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Ammonium salt catalyzed multicomponent transformation: simple route to functionalized spirochromenes and spiroacridines

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ABSTRACT

The combination of isatin or acenaphthoquinone, an activated methylene reagent, and 1,3-dicarbonyl compounds in the presence of catalytic ammonium chloride was found to be a suitable and efficient method for the synthesis of the biologically important spirooxindoles.

1. Introduction

Compounds with an indole moiety exhibit antibacterial and antifungal activities.[1] Furthermore, it has been reported that spiroindoline derivatives have highly enhanced biological activity.[2–4] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[5–9] For example, cytostatic alkaloids as spirotryprostatins A, B, and pteropodine, and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (Fig. 1).[10]

Isatin and its derivatives also have interesting biological properties and are widely used as precursors for many natural products.[11–15] On the basis of biological studies, the existence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal activity remarkably,[16–18] and we intended the synthesis of a series of spirooxindoles with fused chromenes through a three-component reaction of isatin or acenaphthoquinone, malononitrile or ethylcyanoacetate, and 1,3-dicarbonyl compounds in the presence of catalytic ammonium chloride under aqueous conditions. Fused chromenes have received considerable attention due to their wide range of useful biological properties, which include spasmolitic, diuretic, anticoagulant, anticancer, and antianaphylactic activities.[19–23]

There are several reports on multicomponent entries to the synthesis of spirooxindoles. Recently, Shanthi et al. reported a three-component condensation of cyclic 1,3-diketones, isatin, and malononitrile catalyzed by 20 mol % of $InCl_3$.[24] Spirooxindoles were also prepared by electrochemical methods[25] that suffer from technical intricacy. This reaction was carried out in the presence of the surfactant triethylbenzylammonium chloride (TEBA) in water

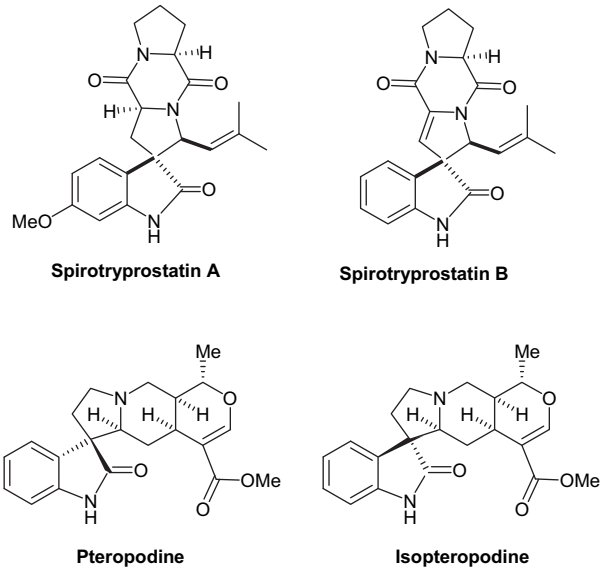

Figure 1. Illustration of spirooxindole-containing compounds.

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medium.[26] An important disadvantage of this approach was the generation of mixtures of pyrans and unsaturated nitriles. Shestopalov et al. have described a three-component Et_3N-catalyzed procedure for the combinatorial synthesis of 2-amino-spiro pyrans under simple conditions.[27] Thus, we tried to utilize a more appropriate and more accessible acidic catalyst, NH_4Cl, and water for these transformations. This method is very expedient and would be useful for the synthesis of different types of spirooxindoles.

Water plays an important role in the formation of the so-called 'chemistry of life'. Its importance in chemistry has decreased in the last century because of the introduction of organic solvents as more convenient reaction media for the preparation of new organic molecules. However, the demands of recent decades for sustainable and ecologically friendlier procedures have again put water at the frontier of organic chemistry.[28,29] Breslow et al. used water in combination with antihydrophobic additives as a mechanistic tool for obtaining information about the nature and structure of transition states in transformations of molecules that are almost completely soluble in water.[30,31] Mayr et al. have recently found an important influence of water on the reactivity of organic molecules, enabling alkylation of aromatic molecules with benzyl halides in a water–acetonitrile mixture without the use of a Friedel–Crafts catalyst.[32,33] Very recently, Sharpless et al.[34] reported the important observation that some organic molecules can react on the surface of water, and in some cases, a very strong enhancement in reaction rates was noticed in comparison to reactions without the solvent. The authors also suggested that water could be a useful reaction medium for reactions where no acceleration of rate was observed, especially in cases of exothermic reactions because of the high heat capacity of water.

In continuation of our investigations into the synthesis of novel heterocyclic compounds under aqueous conditions,[35–37] herein, we wish to report an efficient and green protocol for the three-component synthesis of some chromene derivatives at ambient temperature in excellent yields (Schemes 1 and 2).

2. Results and discussion

In the course of our research and evaluation of different catalysts and various solvent systems, we have found that ammonium chloride has a unique capability to enhance the reaction rate in aqueous medium. The results are summarized in Tables 1 and 2.

While, in some work, we observed that ammonium chloride and other ammonium salts have been used as ammonia generator

Table 1
Solvent effects on the reaction of dimedone (**1a**), isatin (**2a**), and malononitrile (**3a**) in the presence of 20 mol % ammonium chloride

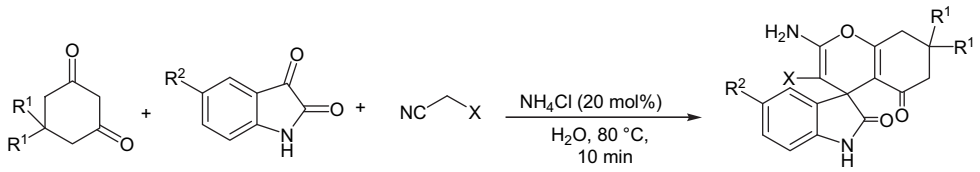
Entry	Solvent[a]	Time (min)	Yield of **4a**[b] (%)
1	CH_3OH[c]	480	60
2	C_2H_5OH[c]	360	75
3	CH_3CN[c]	600	20
4	DMSO[c]	600	Trace
5	DMF[c]	600	Trace
6	CH_3Cl[c]	600	Trace
7	CH_2Cl_2[c]	600	Trace
8	Solvent-free[d]	600	Trace
9	H_2O[d]	10	92

[a] Solvent (5 mL) was used.
[b] Isolated yield.
[c] The reaction was run under reflux condition.
[d] The reaction was run at 80 °C.

Table 2
Synthesis of spirooxindoles using various ammonium salt catalysts

Entry	Ammonium salt	Yield of **4a**[a] (%)
1	NH_4OAc	60
2	$(NH_4)_2CO_3$	57
3	$(NH_4)_2SO_4$	55
4	$(NH_4)_2C_2O_4$	50
5	$(NH_4)_2S$	50
6	NH_4Cl	92

[a] Isolated yield based on 1,3-diketones.



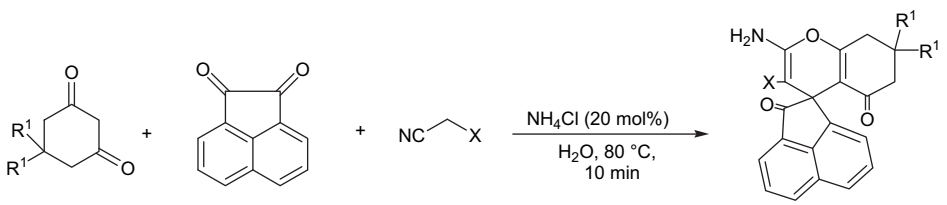
1a, b
a R^1=Me
b R^1=H

2a, b
a R^2=H
b R^2=F

3a, b
a X=CN
b X=CO_2Et

4a-g
a R^1=Me, R^2=H, X=CN
b R^1=Me, R^2=H, X=CO_2Et
c R^1=Me, R^2=F, X=CN
d R^1=Me, R^2=F, X=CO_2Et
e R^1=H, R^2=H, X=CN
f R^1=H, R^2=H, X=CO_2Et
g R^1=H, R^2=F, X=CO_2Et

Scheme 1. Synthesis of spirooxindoles via three-component reaction.



1a, b
a R^1=Me
b R^1=H

5

3a, b
a X=CN
b X=CO_2Et

6a-d
a R^1=Me, X=CN
b R^1=Me, X=CO_2Et
c R^1=H, X=CN
d R^1=H, X=CO_2Et

Scheme 2.

agents,[38–40] in the present exploration, the reaction of 1,3-dicarbonyl compounds (**1a**,**b**), isatin (**2a**,**b**), and activated methylene reagents (**3a**,**b**) in a molar ratio of 1:1:1 in the presence of catalytic ammonium chloride and water at 80 °C for 10 min (Scheme 1) furnished spirooxindoles in moderate yields (Table 3).

Table 3
Synthesis of compounds **4**, **6**, **7**, and **8** in water by the reaction of 1,3-diketones (**1**), isatins (**2**) or acenaphthenequinone (**5**), and activated methylene compounds in the presence of ammonium chloride

Entry	Product	Time (min)	Yield[a] (%)	Mp (°C)
1	**4a**	10	92	268–270[26]
2	**4b**	15	87	257–258
3	**4c**	10	85	270–273
4	**4d**	10	80	240–242
5	**4e**	10	94	251–252[26]
6	**4f**	15	83	263–265
7	**4g**	15	85	273–274
8	**6a**	10	90	260–262
9	**6b**	15	83	261–263
10	**6c**	15	75	245–247
11	**6d**	10	87	225–227
12	**7**	240	65	95–98
13	**8**	240	60	244–245

[a] Isolated yield based on 1,3-diketones. The reactions were run at 80 °C in the presence of 20 mol % NH_4Cl.

We examined this reaction in the absence and presence of ammonium salts. It was observed that the reaction did not occur without any catalyst. We also evaluated the amount of catalyst required for this transformation. It was found that using 20 mol % ammonium chloride in water is sufficient to push the reaction forward. More amount of the catalyst did not increase the yield. In order to evaluate the efficiency of this methodology, dimedone, isatin, and malononitrile were further subjected to reaction using 20 mol % of a diverse type of ammonium salts such as ammonium acetate, ammonium sulfate, ammonium carbonate, ammonium oxalate, and ammonium sulfide as well as ammonium chloride under identical conditions. As seen from Table 2, rate enhancement of the reaction was observed when 20 mol % of ammonium chloride was used. However, use of amount 20 mol % of other ammonium salts led to lower yields (50–60%) after 10 min reaction time.

As shown in Table 3 it was found that this procedure works with a wide variety of substrates. Two types of substituted isatins and 1,3-cyclohexanediones were used in this reaction (Scheme 1). Also the reaction with malononitrile or ethylcyanoacetate worked well. The most probable mechanism of this reaction includes a fast Knoevenagel condensation between isatin and CH-acidic cyanoacetic ester derivatives in the presence of ammonium chloride in water in the first step and a Michael addition of diketones to the unsaturated nitrile, the product of Knovenagel condensation, in the second stage and then the cycloaddition of the hydroxyl group to the cyano moiety to form the desired product.[26] To further expand the scope of this approach, we examined one-pot reactions involving acenaphthoquinone (**5**), instead of isatin. Under these conditions, a variety of desired spirochromenes were also produced in excellent yields (Scheme 2, Table 3). On the other hand, when benzyl cyanide was treated as a substitute for malononitrile or ethylcyanoacetate in this reaction and under similar conditions, not only a highly prolonged time was required, but the products were different. The spectroscopic data of the products confirmed that these structures belong to spiroacridine derivatives (Scheme 3, entries 12 and 13, Table 3).

3. Conclusion

In conclusion, we have developed a clean and simple one-pot three-component reaction for the synthesis of a series of spirochromene derivatives catalyzed by ammonium chloride in water. The utility of the described methodology in MCRs is highly promising as it allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the procedure.

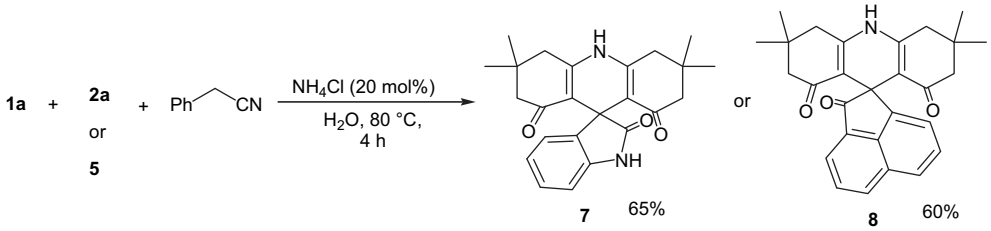
4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a FT-IR 10MB BOMEM spectrometer. Mass spectra were documented on a FINNIGAN-MAT8430 mass spectrometer operating at an ionization potential of 70 eV. The elemental analysis was performed with an Elementar Analysensysteme GmbH VarioEL CHNS mode. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained in solutions of $CDCl_3$ and DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Merck and Fluka Chemical Companies.

4.2. Typical procedure for preparation of 2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4a)

A mixture of isatin (1 mmol, 0.147 g), malononitrile (1 mmol, 0.066 g), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol, 0.141 g), and NH_4Cl (0.2 mmol, 0.01 g) in H_2O (5 mL) was stirred at 80 °C for 10 min. Upon completion, monitored by TLC (*n*-hexane/ethyl acetate:2/1), the reaction mixture was allowed to cool to room temperature. The solid was filtered off and washed with water and cool ethanol to give the desired products. The crude product was recrystallized from EtOH to yield 2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile **4a**: white solid (0.31 g, 92%). Mp 268–270 °C, IR (KBr) (ν_{max}, cm^{-1}): 3378, 3314, 2906, 2191, 1722, 1658, 1221. MS, *m*/*z* (%): 335 (M^+, 50), 251 (100), 210 (25), 83 (23), 66 (23), 39 (35). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 0.99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.08 (1H, d, J=16.1 Hz, CH_AH_B), 2.17 (1H, d, J=15.9 Hz, CH_AH_B), 2.52 (2H, m, CH_2), 6.76–7.15 (4H, m, ArH), 7.22 (2H, s, NH_2), 10.40 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 27.46 (CH_3), 28.06 (CH_3), 32.40, 47.25 (CH_2), 50.44 (CH_2), 57.89, 109.69, 111.22, 117.81 (CN), 122.14, 123.47, 128.63, 134.87, 142.49, 159.22, 164.61, 178.50 (C=O amide), 195.37 (C=O). Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%. Found: C, 67.94; H, 5.23; N, 12.64%.



Scheme 3.

4.3. Ethyl-2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (4b)

White solid (0.33 g, 87%). Mp 257–258 °C, IR (KBr) (ν_{max}, cm^{-1}): 3367, 3189, 2925, 1668, 1611, 1221. MS, *m*/*z* (%): 382(M^+, 90), 309 (100), 281 (25), 83 (25), 41 (23). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 0.78 (3H, t, *J*=6.57 Hz, CH_3), 0.93 (3H, s, CH_3), 1.01 (3H, s, CH_3), 2.00 (1H, d, *J*=15.7 Hz, CH_AH_B), 2.14 (1H, d, *J*=15.7 Hz, CH_AH_B), 2.55 (2H, m, CH_2), 3.69 (2H, q, *J*=5.2 Hz, CH_2), 6.65–7.03 (4H, m, ArH), 7.86 (2H, s, NH_2), 10.14 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 13.55 (CH_3), 27.12 (CH_3), 28.25 (CH_3), 32.0, 47.06 (CH_2), 51.09 (CH_2), 59.3 (CH_2), 76.76, 108.58, 113.54, 120.99, 122.69, 127.63, 136.44, 144.49, 159.56, 162.86, 168.10 (C=O, ester), 180.26 (C=O, amide), 195.11 (C=O). Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33%. Found: C, 65.72; H, 6.03; N, 7.57%.

4.4. 2-Amino-5′-fluoro-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4c)

Light pink solid (0.30 g, 85%). Mp 270–273 °C, IR (KBr) (ν_{max}, cm^{-1}): 3359, 3299, 3161, 2963, 2190, 1726, 1647, 1345, 1223. MS, *m*/*z* (%): 353 (M^+, 30), 269 (100), 227 (55), 42 (75). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 1.00 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.07 (1H, d, *J*=15.9 Hz, CH_AH_B), 2.15 (1H, d, *J*=16.0 Hz, CH_AH_B), 2.51 (2H, m, CH_2), 6.62–6.78 (3H, m, ArH), 7.70 (2H, s, NH_2), 10.24 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 27.35 (CH_3), 28.11 (CH_3), 33.12, 47.35 (CH_2), 51.2 (CH_2), 59.12, 110.15, 112.28, 117.81 (CN), 123.09, 124.45, 129.58, 133.81, 144.52, 160.01, 167.52, 179.45 (C=O, amide), 196.25 (C=O). Anal. Calcd for $C_{19}H_{16}FN_3O_3$: C, 64.58; H, 4.56; N, 11.89%. Found: C, 64.27; H, 4.87; N, 12.14%.

4.5. Ethyl-2-amino-5′-fluoro-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (4d)

White solid (0.32 g, 80%). Mp 240–242 °C, IR (KBr) (ν_{max}, cm^{-1}): 3396, 3350, 2953, 1705, 1688, 1665, 1488, 1170. MS, *m*/*z* (%): 400 (M^+, 25), 327 (100), 299 (22), 83 (25), 41 (45). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 0.77 (3H, t, *J*=6.5 Hz, CH_3), 0.95 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.04 (1H, d, *J*=16.6 Hz, CH_AH_B), 2.13 (1H, d, *J*=15.7 Hz, CH_AH_B), 2.55 (2H, m, CH_2), 3.71 (2H, q, *J*=6.5 Hz, CH_2), 6.63–6.85 (3H, m, ArH), 7.91 (2H, s, NH_2), 10.17 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 13.58 (CH_3), 27.39 (CH_3), 28.05 (CH_3), 31.99, 47.61 (CH_2), 51.07 (CH_2), 59.36, 76.26, 108.85, 110.65, 113.39, 116.66, 138.23, 140.86, 159.62, 163.21, 167.98 (C=O, ester), 180.23 (C=O, amide), 195.22 (C=O). Anal. Calcd for $C_{21}H_{21}FN_2O_5$: C, 62.99; H, 5.29; N, 7.00%. Found: C, 62.74; H, 5.54; N, 7.25%.

4.6. 2-Amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4e)

White solid (0.29 g, 94%). Mp 251–252 °C, IR (KBr) (ν_{max}, cm^{-1}): 3365, 3284, 3161, 2194, 1722, 1653, 1349, 1213. MS, *m*/*z* (%): 307 (M^+, 50), 251 (100), 209 (50), 140 (55), 39 (30). ^1H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 1.90 (2H, br s, CH_2), 2.20 (2H, br s, CH_2), 2.64 (2H, br s, CH_2), 6.75–7.12 (4H, m, ArH), 7.21 (2H, s, NH_2), 10.39 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 20.24 (CH_2), 27.17 (CH_2), 36.81 (CH_2), 47.31, 57.93, 109.58, 112.31 (CN), 122.1, 123.64, 128.57, 134.98, 142.43, 159.06, 166.48, 178.58 (C=O, amide), 195.47 (C=O). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67%. Found: C, 66.31; H, 4.43; N, 13.84%.

4.7. Ethyl-2-amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro-[chromene-4,3′-indoline]-3-carboxylate (4f)

White solid (0.29 g, 83%). Mp 263–265 °C, IR (KBr) (ν_{max}, cm^{-1}): 3368, 3245, 3161, 1696, 1649, 1522, 1298. MS, *m*/*z* (%): 354 (M^+, 40), 281 (100), 253 (25), 55 (30), 39 (30). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 0.78 (3H, t, *J*=7.1 Hz, CH_3), 1.86 (2H, m, CH_2), 2.15 (2H, m, CH_2), 2.63 (2H, m, CH_2), 3.72 (2H, q, *J*=6.1 Hz, CH_2), 6.64–7.06 (4H, m, ArH), 7.85 (2H, s, NH_2), 10.15 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 13.55 (CH_3), 20.11 (CH_2), 27.39 (CH_2), 37.55 (CH_2), 47.16, 59.29, 76.80, 108.48, 114.66, 120.98, 122.89, 127.58, 136.55, 144.47, 159.44, 164.68, 168.11 (C=O, ester), 180.36 (C=O, amide), 195.29 (C=O). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91%. Found: C, 64.08; H, 5.44; N, 8.23%.

4.8. Ethyl-2-amino-5′-fluoro-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (4g)

White solid (0.32 g, 85%). Mp 273–274 °C, IR (KBr) (ν_{max}, cm^{-1}): 3596, 3368, 3161, 1716, 1694, 1656, 1522, 1294. MS, *m*/*z* (%): 372 (M^+, 65), 299 (100), 271 (25), 42 (45). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 0.8 (3H, t, *J*=7.1 Hz, CH_3), 1.87 (2H, m, CH_2), 2.18 (2H, m, CH_2), 2.62 (2H, m, CH_2), 3.71 (2H, q, *J*=6.5 Hz, CH_2), 6.63–6.88 (3H, m, ArH), 7.91 (2H, s, NH_2), 10.19 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 13.57 (CH_3), 20.04 (CH_2), 27.43 (CH_2), 37.5 (CH_2), 47.71 (CH_2), 59.36, 76.31, 108.71, 111, 113.52, 114.11, 138.31, 140.82, 156.60, 159.65, 165.06, 167.99 (C=O, ester), 180.34 (C=O, amide), 195.39 (C=O). Anal. Calcd for $C_{19}H_{17}FN_2O_5$: C, 61.29; H, 4.60; N, 7.52%. Found: C, 61.12; H, 4.77; N, 7.69%.

4.9. 2′-Amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carbonitrile (6a)

Light yellow solid (0.33 g, 90%). Mp 260–262 °C, IR (KBr) (ν_{max}, cm^{-1}): 3369, 3186, 2953, 2192, 1718, 1667, 1598, 1215. MS, *m*/*z* (%): 370 (M^+, 75), 286 (100), 259 (45), 83 (25), 39 (30). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 1.01 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.05 (1H, d, *J*=16.6 Hz, CH_AH_B), 2.12 (1H, d, *J*=16.5 Hz, CH_AH_B), 2.62 (2H, m, CH_2), 7.33 (2H, s, NH_2), 7.37–8.28 (6H, m, ArH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 27.64 (CH_3), 27.93 (CH_3), 32.51, 50.16 (CH_2), 51.42 (CH_2), 58.47, 112.48, 117.97 (CN), 120.29, 121.87, 124.99, 128.93, 129.35, 130.26, 131.91, 132.64, 140.98, 143.66, 159.23, 165.02, 195.77 (C=O), 204.05 (C=O). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56%. Found: C, 74.45; H, 5.15; N, 7.31%.

4.10. Ethyl-2′-amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carboxylate (6b)

White solid (0.35 g, 83%). Mp 261–263 °C, IR (KBr) (ν_{max}, cm^{-1}): 3380, 3269, 2953, 1718, 1687, 1519, 1222. MS, *m*/*z* (%): 418 (M^++1, 25), 344 (100), 271 (30), 83 (25). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 0.53 (3H, t, *J*=7.0 Hz, CH_3), 0.93 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.92 (1H, d, *J*=15.9 Hz, CH_AH_B), 2.07 (1H, d, *J*=16.0 Hz, CH_AH_B), 2.62 (2H, m, CH_2), 7.22–8.12 (6H, m, ArH), 7.94 (2H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 12.66 (CH_3), 27.17 (CH_3), 28.23 (CH_3), 32.15, 50.48 (CH_2), 51.16 (CH_2), 58.86 (CH_2), 77.67, 115.32, 119.46, 119.58, 124.23, 128.17, 128.68, 129.71, 129.89, 136.45, 141.09, 145.76, 159.85, 163.41, 167.91 (C=O, ester), 195.73 (C=O), 205.65 (C=O). Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36%. Found: C, 71.78; H, 5.70; N, 3.95%.

4.11. 2′-Amino-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carbonitrile (6c)

Orange solid (0.26 g, 75%). Mp 245–247 °C, IR (KBr) (ν_{max}, cm^{-1}): 3372, 3189, 2192, 1718, 1672, 1595, 1344, 1205. MS, *m*/*z* (%): 342 (M^+, 23), 230 (70), 202 (50), 175 (40), 84 (30), 42 (100). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 1.92 (2H, m, CH_2), 2.15 (2H, m, CH_2), 2.71 (2H, m, CH_2), 7.32–8.66 (6H, m, ArH), 7.92 (2H, s, NH_2). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 20.27 (CH_2), 27.17

(CH_2), 36.50, 51.46, 58.50, 113.55, 117.99 (CN), 120.47, 121.81, 124.95, 128.90, 129.33, 130.19, 131.86, 132.67, 140.87, 143.82, 159.10, 166.93, 195.87 (C=O), 204.06 (C=O). Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18%. Found: C, 73.54; H, 4.28; N, 8.34%.

4.12. Ethyl-2′-amino-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carboxylate (6d)

Yellow solid (0.34 g, 87%). Mp 225–227 °C, IR (KBr) (ν_{max}, cm^{-1}): 3400, 3295, 2989, 1726, 1677, 1520, 1354. MS, *m*/*z* (%): 389 (M^+, 20), 316 (100), 176 (80), 149 (40), 55 (25). ^1H NMR (300.13 MHz, $CDCl_3$): δ_H (ppm) 0.04 (3H, t, *J*=7.1 Hz, CH_3), 1.47 (2H, m, CH_2), 2.65 (2H, t, *J*=6.2 Hz, CH_2), 3.45 (2H, q, *J*=7.1 Hz, CH_2), 4.52 (2H, t, *J*=7.1 Hz, CH_2), 6.58 (2H, s, NH_2), 7.22–8.48 (6H, m, ArH). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C (ppm) 12.25 (CH_3), 27.43 (CH_2), 36.82 (CH_2), 59.43 (CH_2), 63.40 (CH_2), 75.09, 119.40, 119.90, 122.78, 124.21, 127.80, 127.99, 128.72, 128.83, 129.50, 129.61, 129.71, 132.21, 136.02, 141.23, 164.17 (C=O, ester), 168.32 (C=O), 195.60 (C=O). Anal. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60%. Found: C, 70.75; H, 5.12; N, 3.78%.

4.13. 3,3,6,6-Tetramethyl-3,4,6,7-tetrahydro-1*H*-spiro-[acridine-9,3′-indoline]-1,2′,8(2*H*,5*H*,10*H*)-trione (7)

Yellow solid (0.25 g, 65%). Mp 95–98 °C, IR (KBr) (ν_{max}, cm^{-1}): 3351, 2859, 1720, 1685, 1612, 1368, 1230, 975. MS, *m*/*z* (%): 391 (M^++1, 100), 307 (70), 270 (60), 83 (85), 41 (80). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 0.90–1.04 (12H, 4s, $4CH_3$), 1.86–2.54 (8H, m, $4CH_2$), 4.11 (1H, s, NH), 6.67–7.42 (4H, m, ArH), 10.99 (1H, s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 26.42 (CH_3), 27.27 (CH_3), 29.13 (CH_3), 31.55 (CH_3), 32.78, 33.68, 42.65 (CH_2), 46.86 (CH_2), 47.25 (CH_2), 50.60 (CH_2), 54.19, 59.08, 101.37, 109.80, 111.67, 121.63, 121.95, 127.97, 133.52, 144.72, 168.65, 182.26 (C=O, amide), 194.66 (C=O), 203.90 (C=O). Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17%. Found: C, 73.64; H, 6.89; N, 7.35%.

4.14. 3′,3′,6′,6′-Tetramethyl-3′,4′,6′,7′-tetrahydro-1′*H*,2*H*-spiro-[acenaphthylene-1,9′-acridine]-1′,2,8′(2′*H*,5′*H*,10′*H*)-trione (8)

White solid (0.25 g, 60%). Mp 244–245 °C, IR (KBr) (ν_{max}, cm^{-1}): 3255, 2959, 1718, 1688, 1658, 1612, 1230, 781. MS, *m*/*z* (%): 425 (M^+, 20), 343 (100), 317 (30), 261 (45), 150 (65), 83 (95), 41 (85). ^1H NMR (300.13 MHz, $CDCl_3$): δ_H (ppm) 1.06 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.14 (3H, s, CH_3), 2.00–2.52 (8H, m, $4CH_2$), 3.86 (1H, s, NH), 7.12–8.16 (6H, m, ArH). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C (ppm) 26.92 (CH_3), 26.98 (CH_3), 29.27 (CH_3), 31.50 (CH_3), 33.14, 33.88, 43.10 (CH_2), 47.80 (CH_2), 50.15 (CH_2), 51.40 (CH_2), 54.21, 63.32, 100.68, 114.25, 117.34, 121.02, 125.02, 127.83, 128.23, 130.08, 131.04, 134.81, 141.96, 142.58, 168.51, 195.25 (C=O), 202.70 (C=O), 209.36 (C=O). Anal. Calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29%. Found: C, 78.76; H, 6.67; N, 3.56%.

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Supplementary data

Copy of ^1H NMR and ^{13}C NMR spectra for some compounds is available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.08.070.

References and notes

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, NY, 1996.
2. Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273–324.
3. Joshi, K. C.; Jain, R.; Sharma, K. *J. Indian Chem. Soc.* **1988**, *115*, 202–204.
4. Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, Sh. M. *Bioorg. Med. Chem.* **2004**, *12*, 2483–2488.
5. Dandia, A.; Singh, R.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. *Bioorg. Med. Chem.* **2006**, *14*, 2409–2417.
6. Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715–722.
7. Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.
8. Ma, J.; Hecht, S. M. *Chem. Commun.* **2004**, 1190–1191.
9. Edmondson, S.; Danishefsky, S. J.; Sepp-lorenzinol, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155.
10. Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39–45.
11. Saxton, J. E. *The Monoterpenoid Indole Alkaloids*; Wiley: New York, NY, 1983.
12. Cordell, G. A. *The Alkaloids: Chemistry and Biology*; Academic: San Diego, CA, 1998; Vol. 5.
13. Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651–12666.
14. Xue, J.; Zhang, Y.; Wang, X.-I.; Fun, H. K.; Xu, J.-H. *Org. Lett.* **2000**, *2*, 2583–2586.
15. Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1998**, *63*, 4481–4484.
16. Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacanni, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395–1398.
17. Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. *Mutat. Res.* **1997**, *395*, 47–56.
18. Elagamay, A. G. A.; El-Taweel, F. M. A. A. *Indian J. Chem., Sect. B* **1990**, *29*, 885–886.
19. Skommer, J.; Wlodkowic, D.; Matto, M.; Eray, M.; Pelkonen, J. *Leuk. Res.* **2006**, *30*, 322–331.
20. Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. *Tetrahedron Lett.* **2000**, *41*, 6993–6996.
21. Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517–520.
22. Witte, E. C.; Neubert, P.; Roesch, A. Ger. Offen. DE 3427985, 1986; *Chem. Abstr.* **1986**, *104*, 224915f.
23. Andreani, L. L.; Lapi, E. *Boll. Chim. Farm.* **1960**, *99*, 583–587.
24. Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057–2063.
25. Elinson, M. N.; Ilovaisky, A. I.; Dorofeev, A. S.; Merkulova, V. M.; Stepanov, N. O.; Miloserdov, F. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron* **2007**, *63*, 10543–10548.
26. Zhu, S. L.; Ji, S. J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365–9372.
27. Litvinov, Y. M.; Mortikov, V. Y.; Shestopalov, A. M. *J. Comb. Chem.* **2008**, *10*, 741–745.
28. Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; J. Wiley & Sons: New York, NY, 1997.
29. Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772.
30. Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164.
31. Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471–478.
32. Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5402–5405.
33. Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2004**, *126*, 5174–5181.
34. Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.
35. Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgary, Gh.; Mohammadi, A. A. *Tetrahedron Lett.* **2005**, *46*, 6123–6126.
36. Dabiri, M.; Baghbanzadeh, M.; Nickcheh, M. S.; Arzroomchilar, E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 436–438.
37. Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Agheb, M.; Heydari, S. *Catal. Commun.* **2008**, *9*, 785–788.
38. Barthakur, M. G. *Synlett* **2007**, 1475–1476.
39. Tewari, N.; Dwivedi, N.; Tripath, R. P. *Tetrahedron Lett.* **2004**, *45*, 9011–9014.
40. Salehi, P.; Dabiri, M.; Baghbanzadeh, M.; Bahramnejad, M. *Synth. Commun.* **2006**, *36*, 2287–2292.