Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 2057–2063

A new $InCl_3$-catalyzed, facile and efficient method for the synthesis of spirooxindoles under conventional and solvent-free microwave conditions

Gnanamani Shanthi, Ganesan Subbulakshmi and Paramasivan T. Perumal*

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, Tamilnadu, India

Received 19 September 2006; revised 28 November 2006; accepted 14 December 2006
Available online 17 December 2006

Abstract—A simple and efficient method for the one-pot three-component synthesis of new spirooxindoles under conventional and solvent-free microwave irradiation is described.

1. Introduction

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[1] Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[2–5] For example, spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly,[5] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (Fig. 1).[2]

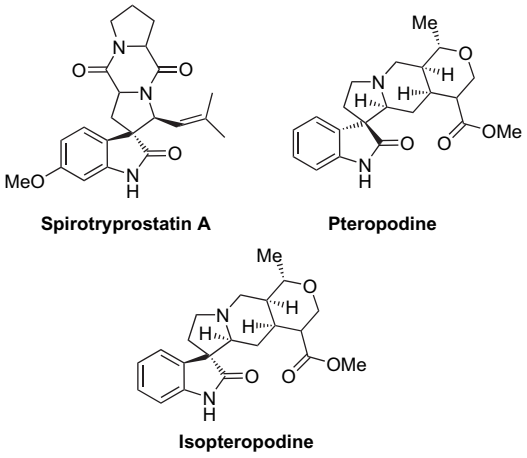


Figure 1. Representatives of spirooxindole-containing compounds.

As part of our endeavor to discover new spirooxindoles of biocidal interest, and guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably, we investigated a three-component reaction involving isatin with malononitrile and α-naphthol, in order to synthesize a new class of spirooxindoles with fused chromenes. Fused chromenes have been found to have a wide spectrum of activities such as antimicrobial,[6] antiviral,[7] mutagenicity,[8] antiproliferative,[9] sex pheromone,[10] antitumor,[11] and central nervous system activities.[12]

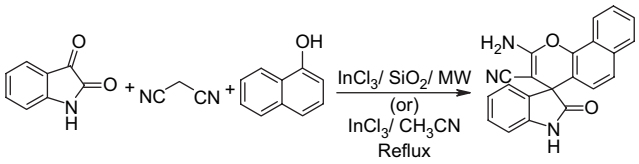
2. Results and discussion

In recent years, indium(III) chloride has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various transformations under mild and convenient conditions, affording the corresponding products in excellent yields with high selectivity. However, there has been no example of spirooxindoles with fused chromenes, so as part of our ongoing interest in indium(III) chloride-catalyzed reactions[13] and surface solid state reactions coupled with microwave irradiation,[14] we herein report for the first time a simple, new, and efficient method for the synthesis of spirooxindoles with fused chromenes, through the three-component condensation of isatin, malononitrile, and α-naphthol/β-naphthol using indium trichloride impregnated silica gel as a catalyst, under solvent-free conditions (Scheme 1).

Initially, evaluation of various catalysts and solvent systems was carried out for the synthesis of spirooxindole with fused chromenes. After systematic screening, indium(III) chloride and acetonitrile were found to be the best. The microwave assisted $InCl_3/SiO_2$-catalyzed method was superior to the

* Corresponding author. Tel.: +91 44 24913289; fax: +91 44 24911589; e-mail: ptperumal@gmail.com

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.12.042



Scheme 1. Synthesis of spirooxindoles.

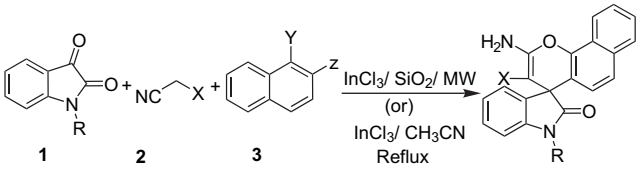
conventional one, as the reaction was high yielding, fast, and clean without any side products. We also evaluated the amount of indium trichloride required for this transformation. As little as 10 mol % of $InCl_3$ catalyzed the reaction but needs a longer reaction time (8–10 min). With silica gel alone, the reaction was extremely slow with very poor yield (10%) (Table 1).

Table 1. The effect of catalysts and a comparison between conventional and microwave assisted methods

Entry	Catalyst	Acetonitrile/reflux[a]		MW (solvent-free)[a]	
		Time (h)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	$ZnCl_2$	3	45	4.5	55
2	$FeCl_3 \cdot 6H_2O$	6	20	5	25
3	$BiCl_3$	5	42	3.5	48
4	$SnCl_2 \cdot 2H_2O$	4	45	3.5	50
5	$InCl_3$	1.5	70	3	88

[a] Reactions carried out on a 1 mmol scale.
[b] Isolated yield.

We then explored the scope and limitations of the one-pot reactions involving isatin, malononitrile/ethyl cyanoacetate with 1-naphthol/2-naphthol (Scheme 2). Results of the investigation involving thermal heating (method A) as well as microwave (method B) irradiation are presented in Table 2.

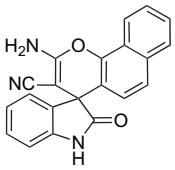
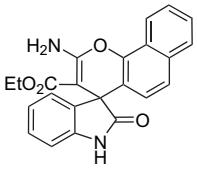
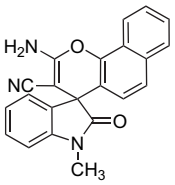
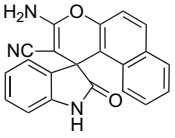
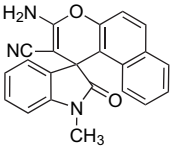
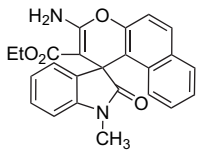


	R	X	Y	Z
6a	H	CN	OH	H
6b	H	CO_2Et	OH	H
6c	CH_3	CN	OH	H
6d	H	CN	H	OH
6e	H	CO_2Et	H	OH
6f	CH_3	CN	H	OH

Scheme 2. Preparation of spirooxindoles from 1-naphthol/2-naphthol.

We propose the following possible mechanism to account for the formation of **6**. The process represents a typical cascade reaction[15] in which the isatin **1** first condenses with malononitrile **2** to afford isatylidene malononitrile derivative **4**. This step can be regarded as a fast Knoevenagel addition. The second step involves the *ortho* C-alkylation of 1-naphthol by reaction with the electrophilic C═C double bond,[16] and the nucleophilic addition of the phenolic OH group on the cyano moiety (Scheme 3).[17]

Table 2. Synthesis of spirooxindoles from 1-naphthol/2-naphthol

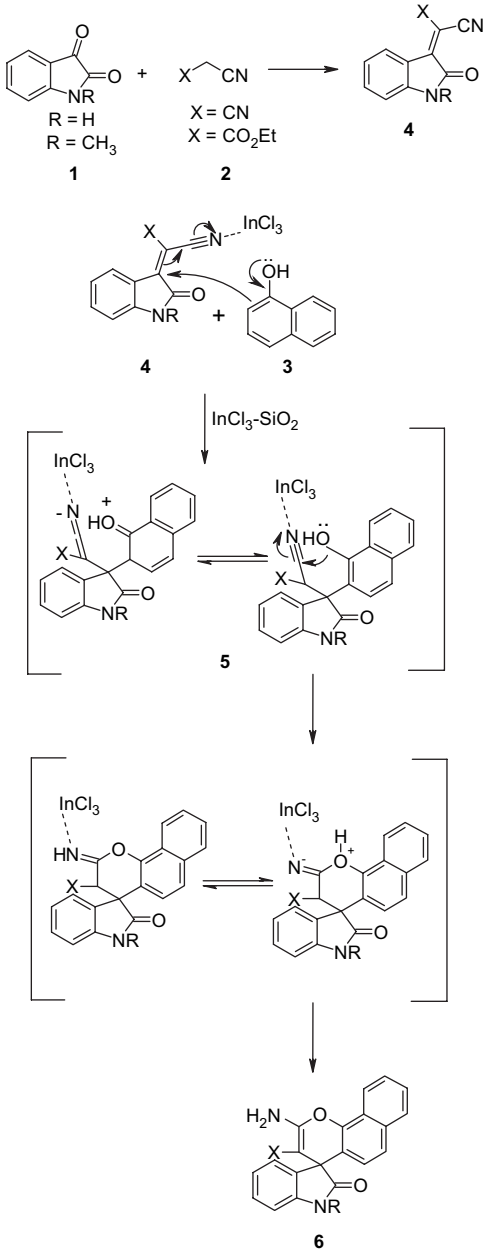
Entry	Product	MW (min)	Yield[a] (%)	Δ (h)	Yield[a] (%)
1	 **6a**	3	88	1.5	70
2	 **6b**	3.5	86	2	68
3	 **6c**	3	90	1.5	75
4	 **6d**	3	87	2	73
5	 **6e**	3	84	1.5	65
6	 **6f**	3.5	89	1.5	71

[a] Isolated yield.

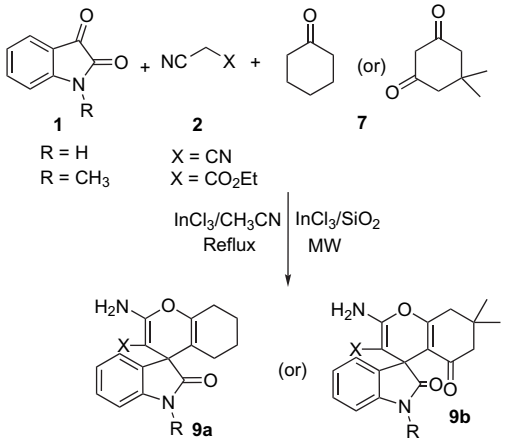
Encouraged by these results, we were delighted to observe that this protocol could be extended to a three-component coupling reaction involving an equimolar quantity of isatin, malononitrile, and cyclohexanone/dimedone (Scheme 4). This gave spirooxindoles **9a**,**b** in excellent yields without the formation of any side products.

To further explore the potential of this protocol for heterocyclic synthesis, we investigated one-pot reactions involving 1-phenyl-3-methyl pyrazolon-5-one and 4-hydroxy coumarin and obtained spirooxindoles in excellent yields (Scheme 5 and Table 3). The X-ray crystal structure of compound **9e** (Fig. 2)[18] adds a sharp evidence for the regioselective formation of spirooxindoles (**6** and **9**).

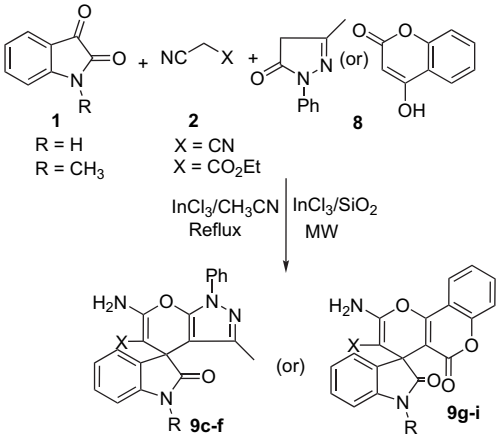
The feasibility of employing anilines instead of naphthols and enones in the reaction was also investigated. Unfortunately, when aniline was used, the reactions were usually very slow and resulted in a complicated mixture of products.



Scheme 3. Plausible mechanism for the reaction of isatin and malononitrile with α-naphthol.



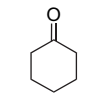
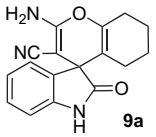
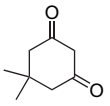
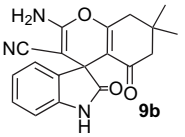
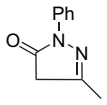
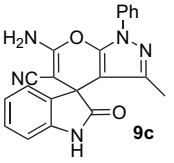
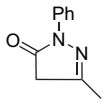
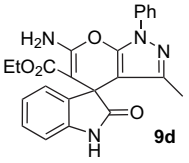
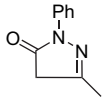
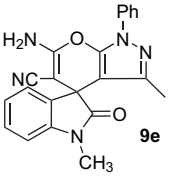
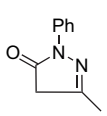
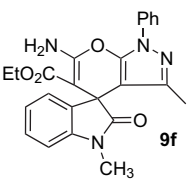
Scheme 4.



Scheme 5. Preparation of spirooxindoles using 1-phenyl-3-methyl pyrazolon-5-one and 4-hydroxy coumarin.

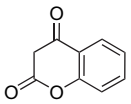
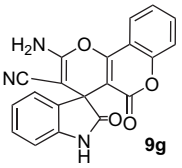
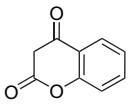
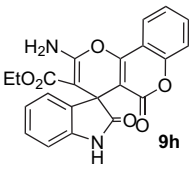
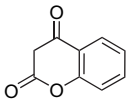
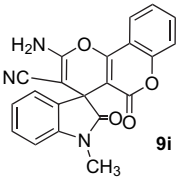
Substituted quinoxaline derivatives are pharmacologically important compounds. Although rarely described in nature, both leromycin and actinomycin possessing a quinoxaline

Table 3. Synthesis of spirooxindoles from enones

Entry	Reactant	Product	MW (min)	Yield[a] (%)	Δ (h)	Yield[a] (%)
1		 **9a**	3.5	88	1.5	70
2		 **9b**	3	93	1.5	75
3		 **9c**	3	90	1.5	73
4		 **9d**	3	90	1.5	70
5		 **9e**	3.5	92	1.5	71
6		 **9f**	3	90	2	75

(*continued*)

Table 3. (*continued*)

Entry	Reactant	Product	MW (min)	Yield[a] (%)	Δ (h)	Yield[a] (%)
7		 **9g**	3.5	92	1.5	72
8		 **9h**	3.5	91	1.5	68
9		 **9i**	3.5	95	1.5	74

[a] Isolated yield.

ring are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors.[19]

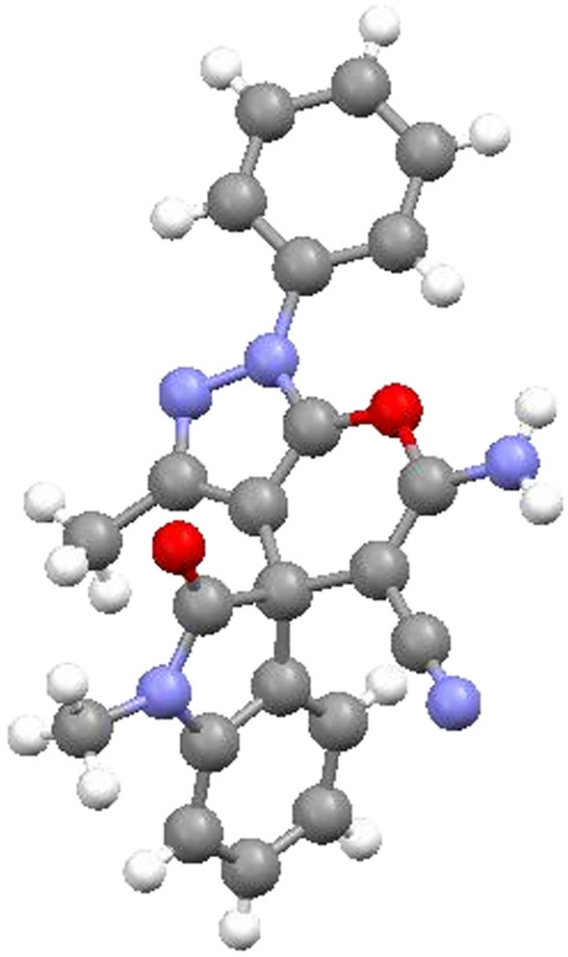
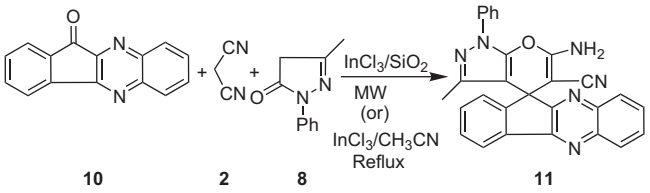


Figure 2. ORTEP diagram of compound **9e**.

Recently, Azizian et al.[20] have utilized the carbonyl group of the indenoquinoxaline **10** in a reaction with 4-hydroxy proline for the synthesis of pyrrolyl indenoquinoxaline derivatives. Taking this into consideration, we replaced isatin with indenoquinoxaline as the carbonyl component. The product spiroindenoquinoxaline **11** was confirmed by mass, IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses (Scheme 6).



Scheme 6. Synthesis of spiroindenoquinoxaline by the three-component condensation of indenoquinoxaline, malononitrile, and 1-phenyl-3-methyl pyrazolon-5-one.

3. Conclusion

In conclusion, we have developed a quick, clean, and simple method for the synthesis of new spirooxindoles and spiroindenoquinoxaline derivatives catalyzed by indium(III) chloride under solvent-free conditions and also by thermal heating. Further merits of this method are its generality, shorter reaction times, and easy work-up. The biological evaluations of these derivatives are underway.

4. Experimental

4.1. General

Zinc(II) chloride, bismuth(III) chloride, ferric chloride hexahydrate, stannous chloride, isatin, α-naphthol, β-naphthol, and malononitrile were obtained from S.D. Fine Chemicals. Indium(III) chloride was purchased from Aldrich. Reagent grade acetonitrile was used. THF was distilled over sodium-benzophenone before use. All melting points are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz, respectively. Mass spectra were recorded on a JEOL DX 303 HF spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer. Column chromatography was performed on silica gel (100–200 mesh, SRL, India). Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

4.2. General procedure for the synthesis of spirooxindoles (6a–f, 9a–i) and spiroindenoquinoxalines (11)

Method A (conventional method). To the reaction mixture containing isatin (0.147 g, 1 mmol), malononitrile (0.066 g, 1 mmol), and α-naphthol (0.144 g, 1 mmol) in acetonitrile (10 mL), indium(III) chloride (20 mol %) was added and stirred at reflux for about 1.5 h. On completion, the reaction mixture was diluted with water and the precipitate formed

was filtered, dried, and purified by column chromatography to afford the pure product in 70% yield. This procedure was followed for the synthesis of all the spirooxindoles (**6a–f** and **9a–i**) and spiroindenoquinoxaline (**11**).

Method B (microwave method). Isatin (0.147 g, 1 mmol), malononitrile (0.066 g, 1 mmol), and α-naphthol (0.144 g, 1 mmol) were added to silica gel impregnated with indium(III) chloride (44 mg, 20 mol %), prepared by adding a solution of $InCl_3$ in a minimum amount of THF to silica gel (2 g, 100–200 mesh activated by heating for 4 h at 150 °C before use), followed by complete evaporation of solvent under vacuum. The whole mixture was stirred for 5 min for uniform mixing and then irradiated in a microwave oven (BPL SANYO) at 300 W for 3 min. On completion, the reaction mixture was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate–hexane (4:6) to afford the pure product in 88% yield as a white solid. This procedure was followed for the synthesis of all the spirooxindoles (**6a–f** and **9a–i**) and spiroindenoquinoxalines (**11**).

4.2.1. 2-Amino spiro[(4*H*)-benzo(*h*)chromen-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carbonitrile 6a (Table 2, entry 1). White solid (298 mg, 88%); mp: 222 °C. ν_{max} (KBr): 3420, 3319, 2196, 1704, 1653, 1170 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.52 (d, 1H, *J*=9.2 Hz), 6.96 (m, 2H), 7.05 (d, 1H, *J*=7.5 Hz), 7.25 (t, 1H, *J*=7.5 Hz), 7.43 (br s, 2H, –NH_2, D_2O exchangeable), 7.53 (d, 1H, *J*=9.2 Hz), 7.58 (t, 1H, *J*=8.0 Hz), 7.63 (t, 1H, *J*=8.1 Hz), 7.85 (d, 1H, *J*=8.0 Hz), 8.24 (d, 1H, *J*=8.1 Hz), 10.67 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.42, 54.8, 110.6, 115.3, 119.1, 121.3, 123.2, 123.3, 123.7, 125.1, 125.6, 127.6, 127.9, 128.2, 129.8, 133.6, 135.2, 142.4, 144.1, 161.6, 179.3. MS (*m*/*z*): 339 (M^+). Anal. Calcd for $C_{21}H_{13}N_3O_2$: C, 74.33; H, 3.86; N, 12.38. Found: C, 74.29; H, 3.81; N, 12.32.

4.2.2. Ethyl 2-amino spiro[(4*H*)-benzo(*h*)chromen-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carboxylate 6b (Table 2, entry 2). Colorless solid (332 mg, 86%); mp: 229 °C. ν_{max} (KBr): 3430, 3325, 1707, 1669, 1170 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.75 (t, 3H, *J*=6.9 Hz, –$CO_2CH_2CH_3$), 3.52 (m, 2H, –$CO_2CH_2CH_3$), 6.42 (d, 1H, *J*=7.4 Hz), 6.86 (d, 1H, *J*=7.4 Hz), 7.05 (t, 1H, *J*=7.5 Hz), 7.12 (d, 1H, *J*=7.5 Hz), 7.20 (d, 1H, *J*=7.5 Hz), 7.32 (t, 1H, *J*=8.0 Hz), 7.44 (br s, 2H, –NH_2, D_2O exchangeable), 7.52 (d, 1H, *J*=8.6 Hz), 7.59 (t, 1H, *J*=8.0 Hz), 7.63 (t, 1H, *J*=8.0 Hz), 8.28 (d, 1H, *J*=8.6 Hz), 10.76 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8, 51.0, 55.2, 66.7, 109.2, 115.5, 118.4, 121.7, 123.3, 123.5, 123.9, 125.2, 125.4, 127.6, 128.0, 130.2, 133.0, 134.4, 143.7, 144.0, 161.8, 168.9, 177.5. MS (*m*/*z*): 386 (M^+). Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.41; H, 4.65; N, 7.20.

4.2.3. 2-Amino-1′-methyl spiro[(4*H*)-benzo(*h*)chromen-4,3′-(3′*H*)-indol]-2′-one-3-carbonitrile 6c (Table 2, entry 3). Colorless solid (318 mg, 90%); mp: 242 °C. ν_{max} (KBr): 3442, 2195, 1704, 1661, 1597, 1133 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.33 (s, 3H, –NMe), 6.79 (d, 1H, *J*=8.6 Hz), 6.96 (d, 2H, *J*=8.0 Hz), 7.20 (br s, 2H, –NH_2, D_2O exchangeable), 7.22 (m, 5H), 7.88 (d, 1H, *J*=8.0 Hz), 7.97 (d, 1H, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 27.0, 50.4, 57.5, 109.9, 111.4, 117.7, 118.2, 122.9, 124.5, 125.5, 128.2, 129.3, 129.8, 130.5, 131.8, 135.1, 142.8, 148.5, 159.9, 177.5. MS (*m*/*z*): 353 (M^+). Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.74; H, 4.22; N, 11.83.

4.2.4. 2-Amino spiro[(4*H*)-benzo(*f*)chromen-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carbonitrile 6d (Table 2, entry 4). White solid (295 mg, 87%); mp: 236 °C. ν_{max} (KBr): 3446, 3321, 2200, 1704, 1653, 1170 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.86 (m, 2H), 7.00 (d, 1H, *J*=8.0 Hz), 7.04 (d, 1H, *J*=8.6 Hz), 7.16 (br s, 2H, –NH_2, D_2O exchangeable), 7.23 (t, 2H, *J*=7.5 Hz), 7.29 (d, 1H, *J*=9.2 Hz), 7.32 (t, 1H, *J*=7.5 Hz), 7.88 (d, 1H, *J*=8.0 Hz), 7.96 (d, 1H, *J*=8.6 Hz), 10.98 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 50.8, 57.8, 110.8, 111.7, 117.7, 118.4, 123.2, 123.4, 124.8, 125.4, 127.9, 129.5, 129.7, 130.7, 131.5, 131.6, 135.9, 141.3, 148.5, 159.9, 179.1. MS (*m*/*z*): 339 (M^+). Anal. Calcd for $C_{21}H_{13}N_3O_2$: C, 74.33; H, 3.86; N, 12.38. Found: C, 74.26; H, 3.80; N, 12.34.

4.2.5. 2-Amino-1′-methyl spiro[(4*H*)-benzo(*f*)chromen-4,3′-(3′*H*)-indol]-2′-one-3-carbonitrile 6e (Table 2, entry 5). White solid (296 mg, 84%); mp: 266 °C. ν_{max} (KBr): 3453, 2191, 1686, 1650, 1174 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.42 (s, 3H, –NMe), 6.85 (d, 1H, *J*=8.6 Hz), 7.38 (br s, 2H, –NH_2, D_2O exchangeable), 7.22 (m, 5H), 7.48 (d, 2H, 8.0 Hz), 7.88 (d, 1H, *J*=8.0 Hz), 7.97 (d, 1H, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 27.8, 51.4, 56.5, 109.1, 112.4, 117.2, 118.8, 123.4, 124.9, 125.5, 128.7, 129.4, 129.9, 130.7, 132.5, 135.8, 142.8, 149.3, 159.2, 178.5. MS (*m*/*z*): 353 (M^+). Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.74; H, 4.23; N, 11.84.

4.2.6. Ethyl 2-amino-1′-methyl spiro[(4*H*)-benzo(*f*)chromen-4,3′-(3′*H*)-indol]-2′-one-3-carboxylate 6f (Table 2, entry 6). Colorless solid (356 mg, 89%); mp: 260 °C. ν_{max} (KBr): 3430, 1705, 1662, 1164 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.71 (t, 3H, *J*=6.9 Hz, –$CO_2CH_2CH_3$), 3.21 (s, 3H, –NMe), 3.55 (m, 2H, –$CO_2CH_2CH_3$), 6.47 (d, 1H, *J*=7.5 Hz), 7.04 (t, 1H, *J*=7.5 Hz), 7.10 (d, 1H, *J*=7.5 Hz), 7.15 (d, 1H, *J*=7.5 Hz), 7.36 (t, 1H, *J*=8.1 Hz), 7.47 (br s, 2H, –NH_2, D_2O exchangeable), 7.51 (d, 1H, *J*=8.6 Hz), 7.57 (t, 1H, *J*=8.1 Hz), 7.64 (t, 1H, *J*=8.1 Hz), 7.86 (d, 1H, *J*=8.6 Hz), 8.24 (d, 1H, *J*=8.6 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.2, 27.1, 51.0, 54.6, 67.6, 109.6, 115.2, 118.9, 121.3, 123.3, 123.8, 125.0, 125.2, 127.6, 128.2, 129.9, 133.6, 134.4, 143.9, 144.2, 161.6, 168.5, 177.6. MS (*m*/*z*): 400 (M^+). Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.95; H, 5.00; N, 6.95.

4.2.7. 2-Amino spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carbonitrile 9a (Table 3, entry 1). Brown solid (258 mg, 88%); mp: 238 °C. ν_{max} (KBr): 3443, 3290, 2194, 1710, 1631, 1470, 1218, 1148 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.24 (m, 8H, –$(CH_2)_4$), 6.79 (d, 1H, *J*=7.6 Hz), 6.82 (br s, 2H, –NH_2, D_2O exchangeable), 6.96 (t, 1H, *J*=7.7 Hz), 7.05 (d, 1H, *J*=7.7 Hz), 7.16 (t, 1H, *J*=7.7 Hz), 10.44 (br s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6,

125 MHz): δ 22.1, 22.4, 23.0, 26.2, 52.3, 54.8, 106.8, 110.1, 119.4, 122.9, 124.8, 129.2, 133.5, 142.3, 145.0, 161.2, 178.9. MS (*m/z*): 293 (M^+). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.56; H, 5.06; N, 14.22. Found: C, 69.61; H, 5.15; N, 14.33.

4.2.8. 2-Amino-5-oxo-7,7-dimethyl spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-carbonitrile 9b (Table 3, entry 2). Colorless solid (312 mg, 93%); mp: 268 °C. ν_{max} (KBr): 3410, 3306, 3136, 2959, 2191, 1719, 1679, 1653, 1601, 1218, 1163 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 0.97 (s, 3H, $-CH_3$), 1.00 (s, 3H, $-CH_3$), 2.05 (d, 1H, *J*=16.1 Hz, $-CH_aH_b$), 2.12 (d, 1H, *J*=16.1 Hz, $-CH_aH_b$), 2.52 (d, 2H, *J*=6.1 Hz, $-CH_2$), 6.75 (d, 1H, *J*=7.7 Hz), 6.84 (t, 1H, *J*=6.9 Hz), 6.94 (d, 1H, *J*=6.9 Hz), 7.09 (t, 1H, *J*=7.7 Hz), 7.19 (br s, 2H, $-NH_2$, D_2O exchangeable), 10.36 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 19.1, 27.6, 28.1, 47.3, 50.5, 56.6, 58.0, 109.8, 111.3, 117.9, 122.2, 123.6, 128.7, 134.9, 142.6, 159.3, 164.7, 178.6, 195.4. MS (*m/z*): 335 (M^+). Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 67.98; H, 5.03; N, 12.42. Found: C, 68.05; H, 5.11; N, 12.53.

4.2.9. 6-Amino-3-methyl-1-phenyl spiro[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*d*)pyrazol]-(1′*H*)-2′-one-5-carbonitrile 9c (Table 3, entry 3). Colorless solid (332 mg, 90%); mp: 248 °C. ν_{max} (KBr): 3446, 3269, 2192, 1686, 1650, 1576, 1174 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.55 (s, 3H, $-CH_3$), 6.95 (d, 1H, *J*=7.4 Hz), 7.02 (t, 1H, *J*=7.5 Hz), 7.17 (d, 1H, *J*=6.9 Hz), 7.28 (t, 1H, *J*=7.5 Hz), 7.35 (t, 1H, *J*=7.5 Hz), 7.51 (t, 2H, *J*=7.5 Hz), 7.58 (br s, 2H, $-NH_2$, D_2O exchangeable), 7.79 (d, 2H, *J*=7.5 Hz), 10.75 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.2, 48.3, 56.7, 96.9, 110.4, 118.5, 120.7, 123.2, 125.4, 127.1, 129.8, 130.0, 132.6, 137.8, 142.1, 144.5, 145.5, 161.6, 178.0. MS (*m/z*): 369 (M^+). Anal. Calcd for $C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96. Found: C, 68.24; H, 4.02; N, 18.90.

4.2.10. Ethyl 6-amino-3-methyl-1-phenyl spiro[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*d*)pyrazol]-(1′*H*)-2′-one-5-carboxylate 9d (Table 3, entry 4). White solid (374 mg, 90%); mp: 208 °C. ν_{max} (KBr): 3441, 1710, 1652, 1601, 1574, 1156 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 0.69 (t, 3H, *J*=6.9 Hz, $-CO_2CH_2CH_3$), 1.56 (s, 3H, $-CH_3$), 3.71 (m, 2H, $-CO_2CH_2CH_3$), 6.82 (m, 2H), 6.93 (d, 1H, *J*=7.5 Hz), 7.12 (t, 1H, *J*=7.5 Hz), 7.29 (t, 1H, *J*=7.5 Hz), 7.46 (t, 2H, *J*=8.0 Hz), 7.77 (d, 2H, *J*=8.0 Hz), 8.19 (br s, 2H, $-NH_2$, D_2O exchangeable), 10.49 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.3, 13.6, 48.0, 59.5, 75.1, 98.7, 109.4, 120.5, 122.3, 123.7, 126.9, 128.3, 129.9, 136.3, 137.9, 142.7, 144.5, 144.8, 161.9, 168.4, 179.8. MS (*m/z*): 416 (M^+). Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45. Found: C, 66.28; H, 4.80; N, 13.39.

4.2.11. 6-Amino-1′,3-dimethyl-1-phenyl spiro[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*d*)pyrazol]-2′-one-5-carbonitrile 9e (Table 3, entry 5). White solid (352 mg, 92%); mp: 200 °C. ν_{max} (KBr): 3450, 2198, 1686, 1603, 1572, 1179 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.43 (s, 3H, $-CH_3$), 3.22 (s, 3H, –NMe), 7.07 (t, 1H, *J*=7.4 Hz), 7.12 (d, 1H, *J*=8.0 Hz), 7.21 (d, 1H, *J*=6.9 Hz), 7.31 (m, 2H), 7.47 (t, 2H, *J*=8.6 Hz), 7.62 (br s, 2H, $-NH_2$, D_2O exchangeable), 7.75 (d, 2H, *J*=8.0 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.2, 27.0, 47.9, 56.2, 96.7, 109.4, 118.4, 120.7, 123.9, 125.1, 127.1, 129.9, 131.9, 137.7, 143.6, 144.4, 145.5, 161.7, 176.3. MS (*m/z*): 383 (M^+). Anal. Calcd for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 5.15; N, 13.02. Found: C, 8.87; H, 5.10; N, 12.97.

4.2.12. Ethyl 6-amino-1′,3-dimethyl-1-phenyl spiro-[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*d*)pyrazol]-2′-one-5-carboxylate 9f (Table 3, entry 6). White solid (387 mg, 90%); mp: 256 °C. ν_{max} (KBr): 3416, 1708, 1652, 1579, 1181 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 0.67 (t, 3H, $-CO_2CH_2CH_3$), 1.49 (s, 3H, $-CH_3$), 3.23 (s, 3H, –NMe), 3.65 (m, 2H, $-CO_2CH_2CH_3$), 6.97 (t, 1H, *J*=7.5 Hz), 7.03 (t, 2H, *J*=7.5 Hz), 7.28 (t, 1H, *J*=7.5 Hz), 7.33 (t, 1H, *J*=7.4 Hz), 7.50 (t, 2H, *J*=8.1 Hz), 7.81 (d, 2H, *J*=7.5 Hz), 8.27 (br s, 2H, $-NH_2$, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.2, 13.9, 26.7, 47.5, 59.4, 74.8, 98.5, 108.3, 120.5, 123.1, 123.4, 126.9, 128.5, 129.9, 135.5, 137.8, 143.9, 144.5, 144.6, 161.9, 168.3, 178.0. MS (*m/z*): 430 (M^+). Anal. Calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.02. Found: C, 66.92; H, 5.09; N, 12.96.

4.2.13. 2-Amino-5-oxaspiro[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile 9g (Table 3, entry 7). Off-white solid (328 mg, 92%); mp: 250 °C. ν_{max} (KBr): 3301, 2203, 1714, 1671, 1169 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.82 (d, 1H, *J*=7.5 Hz), 6.89 (t, 1H, *J*=7.5 Hz), 7.17 (m, 2H), 7.45 (d, 1H, *J*=8.6 Hz), 7.49 (t, 1H, *J*=8.1 Hz), 7.66 (br s, 2H, $-NH_2$, D_2O exchangeable), 7.72 (t, 1H, *J*=7.5 Hz), 7.91 (d, 1H, *J*=8.0 Hz), 10.67 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 48.1, 57.5, 101.9, 110.1, 112.9, 117.5, 122.6, 123.2, 124.7, 125.6, 129.5, 133.6, 134.2, 142.7, 152.6, 155.6, 158.8, 158.9, 177.7. MS (*m/z*): 357 (M^+). Anal. Calcd for $C_{20}H_{11}N_3O_4$: C, 67.23; H, 3.10; N, 11.76. Found: C, 67.19; H, 3.04; N, 11.71.

4.2.14. Ethyl 2-amino-5-oxaspiro[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carboxylate 9h (Table 3, entry 8). Off-white solid (368 mg, 91%); mp: 210 °C. ν_{max} (KBr): 3408, 3302, 1716, 1669, 1607, 1175 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 0.79 (t, 3H, *J*=6.9 Hz, $-CO_2CH_2CH_3$), 3.73 (m, 2H, $-CO_2CH_2CH_3$), 6.72 (m, 2H), 6.98 (m, 2H), 7.39 (m, 2H), 7.69 (m, 1H), 7.99 (m, 1H), 8.11 (br s, 2H, $-NH_2$, D_2O exchangeable), 10.40 (s, 1H, –NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.7, 47.9, 59.7, 76.1, 104.4, 108.9, 112.9, 116.9, 121.5, 123.4, 123.7, 125.4, 128.4, 133.9, 135.2, 144.6, 152.4, 154.3, 158.3, 159.1, 167.7, 179.4. MS (*m/z*): 404 (M^+). Anal. Calcd for $C_{22}H_{16}N_2O_6$: C, 65.34; H, 3.99; N, 6.93. Found: C, 65.29; H, 3.92; N, 6.88.

4.2.15. 2-Amino-1′-methyl-5-oxaspiro[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*c*)chromen]-2′-one-3-carbonitrile 9i (Table 3, entry 9). Off-white solid (352 mg, 95%); mp: 244 °C. ν_{max} (KBr): 3452, 2195, 1712, 1672, 1601, 1168 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.17 (s, 3H, –NMe), 6.98 (t, 1H, *J*=7.5 Hz), 7.04 (d, 1H, *J*=8.1 Hz), 7.25 (d, 1H, *J*=7.4 Hz), 7.28 (t, 1H, *J*=7.4 Hz), 7.45 (d, 1H, *J*=8.6 Hz), 7.50 (t, 1H, *J*=7.5 Hz), 7.71 (br s, 2H, $-NH_2$, D_2O exchangeable), 7.73 (m, 1H), 7.91 (d, 1H, *J*=7.5 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 27.1, 47.8, 57.1, 101.8,

109.1, 112.9, 117.2, 117.4, 123.3, 123.4, 124.4, 125.6, 129.7, 132.8, 134.3, 144.2, 152.6, 155.7, 158.8, 159.1, 176.2. MS (*m/z*): 371 (M^+). Anal. Calcd for $C_{21}H_{13}N_3O_4$: C, 67.92; H, 3.53; N, 11.32. Found: C, 67.87; H, 3.47; N, 11.26.

4.2.16. 2-Amino-5-methyl-7-phenyl spiro[(11′*H*)-indeno(1,2-*b*)quinoxalin-11′,4-4(*H*)-pyrano(3,2-*d*)pyrazol]-3-carbonitrile (11). Pale yellow solid (363 mg, 80%); mp: 236 °C. ν_{max} (KBr): 3313, 2199, 1653, 1594, 1130 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.07 (s, 3H, $-CH_3$), 7.33 (t, 1H, J=7.5 Hz), 7.49 (t, 2H, J=7.5 Hz), 7.62 (m, 3H), 7.65 (br s, 2H, $-NH_2$, D_2O exchangeable), 7.78 (m, 4H), 8.09 (d, 1H, J=8.1 Hz), 8.16 (t, 2H, J=7.4 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.4, 48.4, 58.1, 97.8, 118.6, 120.7, 122.3, 126.7, 127.1, 129.6, 129.7, 130.0, 130.3, 130.5, 131.1, 133.6, 136.3, 137.8, 141.9, 142.7, 144.4, 145.7, 150.8, 153.5, 161.6, 163.5, 164.1. MS (*m/z*): 454 (M^+). Anal. Calcd for $C_{28}H_{18}N_6O$: C, 74.00; H, 3.99; N, 18.49. Found: C, 73.95; H, 3.96; N, 18.44.

Acknowledgements

One of the authors (G. Shanthi) thanks CSIR, New Delhi for financial support.

References and notes

1. Houlihan, W. J.; Remers, W. A.; Brown, R. K. *Indoles: Part I*; Wiley: New York, NY, 1992.
2. Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39.
3. (a) Ma, J.; Hecht, S. M. *Chem. Commun.* **2004**, 1190; (b) Edmondson, S.; Danishefsky, S. J.; Sepp-lorenzinol, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147.
4. Usui, T.; Kondoh, M.; Cui, C.-B.; Mayumi, T.; Osada, H. *Biochem. J.* **1998**, *333*, 543.
5. Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715.
6. Smith, W. P.; Sollis, L. S.; Howes, D. P.; Cherry, C. P.; Starkey, D. I.; Cobley, N. K. *J. Med. Chem.* **1998**, *41*, 787.
7. Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. *Mutat. Res.* **1997**, *395*, 47.
8. Dell, C. P.; Smith, C. W. Eur. Pat. Appl. EP 537949; *Chem. Abstr.* **1993**, *119*, 139102d.
9. Bianchi, G.; Tava, A. *Agric. Biol. Chem.* **1987**, *51*, 2001.
10. Mohr, S. J.; Chirigos, M. A.; Fuhrman, F. S.; Pryor, J. W. *Cancer Res.* **1975**, *35*, 3750.
11. Elagamay, A. G. A.; El-Taweel, F. M. A. A. *Indian J. Chem., Sect. B* **1990**, *29*, 885.
12. Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacanni, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395.
13. (a) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16; (b) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 5025; (c) Babu, G.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 1627; (d) Babu, G.; Nagarajan, R.; Perumal, P. T. *Synthesis* **2000**, 661.
14. (a) Shanmugam, P.; Annie, G.; Perumal, P. T. *J. Heterocycl. Chem.* **2003**, *40*, 879; (b) Hemanth Kumar, K.; Muralidharan, D.; Perumal, P. T. *Synthesis* **2004**, 63.
15. Domling, A.; Herdtweck, E.; Ugi, I. *Acta Chem. Scand.* **1998**, *52*, 107; (b) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937; (c) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.
16. Abdel-Latif, F. F. *Indian J. Chem.* **1990**, *29B*, 664.
17. Martin, N.; Seoane, C.; Soto, J. L. *Tetrahedron* **1988**, *44*, 5861.
18. The X-ray data have been deposited in CCDC with number 611343.
19. (a) Dell, A.; William, D. H.; Morris, H. R.; Smith, G. A.; Feeney, J.; Roberts, G. C. K. *J. Am. Chem. Soc.* **1975**, *97*, 2497; (b) Bailly, C.; Echepare, S.; Gago, F.; Waring, M. *Anti-Cancer Drug Des.* **1999**, *15*, 291; (c) Sato, S.; Shiratori, O.; Katagiri, K. *J. Antibiot.* **1967**, *20*, 270.
20. Azizian, J.; Ali, R. K.; Zahra, K.; Ali, A. M.; Mohammad, R. M. *Tetrahedron Lett.* **2005**, *46*, 6155.