Facile Synthesis and Anticancer Activity Study of Novel Series of Substituted and Fused Coumarin Derivatives

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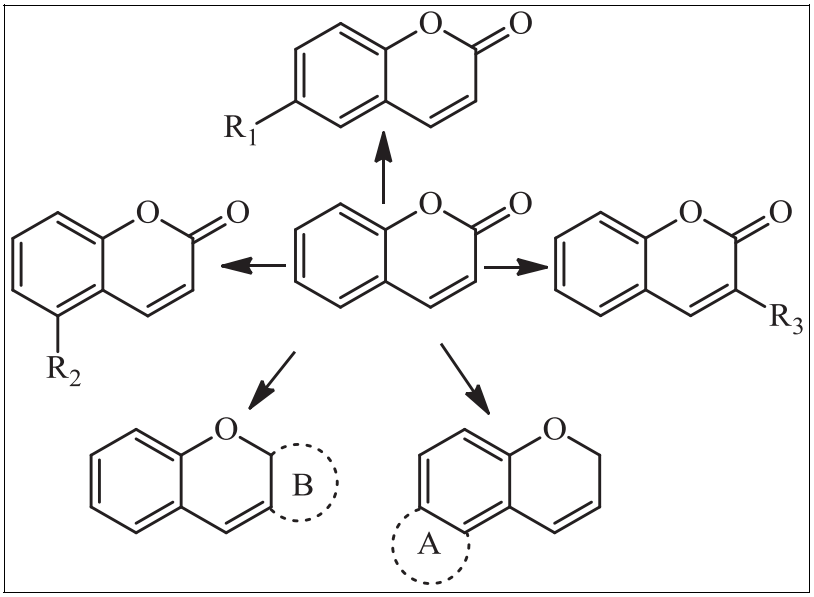

Various new substituted and fused coumarin analogues have been synthesized *via* different synthetic pathways. Among which are variable substituted coumarin derivatives bearing either biologically active side chains or rings at 5, 6, and 3 positions of the coumarin nucleus as indicated in compounds **10**, **12**, **13**, **16–19**, **21**, **23–32**, **38**, and **42–45**. In addition, different pyranocoumarin derivatives either substituted as in compounds **2**, **3**, and **6** or fused as compounds **33–36**, pyranoxanthene analogues such as compounds **4** and **46**, coumarinotriazolothiadiazine derivative **8**, coumarinonaphthodiazocin analogue **39** and coumarinopyrazolone derivative **40** were synthesized. Thirty-eight of the synthesized compounds were subjected to *in vitro* anticancer screening against mammalian liver carcinoma HepG2 and breast carcinoma MCF7 cell lines using Cisplatin as a standard reference. The anticancer activity screening results revealed that, among the tested compounds, compounds **16**, **40**, and **43** bearing 4-chlorophenyl-2-aminopyridine-3-carbonitrile attached to C_6 position, fused pyrazolone ring or attached to 4-chlorophenyl-2-oxo-dihydropyridine-3-carbonitrile at C_3 position of the coumarin nucleus, respectively, exhibited moderate to strong activity against both cell lines.

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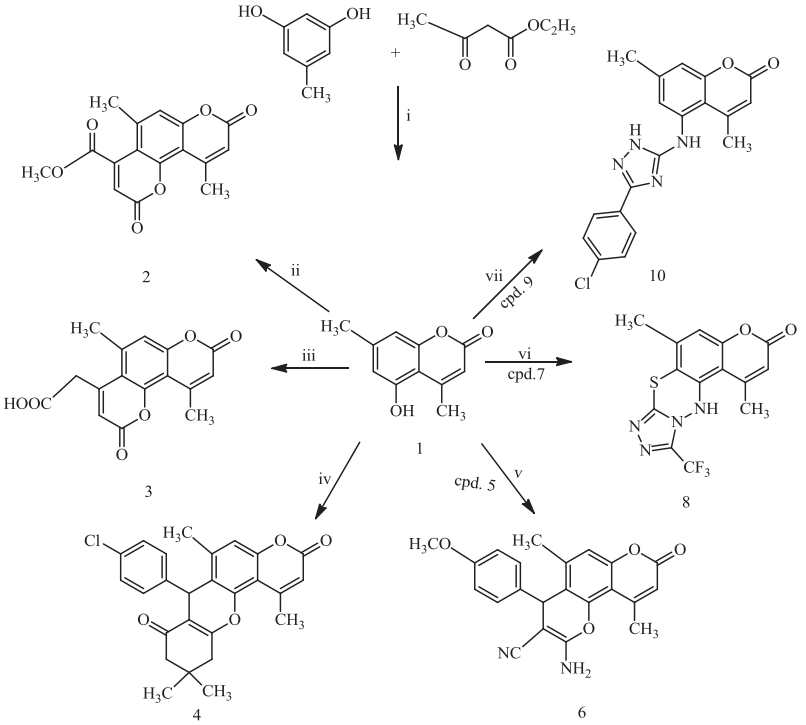
INTRODUCTION

Coumarins and their derivatives comprise a class of heterocyclic compounds of valuable medicinal importance. Anticancer [1–3], antibacterial [4], antiviral [5], anti-inflammatory [6], anticoagulant [7], acetyl, and butyryl cholinesterase inhibitory activity [8,9] are widely reported biological activities of various coumarin derivatives. Therefore, it was designed to synthesize different novel substituted and fused coumarin derivatives and investigate their anticancer activity.

RESULTS AND DISCUSSION

Chemistry. Literature survey revealed the significant anticancer activity of different coumarin derivatives against various cancer cell lines including HepG2 and MCF7 cell lines [10–18]. Therefore, Novel pyranocoumarin-4-carboxylate derivative **2** was prepared by fusion of the 5-hydroxycoumarin derivative **1** [19] and dimethyl acetylenedicarboxylate (Scheme 1). The reaction was suggested to proceed through the interaction of the activated ortho position of the phenolic coumarin

Scheme 1. Reagents and conditions: (i) conc.H2SO4, R.T.; (ii) DMAD/fusion; (iii) citric acid/fusion; (iv) Dimedone, 4-chlorobenzaldehyde, piperdine, C2H5OH/reflux; (v) piperidine, C2H5OH/reflux; (vi) DMSO/reflux; (vii) DMSO/reflux.



function and dimethyl acetylenedicarboxylate triple bond with the subsequent intramolecular lactonization through elimination of a methanol moiety. The IR spectrum of compound **2** was devoid of the characteristic OH absorption band of its precursor **1**.

Novel pyranocoumarin acetic acid derivative **3** was obtained by fusion of equivalent amounts of 5-hydroxycoumarin derivative **1** and citric acid. ^{1}H NMR spectrum of compound **3** revealed a singlet signal at δ 6.59 ppm attributed to the pyranocoumarin C_3 proton which was not observed in its precursor compound **1**.

Building up a xanthene moiety on the pyran ring in compound **4** was carried out *via* the multicomponent cyclocondensation of equimolar amounts of the 5-hydroxycoumarin derivative **1**, 4-chlorobenzaldehyde and dimedone in ethanol containing piperidine as a catalyst. A conceivable mechanism for the formation of a pyranoxanthene system was reported to proceed either through the knoevenagel condensation between the aldehyde and dimedone followed by Michael addition of the α-position of the hydroxy group of the coumarin [20] or through formation of the intermediate *via* the nucleophilic addition of the activated α-position of the hydroxycoumarin to the aldehyde followed by subsequent Michael addition of the dimedone [4]. In both cases, subsequent intramolecular cyclization afforded the corresponding pyranoxanthene derivative **4**. The ^{1}H NMR spectrum of compound **4** revealed singlet signals at δ 0.87 and 1.06 ppm attributed to the dihydropyranoxanthene-C_{10}-$(CH_3)_2$ protons. In addition, three singlet signals at δ 2.29, 2.70, and 5.03 ppm due to dihydropyranoxanthene-C_{11}, C_9, and C_7 protons, respectively, which were not observed in its precursor compound **1**.

Furthermore, 2-aminopyranocoumarin-3-carbonitrile derivative **6** was prepared *via* the reaction of equivalent amounts of the 2-(4-methoxybenzylidene)malononitrile **5** [21] and 5-hydroxy- coumarin derivative **1** in ethanol containing piperidine as a catalyst. ^{1}H NMR spectrum of compound **6** displayed a deuterium oxide exchangeable singlet signal at δ 3.89 ppm due to NH_2 protons and a singlet signal at δ 4.03 ppm corresponding to pyranocoumarin-C_4 proton.

The reaction of compound **1** with two equivalents of 4-amino-5-trifluromethyl-4*H*-1,2,4-triazole-3-thiol **7** [22] in dimethyl sulfoxide under reflux condition led to the novel coumarinotriazolothiadiazine **8** through the addition of the bis(o-amino aryl)disulfide on the substituted hydroxycoumarin accompanied by elimination of a water molecule. The bis(o-aminoaryl) disulfide was cleaved and intramolecular cyclization occurred (Fig. 1). The IR spectrum of compound **8** showed two characteristic absorption bands at 3427 and 1700 cm^{-1} due to NH and carbonyl functions, respectively.

5-Hydroxycoumarin derivative **1** upon heating under reflux with one equivalent of 3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-amine **9** [23] in dimethyl sulfoxide yielded

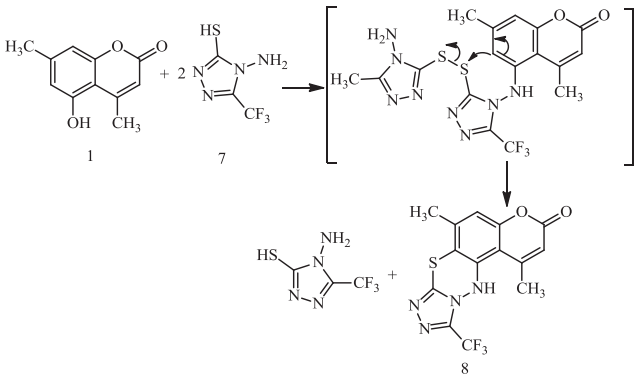


Figure 1. Postulated mechanism for synthesis of compound **8.**

the novel (1*H*-1,2,4-triazol-5-ylamino)coumarin derivative **10**. The ^{1}H NMR spectrum of compound **10** displayed two deuterium oxide exchangeable singlet signals at δ 8.12 and 12.24 ppm due to coumarin-C_5 NH and triazole NH protons, respectively.

Furthermore, cinnamoyl-5-hydroxycoumarin derivative **12** was obtained through fusion of equivalent amounts of cinnamoyl chloride **11** [24] and compound **1**. ^{1}H NMR spectrum of compound **12** displayed two multiplet signals at δ 6.56–6.60 and δ 7.07–7.14 due to the vinylic protons, as well as a deuterium oxide exchangeable singlet signal at δ 10.49 ppm due to OH proton.

Our scope was extended to study the anticancer activity of different substituted coumarines, therefore, bis-hydroxycoumarin derivative **13** was prepared *via* heating 4-methoxybenzaldehyde with two equivalents of 5-hydroxycoumarin derivative **1** (Scheme 2). The ^{1}H NMR spectrum of compound **13** revealed two singlet signals at δ 3.68 and 6.03 ppm corresponding to $–OCH_3$ and $–CH-(coumarin)_2$ protons, respectively.

The multicomponent reaction of the acetylcoumarin derivative **15** [18], malononitrile, ammonium acetate, and 4-chlorobenzaldehyde in ethanol under reflux condition furnished the target 2-aminocoumarinylnicotinonitrile derivative **16**. The reaction mechanism was postulated to proceed through initial formation of the coumarin chalcone followed by the nucleophilic attack of malononitrile on the chalcone double bond. Ammonium acetate introduces a nitrogen atom and elimination of a water molecule occurs followed by subsequent intramolecular cyclization. The ^{1}H NMR spectrum of compound **16** displayed a deuterium oxide exchangeable singlet signal at δ 7.28 ppm corresponding to OH and NH_2 protons, in addition to a singlet signal at δ 7.46 ppm corresponding to the pyridine-C_5 proton.

The target 1,3-diketone derivative **17** was prepared *via* heating an equimolar mixture of compound **15** and benzoyl chloride in pyridine containing potassium hydroxide. ^{1}H NMR spectrum of compound **17** revealed a deuterium oxide exchangeable singlet signal at δ 12.87 ppm corresponding to OH proton.

In addition, 5-hydroxycoumarin-6-carboxamidine derivative **18** was prepared upon fusion of compund **1** and cyanamide through the nucleophilic addition of the activated ortho position of the phenolic 5-hydroxy function to the cyano triple bond. ^{1}H NMR spectrum of compound **18** showed three deuterium oxide exchangeable singlet signals at δ 2.53, 6.09, and 10.52 ppm due to NH_2, imine NH, and OH protons, respectively.

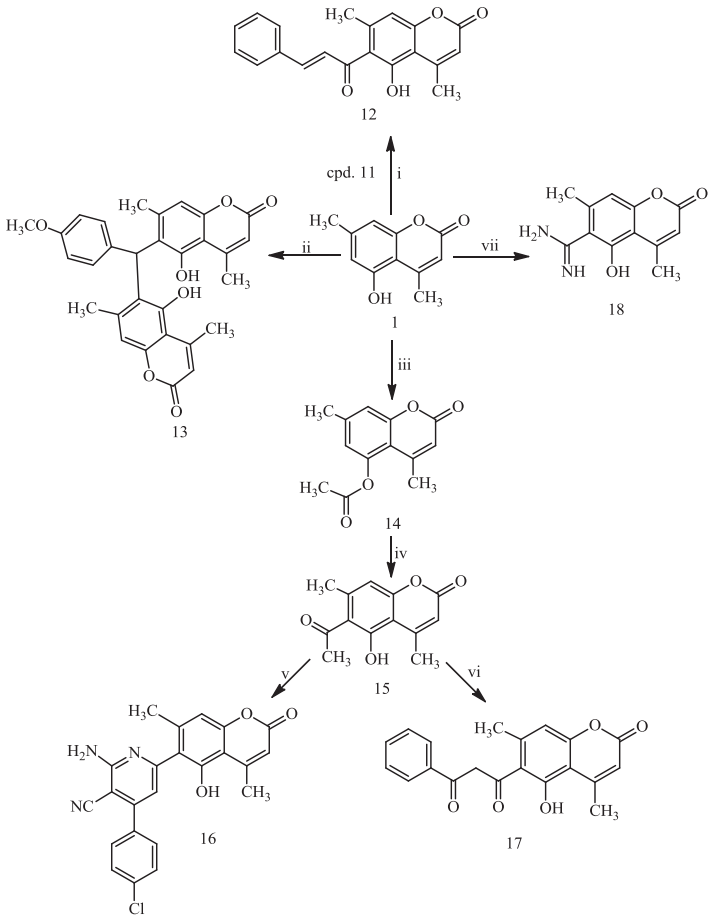
Moreover, refluxing equivalent amounts of compound **1** and 1,3-dichloroacetone in ethanolic sodium ethoxide yielded 2-oxo-propoxycoumarin derivative **19** (Scheme 3). The IR spectrum of compound **19** showed broad absorption band at 3390 cm^{-1} due to tautomeric OH function, in addition to two characteristic absorption bands at 1722 and 1681 cm^{-1} attributed to two carbonyl functions.

In our recent study, the chromenyloxyacetylthiosemicarbazide derivative **21** was obtained by heating equivalent amounts of methyl coumarinylacetate derivative **20** [25] and thiosemicarbazide in pyridine under reflux. ^{1}H NMR spectrum of compound **21** showed three deuterium oxide exchangeable singlet signals at δ 6.81, 6.92, and 10.52 ppm due to NH_2 and two NH protons, respectively.

In attempts to develop various side chains attached to C_5 of the coumarin nucleus, the potassium hydrazincarbodithioate derivative **23** was prepared by stirring equivalent amounts of the acid hydrazide derivative **22** [25] and carbon disulfide in presence of potassium hydroxide which was heated in absolute ethanol to afford the target oxadiazolethione derivative **24**. ^{1}H NMR spectrum of compound **24** displayed a deuterium oxide exchangeable singlet signal at δ 6.47 ppm due to NH proton.

However, the target 1,3,4 thiadiazole derivative **25** was obtained *via* stirring the potassium salt **23** with concentrated sulfuric acid in ethanol at room temperature.

Scheme 2. Reagents and conditions: (i) fusion; (ii) 4-methoxybenzaldehyde/fusion; (iii) AC2O/reflux; (iv) AlC13/fusion; (v) 4-chlorobenzaldehyde, malononitrile, NH4OAc, C2H5OH/reflux; (vi) PhCOC1, KOH, pyridine/reflux; (vii) cyanamide/fusion.



^{1}H NMR spectrum of compound **25** displayed a deuterium oxide exchangeable singlet signal at δ 12.99 ppm attributed to NH proton.

Fusion of the potassium salt **23** with hydrazine hydrate led to formation of 4-amino[1,2,4]triazole-5-thione derivative **26**. The IR spectrum of compound **26** revealed absorption bands at 3394, 3356, 3336, and 1700 cm^{-1} attributed NH, NH_2, and carbonyl functions, respectively. Furthermore, coumarinyloxyhydroxyethylacetamide derivative **27** was obtained by fusion of the methyl coumarinylacetate derivative **20** with ethanolamine. IR spectrum of compound **27** revealed broad absorption bands at 3421 and 3300 cm^{-1} corresponding to OH and NH functions, in addition to two absorption bands at 1743 and 1685 cm^{-1} due to two carbonyl functions.

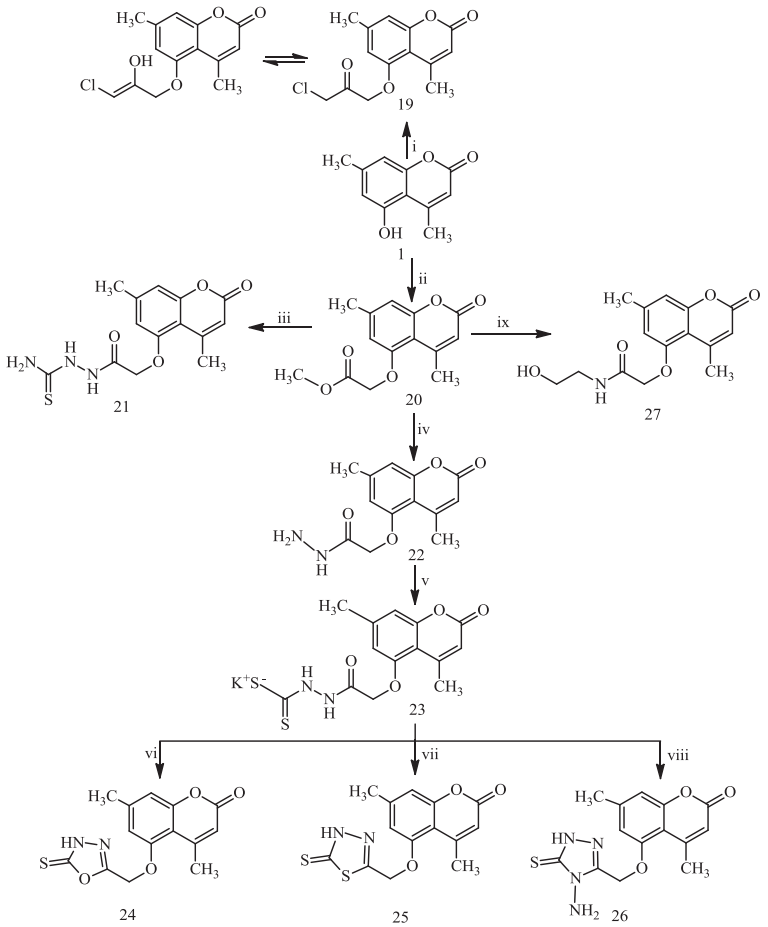
Acetylacetone was utilized in the synthesis of dimethyl pyrazolyloxoethoxycoumarinone derivative **28** *via* fusion with the acetohydrazide derivative **22** (Scheme 4). ^{1}H NMR spectrum of compound **28** revealed two singlet signals at δ 2.52 and 2.58 ppm corresponding to pyrazole-C_3 and pyrazole-C_5 CH_3 protons, respectively, in addition to a deuterium oxide exchangeable singlet signal at δ 10.51 due to tautomeric OH half proton.

The reaction of compound **22** with ethyl cyanoacetate by heating under reflux in dimethyl formamide afforded the corresponding amino pyrazolyloxoethoxycoumarin derivative **29**. ^{1}H NMR spectrum of compound **29** displayed two deuterium oxide exchangeable singlet signals at δ 3.75 and 10.28 ppm corresponding to NH_2 and OH protons, respectively. However, a singlet signal appeared at 7.92 ppm due to pyrazole-C_4 proton.

Furthermore, the target pyrazolyloxoethoxychromenone derivative **30** was prepared by fusion of equivalent amounts of the compound **22** and ethyl acetoacetate. ^{1}H NMR spectrum of compound **30** revealed a singlet signal at δ 7.34 ppm attributed to pyrazole-C_4 proton and a deuterium oxide exchangeable singlet signal at δ 10.49 ppm corresponding to OH proton.

In addition, the target 3,5-dioxopyrazolidine derivative **31** was prepared by fusion of equivalent amounts of the acetohydrazide derivative **22** and diethyl malonate. ^{1}H NMR spectrum of compound **31** displayed two deuterium oxide exchangeable singlet signal at δ 9.61 and

Scheme 3. Reagents and conditions: (i) 1,3-dichloroacetone, NaOC2H5, C2H5OH/reflux; (ii) methyl bromoacetate, K2CO3, acetone/reflux; (iii) thiosemicarbazide, pyridine/reflux; (iv) NH2NH2 99%, C2H5OH/R.T.; (v) CS2, KOH, C2H5OH/R.T.; (vi) C2H5OH/reflux; (vii) conc.H2SO4, C2H5OH, R.T.; (viii) NH2NH2 99%/fusion; (ix) ethanolamine/fusion.



10.23 ppm each integrated for half proton attributed to tautomeric OH and NH proton, respectively.

The acetohydrazide derivative **22** afforded its corresponding acetyl benzohydrazide derivative **32** upon fusion with one equivalent of benzoyl chloride. IR spectrum of compound **32** absorption bands at 1743, 1680, and 1658 cm^{-1} attributed to the carbonyl functions.

Iminopyranochromenopyrimidine-2-thione derivative **33** was synthesized by heating equimolar amounts of the 2-aminopyranocoumarin-3-carbonitrile derivative **6** and phenyl isothiocyanate in refluxing pyridine (Scheme 5).

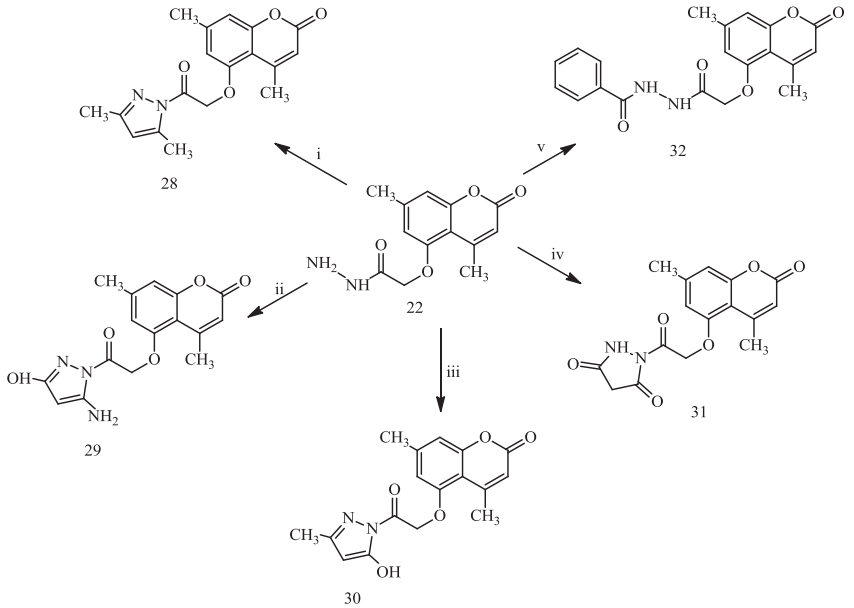
IR spectrum of compound **33** revealed absorption bands at 3380, 3360, and 1716 cm^{-1} corresponding to two NH and the carbonyl functions, respectively, in addition to absorption bands at 1543, 1438, 1253, and 1029 cm^{-1} due to the four bands of –N–C═S function (Fig. 2).

In addition, the target 4-aminopyranochromenopyrimidine derivative **34** was formed by refluxing compound **6** in excesss formamide first through o-cyanoformamidine formation followed by intramolecular cyclization *via* nucleophilic attack of the lone pair of the formamide amino group on the electrophilic nitrile carbon. IR spectrum of compound **34** revealed absorption bands at 3309 and 3163 cm^{-1} attributed to NH_2 function and absorption band at 1680 cm^{-1} attributed to the carbonyl function.

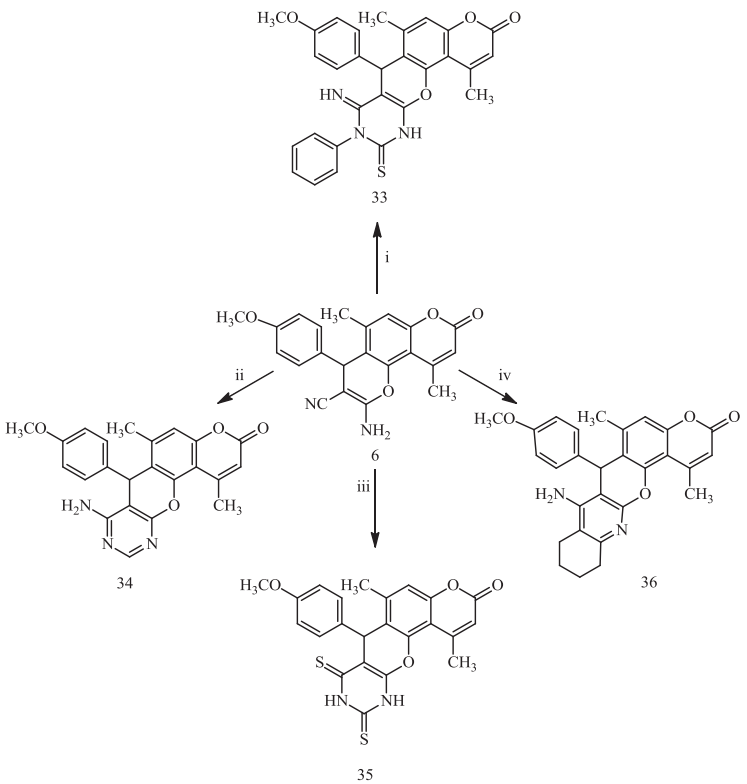
Furthermore, refluxing a mixture of compound **6** and carbon disulfide in absolute ethanol containing potassium hydroxide afforded pyranochromenopyrimidinedithione derivative **35** (Fig.3). IR spectrum of compound **35** showed absorption bands at 3390 and 3292 cm^{-1} due to two NH functions and absorption band at 1654 cm^{-1} attributed to the carbonyl function.

Friedlander cyclocondensation [26] of compound **6** and cyclohexanone in refluxing dimethyl formamide containing anhydrous zinc chloride as a lewis acid atalyst yielded the target tetrahydropyranochromenoquinoline derivative **36**. ^1H NMR spectrum of compound **36** displayed the tetrahydropyranochromenoquinoline-$C_{8,9}$ and tetrahydropyranochromenoquinoline-$C_{7,10}$ multiplets at 1.19–1.29 and 1.55–1.72 ppm, respectively.

Scheme 4. Reagents and conditions: (i) acetylacetone/fusion; (ii) ethyl cyanoacetate, DMF/reflux; (iii) ethyl acetoacetate/fusion; (iv) diethyl malonate/fusion; (v) PhCOC1/fusion.



Scheme 5. Reagents and conditions: (i) PhNCS, pyridine/reflux; (ii) excess formamide/reflux; (iii) CS2, KOH, C2H5OH/reflux; (iv) cyclohexanone, ZnCl2, DMF/reflux.



Moreover, heating equimolar amounts of the ethyl ester derivative **37** [27] and 5-bromosalicylaldehyde in absolute ethanol containing a catalytic amount of potassium hydroxide led to the formation of 2-formylphenylchromene-3-carboxylate **38** (Scheme 6). ^{1}H NMR spectrum of compound **38** lacked signals due to ethyl ester protons.

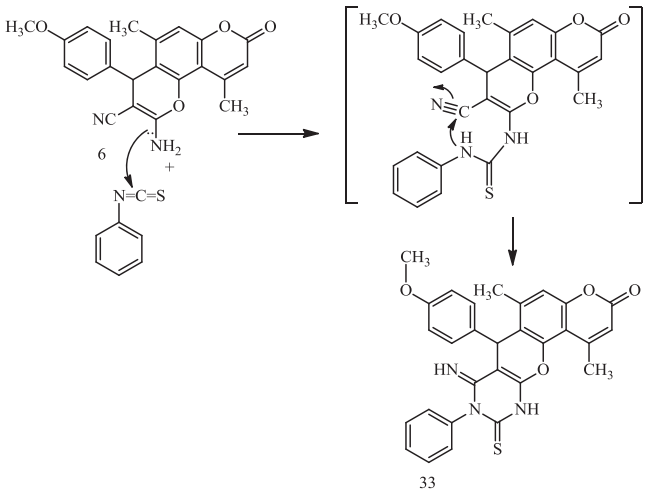


Figure 2. Postulated mechanism for synthesis of compound **33.**

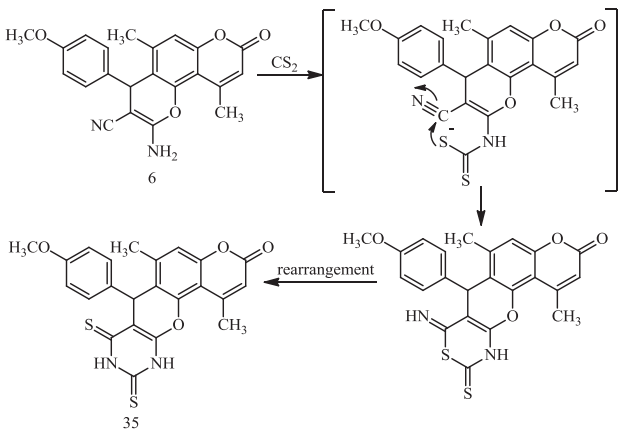


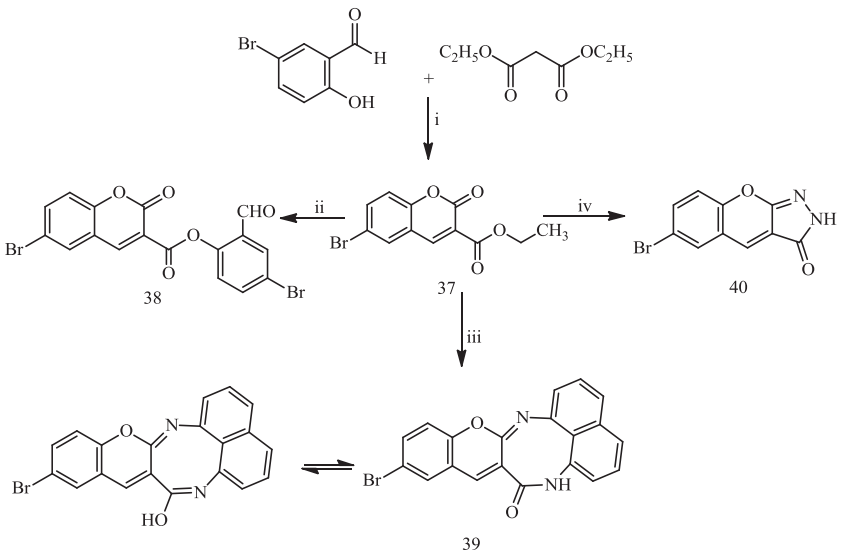
Figure 3. Postulated mechanism for synthesis of compound **35**.

However, it displayed a singlet signal at δ 7.81 ppm attributed to CHO proton.

In our investigation, the target chromenonaphthodiazocine derivative **39** was prepared by fusion of the ester derivative **37** with one equivalent of 1,8-diaminonaphthalene. IR spectrum of compound **39** lacked the absorption band of the coumarin carbonyl function and displayed absorption bands at 3446 and 3387 cm^{-1} due to tautomeric OH and NH functions, respectively, as well as absorption band at 1685 cm^{-1} attributed to the amidic carbonyl function.

The reaction of equivalent amounts of compound **37** and hydrazine hydrate in absolute ethanol yielded the chromenopyrazolone derivative **40** *via* the initial formation of the hydrazide intermediate which undergoes subsequent intramolecular condensation to yield the

Scheme 6. Reagents and conditions: (i) pipridine, gl.AcOH, C2H5OH/reflux; (ii) 5-bromosalicylaldehyde, KOH, C2H5OH/reflux; (iii) 1,8-diaminonaphthalene/fusion; (iv) NH2NH2 99%, C2H5OH/reflux.



cyclic compound **40**. IR spectrum of compound **40** lacked the absorption band characteristic for the coumarin carbonyl functions and revealed absorption bands at 3383 and 1685 cm^{-1} due to NH and amidic carbonyl function, respectively.

While the ^1H NMR spectrum of compound **40** revealed a deuterium oxide exchangeable singlet signal at δ 11.10 ppm due to NH proton.

In continuation for our study of different C_3-substituted coumarin derivatives, we carried out the synthesis of the oxiranylpropanoylcoumarin derivative **42** by refluxing equimolar amounts of epichlorohydrin and acetylcoumarin derivative **41** [28] in dimethylformamide in presence of potassium hydroxide (Scheme 7). IR spectrum of compound **42** revealed absorption bands at 3402 and 1725 cm^{-1} due to tautomeric OH and carbonyl functions, respectively.

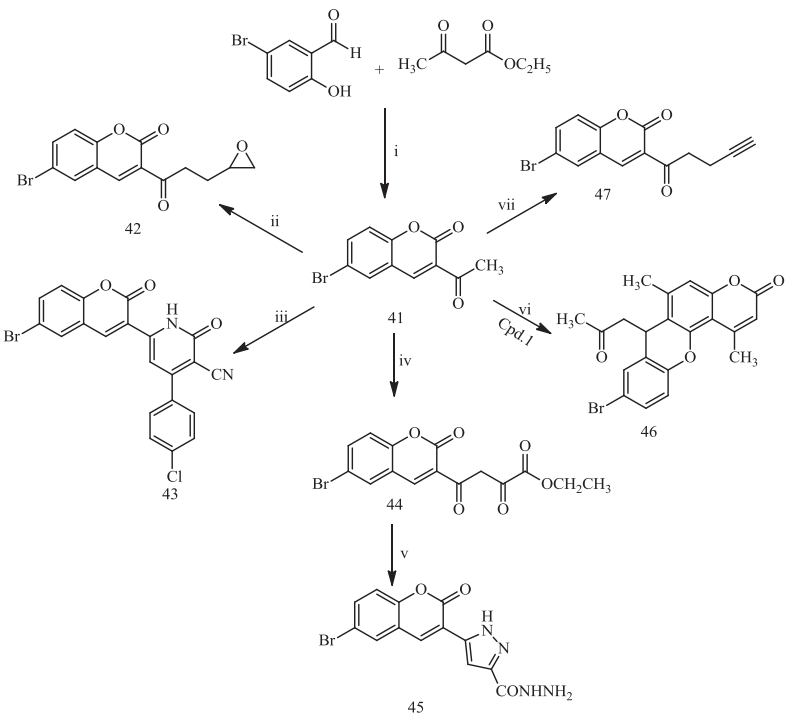
However, the target coumarinylpyridinone-3-carbonitrile derivative **43** was synthesized through the multicomponent condensation reaction of the acetylcoumarin derivative **41**, ethyl cyanoacetate, 4-chlorobenzaldehyde, and ammonium acetate in refluxing ethanol. ^1H NMR spectrum of compound **43** revealed a singlet signal at δ 7.00 ppm due to pyridine C_5 proton and two deuterium oxide exchangeable singlet signals at δ 8.15 and 9.80 ppm each integrated for half proton attributed to tautomeric OH and NH proton, respectively.

Ethyl coumarin-2,4-dioxobutanoate derivative **44** was prepared *via* Claisen condensation of equivalent amounts of the acetylcoumarin derivative **41** and diethyl oxalate by fusion. However, compound **44** upon reflux with excess hydrazine hydrate yielded the pyrazole-3-carbohydrazide analogue **45**. IR spectrum of compound **44** showed absorption bands at 1732 and 1693 cm^{-1} corresponding to carbonyl functions. While the IR spectrum of compound **45** showed absorption bands 3390, 3367, and 3128 cm^{-1} due NH and NH_2 functions. ^1H NMR spectrum of compound **45** revealed three deuterium oxide exchangeable singlet signals at δ 6.98, 7.11, and 7.23 ppm due to NH_2, amide NH, and pyrazole NH protons, respectively.

In addition, pyranoxanthene derivative **46** was prepared *via* refluxing equivalent amounts of the 5-hydroxycoumarin derivative **1** and acetylcoumarin derivative **41** in methanolic sodium methoxide (Fig. 4). ^1H NMR spectrum of compound **46** revealed a multiplet signal at δ 2.68–2.73 ppm corresponding to CH_2 proton, in addition to a deuterium oxide exchangeable singlet signals at δ 2.27 ppm due to tautomeric OH half proton.

Finally, pentynoylcoumarin derivative **47** was prepared *via* heating equimolar amounts of compound **41** and propargyl bromide in ethanolic sodium ethoxide. ^1H NMR spectrum of compound **47** displayed a singlet signal at δ 2.25 ppm due to the terminal acetylenic

Scheme 7. Reagents and conditions: (i) piperidine, R.T.; (ii) epichlorohydrin, KOH, DMF/reflux; (iii) 4-chlorobenzaldehyde,ethyl cyanoacetat, NH4OAc, C2H5OH/reflux; (iv) diethyl oxalate/fusion; (v) excess NH2NH2 99%/reflux; (vi) NaOCH3, CH3OH/reflux; (vii) propargyl bromide, NaOC2H5, C2H5OH/reflux.



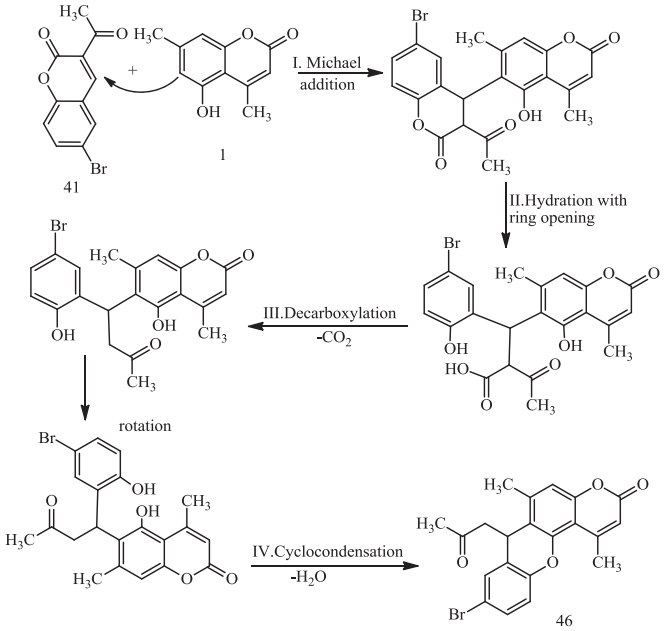


Figure 4. Postulated mechanism for synthesis of compound **46**.

Table 1

Six dose growth inhibition percent and IC_{50} values of the tested compounds against HepG2 cell line.

Sample concentration (μg/mL) Compound no.	Growth inhibition (%)						
	500	250	125	62.5	31.25	15.6	IC_{50} (μg/mL)
1	79.18	65.75	54.36	41.81	27.37	10.49	103
2	16.14	5.35	1.27	0	0	0	>500
3	69.11	38.58	21.04	8.53	2.75	0	344
4	63.07	31.83	15.35	7.69	1.56	0	395
6	81.24	76.98	71.09	63.51	57.65	38.07	25.1
8	58.28	17.94	10.72	3.63	0.59	0	449
10	37.51	15.29	7.65	1.28	0	0	>500
12	74.29	61.82	53.05	38.46	25.81	16.94	112
13	68.46	30.38	14.87	6.96	1.22	0	379
16	91.98	87.69	81.33	75.44	67.21	61.28	7.65
17	85.53	76.11	62.75	56.09	35.46	18.55	53.3
18	70.58	56.09	38.52	23.61	14.58	8.65	207
19	57.82	31.04	18.52	9.33	1.75	0	427
21	76.06	61.37	32.72	15.81	7.63	1.96	200
24	80.22	64.74	31.53	14.77	5.98	2.76	195
25	91.66	84.02	72.88	61.11	30.75	12.69	51.1
26	24.86	12.02	5.88	0.24	0	0	>500
27	78.63	67.94	40.82	23.77	10.43	5.88	167
28	63.26	39.08	25.83	11.51	5.93	2.38	363
29	68.22	35.71	18.34	7.55	1.37	0	360
30	59.35	36.82	20.96	8.57	1.24	0	396
31	57.04	27.18	14.81	7.64	1.29	0	441
32	71.66	30.88	11.53	5.84	0.22	0	367
33	61.84	53.62	21.96	13.59	4.87	1.28	236
34	69.35	51.74	20.38	9.87	2.58	0	243
35	89.76	78.61	69.18	54.77	35.82	21.35	54.6
36	86.18	71.24	60.92	25.83	14.78	6.86	106
37	88.64	79.42	68.21	55.37	38.73	27.87	52.4
38	70.39	51.71	20.87	13.96	7.65	1.38	243

(*Continues*)

Table 1

(*Continued*)

Sample concentration (μg/mL) Compound no.	Growth inhibition (%) 500	250	125	62.5	31.25	15.6	IC_{50} (μg/mL)
39	84.17	75.94	67.21	51.84	27.13	10.88	60.2
40	93.04	87.66	83.72	77.37	68.02	61.93	6.89
41	90.53	84.11	76.39	68.28	59.46	52.74	13.6
42	82.18	61.69	50.35	31.52	18.36	9.64	124
43	90.86	84.17	76.28	67.03	61.59	50.36	15.5
44	66.38	37.09	24.15	16.83	7.24	1.41	360
45	63.75	29.84	15.09	7.63	0.52	0	399
46	85.94	79.02	73.83	65.42	51.67	36.52	29.5
47	94.63	87.06	75.39	65.44	52.32	27.61	29.7
Cisplatin	96.92	95.69	93.25	87.61	77.02	68.13	3.67

Table 2

Six dose growth inhibition percent and IC_{50} values of the tested compounds against MCF7 cell line.

Sample concentration (μg/mL) Compound no.	Growth inhibition (%) 500	250	125	62.5	31.25	15.6	IC_{50} (μg/mL)
1	75.43	61.53	47.07	29.18	13.85	4.53	150
2	7.63	2.15	0	0	0	0	>500
3	63.51	34.88	18.02	9.33	1.96	0	382
4	51.94	20.72	8.57	1.33	0	0	484
6	69.18	60.25	51.37	37.66	21.85	7.51	119
8	27.19	10.48	3.93	0.16	0	0	>500
10	14.86	6.13	0.79	0	0	0	>500
12	63.11	46.79	25.62	14.87	8.26	2.02	299
13	79.58	61.83	45.04	19.37	8.52	1.24	162
16	90.38	85.44	77.63	69.58	61.25	37.62	23.8
17	78.64	65.82	54.78	32.71	18.57	9.33	111
18	61.27	49.32	30.59	11.28	4.87	1.08	264
19	78.26	59.63	27.82	10.44	3.59	0	212
21	70.52	59.15	26.06	10.85	1.94	0	215
24	86.15	71.26	60.38	52.11	18.53	4.78	60.5
25	93.72	85.64	76.09	64.77	32.18	15.84	48.3
26	35.19	19.38	5.97	0.24	0	0	>500
27	69.75	57.41	21.88	9.33	1.87	0	224
28	40.33	18.52	3.77	1.24	0	0	>500
29	68.46	52.72	28.04	10.96	3.77	0.53	236
30	62.11	35.85	13.77	5.92	0.35	0	385
31	91.69	83.24	67.52	54.98	26.71	10.3	57
32	73.03	24.38	13.77	4.64	0.58	0	382
33	50.48	25.81	10.47	3.22	0.59	0	495
34	58.33	37.66	18.05	7.63	1.48	0	399
35	72.14	60.33	47.66	29.15	15.69	7.94	148
36	89.26	78.13	65.38	31.07	20.44	5.82	97
37	82.11	73.57	59.15	47.12	29.08	13.59	77.5
38	61.26	43.15	18.58	7.63	2.02	0	345
39	73.66	62.19	54.81	37.62	20.44	8.58	108
40	91.25	85.11	77.64	68.16	60.47	53.22	14
41	91.21	81.96	73.25	61.59	50.75	38.68	30.2
42	78.4	63.43	25.72	12.85	5.74	1.28	205
43	89.06	82.18	73.27	64.72	52.75	29.41	29.4
44	63.08	30.12	12.79	2.96	0.14	0	401
45	67.44	52.87	29.71	13.88	4.78	0.53	235

(*Continues*)

Table 2

(*Continued*)

Sample concentration (μg/mL) Compound no.	Growth inhibition (%) 500	250	125	62.5	31.25	15.6	IC_{50} (μg/mL)
46	83.21	76.25	71.44	60.37	47.62	28.76	37.1
47	90.17	79.52	72.31	60.15	39.29	17.57	47.3
Cisplatin	96.28	95.02	92.17	85.32	76.21	65.38	5.71

proton and a multiplet due to two CH_2 protons at δ 3.20–3.58 ppm.

Anticancer screening. Thirty eight of the synthesized compounds were subjected to *in vitro* anticancer screening and six dose growth inhibition percent and IC_{50} values were calculated against mammalian hepatocellular carcinoma HepG2 and breast carcinoma MCF7 cell lines. Cytotoxicity evaluation using viability assay [29,30] was carried out in the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. Cisplatin was used as the reference drug in this study.

As revealed from the anticancer screening results presented in Tables 1 and 2, the 5-hydroxycoumarin derivative **1** did not exhibit anticancer activity against HepG2 and MCF7 cell lines. However, fusion of substituted pyran ring to the 5-hydroxycoumarin backbone as in compounds **2**, **3**, and **6** showed only weak anticancer activity of compound **6** against liver cancer HepG2 cell line. While attachment of another chromene nucleus to the coumarin backbone as in compounds **4** and **46** led only to the moderate to weak anticancer agent **46** against both cell lines. However, triazolothiadiazine moiety attached to the 5-hydroxycoumarin skeleton as in compound **8** diminished the anticancer activity against both cell lines. Structure modification of the moderately active pyranocoumarin derivative **6** by fusion with different substituted pyrimidine rings as in compounds **33–35** or tetrahydroquinoline as in compound **36** was found to diminish the anticancer activity against both HepG2 and MCF7 cell lines. Furthermore, attachement of a naphthodiazinone moiety to the chromene back bone led to very weak anticancer activity against both cell lines. However, fusion of substituted pyrazolone nucleus to the coumarin backbone in compound **40** led to highly potent anticancer activity against HepG2 cell line which showed nearly half potency of the reference drug Cisplatin and strong anticancer activity against MCF7 cell line. Finally, our attempts were extended to study the anticancer activity of compounds having different side chains or rings attached at 5, 6, or 3 positions of the coumarin nucleus as in compounds **10**, **12**, **13**, **16–19**, **21**, **23–32**, **38**, and **42–45**. It has been revealed that only compound **16** bearing 2-amino-4-(4-chlorophenyl)nicotinonitrile side chain attached to C_6 position of the coumarine backbone exhibited nearly half potency of the reference drug Cisplatin against HepG2 cell line and good anticancer activity against MCF7 cell line. Moreover, attachment of 4-chlorophenyl-2-hydroxypyridine-3-carbonitrile moiety at C_3 position of coumarin skeleton as in compound **43** resulted in strong activity against HepG2 and moderate activity against MCF7 cell lines, respectively. However, other substituted coumarin derivatives showed either very weak potency or inactivity against both cancer cell line.

CONCLUSIONS

It could be concluded that, among the tested compounds, compound **16**, **40**, and **43** bearing 2-amino-4-(4-chlorophenyl)nicotinonitrile side chain attached to C_6 position, fused pyrazolone ring or 4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile side chain attached at C_3 position of the coumarin backbone, respectively, exhibited moderate to highly potent anticancer activity against both HepG2 with IC_{50} values 6.89–15.5 μg/mL and MCF7cell lines with IC_{50} values 14–29.4 μg/mL.

EXPERIMENTAL

Chemistry. All melting points were taken on Electro thermal LA 9000 SERIS, Digital Melting Point Apparatus and were uncorrected. IR Spectra were determined using KBr disk technique on Nikolet IR 200 FT IR Spectrophotometer at Pharmaceutical Analytical Unit, Faculty of Pharmacy, Cairo University, and values are represented in cm^{-1}. The ^1H NMR Spectra was recorded in Varian Gemini EM-300 MHz, NMR Spectrometer at laboratories of the nuclear magnetic resonance, Chemical Warfare Department, Ministry of Defense, DMSO-d_6 was used as a solvent and Chemical shifts were measured in δ ppm, relative to TMS as internal standard. Mass Spectra were recorded at 70 ev on DI-50 unit of Schimadzu GC/MS-QP5050A Spectrometer at Regional Center for Mycology and

Biotechnology, Al-Azhar University. Microanalyses were carried out at Regional Center for Mycology and Biotechnology, Al-Azhar University.

Methyl 5,10-dimethyl-2,8-dioxo-2H,8H-pyrano[3,2-e]chromen-4-carboxylate (2). A mixture of 5-hydroxycoumarin derivative **1** (0.19 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.21 g, 0.18 mL, 1.5 mmol) was fused at 200–210°C for 5 h. The reaction mixture was allowed to cool then triturated with ethanol. The obtained precipitate was filtered, washed with ethanol, dried, and crystalized from ethanol/acetone mixture (3:1) to yield compound **2**. Brown powder; yield: 0.25 g (83%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{16}H_{12}O_6$ (300.26): C, 64.00; H, 4.03. Found (%): C, 64.36; H, 3.96. IR (KBr, cm^{-1}): 3003, 2954 (CH-aromatic); 2848 (CH-aliphatic); 1735, 1720 (C═O); 1560 (C═C). Mass spectrum, m/z (%): 300 ($M^{+\cdot}$, 1.67); 299 ($M^{+\cdot}-1$, 6.2); 43(100).

5,10-Dimethyl-2,8-dioxo-2H,8H-pyrano[3,2-e]chromen-4-acetic acid (3). An equimolar mixture of compound **1** (0.19 g, 1 mmol) and citric acid (0.19 g, 1 mmol) was fused at 200–210°C for 3 h. The reaction mixture was allowed to cool, then triturated with ethanol, the precipitated solid was filtered, washed with ethanol, and crystallized from dimethyl formamide to yield compound **3**. Dark brown powder; yield: 0.09 g (30%); m. p.: > 300°C. *Anal.* Calcd. (%) for $C_{16}H_{12}O_6$ (300.26): C, 64.00; H, 4.03. Found (%): C, 63.95; H, 4.11. IR (KBr, cm^{-1}): 3406 (broad OH); 3070, 2924 (CH-aromatic); 2854 (CH-aliphatic); 1720, 1700, 1674 (C═O); 1616 (C═C); 1273, 1087 (C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.25 (s, 3H, pyranocoumarin-C_5–CH_3); 2.50–2.53 (m, 5H, pyranocoumarin-C_{10}–CH_3 & CH_2); 6.02 (s, 1H, pyranocoumarin-C_9–H); 6.55 (s, 1H, pyranocoumarin-C_6–H); 6.59 (s, 1H, pyranocoumarin-C_3–H); 10.49 (s, 1H, OH, D_2O exchangeable). Mass spectrum, m/z (%): 300 ($M^{+\cdot}$, 1.38); 162 (100).

7-(4-Chlorophenyl)-1,6,10,10-tetramethyl-10,11-dihydropyrano[2,3-c]xanthene-3,8(7H,9H)-dione (4). An equimolar mixture of compound **1** (0.19 g, 1 mmol), dimedone (0.14 g, 1 mmol), and 4-chlorobenzaldehyde (0.14 g, 1 mmol) in absolute ethanol (20 mL) was heated under reflux in presence of a catalytic amount of piperidine (2 drops) for 12 h. The reaction mixture was left to cool, the obtained precipitate was filtered, washed with ethanol, and crystallized from ethanol to yield compound **4**. Yellow crystals; yield: 0.15 g (35%); m.p.: 253-255°C. *Anal.* Calcd. (%) for $C_{26}H_{23}ClO_4$ (434.91): C, 71.80; H, 5.33. Found (%): C, 72.07; H, 5.35. IR (KBr, cm^{-1}): 3070, 3061, 3045 (CH-aromatic); 2922, 2899 (CH-aliphatic); 1716, 1666 (C═O); 1614, 1591 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 0.87 (s, 3H, dihydropyranoxanthene-C_{10}–CH_3); 1.06 (s, 3H, dihydropyranoxanthene-C_{10}–CH_3); 2.18 (s, 3H, dihydropyranoxanthene-C_1–CH_3); 2.29 (s, 2H, dihydropyranoxanthene-C_{11}–H); 2.63 (s, 3H, dihydropyranoxanthene-C_6–CH_3); 2.70 (s, 2H, dihydropyranoxanthene-C_9–H); 5.03 (s, 1H, dihydropyranoxanthene-C_7–H); 6.33 (s, 1H, dihydropyranoxanthene-C_2–H); 7.06 (s, 1H, dihydropyranoxanthene-C_5–H); 7.19 (d, 2H, J = 8 Hz, 4-Cl–C_6H_4–$C_{2,6}$–H); 7.29 (d, 2H, J = 8 Hz, 4-Cl–C_6H_4–$C_{3,5}$–H).

2-Amino-5,10-dimethyl-4-(4-methoxyphenyl)-8-oxo-4H-pyrano[2,3-f]chromen-3-carbonitrile (6). An equimolar mixture of compound **1** (0.19 g, 1 mmol) and 2-(4-methoxybenzylidene)malononitrile **5** (0.18 g, 1 mmol) was heated under reflux in absolute ethanol (20 mL) in presence of a catalytic amount of piperidine (3 drops) for 3 h. The reaction mixture was left to cool, the obtained precipitate was filtered, washed with ethanol, and crystallized from ethanol to yield compound **6**. Yellow crystals; yield: 0.13 g (35%); m.p.: 260-262°C. *Anal.* Calcd. (%) for $C_{22}H_{18}N_2O_4$ (374.39): C, 70.58; H, 4.85; N, 7.48. Found (%): C, 70.81; H, 4.92; N, 7.76. IR (KBr, cm^{-1}): 3444, 3390 (NH_2); 3068, 3051, 3030 (CH-aromatic); 2929, 2820 (CH-aliphatic); 2222 (CN); 1690 (C═O); 1604 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.28 (s, 3H, pyranocoumarin-C_{10}–CH_3); 2.55 (s, 3H, pyranocoumarin-C_5–CH_3); 3.25 (s, 3H, OCH_3, under DMSO); 3.89 (s, 2H, NH_2, D_2O exchangeable); 4.03 (s, 1H, pyranocoumarin-C_4-H); 6.03 (s, 1H, pyranocoumarin-C_9–H); 6.58 (s, 1H, pyranocoumarin-C_6–H); 7.18 (d, 2H, J = 8.5 Hz, 4-OCH_3–C_6H_4–$C_{3,5}$–H); 7.98 (d, 2H, J = 8.5 Hz, 4-OCH_3–C_6H_4–$C_{2,6}$–H).

1,6-Dimethyl-10-(trifluoromethyl)chromeno[5,6-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3(12H)-one (8). A mixture of compound **1** (0.19 g, 1 mmol) and the amino triazole derivative **7** (0.37 g, 2 mmol) was heated under reflux in dimethylsulfoxide (15 mL) for 10 h. The precipitated solid was filtered while hot, washed with various solvents, and dried to yield compound **8**. Dark brown powder; yield: 0.3 g (86%); m. p.: >300°C. *Anal.* Calcd. (%) for $C_{14}H_9F_3N_4O_2S$ (354.31): C, 47.46; H, 2.56; N, 15.81; S, 9.05. Found (%): C, 47.69; H, 2.54; N, 16.07; S, 9.17. IR (KBr, cm^{-1}): 3427 (NH); 2924 (CH-aromatic); 2852, 2810 (CH-aliphatic); 1700 (C═O); 1618 (C═N); 1570 (C═C). Mass spectrum, m/z (%): 356 ($M^{+\cdot}$+2, 3.95); 354 ($M^{+\cdot}$, 7.35); 55 (100).

5-(3-(4-Chlorophenyl)-1H-1,2,4-triazol-5-ylamino)-4,7-dimethyl-2H-chromen-2-one (10). A mixture of compound **1** (0.19 g, 1 mmol) and the aminotriazole derivative **9** (0.19 g, 1 mmol) was heated under reflux in dimethyl sulfoxide (15 mL) for 10 h. The reaction mixture was allowed to cool, then triturated with ethanol. The precipitated solid was filtered, washed with various solvents, and dried to yield compound **10**. Yellow powder; yield: 0.08 g (22%), m.p.: >300°C. *Anal.* Calcd. (%) for $C_{19}H_{15}ClN_4O_2$ (366.8): C, 62.21; H, 4.12; N, 15.27. Found (%): C, 62.44; H, 4.20; N, 15.56. IR (KBr, cm^{-1}): 3400, 3240 (NH); 3060, 2932 (CH-aromatic);

2880, 2840 (CH-aliphatic); 1700 (C═O); 1600 (C═N); 1570 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.23 (s, 3H, coumarin-C_4–CH_3); 2.03 (s, 3H, coumarin-C_7–CH_3); 7.55–7.70 (m, 3H, coumarin-$C_{3,6,8}$–H); 7.92–8.00 (m, 4H, 4-Cl–C_6H_4); 8.12 (s, 1H, coumarin-C_5–NH, D_2O exchangeable); 12.24 (s, 1H, triazole-NH, D_2O exchangeable). Mass spectrum, m/z (%): 368 ($M^{+\cdot}$ +2, 1.80); 366 ($M^{+\cdot}$, 3.59); 71 (100).

6-Cinnamoyl-5-hydroxy-4,7-dimethyl-2H-chromen-2-one (12). An equimolar mixture of compound **1** (0.19 g, 1 mmol) and cinamoyl chloride **11** (0.17 g, 1 mmol) was fused at 190–205°C for 10 h. The reaction mixture was allowed to cool, then triturated with ethanol and the obtained solid was filtered, washed with ethanol, dried, and crystallized from dimethyl formamide to yield compound **12**. Dark brown powder; yield: 0.1 g (31%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{20}H_{16}O_4$ (320.34): C, 74.99; H, 5.03. Found (%): C, 75.23; H, 5.08. IR (KBr, cm^{-1}): 3427 (broad OH); 3000, 2990 (CH-aromatic); 2924 (CH-aliphatic); 1732, 1716 (C═O); 1614 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.21 (s, 3H, coumarin-C_4–CH_3); 2.27 (s, 3H, coumarin-C_7–CH_3); 6.02 (s, 1H, coumarin-C_3–H); 6.32 (s, 1H, coumarin-C_8–H); 6.56–6.60 (m, 1H, –CH═CH–C_6H_5); 7.07–7.14 (m, 1H, –CH═CH–C_6H_5); 7.20–7.40 (m, 3H, C_6H_5–$C_{3,4,5}$–H); 7.42–7.59 (m, 2H, C_6H_5–$C_{2,6}$–H); 10.49 (s, 1H, OH, D_2O exchangeable). Mass spectrum, m/z (%): 320 ($M^{+\cdot}$, 3.75); 44 (100).

6,6′-((4-Methoxyphenyl)methylene)bis(5-hydroxy-4,7-dimethyl-2H-chromen-2-one) (13). A mixture of compound **1** (0.38 g, 2 mmol) and 4-methoxybenzaldehyde (0.14 g, 0.13 mL, 1 mmol) was fused at 200–210°C for 5 h. The reaction mixture was allowed to cool, then triturated with ethanol. The precipitated solid was filtered, washed with ethanol, dried, and crystallized from dimethyl formamide to yield compound **13**. Dark brown powder; yield: 0.4 g (40%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{30}H_{26}O_7$ (498.52): C, 72.28; H, 5.26. Found (%): C, 72.49; H, 5.34. IR (KBr, cm^{-1}): 3406 (broad OH); 3066, 2951 (CH-aromatic); 2927, 2860 (CH-aliphatic); 1720 (C═O); 1604 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.16 (s, 6H, two coumarin-C_4–CH_3); 2.26 (s, 6H, two coumarin-C_7–CH_3); 3.68 (s, 3H, OCH_3); 6.03 (s, 1H, -CH-(coumarin)); 6.56 (s, 2H, two coumarin-C_3–H); 6.60 (s, 2H, two coumarin-C_8–H); 6.98–7.05 (m, 2H, 4-OCH_3–C_6H_4–$C_{3,5}$–H); 7.41–7.60 (m, 2H, 4-OCH_3–C_6H_4–$C_{2,6}$–H); 10.14 (s, 1H, OH, D_2O exchangeable); 10.51 (s, 1H, H-bonded-OH, D_2O exchangeable). Mass spectrum, m/z (%): 498 ($M^{+\cdot}$, 1); 162 (100).

2-Amino-4-(4-chlorophenyl)-6-(5-hydroxy-4,7-dimethyl-2-oxo-2H-chromen-6-yl)nicotine-nitrile (16). A mixture of 6-acetyl-5-hydroxy-coumarin derivative **15** (1.16 g, 5 mmol), malononitrile (0.33 g, 5 mmol), 4-chlorobenzaldehyde (0.7 g, 5 mmol), and ammonium acetate (0.77 g, 10 mmol) was heated under reflux in absolute ethanol (20 mL) for 30 h. The reaction mixture was left to cool and poured onto crushed ice; the obtained precipitate was filtered, washed with water, dried, and crystallized from ethanol to yield compound **16**. Brown powder; yield: 1.5 g (72%); m.p.: 228–230°C. *Anal.* Calcd. (%) for $C_{23}H_{16}ClN_3O_3$ (417.84): C, 66.11; H, 3.86; N, 10.06. Found (%): C, 66.42; H, 3.89; N, 10.40. IR (KBr, cm^{-1}): 3428 (OH); 3342, 3214 (NH_2); 3000, 2950 (CH-aromatic); 2880, 2860 (CH-aliphatic); 2205 (CN); 1700 (C═O); 1638 (C═N); 1549 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.23 (s, 3H, coumarin-C_4–CH_3); 2.30 (s, 3H, coumarin-C_7–CH_3); 6.90 (s, 1H, coumarin-C_3–H); 7.28 (s, 3H, OH & NH_2, D_2O exchangeable); 7.36 (s, 1H, coumarin-C_8–H); 7.46 (s, 1H, pyridinyl-C_5–H); 7.50 (d, 2H, J = 8.7 Hz, 4-Cl–C_6H_4–$C_{3,5}$–H); 7.58 (d, 2H, J = 8.7 Hz, 4-Cl–C_6H_4–$C_{2,6}$–H). Mass spectrum, m/z (%): 419 ($M^{+\cdot}$ +2, 1.77); 417 ($M^{+\cdot}$, 4.43); 81 (100).

1-(5-Hydroxy-4,7-dimethyl-2oxo-2H-chromen-6-yl)-3-phenylpropane-1,3-dione (17). Equimolar amounts of compound **15** (0.23 g, 1 mmol) and benzoyl chloride (0.14 g, 0.12 mL, 1 mmol) were heated under reflux in pyridine (15 mL) in presence of potassium hydroxide (0.084 g, 1.5 mmol) for 10 h. The reaction mixture was left to cool and poured onto crushed ice; the obtained precipitate was filtered, washed with water, dried, and recrystallized from hexane to yield compound **17**. White crystals; yield: 0.25 g (74%); m.p.:136–138°C. *Anal.* Calcd. (%) for $C_{20}H_{16}O_5$ (336.34): C, 71.42; H, 4.79. Found (%): C, 71.68; H, 4.87. IR (KBr, cm^{-1}): 3400 (broad OH); 3070, 3012, 2956 (CH-aromatic); 2883, 2837 (CH-aliphatic); 1710, 1685 (C═O); 1610 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.23 (s, 3H, coumarin-C_4–CH_3); 2.40 (s, 3H, coumarin-C_7–CH_3); 3.27 (s, 2H, CH_2, under DMSO); 7.40–7.56 (m, 2H, coumarin-$C_{3,8}$–H); 7.59–7.64 (m, 3H, C_6H_5–$C_{3,4,5}$–H); 7.91 (d, 2H, J = 8.1 Hz, C_6H_5–$C_{2,6}$–H); 12.87 (s, 1H, OH, D_2O exchangeable). Mass spectrum, m/z (%): 337 ($M^{+\cdot}$ +1, 3.43); 336 ($M^{+\cdot}$, 10.78); 71 (100).

5-Hydroxy-4,7-dimethyl-2-oxo-2H-chromene-6-carboxamidine (18). An equimolar mixture of compound **1** (2.35 g, 12.4 mmol) and cyanamide (1.04 g, 24.8 mmol) was fused at 200–210°C for 12 h. The reaction mixture was allowed to cool, then triturated with ethanol and the obtained solid product was filtered, washed with ethanol, dried, and crystallized from dimethyl formamide to yield compound **18**. Brown powder; yield: 1.9 g (66%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{12}H_{12}N_2O_3$ (232.24): C, 62.06; H, 5.21; N, 12.06. Found (%): C, 62.23; H, 5.27; N, 12.19. IR (KBr, cm^{-1}): 3417 (OH); 3334, 3200, 3130 (NH & NH_2); 1680 (C═O); 1622 (C═N); 1548 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.90 (s, 3H, coumarin-C_4–CH_3); 2.27 (s, 3H, coumarin-C_7–CH_3); 2.53 (s, 2H, NH_2, D_2O exchangeable); 6.04 (s, 1H, coumarin-C_3–H); 6.09

(s, 1H, imine NH, D_2O exchangeable); 6.57 (s, 1H, coumarin-C_8–H); 10.52 (s, 1H, OH, D_2O exchangeable).

5-(3-Chloro-2-oxopropoxy)-4,7-dimethyl-2H-chromen-2-one (19). An equimolar mixture of compound **1** (0.19 g, 1 mmol) and 1,3-dichloroacetone (0.13 g, 1 mmol) was heated under reflux in ethanolic sodium ethoxide [prepared by dissolving (0.05 g, 2 mmol) of sodium metal in 5 mL ethanol] for 24 h. The reaction mixture was allowed to cool, then poured onto crushed ice. The formed precipitate was filtered, washed with water, dried, and crystallized from toluene/ethanol mixture (3:1) to yield compound **19**. Brown powder; yield: 0.15 g (54%); m.p.: > 300°C. *Anal.* Calcd. (%) for $C_{14}H_{13}ClO_4$ (280.70): C, 59.90; H, 4.67; Found (%): C, 60.27; H, 4.78. IR (KBr, cm^{-1}): 3390 (broad OH); 2960, 2926 (CH-aromatic); 2854 (CH-aliphatic); 1722, 1681 (C═O); 1620 (C═C). Mass spectrum, m/z (%): 282 ($M^{+\cdot}$ +2, 0. 85); 280 ($M^{+\cdot}$, 4.58); 78 (100).

1-(2-(4,7-Dimethyl-2-oxo-2H-chromen-5-yloxy)acetyl) thiosemicarbazide (21). An equimolar mixture of the methyl acetate derivative **20** (0.26 g, 1 mmol) and thiosemicarbazide (0.09 g, 1 mmol) was heated under reflux in pyridine (15 mL) for 5 h. The reaction mixture was allowed to cool, then poured onto crushed ice; the obtained precipitate was filtered, washed with water, dried, and crystalized from dimethyl formamide to yield compound **21**. Brown powder; yield: 0.18 g (56%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{14}H_{15}N_3O_4S$ (321.35): C, 52.33; H, 4.70; N, 13.08. Found (%): C, 52.61; H, 4.79; N, 13.34. IR (KBr, cm^{-1}): 3363, 3300, 3280, 3213 (NH & NH_2); 2974, 2924 (CH-aromatic); 2854 (CH-aliphatic); 1724, 1670 (C═O); 1604 (C═C). ^1H NMR (DMSO-d_6, δ ppm): 1.33 (s, 3H, coumarin-C_4–CH_3); 2.27 (s, 3H, coumarin-C_7–CH_3); 4.55 (s, 2H, CH_2); 6.03 (s, 1H, coumarin-C_3–H); 6.56 (s, 1H, coumarin-C_6–H); 6.60 (s, 1H, coumarin-C_8–H); 6.81 (s, 2H, NH_2, D_2O exchangeable); 6.92 (s, 1H, –CS–NH, D_2O exchangeable); 10.52 (s, 1H, –NHCO, D_2O exchangeable). Mass spectrum, m/z (%): 322 ($M^{+\cdot}$ +1, 6.14); 321 ($M^{+\cdot}$, 18.89); 54 (100).

Potassium2-(2-(4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)-acetyl)hydrazinecarbodithioate (23). A mixture of the acetohydrazide derivative **22** (0.26 g, 1 mmol) in absolute ethanol (15 mL) containing potassium hydroxide (0.06 g, 1 mmol) was treated with carbon disulfide (0.07 g, 0.06 mL, 1 mmol) and stirred at room temperature for 12 h. The obtained precipitate was filtered, washed with ethanol, and dried to yield compound **23** that was used as such in the next steps. White powder; yield: 0.15 g (39%); m.p.: >300°C.

4,7-Dimethyl-5-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) methoxy)-2H-chromen-2-one (24). A solution of the potassium salt of the hydrazinecarbodithioate derivative **23** (0.38 g, 1 mmol) in absolute ethanol (20 mL) was heated under reflux for 20 h. The reaction mixture was filtered while hot and the filtrate was concentrated. The filtrate was allowed to stand overnight to yield a precipitate that was collected, washed with ethanol, dried, and crystallized from dimethyl formamide to yield compound **24**. White powder, yield: 0.12 g (40%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{14}H_{12}N_2O_4S$ (304.32): C, 55.25; H, 3.97; N, 9.21. Found (%): C, 55.38; H, 4.11; N, 9.43. IR (KBr, cm^{-1}): 3250 (NH); 2958, 2927 (CH-aromatic); 2885 (CH-aliphatic); 1720 (C═O); 1620 (C═N); 1570 (C═C); 1570, 1492, 1296, 941 (I, II, III, IV bands of N–C═S). ^1H NMR (DMSO-d_6, δ ppm): 1.69 (s, 3H, coumarin-C_4–CH_3); 2.35 (s, 3H, coumarin-C_7–CH_3); 5.15 (s, 2H, CH_2); 6.12 (s, 1H, coumarin-C_3–H); 6.47 (s, 1H, NH, D_2O exchangeable); 6.82 (s, 1H, coumarin-C_6–H); 6.95 (s, 1H, coumarin-C_8–H). Mass spectrum, m/z (%): 305 ($M^{+\cdot}$ +1, 2.49); 304 ($M^{+\cdot}$, 6.32); 162 (100).

4,7-Dimethyl-5-((5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl) methoxy)-2H-chromen-2-one (25). Compound **23** (0.38 g, 1 mmol) was stirred at room temperature for 20 h in absolute ethanol/concentrated sulfuric acid mixture (8:2) (10 mL). The reaction mixture was poured onto distilled water and the obtained precipitate was filtered, washed with water, dried, and crystallized from dimethyl formamide to yield compound **25**. White powder; yield: 0.22 g (69%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{14}H_{12}N_2O_3S_2$ (320.39): C, 52.48; H, 3.78; N, 8.74. Found (%): C, 52.76; H, 3.72; N, 8.98. IR (KBr, cm^{-1}): 3220 (NH); 2927 (CH-aromatic); 2854 (CH-aliphatic); 1720 (C═O); 1640 (C═N); 1620 (C═C); 1555, 1485, 1280, 940 (I, II, III, IV bands of N–C═S). ^1H NMR (DMSO-d_6, δ ppm): 2.33 (s, 3H, coumarin-C_4–CH_3); 2.58 (s, 3H, coumarin-C_7–CH_3); 4.80 (s, 2H, CH_2); 6.12 (s, 1H, coumarin-C_3–H); 6.74 (s, 1H, coumarin-C_6–H); 6.80 (s, 1H, coumarin-C_8–H); 12.99 (s, 1H, NH, D_2O exchangeable). Mass spectrum, m/z (%): 321 ($M^{+\cdot}$ +1, 15.24); 320 ($M^{+\cdot}$, 28.73); 313 (100).

5-((4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methoxy)-4,7-dimethyl-2H-chromen-2-one (26). Compound **23** (0.38 g, 1 mmol) was fused with hydrazin hydrate (0.03 g, 0.03 mL, 1 mmol) at 230–240°C for 5 h. The reaction mixture was allowed to cool, then triturated with ethanol, the formed precipitate was filtered, washed with ethanol, and boiled in different solvents to yield compound **26**. Dark brown powder; yield: 0.25 g (78%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{14}H_{14}N_4O_3S$ (318.35): C, 52.82; H, 4.43; N, 17.60. Found (%): C, 53.07; H, 4.52; N, 17.89. IR (KBr, cm^{-1}): 3394, 3356, 3336 (NH & NH_2); 3032, 3012 (CH-aromatic); 2924, 2854 (CH-aliphatic); 1700 (C═O); 1640 (C═N); 1600 (C═C). Mass spectrum, m/z (%): 318 ($M^{+\cdot}$, 4.11); 42 (100).

2-(4,7-Dimethyl-2-oxo-2H-chromen-5-yloxy)-N-(2-hydroxyethyl) acetamide (27). A mixture of compound **20** (1.37 g, 5 mmol) and ethanolamine (0.037 g, 0.37 mL, 6 mmol) was fused at 140–145°C for 10 h. The reaction mixture

was allowed to cool, then poured onto crushed ice; the obtained precipitate was filtered, washed with water, dried, and washed with different solvents to yield compound **27**. Yellow powder; yield: 0.6 g (40%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{15}H_{17}NO_5$ (291.30): C, 61.85; H, 5.88; N, 4.81. Found (%): C, 62.17; H, 5.92; N, 4.89. IR (KBr, cm^{-1}): 3421 (broad OH); 3300 (NH); 2924 (CH-aromatic); 2854 (CH-aliphatic); 1743, 1685 (C═O); 1595 (C═C). Mass spectrum, m/z (%): 292 ($M^{+\cdot}$ +1, 2.29); 291 ($M^{+\cdot}$, 2.59); 43 (100).

5-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4,7-dimethyl-2H-chromen-2-one (28). A mixture of compound **22** (0.26 g, 1 mmol) and acetylacetone (0.2 g, 0.2 mL, 2 mmol) was fused for 5 h. The reaction mixture was allowed to cool, then triturated with ethanol to precipitate a solid that was filtered, washed with ethanol, dried, and crystalized from dimethyl formamide to yield compound **28**. Dark brown powder; yield: 0.2 g (61%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{18}H_{18}N_2O_4$ (326.35): C, 66.25; H, 5.56; N, 8.58. Found (%): C, 66.13; H, 5.67; N, 8.90. IR (KBr, cm^{-1}): 3420 (broad OH tautomer); 3097, 3066 (CH-aromatic); 2924, 2854 (CH-aliphatic); 1716, 1678 (C═O); 1612 (C═N); 1590 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.26 (s, 3H, coumarin-C_4–CH_3); 2.33 (s, 3H, coumarin-C_7–CH_3); 2.52 (s, 3H, pyrazole-C_3–CH_3); 2.58 (s, 3H, pyrazole-C_5–CH_3); 4.79 (s, 1H, CH_2); 6.03 (s, ½ H, –CH═C(OH) tautomer); 6.12 (s, 1H, coumarin-C_3–H); 6.55 (s, 1H, coumarin-C_6–H); 6.60 (s, 1H, coumarin-C_8–H); 6.74 (s, 1H, pyrazole-C_4–H); 10.51 (s, ½H, OH tautomer, D_2O exchangeable). Mass spectrum, m/z (%): 326 ($M^{+\cdot}$, 5.57); 43 (100).

5-(2-(5-Amino-3-hydroxy-1H-pyrazol-1-yl)-2-oxoethoxy)-4,7-dimethyl-2H-chromen-2-one (29). An equimolar mixture of compound **22** (0.26 g, 1 mmol) and ethyl cyanoacetate (0.11 g, 0.11 mL, 1 mmol) in dimethyl formamide (10 mL) was heated under reflux for 5 h. The reaction mixture was allowed to cool, the obtained precipitate was filtered while hot, washed with ethanol, dried, and crystalized from dimethyl formamide to yield compound **29**. Brown powder; yield: 0.25 g (76%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{16}H_{15}N_3O_5$ (329.31): C, 58.36; H, 4.59; N, 12.76. Found (%): C, 58.64; H, 4.67; N, 13.02. IR (KBr, cm^{-1}): 3406 (OH); 3300, 3200 (NH_2); 3020, 2924 (CH-aromatic); 2854 (CH-aliphatic); 1727, 1654 (C═O); 1616 (C═N); 1570 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.33 (s, 3H, coumarin-C_4–CH_3); 2.56 (s, 3H, coumarin-C_7–CH_3); 3.75 (s, 2H, NH_2, D_2O exchangeable); 4.75 (s, 2H, CH_2); 6.13 (s, 1H, coumarin-C_3–H); 6.73 (s, 1H, coumarin-C_6–H); 6.82 (s, 1H, coumarin-C_8–H); 7.92 (s, 1H, pyrazole-C_4–H); 10.28 (s, 1H, OH, D_2O exchangeable). Mass spectrum, m/z (%): 329 ($M^{+\cdot}$, 1.06); 72 (100).

5-(2-(5-Hydroxy-3-methyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4,7-dimethyl-2H-chromen-2-one (30). An equimolar mixture of the acetohydrazide derivative **22** (0.26 g, 1 mmol) and ethyl acetoacetate (0.13 g, 0.13 mL, 1 mmol) was fused at 170–180°C for 5 h. The reaction mixture was allowed to cool, then triturated with ethanol, the obtained precipitate was filtered, washed with ethanol, dried, and boiled in different solvents to yield compound **30**. Dark brown powder; yield: 0.21 g (64%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{17}H_{16}N_2O_5$ (328.32): C, 62.19; H, 4.91; N, 8.53. Found (%): C, 62.43; H, 4.98; N, 8.71. IR (KBr, cm^{-1}): 3421 (broad OH); 3097, 3062 (CH-aromatic); 2924, 2854 (CH-aliphatic); 1716, 1685 (C═O); 1612 (C═N); 1565 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.20 (s, 3H, coumarin-C_4–CH_3); 2.25 (s, 3H, coumarin-C_7–CH_3); 2.31 (s, 3H, pyrazole-C_3–CH_3); 4.87 (s, 2H, CH_2); 6.11 (s, 1H, coumarin-C_3–H); 6.54 (s, 1H, coumarin-C_6–H); 6.79 (s, 1H, coumarin-C_8–H); 7.34 (s, 1H, pyrazole-C_4–H); 10.49 (s, 1H, OH, D_2O exchangeable). Mass spectrum, m/z (%): 329 ($M^{+\cdot}$ +1, 1.01); 328 ($M^{+\cdot}$, 1.58); 276 (100).

1-(2-(4,7-Dimethyl-2-oxo-2H-chromen-5-yloxy)acetyl) pyrazolidine-3,5-dione (31). An equimolar mixture of the acetohydrazide derivative **22** (0.26 g, 1 mmol) and diethyl malonate (0.16 g, 0.15 mL, 1 mmol) was fused at 170–180°C for 5 h. The reaction mixture was allowed to cool, then triturated with ethanol, the obtained precipitate was filtered, washed with ethanol, dried, and crystalized from dimethyl formamide to yield compound **31**. Yellow powder; yield: 0.23 g (70%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{16}H_{14}N_2O_6$ (330.29): C, 58.18; H, 4.27; N, 8.48. Found (%): C, 58.40; H, 4.31; N, 8.65. IR (KBr, cm^{-1}): 3402 (NH); 3070, 2974 (CH-aromatic); 2924, 2854 (CH-aliphatic); 1724, 1697, 1658 (C═O); 1620 (C═N); 1600 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.33 (s, 3H, coumarin-C_4–CH_3); 2.57 (s, 3H, coumarin-C_7–CH_3); 4.75 (s, 2H, CH_2); 4.82 (s, 2H, pyrazole-CH_2); 6.13 (s, 1H, coumarin-C_3–H); 6.74 (s, 1H, coumarin-C_6–H); 6.82 (s, 1H, coumarin-C_8–H); 9.61 (s, ½H, OH, D_2O exchangeable); 10.23 (s, ½H, NH, D_2O exchangeable). Mass spectrum, m/z (%): 330 ($M^{+\cdot}$, 1.13); 43 (100).

N-(2-(4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetyl) benzohydrazide (32). An equimolar mixture compound **22** (0.26 g, 1 mmol) and benzoyl chloride (0.14 g, 0.12 mL, 1 mmol) was fused at 170–180°C for 5 h. The reaction mixture was allowed to cool, then triturated with ethanol, the obtained precipitate was filtered, washed with ethanol, dried, and boiled in different solvents to yield compound **32**. Dark brown powder; yield: 0.22 g (59%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{20}H_{18}N_2O_5$ (366.37): C, 65.57; H, 4.95; N, 7.65. Found (%): C, 65.82; H, 4.89; N, 7.89. IR (KBr, cm^{-1}): 3429 (OH); 3300, 3220 (NH); 3059, 3032, 2978 (CH-aromatic); 2854 (CH-aliphatic); 1743, 1680, 1658 (C═O); 1597 (C═N); 1577 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.70 (s, 3H, coumarin-C_4–CH_3); 2.86 (s, 3H, coumarin-C_7–CH_3); 4.28 (s, 2H, CH_2); 7.32 (s, 1H, coumarin-C_3–H); 7.40–750 (m, 4H, coumarin-$C_{6,8}$–H & two NH); 7.51–7.68 (m, 3H,

C_6H_5–$C_{3,4,5}$–H); 7.85–8.00 (m, 2H, C_6H_5–$C_{2,6}$–H). Mass spectrum, m/z (%): 367 ($M^{+\cdot}$ + 1, 11.51); 366 ($M^{+\cdot}$, 21.58); 365 ($M^{+\cdot}-1$, 7.21); 43 (100).

4-Imino-6,11-dimethyl-5-(4-methoxyphenyl)-9-oxo-3-phenyl-pyrano[2⁻,3⁻:2,3]chromeno [2,3-d]-pyrimidine-2-(1H,5H)thione (33). An equimolar mixture of the 2-aminopyrano-coumarin-3-carbonitrile derivative **6** (0.37 g, 1 mmol) and phenyl isothiocyanate (0.14 g, 0.13 mL, 1 mmol) was heated under reflux in pyridine (10 mL) for 10 h. The reaction mixture was allowed to cool, poured onto crushed ice, and triturated with few drops of dilute hydrochloric acid (10%), the precipitated solid was filtered, washed with water, dried, and boiled in different solvents to yield compound **33**. Dark brown powder; yield: 0.27 g (53%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{29}H_{23}N_3O_4S$ (509.58): C, 68.35; H, 4.55; N, 8.25; S, 6.29. Found (%): C, 68.57; H, 4.51; N, 8.49; S, 6.34. IR (KBr, cm^{-1}) 3380, 3360 (NH); 3062, 2924 (CH-aromatic); 2854 (CH-aliphatic); 1716 (C═O); 1625 (C═N); 1597 (C═C); 1543, 1438, 1253, 1029 (I, II, III, IV bands of N–C═S). Mass spectrum, m/z (%): 509 ($M^{+\cdot}$, 1); 57 (100).

4-Amino-6,11-dimethyl-5-(4-methoxyphenyl)-9-oxo-5H-pyrano [2⁻,3⁻:2,3]chromeno[2,3-d] pyrimidine (34). Compound **6** (0.37 g, 1 mmol) was heated under reflux in excess formamide solution (5 mL) for 2 h. The reaction mixture was allowed to cool, then triturated with ethanol and the precipitated solid was filtered, washed with ethanol, boiled in different solvents to yield compound **34**. Dark brown powder; yield: 0.3 g (75%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{23}H_{19}N_3O_4$ (401.41): C, 68.82; H, 4.77; N, 10.47. Found (%): C, 69.04; H, 4.85; N, 10.69. IR (KBr, cm^{-1}): 3309, 3163 (NH_2); 3088, 3066, 3014 (CH-aromatic); 2900, 2882 (CH-aliphatic); 1680 (C═O); 1640 (C═N); 1595 (C═C). Mass spectrum, m/z (%): 401 ($M^{+\cdot}$, 1); 69 (100).

6,11-Dimethyl-5-(4-methoxyphenyl)-9-oxo-pyrano[2⁻,3⁻:2,3] chromeno[2,3-d]pyrimidine-2,4(1H,3H,5H)dithione (35). To a solution of compound **6** (0.37 g, 1 mmol) in absolute ethanol (15 mL), carbon disulfide (0.08 g, 0.06 mL,1 mmol) and potassium hydroxide (0.06 g, 1 mmol) were added. The reaction mixture was heated under reflux for 20 h. The reaction mixture was allowed to cool and then poured onto crushed ice; the precipitated solid was filtered, washed with water, dried, and crystallized from ethanol to yield compound **35**. Yellow powder; yield: 0.34 g (76%); m.p.: 260–262°C. *Anal.* Calcd. (%) for $C_{23}H_{18}N_2O_4S_2$ (450.53): C, 61.32; H, 4.03; N, 6.22; S, 14.23. Found (%): C, 61.47; H, 4.01; N, 6.30; S, 14.37. IR (KBr, cm^{-1}): 3390, 3292 (NH); 3049, 3014 (CH-aromatic); 2887, 2872 (CH-aliphatic); 1654 (C═O); 1612 (C═N); 1558 (C═C); 1512 1448, 1296, 1099 (I, II, III, IV bands of N–C═S). Mass spectrum, m/z (%): 452 ($M^{+\cdot}$ +2, 5.80); 450 ($M^{+\cdot}$, 6.18); 73 (100).

11-Amino-4,13-dimethyl-12-(4-methoxyphenyl)-7,8,9,10-tetrahydro-2-oxo-12H-pyrano[2⁻,3⁻ :2,3]chromeno[2,3-b]quinoline (36). An equimolar mixture of compound **6** (3.7 g, 10 mmol) and cyclohexanone (0.98 g, 1 mL, 10 mmol) was heated under reflux in dimethyl formamide (10 mL) containing zinc chloride (0.68 g, 5 mmol) for 5 h. The reaction mixture was allowed to cool, poured onto crushed ice, and triturated with few drops of dilute hydrochloric acid (10%); the obtained solid was filtered, washed with water, dried, and crystallized from dimethyl formamide to yield compound **36**. Brown powder; yield: 3.5 g (77%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{28}H_{26}N_2O_4$ (454.52): C, 73.99; H, 5.77; N, 6.16. Found (%): C, 74.23; H, 5.85; N, 6.42. IR (KBr, cm^{-1}): 3392, 3213 (NH_2); 3070 (CH-aromatic); 2854, 2926 (CH-aliphatic); 1674 (C═O); 1616 (C═N); 1585 (C═C).^{1}H NMR (DMSO-d_6, δ ppm): 1.19–1.29 (m, 4H, tetrahydropyranochromenoquinoline-$C_{8,9}$–H); 1.55–1.72 (m, 4H, tetrahydropyranochromeno-quinoline-$C_{7,10}$–H); 2.28 (s, 3H, tetrahydropyranochromenoquinoline-C_4–CH_3); 2.54 (s, 3H, tetrahydropyranochromenoquinoline-C_{13}–CH_3); 2.89 (s, 3H, OCH_3); 4.15 (s, 1H, tetrahydro-pyranochromenoquinoline-C_{12}–H); 6.03 (s, 1H, tetrahydropyranochromenoqunoline-C_3–H); 6.57 (s, 1H, tetrahydropyranochromeno-quinoline-C_{14}–H); 7.62–7.78 (m, 2H, 4-OCH_3–C_6H_4–$C_{3,5}$–H); 7.90–7.99 (m, 2H, 4-OCH_3–C_6H_4–$C_{2,6}$–H); 10.52 (s, 2H, NH_2, D_2O exchangeable). Mass spectrum, m/z (%): 454 ($M^{+\cdot}$, 2.1); 44 (100).

4-Bromo-2-formylphenyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (38). An equimolar mixture of ethyl coumarin-3-carboxylate **37** (0.3 g, 1 mmol) and 5-bromosalicylaldehyde (0.2 g, 1 mmol) was heated under reflux in absolute ethanol (10 mL) containing potassium hydroxide (0.06 g, 1 mmol) for 20 h. The reaction mixture was allowed to cool and poured onto crushed ice; the formed precipitate was filtered, washed with water, dried, and crystallized from dimethyl formamide to yield compound **38**. Yellow powder; yield: 0.32 g (71%) m.p.: >300°C. *Anal.* Calcd. (%) for $C_{17}H_8Br_2O_5$ (452.05): C, 45.17; H, 1.78. Found (%): C, 45.41; H, 1.89. IR (KBr, cm^{-1}): 3053, 2960 (CH-aromatic); 1734, 1716, 1695 (C═O); 1616 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 7.26 (s, 1H, coumarin-C_4–H); 7.29 (s, 2H, coumarin-C_5–H & 4-Br–C_6H_3–C_3–H); 7.62–7.65 (m, 2H, coumarin-C_8–H & 4-Br–C_6H_3–C_6–H); 7.66–7.77 (m, 1H, coumarin-C_7–H); 7.81 (s, 1H, CHO); 7.93–7.96 (m, 1H, 4-Br–C_6H_3–C_5–H). Mass spectrum, m/z (%): 456 ($M^{+\cdot}$ +4, 2.21); 453 ($M^{+\cdot}$ +1, 32.2); 452 ($M^{+\cdot}$, 11); 155 (100).

11-Bromochromeno[2,3-f]naphtho[1,8-bc][1,5]diazocin-8(7H) one (39). An equimolar mixture of compound **37** (0.3 g, 1 mmol) and 1,8-diaminonaphthalene (0.16 g, 1 mmol) was fused at 145–150°C for 3 h. The reaction mixture was allowed to cool, then triturated with ethanol and the formed precipitate was filtered, washed with ethanol, dried, and crystallized from toluene/dimethyl formamide mixture (3:1) to yield compound **39**. Dark brown powder; yield: 0.3 g (77%) m.p.: >300°C. *Anal.* Calcd. (%) for $C_{20}H_{11}BrN_2O_2$

(391.22): C, 61.40; H, 2.83; N, 7.16. Found (%): C, 61.59; H, 2.88; N, 7.34. IR (KBr, cm^{-1}): 3446 (OH tautomer); 3387 (NH); 3049, 2924 (CH-aromatic); 1685 (C═O); 1627 (C═N); 1558 (C═C). Mass spectrum, m/z (%): 391 ($M^{+\cdot}$, 7.33); 298 (100).

6-Bromochromeno[2,3-c]pyrazol-3(2H)one (40). An equimolar mixture of compound **37** (0.3 g, 1 mmol) and hydrazine hydrate (0.032 g, 0.03 mL, 1 mmol) was heated under reflux in absolute ethanol for 3 h. The formed precipitate was filtered, washed with ethanol, dried, and crystallized from dimethyl formamide to yield compound **40**. Yellow powder; yield: 0.2 g (74%) m.p.: >300°C. *Anal.* Calcd. (%) for $C_{10}H_5BrN_2O_2$ (265.06): C, 45.31; H, 1.90; N, 10.57. Found (%): C, 45.48; H, 1.87; N, 10.76. IR (KBr, cm^{-1}): 3383 (NH); 3007, 2954, 2924 (CH-aromatic); 1685 (C═O); 1624 (C═N); 1564 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 6.96 (d, 1H, J = 8.8 Hz, chromenopyrazolone-C_8–H); 7.55 (d, 1H, J = 8.8 Hz, chromenopyrazolone-C_7–H); 7.91 (s, 1H, chromenopyrazolone-C_4–H); 8.95 (s, 1H, chromenopyrazolone-C_5–H); 11.10 (s, 1H, NH, D_2O exchangeable).

3-(3-(Oxiran-2-yl)propanoyl)-6-bromo-2H-chromen-2-one (42). An equimolar mixture of the acetylcoumarin derivative **41** (0.27 g, 1 mmol) and epichlorohydrin (0.09 g, 0.08 mL, 1 mmol) was heated under reflux in dimethyl formamide (5 mL) containing potassium hydroxide (0.06 g, 1 mmol) for 10 h. The reaction mixture was allowed to cool, poured onto crushed ice, and the obtained solid product was filtered, washed with water, dried, and crystallized from dimethyl formamide to yield compound **42**. Brown powder; yield; 0.21 g (65%), m.p.: >300°C. *Anal.* Calcd. (%) for $C_{14}H_{11}BrO_4$ (323.14): C, 52.04; H, 3.43; Found (%): C, 52.31; H, 3.50. IR (KBr, cm^{-1}): 3402 (broad OH tautomer); 3040, 2927 (CH-aromatic); 2877 (CH-aliphatic) 1725 (C═O); 1589 (C═C). Mass spectrum, m/z (%): 325 ($M^{+\cdot}$ +2, 5.61); 323 ($M^{+\cdot}$, 11.36); 55 (100).

6-(6-Bromo-2-oxo-2H-chromen-3-yl)-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (43). A mixture of compound **41** (1.3 g, 5 mmol), ethyl cyanoacetate (0.57 g, 0.53 mL, 5 mmol), 4-chlorobenzaldehyde (0.7 g, 5 mmol), and ammonium acetate (0.77 g, 10 mmol) was heated under reflux in absolute ethanol (20 mL) for 60 h. The reaction mixture was allowed to cool and poured onto crushed ice. The obtained solid product was filtered, washed with water, dried, and crystallized from ethanol to yield compound **43**. Yellow powder; yield: 1.5 g (66%); m.p.: >300°C. *Anal.* Calcd. (%) for: $C_{21}H_{10}BrClN_2O_3$ (453.67): C, 55.60; H, 2.22; N, 6.17. Found (%): C, 55.89; H, 2.18; N, 6.34. IR (KBr, cm^{-1}): 3390 (broad OH tautomer); 3277 (NH); 3080, 2980 (CH-aromatic); 2220 (CN); 1732 (C═O); 1645 (C═N); 1575 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 6.75 (d, 1H, J = 9 Hz, coumarin-C_8–H); 7.00 (s, 1H, pyridine-C_5–H); 7.22–7.31 (m, 1H, coumarin-C_7–H); 7.32–7.39 (m, 2H, 4-Cl–C_6H_4–$C_{3,5}$–H); 7.40–7.50 (m, 3H, coumarin-C_5–H & 4-Cl–C_6H_4–$C_{2,6}$–H); 8.04 (s, 1H, coumarin-C_4–H); 8.15 (s, ½ H, OH tautomer, D_2O exchangeable); 9.80 (s, ½ H, NH, D_2O exchangeable). Mass spectrum, m/z (%): 457 ($M^{+\cdot}$ + 4, 0.99); 455 ($M^{+\cdot}$ + 2, 1.48); 453 ($M^{+\cdot}$, 13.97); 44 (100).

Ethyl 4-(6-bromo-2-oxo-2H-chromen-3-yl)-2,4-dioxobutanoate (44). An equimolar mixture of compound **41** (0.27 g, 1 mmol) and diethyl oxalate (0.15 g, 0.14 mL, 1 mmol) was fused at 200–210°C for 10 h. The reaction mixture was allowed to cool, then triturated with ethanol, and the obtained solid product was filtered, washed with ethanol, dried, and crystallized from dimethyl formamide to yield compound **44**. Dark brown powder; yield: 0.19 g (51%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{15}H_{11}BrO_6$ (367.15): C, 49.07; H, 3.02. Found (%): C, 49.31; H, 3.11. IR (KBr, cm^{-1}): 3059 (CH-aromatic); 2890 (CH-aliphatic); 1732, 1693 (C═O); 1624 (C═C); 1265, 1068 (C–O–C); 817 (C–Br). Mass spectrum, m/z (%): 370 ($M^{+\cdot}$ +3, 1.00); 368 ($M^{+\cdot}$ +1, 1.51); 367 ($M^{+\cdot}$, 2.07); 43 (100).

5-(6-Bromo-2-oxo-2H-chromen-3-yl)-1H-pyrazole-3-carbohydrazide (45). The ethyl butanoate derivative **44** (0.37 g, 1 mmol) was fused with excess hydrazine hydrate (1 mL) for 10 h. The reaction mixture was allowed to cool, triturated with ethano; and the obtained solid product was filtered, washed with several solvents, and dried to yield compound **45**. Dark brown powder; yield: 0.27 g (77%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{13}H_9BrN_4O_3$ (349.14): C, 44.72; H, 2.60. N, 16.05. Found (%): C, 45.05; H, 2.57; N, 16.37. IR (KBr, cm^{-1}): 3390, 3367, 3128 (NH & NH_2); 3032, 2935 (CH-aromatic); 1678 (C═O); 1625 (C═N); 1600 (C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 6.87 (d, 1H, J = 6.4 Hz, coumarin-C_8–H); 6.98 (s, 2H, CONH$\underline{NH_2}$, D_2O exchangeable); 7.11 (s, 1H, CO$\underline{NH}NH_2$, D_2O exchangeable); 7.23 (s, 1H, pyrazole-$\underline{NH}$, D_2O exchangeable); 7.26 (s, 1H, pyrazole-C_4–H); 7.31 (d, 1H, J = 6.4 Hz, coumarin-C_7–H); 7.93 (s, 1H, coumarin-C_5–H); 8.07 (s, 1H,coumarin-C_4–H). Mass spectrum, m/z (%): 351 ($M^{+\cdot}$ +2, 1.33); 349 ($M^{+\cdot}$, 3.97); 43 (100).

9-Bromo-1,6-dimethyl-7-(2-oxopropyl)pyrano[2,3-c]xanthen-3(7H)-one (46). An equimolar mixture of compound **41** (0.27 g, 1 mmol) and 5-hydroxycoumarin derivative **1** (0.19 g, 1 mmol) was heated under reflux in methanolic sodium methoxide [prepared by dissolving 0.07 g, 3 mmol of sodium metal in absolute methanol (10 mL)] for 60 h. The reaction mixture was allowed to cool, poured onto crushed ice; and the obtained solid product was filtered, washed with water, dried, and crystallized from toluene/ethanol mixture (4:1) to yield compound **46**. Brown powder; yield: 0.25 g (61%), m.p.: >300°C. *Anal.* Calcd. (%) for $C_{21}H_{17}BrO_4$ (413.26): C, 61.03; H, 4.15. Found (%): C, 61.29; H, 4.19. IR (KBr, cm^{-1}): 3442 (broad OH tautomer); 3084, 3066, 3034 (CH-aromatic); 2872, 2854 (CH-aliphatic); 1701, 1685 (C═O); 1608

(C═C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.17 (t, 1H, pyranoxanthene-C_7–H); 1.23 (s, 3H, pyranoxanthene-C_1–CH_3); 1.98 (s, 3H, pyranoxanthene-C_6-CH_3); 2.27 (s, ½ H, OH tautomer, D_2O exchangeable); 2.30 (s, 3H, CH_3–C═O); 2.68–2.73 (m, 1H,CH_3–CO–$\underline{CH_2}$); 2.89 (s, ½H, –C(OH)═CH tautomer); 6.04 (s,1H, pyranoxanthene-C_2–H); 6.57 (s, 1H, pyranoxanthene-C_5–H); 6.62 (s,1H, pyranoxanthene-C_8-H); 7.10–7.20 (m, 1H, pyranoxanthene-C_{11}–H); 7.21–7.30 (m, 1H, pyranoxanthene-C_{10}–H). Mass spectrum, m/z (%): 415 ($M^{+\cdot}$ +2, 0.75); 413 ($M^{+\cdot}$, 2.26); 111 (100).

6-Bromo-3-(pent-4-ynoyl)-2H-chromen-2-one (47). An equimolar mixture of compound **41** (0.27 g, 1 mmol) and propargyl bromide (0.12 g, 0.08 mL, 1 mmol) was heated under reflux in ethanolic sodium ethoxide [prepared by dissolving 0.07 g, 3 mmol of sodium metal in absolute ethanol (10 mL)] for 10 h. The reaction mixture was allowed to cool and poured onto crushed ice; the obtained solid product was filtered, washed with water, dried, and crystallized from toluene/ethanol mixture (4:1) to yield compound **47**. Brown powder; yield: 0.2 g (67%); m.p.: >300°C. *Anal.* Calcd. (%) for $C_{14}H_9BrO_3$ (305.12): C, 55.11; H, 2.97; Found (%): C, 55.38; H, 2.94. IR (KBr, cm^{-1}): 3410 (broad, OH tautomer); 3032, 2958, 2927 (CH-aromatic); 2873 (CH-aliphatic) 1725, 1685 (C═O); 1600 (C═C).^{1}H NMR (DMSO-d_6, δ ppm): 2.25 (s, 1H, –C≡CH); 3.20–3.58 (m, 4H, –CO–$\underline{CH_2}$–$\underline{CH_2}$–); 6.60–7.10 (m, 1H, coumarin-C_8–H); 7.20–7.70 (m, 2H, coumarin-$C_{5,7}$–H); 7.77 (s, 1H, coumarin-C_4–H). Mass spectrum, m/z (%): 307 ($M^{+\cdot}$ +2, 0.93); 305 ($M^{+\cdot}$, 0.86); 43 (100).

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