), H–C(9)); 7.93 (*d*, *J* = 8.5, H–C(5)); 8.04 (*d*, *J* = 8.5, H–C(6)); 8.11 (*d*, *J* = 8.0, H–C(7)); 8.31 (*d*, *J* = 8.0, H–C(10)); 10.82 (br. *s*, NH). Anal. calc. for $C_{24}H_{12}BrN_3O_4$ (486.27): C 59.28, H 2.49, N 8.64; found C 59.42, H 2.64, N 8.91.

*2′-Amino-1,2-dihydro-2,5′-dioxo-5-(pyrrolidin-1-ylsulfonyl)-5′*H-*spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4n**). IR: 3400, 3278 (NH_2), 3215 (NH), 2202 (CN), 1714 (C=O), 1671 (C=O), 1362, 1150 (SO_2). ^{1}H-NMR (500 MHz): 1.52 (br. *s*, 2 CH_2 of pyrolidine); 3.07 (br. *s*, 2 CH_2N of pyrolidine); 7.06 (*d*, *J* = 7.5, H–C(7′)); 7.51 (*d*, *J* = 6.8, H–C(7)); 7.52 (*t*, *J* = 7.5, H–C(9′)); 7.69 (*d*, *J* = 7.5, H–C(10′)); 7.71 – 7.82 (*m*, NH_2, H–C(8′)); 7.84 (*s*, H–C(4)); 7.95 (*d*, *J* = 6.8, H–C(6)); 11.15 (br. *s*, NH). ^{13}C-NMR (125 MHz): 24.5; 47.8; 55.9; 95.3; 100.4; 109.6; 112.7; 116.6; 122.7; 123.5; 124.9; 129.2; 129.4; 133.6; 133.9; 146.4; 152.1; 155.6; 158.5; 158.6; 177.5. Anal. calc. for $C_{24}H_{18}N_4O_6S$ (490.49): C 58.77, H 3.70, N 11.42; found C 58.51, H 3.55, N 11.72.

*2′-Amino-1,2-dihydro-5-(morpholin-4-ylsulfonyl)-2,5′-dioxo-5′*H-*spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4o**). IR: 3379, 3288 (NH_2), 3141 (NH), 2193 (CN), 1722 (C=O), 1675 (C=O), 1362, 1158 (SO_2). ^{1}H-NMR (500 MHz): 2.77 (br. *s*, 2 CH_2N of morpholine); 3.56 (br. *s*, 2 CH_2O of morpholine); 7.10 (*d*, *J* = 7.5, H–C(7′) of chromene); 7.55 – 7.80 (*m*, H–C(4), H–C(6), H–C(7), H–C(8′), H–C(9′), H–C(10′), NH_2); 11.22 (br. *s*, NH). ^{13}C-NMR (125 MHz): 45.9; 47.7; 55.9; 90.9; 100.4; 109.8; 112.7; 116.7; 122.7; 124.0; 125.0; 127.8; 129.7; 133.7; 133.9; 146.8; 152.1; 155.7; 158.6; 158.7; 177.5. Anal. calc. for $C_{24}H_{18}N_4O_7S$ (506.49): C 56.91, H 3.58, N 11.06; found C 56.73, H 3.40, N 11.33.

*2-(2′-Amino-3′-cyano-2,5′-dioxo-5′*H-*spiro[indole-3,4′-pyrano[3,2-*c*]chromen]-1(2*H*)-yl)-*N*-benzylacetamide* (**4p**). IR: 3451, 3361 (NH_2), 3119 (NH), 2200 (CN), 1703 (C=O), 1664 (C=O). ^{1}H-NMR (500 MHz): 4.29 (*s*, PhCH_2); 4.47 (*s*, CH_2CO); 7.01 – 7.08 (*m*, H–C(5), H–C(7)); 7.09 – 7.22 (*m*, H–C(4), H–C(6)); 7.53 (*d*, *J* = 7.0, H–C(7′)); 7.58 (*t*, *J* = 7.0, H–C(9′)); 7.81 (br. *s*, NH_2); 7.97 (*d*, *J* = 7.0, H–C(10′)); 8.09 (*t*, *J* = 7.0, H–C(8′)). ^{13}C-NMR (125 MHz): 41.8; 43.7; 57.5; 95.8; 101.4; 109.4; 111.8; 112.9; 117.2; 123.3; 123.9; 124.7; 125.7; 128.6; 129.3; 129.6; 131.8; 132.2; 134.4; 138.2; 142.6; 152.4; 156.1; 159.0; 159.6; 166.5; 176.1. Anal. calc. for $C_{29}H_{20}N_4O_5$ (504.49): C 69.04, H 4.00, N 11.11; found C 68.85, H 4.21, N 11.37.

*2′-Amino-1,2-dihydro-8′-hydroxy-5-(morpholin-4-ylsulfonyl)-2,5′-dioxo-5′*H-*spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4q**). 3460 (OH), 3317, 3281 (NH_2), 3149 (NH), 2195 (CN), 1724 (C=O), 1674 (C=O), 1366, 1173 (SO_2). ^{1}H-NMR (500 MHz): 2.77 (br. *s*, 2 CH_2N of morpholine); 3.56

(br. *s*, 2 CH_2O of morpholine); 6.75 (*s*, H–C(7′)); 6.82–7.42 (*m*, H–C(9′), H–C(10′)); 7.51–7.73 (*m*, H–C(4), H–C(6), H–C(7), NH_2); 10.9 (br. *s*, OH), 11.16 (br. *s*, NH). ^{13}C-NMR (125 MHz): 45.9; 56.0; 65.1; 96.7; 102.3; 104.3; 109.7; 113.8; 116.8; 123.7; 124.2; 127.7; 129.6; 134.1; 146.8; 154.2; 156.1; 158.7; 159.0; 162.6; 177.8. Anal. calc. for $C_{24}H_{18}N_4O_8S$ (522.49): C 55.17, H 3.47, N 10.72; found C 55.41, H 3.60, N 10.81.

*2′-Amino-1,2-dihydro-8′-hydroxy-2,5′-dioxo-5-(pyrrolidin-1-ylsulfonyl)-5′*H*-spiro[indole-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**4r**). IR: 3397 (OH), 3325, 3310 (NH_2), 3212 (NH), 2199 (CN), 1723 (C=O), 1666 (C=O), 1366, 1152 (SO_2). ^{1}H-NMR (500 MHz): 1.52 (br. *s*, 2 CH_2 of pyrolidine); 3.06 (br. *s*, 2 CH_2N of pyrolidine); 6.78 (*s*, H–C(7′)); 6.96 (*d, J* = 7.8, H–C(9′)); 7.04 (*d*, *J* = 7.8, H–C(10′)); 7.68 (*d*, *J* = 8.0, H–C(7)); 7.71 (br. *s*, NH_2); 7.75–7.77 (*m*, H–C(4), H–C(6)); 10.92 (br. *s*, OH), 11.10 (br. *s*, NH). ^{13}C-NMR (125 MHz): 24.5; 47.0; 55.9; 96.7; 102.3; 104.4; 109.6; 113.8; 116.9; 123.3; 124.2; 129.1; 129.4; 134.2; 146.4; 154.1; 156.1; 158.7; 159.0; 162.6; 177.8. Anal. calc. for $C_{24}H_{18}N_4O_7S$ (506.49): C 56.91, H 3.58, N 11.06; found C 57.15, H 3.36, N 10.85.

2-Amino-1′,2′,5,6,7,8-hexahydro-7,7-dimethyl-2′,5-dioxo-5′-(morpholin-4-ylsulfonyl)spiro[chromene-4,3′-indole]-3′-carbonitrile (**4s**). IR: 3364, 3300 (NH_2), 3172 (NH), 2196 (CN), 1727 (C=O), 1669 (C=O), 1351, 1158 (SO_2). ^{1}H-NMR (500 MHz): 1.02 (*s*, 2 Me); 2.08–2.25 (*s*, CH_2 of chromene); 2.58 (*s*, CH_2CO); 2.72 (br. *s*, 2 CH_2N of morpholine); 3.57 (br. *s*, 2 CH_2O of morpholine); 7.04 (*d*, *J* = 6.8, H–C(7) of indole); 7.36 (*s*, H–C(4) of indole); 7.42 (br. *s*, NH_2); 7.56 (*d*, *J* = 6.8, H–C(6) of indole); 10.97 (br. *s*, NH). ^{13}C-NMR (125 MHz): 26.8; 27.5; 30.6; 31.9; 45.8; 49.8; 56.0; 65.1; 96.0; 109.5; 110.02; 117.0; 122.4; 129.1; 135.2; 146.7; 158.9; 164.9; 178.2; 195.1. Anal. calc. for $C_{23}H_{24}N_4O_6S$ (484.52): C 57.01, H 4.99, N 11.56; found C 56.92, H 5.26, N 11.35.

2-Amino-1′,2′,5,6,7,8-hexahydro-7,7-dimethyl-2′,5-dioxo-5′-(pyrrolidin-1-ylsulfonyl)spiro[chromene-4,3′-indole]-3′-carbonitrile (**4t**). IR: 3380, 3296 (NH_2), 3170 (NH), 2192 (CN), 1739 (C=O), 1670 (C=O), 1354, 1152 (SO_2). ^{1}H-NMR (500 MHz): 1.01 (*s*, 2 Me); 1.50 (*s*, 2 CH_2); 2.58 (*s*, CH_2CO); 3.02 (br. *s*, 2 CH_2N of pyrolidine); 7.01 (*d*, *J* = 6.9, H–C(7) of indole); 7.41 (br. *s*, NH_2); 7.44 (*s*, H–C(4) of indole); 7.61 (*d*, *J* = 6.9, H–C(6) of indole); 10.91 (br. *s*, NH). ^{13}C-NMR (125 MHz): 24.5; 27.0; 27.4; 31.8; 46.8; 47.0; 49.8; 56.1; 95.3; 109.3; 110.0; 117.0; 122.0; 128.6; 135.2; 146.3; 158.9; 164.8; 178.1; 195.1. Anal. calc. for $C_{23}H_{24}N_4O_5S$ (468.53): C 58.96, H 5.16, N 11.96; found C 59.18, H 5.42, N 11.65.

*7′-Amino-1,1′,2′,3,3′,4′-hexahydro-1,2′,3,4′-tetraoxospiro[indene-2,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**6a**). IR: 3381, 3308 (NH_2), 3180 (NH), 2210 (CN), 1639 (C=O), 1673 (C=O), 1685 (C=O), 1725 (C=O). ^{1}H-NMR (400 MHz): 7.81 (br. *s*, NH_2); 8.04 (br. *s*, 4 H of indene); 11.38 (*s*, NH).

*7′-Amino-1,1′,2′,3,3′,4′-hexahydro-1′,3′-dimethyl-1,2′,3,4′-tetraoxospiro[indene-2,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**6b**). IR: 3384, 3296 (NH_2), 3237 (NH), 2194 (CN), 1713 (C=O). ^{1}H-NMR (400 MHz): 3.00 (*s*, MeN); 3.37 (*s*, MeN); 7.97 (br. *s*, NH_2); 7.99–8.06 (*m*, 4 H of indene).

*2′-Amino-1,3-dihydro-1,3,5′-trioxospiro[indene-2,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile* (**6c**). IR: 3372, 3289 (NH_2), 3198 (NH), 2199 (CN), 1660 (C=O), 1713 (C=O). ^{1}H-NMR (500 MHz): 5.00 (br. *s*, NH_2); 7.39–8.10 (*m*, 8 H of indene and chromene).

2-Amino-1′,3′,5,6,7,8-hexahydro-7,7-dimethyl-1′,3′,5-trioxospiro[chromene-4,2′-indene]-3-carbonitrile (**6d**). IR: 3375, 3308 (NH_2), 3196 (NH), 2190 (CN), 1717 (C=O), 1687 (C=O). ^{1}H-NMR (400 MHz): 1.15 (*s*, 2 Me); 2.20 (*s*, CH_2); 2.50 (*s*, CH_2CO of chromene); 4.8 (br. *s*, NH_2); 7.88–7.92 (*m*, H–C(5), H–C(6)); 8.00–8.05 (*m*, H–C(4), H–C(7)).

REFERENCES

[1] Y. Huang, F. Yang, C. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16386.
[2] W. O. Foye, 'Principal di Chemico Farmaceutica', Piccin, Padova, Italy, 1991, p. 416.
[3] Y. Abe, H. Ebara, S. Okada, R. Akaki, T. Horii, R. Nakao, *Dyes Pigm.* **2002**, *52*, 23.
[4] C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, *63*, 2209.
[5] S. P. Baran, R. M. Richter, *J. Am. Chem. Soc.* **2005**, *127*, 15394.
[6] S. T. Hilton, T. C. T. Ho, G. Pljevaljcic, K. Jones, *Org. Lett.* **2000**, *2*, 2639.
[7] C. B. Cui, H. Kakeya, G. Okada, R. Onose, H. Osada, *J. Antibiot.* **1996**, *49*, 527.
[8] M. Dabiri, M. Bahramnnejad, M. Baghbanzadeh, *Tetrahedron* **2009**, *65*, 9443.

[9] Y. R. Lee, G. S. Hari, *Synthesis* **2010**, *3*, 453.
[10] L.-M. Wang, N. Jiao, J. Qiu, J- J. Yu, J.-Q. Liu, F.-L. Guo, Y. Liu, *Tetrahedron* **2010**, *66*, 339.
[11] Y. Li, H. Chen, C. Shi, D. Shi, S. Ji, *J. Comb. Chem.* **2010**, *12*, 231.
[12] S.-L. Zhu, S.-J. Ji, Y. Zhang, *Tetrahedron* **2007**, *63*, 9365.
[13] R. Sridhar, B. Srinivas, B. Madhav, V. P. Reddy, Y. V. D. Nageswar, K. R. Rao, *Can. J. Chem*. **2009**, *87*, 1704.
[14] G. Shanthi, G. Subbulakshmi, P. T. Perumal, *Tetrahedron* **2007**, *63*, 2057.
[15] Y. M. Litvinov, V. Y. Mortikov, A. M. Shestopalov, *J. Comb. Chem*. **2008**, *10*, 741.
[16] A. S. El-Ahl, H. Afeefy, M. A. Metwally, *J. Chem. Res. (S)* **1994**, 14.
[17] M. N. Elinson, A. I. Ilovaisky, A. S. Dorofeev, V. M. Merkulova, N. O. Stepanov, F. M. Miloserdov, Y. N. Ogibin, G. I. Nikishin, *Tetrahedron* **2007**, *63*, 10543.
[18] A. R. Karimi, F. Sedaghatpour, *Synthesis* **2010**, 1731.
[19] M. Kidwai, A. Jain, S. Bhardwaj, *Mol. Diversity* **2012**, *16*, 121.
[20] L. Zhao, B. Zhou, Y. Li, *Heteroatom Chem*. **2011**, *22*, 673.
[21] M. Khoobi, L. Ma'mani, F. Rezazadeh, Z. Zareie, A. Foroumadi, A. Ramazani, A. Shafiee, *J. Mol. Catal. A: Chem.* **2012**, *359*, 74.
[22] Y. Zhang, Y. Zhao, C. Xia, *J. Mol. Catal A: Chem.* **2009**, *306*, 107.
[23] A. F. Mahmoud, F. F. Abd El-Latif, A. M. Ahmed, *Chin. J. Chem.* **2010**, *28*, 91.
[24] H. M. Meshram, D. A. Kumar, B. R. V. Prasad, P. R. Goud, *Helv. Chim. Acta* **2010**, *93*, 648.
[25] D. S. Raghuvanshi, S. Krishna Nand, *J. Heterocycl. Chem.* **2010**, *47*, 1323.
[26] Y. He, H. Guo, J. Tian, *J. Chem. Res.* **2011**, *35*, 528.

Received September 11, 2012