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Original article

Synthesis, anticancer activity and photophysical properties of novel substituted 2-oxo-2*H*-chromenylpyrazolecarboxylates

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ABSTRACT

2-Oxo-2*H*-chromenylpyrazolecarboxylates (**8a**–**h** and **12a**–**zb**) have been synthesized by [3 + 2] cycloaddition of 2*H*-chromenophenylhydrazones (**7a**–**h** and **11a**–**w**) with diethyl/dimethylbut-2-ynedioates. Phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones (**13i**–**n**) were prepared from corresponding phenylhydrazones (**7a**–**h**) with catalytic amount of piperidine in presence of pyridine as a solvent at 100 °C. All the synthesized compounds (**8a**–**h**, **12a**–**zb** and **13a**–**n**) were screened for anticancer activity against three human cancer cell lines such as prostate (DU-145), lung adenocarcinoma (A549), and cervical (HeLa) by standard MTT assay method. Further, photophysical properties (UV and fluorescence) for these compounds were discussed.

1. Introduction

Pyrazoles and their derivatives are an important heterocyclic compounds [1], have been found an extensive use in the pharmaceutical industry, for example, Viagra, an inhibitor of 5-phosph odiesterase used for the treatment of erectile dysfunction. Celebrex [2], an inhibitor of cyclooxygenase-2 (Cox-2) used as potent anti-inflammatory (Fig. 1), and Acomplia [3] antagonist of the CB-1 cannabinoid receptor, used for the treatment of obesity (Fig. 1). Researchers at the GlaxoSmithKline, reported 1,2,4-triazol-3-yl-thiopropyl-tetrahydrobenzazepines having pyrazole moiety (Fig. 1) as selective dopamine D_3 receptor antagonist [4]. On the other hand, coumarin and its derivatives have attracted considerable attention due to their potential biological and pharmacological activities [5–13]. In the course of our efforts on synthesis [14] and biological activities of 2*H*-chromenones [15] and 4*H*-chromenone derivatives [16], the present manuscript describes the synthesis of substituted 2-oxo-2*H*-chromenylpyrazolecarboxylates and phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones by applying various synthetic methods and their anticancer activity as well as structure–activity relationship for the first time. Further, we report UV and fluorescence photophysical studies for these 2-oxo-2*H*-chromenylpyrazolecarboxylates.

2. Chemistry

Scheme 1 describes the synthesis of 4-chloro-3-form ylcoumarins **5a** and **5b** starting from substituted phenols. Acetylation of phenols **1a**–**b** with acetyl chloride gives **2a**–**b** and subsequent $AlCl_3$ mediated Fries rearrangement afforded **3a**–**b**. Annulation reaction of **3a**–**b** with diethyl carbonate [17] in presence of NaH afforded 4-hydroxycoumarins **4a**–**b**. Formylation of **4a** and **4b** with DMF/$POCl_3$ under Vilsmeier–Haack conditions [18] afforded **5a** and **5b**. Condensation of 4-chloro-3-formylcoumarin **5a** with phenylhydrazine hydrochloride **6a** in methanol solvent in presence of AcOH and H_2O medium afforded the corresponding 2*H*-chromenophenylhydrazone **7a** [19]. [3 + 2] Cycloaddition reaction of **7a** [20] with diethyl but-2-ynedioate at 130 °C afforded corresponding 2-oxo-2*H*-chromenylphenyl-1*H*-pyrazole-4,5-dicarboxylate **8a** in 62% yield as pale yellow solid (Scheme 2). The IR spectra of compound **8a** has shown absorption bands at ν_{max} = 1604, 1722 cm^{-1} corresponds two carbonyls ketone and ester. The absorption band at

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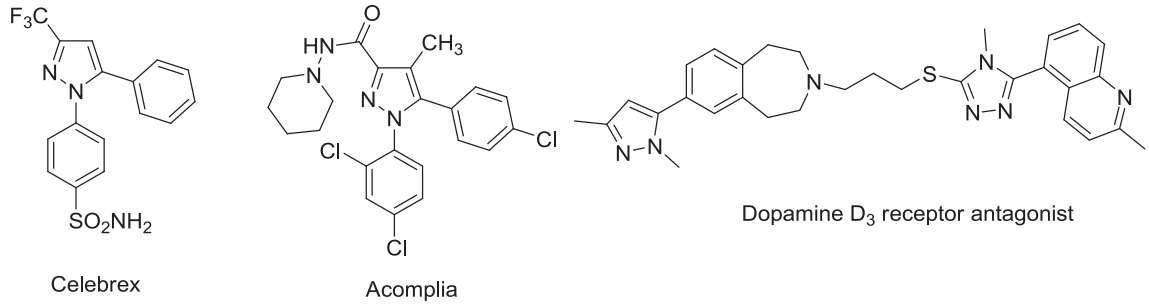


Fig. 1. Structures of pyrazole drugs.

$\nu_{max} = 1543\ cm^{-1}$ has shown the presence of imine (C=N stretching). ^1H NMR spectra of compound **8a** shown two quartets at δ 4.34 and 4.21 ppm correspond to OCH_2 protons of two ester carbonyl groups. A doublet at δ 7.97 ppm ($J = 7.93$ Hz) and multiplet at δ 7.33–7.68 ppm correspond to aromatic protons. Compound **8a** was further confirmed by ^{13}C NMR spectroscopy, the signal at δ 160.33 ppm corresponds to coumarin carbonyl carbon and two separate signals at δ 161.02 and 158.42 ppm correspond to two ester carbonyl carbons of pyrazole. The signal at δ 152.0 ppm corresponds to C-4 of chloro substituted coumarin. The C-3 coumarin carbon having pyrazole moiety shown the signal at δ 133.3 ppm. The pyrazole carbon C-3 displayed at δ 138.0 ppm due to the presence of nitrogen adjacent to the carbon. The ester attached olefin carbons C-4 and C-5 of pyrazole moiety appeared at δ 129.24 and 129.14 ppm. The mass spectrum (ESI-MS) of compound shown molecular ion MS (ESI) m/z 467 $(M + H)^+$, and further confirmed by HRMS (m/z calculated for $C_{24}H_{20}ClN_2O_6$ is 467.1004 and found 467.0979). Finally, the compound **8a** was crystallized in ethanol solvent [21] and its structure confirmed by X-ray crystallography (Fig. 2). Under optimized conditions, the compounds 2-oxo-2*H*-chromenyl-phenyl-1*H*-pyrazole-4,5-dicarboxylates **8b**–**h** were prepared by the [3 + 2] cycloaddition of phenylhydrazones **7b**–**h** with diethyl but-2-ynedioate. Thus synthesized compounds are new and well characterized by spectral data (Scheme 2).

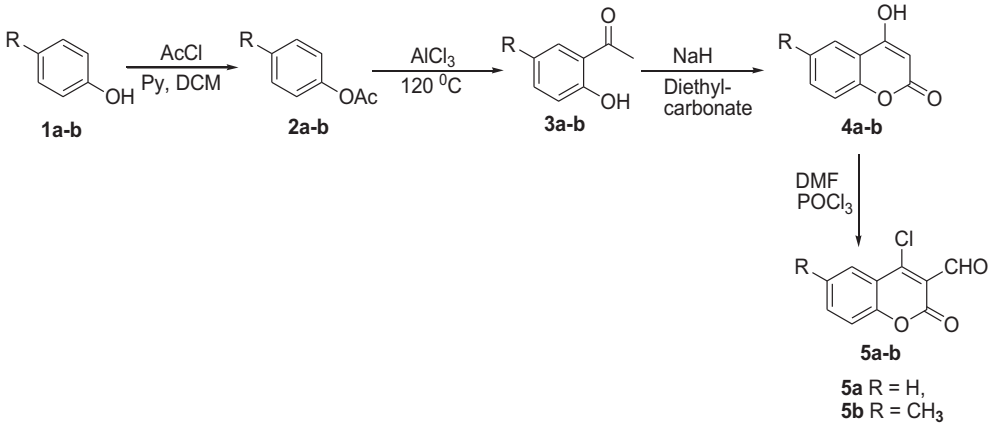
Having succeeded in the synthesis of 2-oxo-2*H*-chromenyl-phenyl-1*H*-pyrazole-4,5-dicarboxylates **8a**–**h**, we extended this protocol to prepare **12a**–**v** from 3-acetylcoumarin derivatives (Schemes 3–6). *Knoevenagel* condensation of substituted salicylaldehydes **9a**–**d** with ethyl 3-oxobutanoate in presence of piperidine in dry dichloromethane afforded substituted 3-acetylcoumarins **10a**–**d**. Condensation of **10a**–**d** with various substituted phenylhydrazine hydrochlorides **6a**–**h** afforded corresponding phenylhydrazones **11a**–**q** and subsequent [3 + 2] cycloaddition of **11a**–**q** with diethyl but-2-ynedioate and dimethyl but-2-ynedioate under optimized conditions, afforded **12a**–**v** in 66–89% yields. In addition to these pyrazole derivatives **12a**–**v**, the self cyclized compounds phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones **13a**–**h** were obtained with low yields (10–20%, Scheme 3). These derivatives are separated by column chromatography and well characterized by spectral data.

Next, the method was applied for the preparation of **12w**–**zb** from acetyl derivatives **10e** and **10f**. *Knoevenagel* condensation of **9e** and **9g** with ethyl 3-oxobutanoate in presence of piperidine in dry dichloromethane afforded **10e** and **10f** (Schemes 4–5). Condensation of **10e** and **10f** with substituted phenylhydrazine hydrochlorides **6a**–**c** afforded corresponding phenylhydrazones **11r**–**w** and subsequent [3 + 2] cycloaddition reaction of **11r**–**w** with diethyl but-2-ynedioate afforded **12w**–**zb** (Scheme 6).

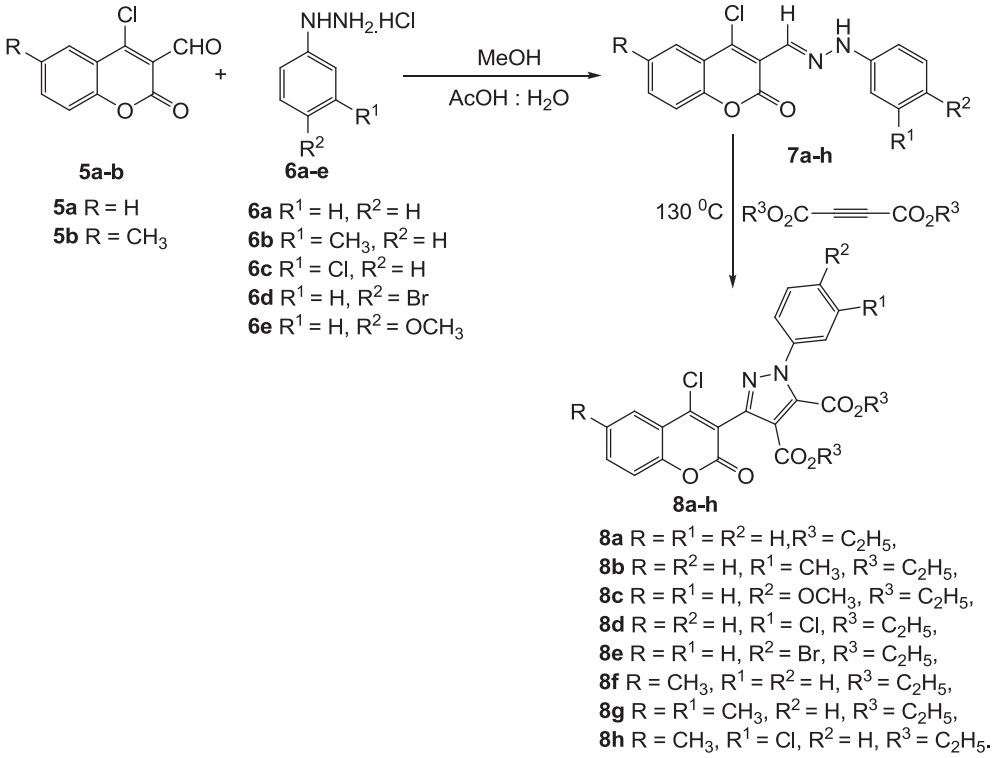
Phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones **13a**–**h** were obtained with low yields (Scheme 3) during the cycloaddition reaction of phenylhydrazones **11a**–**h** with diethyl but-2-ynedioate when substituent's present on phenylhydrazines. To see the feasibility of the formation of these derivatives, various (*E*)-4-chloro-3-((2-phenylhydrazono)methyl)-2*H*-chromen-2-ones **7a**–**h** were heated at 100 °C with catalytic amount of piperidine in pyridine solvent. The reactions were undergo smoothly to give substituted phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones **13i**–**n** in good yields (Scheme 7). All the synthesized compounds are new and well characterized by spectral data.

3. Biology

Thus synthesized 2-oxo-2*H*-chromenylpyrazolecarboxylate derivatives **8a**–**h**, **12a**–**zb** and **13a**–**n** were screened for their *in vitro* cytotoxicity on three human cancer cell lines such as prostate (DU-145), lung adenocarcinoma (A549), and cervical (HeLa) by standard



Scheme 1. Synthesis of compounds **5a**–**b**.



Scheme 2. Synthesis of compounds **8a**–**h**.

MTT assay method [16,22] and compared with the standard drugs Doxorubicin and Nocodazole.

4. Results and discussion

4.1. Anticancer activity of 2H-chromenylpyrazolecarboxylates and phenylchromeno[4,3-c]pyrazol-4(1H)-ones

The IC_{50} values for compounds **8a**–**h**, **12a**–**zb** and **13a**–**n** were presented in Tables 1–2; based on IC_{50} values the structure–activity relationships were discussed below. The compound **8a** displayed the very good activity on human prostate cancer, and lung adenocarcinoma, however, displayed moderate activity on cervical cancer cell lines. Methyl **8b**, methoxy **8c**, chloro **8d**, and bromo **8e** substitutions on pyrazole displayed very good activity on all the tested cell lines. The methyl substituted 2*H*-chromene **8f** displayed good activity on DU-145, moderate activity on A549 and HeLa. Further, methyl **8g** or chloro **8h** substitution on pyrazole with intact of methyl substitution on 2*H*-chromene could not improve the activity. The result indicating that the presence of electron donating or withdrawing groups present on pyrazole **8b**–**e** displayed very good activity when compared to substitution present on 2*H*-chromene **8f**–**h**.

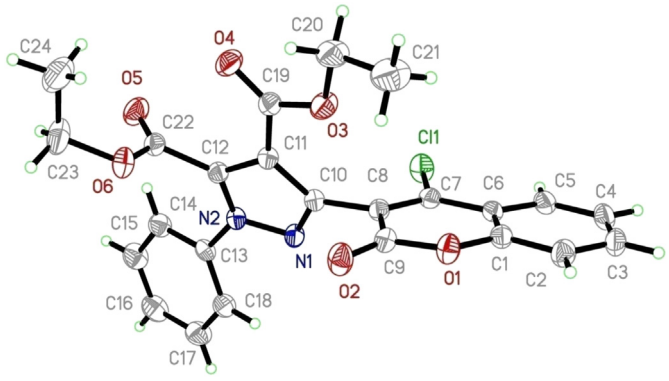
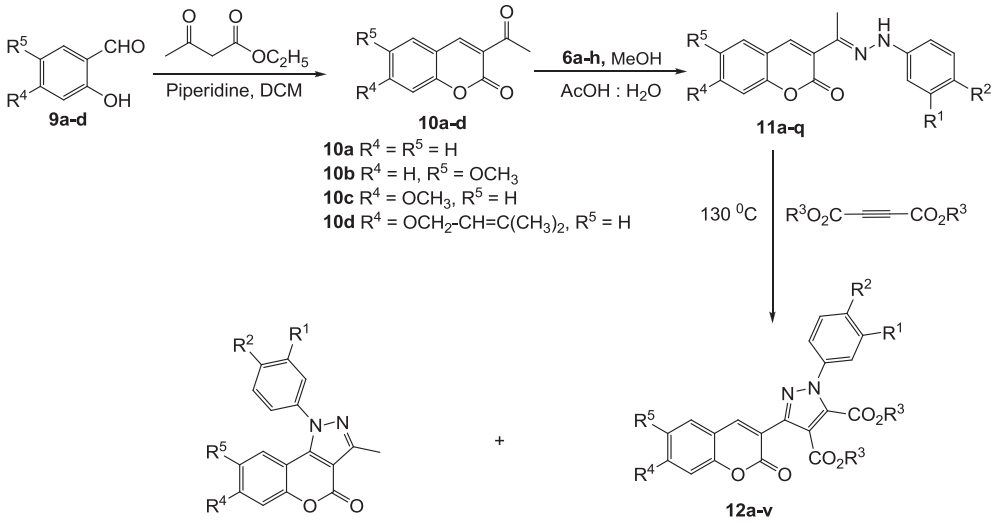


Fig. 2. The molecular structure of **8a**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level Schemes.

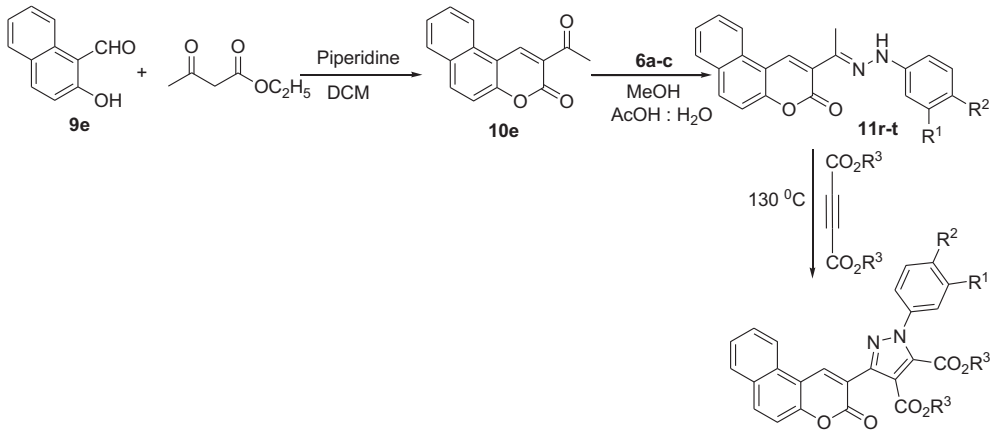
Pyrazolecarboxylate derivatives without chloro substitution at 4th position on 2*H*-chromene **12a**–**s** were tested on all the cell lines and are presented below. Most of the compounds were displayed very good activity on human prostate cancer, lung carcinoma and moderate activity on cervical cancer. The methyl substituted pyrazoles **12c**–**e**, compound **12d** displayed very good activity on all the tested cell lines, however, **12c** displayed good on human prostate cancer, lung carcinoma and moderate on cervical cancer. Further the presence of another methyl substitution on pyrazole **12e** enhanced the activity on human cervical cancer when compared to **12c**. The methoxy substituted pyrazole **12f** displayed very good activity on human prostate cancer and moderate activity on A549 and HeLa. The halo substituted pyrazoles **12g**–**m**, fluoro and chloro substituted 2*H*-chromenepyrazolecarboxylates **12g**–**k** were displayed better activity in all the tested cell lines when compared to bromo substitution **12l** and **12m**. The methoxy substitution at 6th position on 2*H*-chromenone **12n** displayed very good activity on human prostate cancer, lung carcinoma and moderate activity on cervical cancer cell lines. Further methyl and chloro substituted pyrazoles **12o**–**p** displayed good activity on DU-145 and moderate activity on A549 and HELA. Methoxy substitution at 7th position on 2*H*-chromenone **12q** displayed good activity on DU-145, however, moderate activity on A549 and HeLa. The presence of methyl substituted pyrazole with the intact of methoxy substitution on chromene **12r** displayed good activity on both the cell lines DU-145 and Hela, however, chloro substitution **12s** displayed good activity on DU-145. The prenyl **12t**–**v**, benzochromenyl **12w**–**y** and



13a $R^1 = R^2 = R^4 = R^5 = H$
13b $R^1 = CH_3$, $R^2 = R^4 = R^5 = H$
13c $R^1 = R^4 = R^5 = H$, $R^2 = OCH_3$
13d $R^1 = Cl$, $R^2 = R^4 = R^5 = H$
13e $R^1 = R^4 = R^5 = H$, $R^2 = Cl$
13f $R^1 = F$, $R^2 = R^4 = R^5 = H$
13g $R^1 = R^4 = R^5 = H$, $R^2 = Br$
13h $R^1 = R^2 = R^4 = H$, $R^5 = OCH_3$

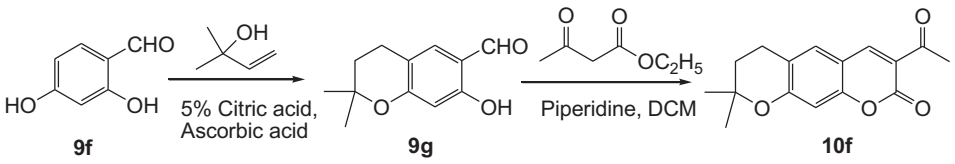
12a $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = C_2H_5$,
12b $R^1 = R^2 = R^4 = R^5 = H$, $R_3 = CH_3$,
12c $R^1 = CH_3$, $R^2 = R^4 = R^5 = H$, $R^3 = C_2H_5$,
12d $R^1 = R^3 = CH_3$, $R^2 = R^4 = R^5 = H$,
12e $R^1 = R^2 = CH_3$, $R^3 = C_2H_5$, $R^4 = R^5 = H$,
12f $R^1 = R^4 = R^5 = H$, $R^2 = OCH_3$, $R^3 = C_2H_5$,
12g $R^1 = Cl$, $R^2 = R^4 = R^5 = H$, $R^3 = C_2H_5$,
12h $R^1 = Cl$, $R^2 = R^4 = R^5 = H$, $R^3 = CH_3$,
12i $R^1 = F$, $R^2 = R^4 = R^5 = H$, $R^3 = C_2H_5$,
12j $R^1 = F$, $R^2 = R^4 = R^5 = H$, $R^3 = CH_3$,
12k $R^1 = R^4 = R^5 = H$, $R^2 = Cl$, $R^3 = C_2H_5$,
12l $R^1 = R^4 = R^5 = H$, $R^2 = Br$, $R^3 = C_2H_5$,
12m $R^1 = R^4 = R^5 = H$, $R^2 = Br$, $R^3 = CH_3$,
12n $R^1 = R^2 = R^4 = H$, $R^3 = C_2H_5$, $R^5 = OCH_3$,
12o $R^1 = CH_3$, $R^2 = R^4 = H$, $R^3 = C_2H_5$, $R^5 = OCH_3$,
12p $R^1 = Cl$, $R^2 = R^4 = H$, $R^3 = C_2H_5$, $R^5 = OCH_3$,
12q $R^1 = R^2 = R^5 = H$, $R^3 = C_2H_5$, $R^4 = OCH_3$,
12r $R^1 = CH_3$, $R^2 = R^5 = H$, $R^3 = C_2H_5$, $R^4 = OCH_3$,
12s $R^1 = Cl$, $R^2 = R^5 = H$, $R^3 = C_2H_5$, $R^4 = OCH_3$,
12t $R^1 = R^2 = R^5 = H$, $R^3 = C_2H_5$, $R^4 = Prenyl$,
12u $R^1 = CH_3$, $R^2 = R^5 = H$, $R^3 = C_2H_5$, $R^4 = Prenyl$,
12v $R^1 = Cl$, $R^2 = R^5 = H$, $R^3 = C_2H_5$, $R^4 = Prenyl$,

Scheme 3. Synthesis of compounds **12a**–**v** and **13a**–**h**.



12w $R^1 = R^2 = H$, $R^3 = C_2H_5$
12x $R^1 = CH_3$, $R^2 = H$, $R^3 = C_2H_5$
12y $R^1 = Cl$, $R^2 = H$, $R^3 = C_2H_5$

Scheme 4. Synthesis of compounds **12w**–**y**.



Scheme 5. Synthesis of compound **10f**.

dihydropyran **12z**–**zb** substituted pyrazoles displayed moderate activity on all the tested cell lines.

The chromenopyrazole-4-(1*H*)-ones **13a**–**n** were also tested on DU-145, A549 and HeLa cancer cell lines (Table 2). Methyl and methoxy substituted pyrazoles **13b**–**c** displayed good activity on human lung carcinoma, however, moderate activity on DU-145 and HeLa when compared to halo substitution **13d**–**g**. Methoxy substitution at 6th position on 2*H*-chromene **13h** could not improve the activity. The compounds **13j**–**n** displayed moderate activity on all tested cell lines.

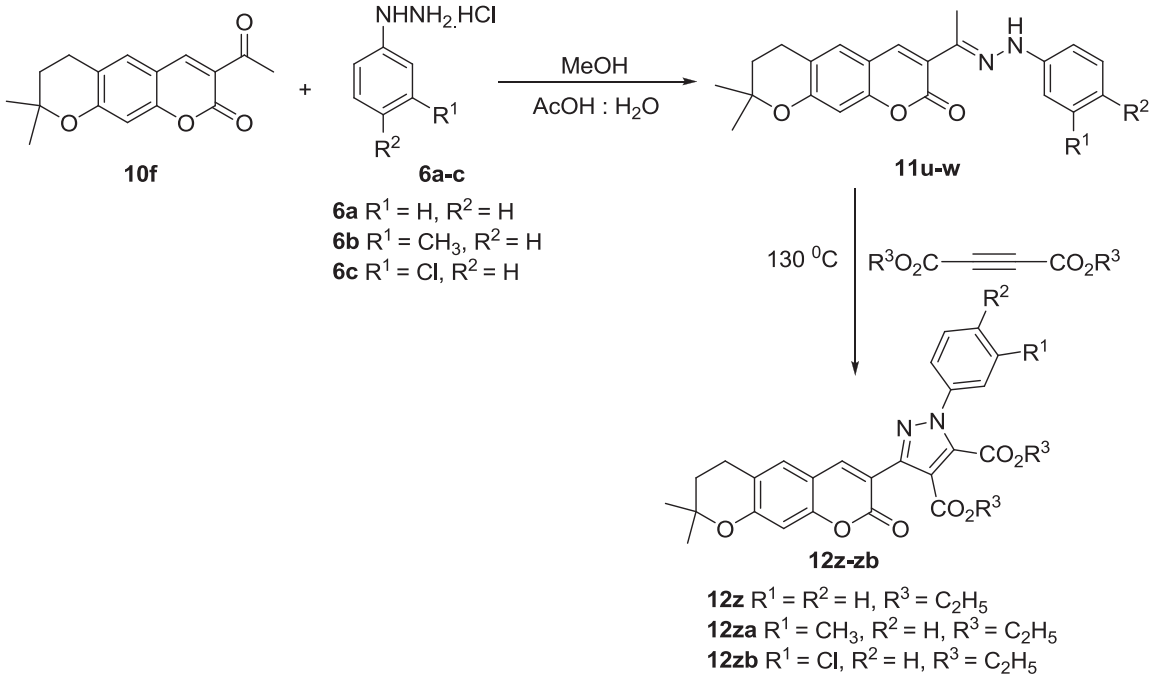
Overall in present series of compounds **8a**–**h**, **12a**–**zb**, compounds **8b**–**d**, **12b**, **12d**, and **12g** displayed very good activity in all the tested cancer cell lines, whereas, compounds **8e**, **12c**, **12h**, **12j**, **12k**, and **12n** displayed good activity on DU-145 and A549 cell lines. The compounds **8f**, **12a**, and **12o**–**s** were selectively displayed the good activity on DU-145 cell line.

5. Photophysical properties

Coumarins have been widely used in the field of biology, medicine, cosmetics and fluorescent dyes. They are efficient fluorophores [23] characterized by good emission quantum yields and are used as materials for lasers in organic light emitting devices (OLED) [24], optical brighteners [25], non-linear optical chromophores and fluorescent labels [26]. Due to the importance of these properties, we have initiated to study the photophysical properties [27] for the 2*H*-chromenylpyrazolecarboxylates. The optical properties will help in future to develop assays for the identified hits and lead compounds of these investigations.

The UV (absorption) and fluorescence (emission) properties of 2*H*-chromenylpyrazolecarboxylates **8a**–**h** and **12a**–**zb** are summarized in Supporting information (Figs. 3–11 and Table 3). From the UV spectroscopy it is observed that the longest absorption maxima of these derivatives are found in the UV region between 321 and 361 nm. The absorption maxima wavelength varied depending on the functional groups present on pyrazole and chromenone. There is no considerable change in absorption maxima (321–325 nm), when the substitutions such as methyl (**8b**, **12c**–**e**), methoxy (**8c**, **12f**), chloro (**8d**, **12g**–**h**), fluoro (**12i**–**j**), and bromo (**8e**, **12l**–**m**) present on pyrazole ring. However, substitutions present on chromene ring such as methoxy (**12n**–**s**), prenyl (**12t**–**v**), naphthyl (**12w**–**y**) and pyran (**12z**–**zb**) absorption maxima was displayed between 337 and 361 nm due to the presence of electron donating and conjugation effect (~40 nm).

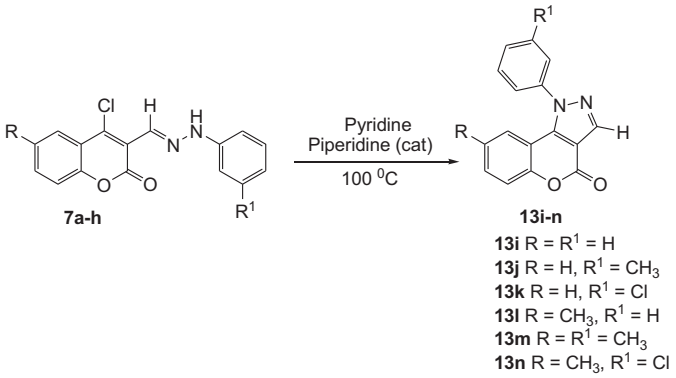
The fluorescence studies of synthesized compounds **8a**–**h** and **12a**–**zb** were performed in dichloromethane at 1×10^{-5} M concentration. Fluorescence spectra for all the compounds are excited at their maximum longest absorption wavelengths. Among the 4-chloro substituted 2*H*-chromenylpyrazolecarboxylates **8a**–**h**, the compound **8c** exhibited longer emission at 484 nm having methoxy substitution on 2*H*-chromene. The compounds **8f**–**h** displayed emission at 417–420 nm due to presence of mild donating methyl substitution at 6th position on chromenone. In the series of 2*H*-chromenylpyrazolecarboxylates **12a**–**v**, compounds **12a**–**e** were exhibited at 401–408 nm. Compound **12f** having methoxy



6a $R^1 = H$, $R^2 = H$
6b $R^1 = CH_3$, $R^2 = H$
6c $R^1 = Cl$, $R^2 = H$

12z $R^1 = R^2 = H$, $R^3 = C_2H_5$
12za $R^1 = CH_3$, $R^2 = H$, $R^3 = C_2H_5$
12zb $R^1 = Cl$, $R^2 = H$, $R^3 = C_2H_5$

Scheme 6. Synthesis of compounds **12z**–**zb**.



Scheme 7. Synthesis of compounds **13i**–**n**.

substitution on pyrazole displayed longer emission at 457 nm. However compounds having fluoro **12i**–**j**, chloro **12k** and bromo **12l**–**m** substitutions on pyrazole displayed emission at 400–402 nm. The 2*H*-chromenone having methoxy substitution at 6th position **12n** displayed emission at 451 nm, however, the presence of methyl substitution on pyrazole **12o** displayed at 444 nm and chloro substitution **12p** at 445 nm. The methoxy **12q**–**s** and prenyl **12t**–**v** substitutions at 7th position on chromenepyrazole displayed at 421–426 nm. Benzochromenylpyrazole derivatives **12w**–**y** were displayed at 440–442 nm, where as pyran substituted chromenone **12z**–**zb** displayed at 428–432 nm. The intensity of these UV visible and fluorescence studies can be exploited as a core structure for fluorescent sensors and dye stuffs.

Table 1
Anticancer activity of 2-oxo-2*H*-chromenylpyrazolecarboxylates **8a**–**h** and **12a**–**zb**.

Entry	Compounds	Cytotoxicity [IC_{50} (μM)][a]		
		DU145	A549	HeLa
1	**8a**	48 ± 6.8	34 ± 4.2	100 ± 5.5
2	**8b**	32 ± 1.9	36 ± 2.9	30 ± 3.5
3	**8c**	25 ± 2.5	18 ± 4.2	27 ± 3.4
4	**8d**	24 ± 2.7	38 ± 5.2	40 ± 3.2
5	**8e**	32 ± 3.3	30 ± 1.9	500 ± 2.5
6	**8f**	50 ± 5.1	108 ± 4.1	228 ± 3.3
7	**8g**	103 ± 4.6	115 ± 2.9	115 ± 3.2
8	**8h**	156 ± 5.2	128 ± 3.9	125 ± 2.1
9	**12a**	57 ± 1.2	100 ± 2.8	100 ± 4.2
10	**12b**	30 ± 2.1	28 ± 3.8	35 ± 2.9
11	**12c**	47 ± 3.2	52 ± 4.5	245 ± 3.5
12	**12d**	35 ± 2.2	51 ± 1.5	45 ± 3.2
13	**12e**	40 ± 4.5	52 ± 3.3	50 ± 1.6
14	**12f**	39 ± 5.1	86 ± 3.5	90 ± 4.4
15	**12g**	35 ± 2.2	28 ± 4.2	22 ± 4.4
16	**12h**	32 ± 2.8	30 ± 3.5	76 ± 4.4
17	**12i**	32 ± 2.4	59 ± 3.9	68 ± 4.4
18	**12j**	37 ± 1.5	50 ± 3.2	76 ± 2.5
19	**12k**	26 ± 2.2	35 ± 1.9	87 ± 3.6
20	**12l**	61 ± 3.2	100 ± 3.2	250 ± 4.5
21	**12m**	93 ± 5.1	165 ± 4	120 ± 3.1
22	**12n**	27 ± 3.7	35 ± 2.2	145 ± 3.1
23	**12o**	31 ± 4.2	102 ± 2.9	155 ± 2.4
24	**12p**	29 ± 2.8	148 ± 3.9	160 ± 3.1
25	**12q**	33 ± 2.6	132 ± 3.2	140 ± 3.8
26	**12r**	35 ± 3.7	171 ± 1.5	35 ± 2.9
27	**12s**	38 ± 5.5	221 ± 3.5	205 ± 4.5
28	**12t**	75 ± 1.8	136 ± 1.4	130 ± 2.9
29	**12u**	125 ± 2.4	178 ± 1.9	150 ± 3.5
30	**12v**	139 ± 3.4	163 ± 2.9	110 ± 4.4
31	**12w**	80 ± 3.9	136 ± 2.8	120 ± 3.4
32	**12x**	259 ± 4.2	179 ± 2.6	155 ± 3.8
33	**12y**	257 ± 5.5	165 ± 4.2	170 ± 1.2
34	**12z**	209 ± 1.6	189 ± 2.2	125 ± 3.9
35	**12za**	67 ± 1.9	175 ± 1.5	105 ± 2.5
36	**12zb**	74 ± 2.5	146 ± 1.8	145 ± 2.6
37	**Doxorubicin**	6 ± 2.76	4 ± 1.9	4.1 ± 2.2
38	**Nocodazole**	2.8 ± 1.3	2.31 ± 1.4	0.71 ± 0.05

[a] IC_{50} values are indicates mean ± SD (standard deviation) of three independent experiments.

Table 2
Anticancer activity of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones and 1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones **13a**–**n**.

Entry	Compounds	Cytotoxicity [IC_{50} (μM)][a]		
		DU145	A549	HeLa
1	**13a**	120 ± 6.1	119 ± 3.8	120 ± 2.3
2	**13b**	150 ± 4.4	43 ± 3.5	154 ± 2.1
3	**13c**	175 ± 4.9	27 ± 1.9	190 ± 3.6
4	**13d**	139 ± 2.8	85 ± 2.5	175 ± 4.4
5	**13e**	121 ± 5.1	136 ± 2.2	83 ± 2.9
6	**13f**	134 ± 3.4	125 ± 4.1	276 ± 3.2
7	**13g**	53 ± 1.2	130 ± 2.6	130 ± 4.5
8	**13h**	150 ± 3.2	150 ± 3.8	115 ± 3.9
9	**13i**	125 ± 5.5	175 ± 4.2	165 ± 1.9
10	**13j**	100 ± 4.2	160 ± 3.8	135 ± 2.8
11	**13k**	60 ± 3.2	110 ± 3.5	110 ± 2.9
12	**13l**	110 ± 5.2	125 ± 1.9	192 ± 6.2
13	**13m**	130 ± 5.2	145 ± 2.5	150 ± 4.2
14	**13n**	105 ± 2.2	150 ± 4.1	120 ± 2.2
15	**Doxorubicin**	6 ± 2.76	4 ± 1.9	4.1 ± 2.2
16	**Nocodazole**	2.8 ± 1.3	2.31 ± 1.4	0.71 ± 0.05

[a] IC_{50} values are indicates mean ± SD (standard deviation) of three independent experiments.

6. Conclusion

In conclusion, compounds **8a**–**h**, **12a**–**zb** and **13a**–**n** were synthesized by applying various synthetic methods such as Fries rearrangement, Vilsmeier–Haack, *Knoevenagel* condensation, and [3 + 2] cycloaddition reaction. All the compounds were screened for their anticancer activity against three human cancer cell lines by standard MTT assay method and compared with the standard drugs Doxorubicin and Nocodazole. Compounds **8b**–**d**, **12b**, **12d**–**e** and **12g** displayed very good anticancer activity on all the tested cell lines, however, compounds **8a**, **8e**, **12c**, **12k** and **12n** selectively displayed very good anticancer activity on DU 145 and A 549. Fluorescence property for the compounds **8c**, **12f** and **12n**–**p** having methoxy substitution exhibited longer emission at 444–484 nm. The synthetic methodology applied in this report and assignment of anticancer and UV, fluorescence data to all these derivatives is new aspect. This study further presents 2-oxo-2*H*-chromenylpyrazolecarboxylate derivatives as new class of anticancer agents and it may serve as a model compounds for design and development of therapeutic based anticancer inhibitors. The synthesis and biological activities of 2*H*-chromene derived heterocyclic compounds are under investigation.

7. Experimental section

7.1. General

Salicylaldehydes and diethyl/methyl but-2-ynedioates were procured from Sigma–Aldrich. Phenylhydrazine hydrochlorides, piperidine, and solvents were obtained from local suppliers. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh); spots were visualized under UV light. Column chromatographic separations were carried out on silica gel (60–120 mesh). Melting points were determined on a *Mettler-Temp* apparatus and are uncorrected. An IR spectrum was recorded with a *Thermo Nicolet Nexus* 670 spectrometer. ^{1}H NMR

and ^{13}C NMR spectra were recorded on a *Gemini 200* MHz, *Bruker Avance* 300 MHz spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as internal standard. EIMS obtained on *7070H spectrometer* operating at 70 eV using a direct inlet system. HRMS were carried out on Agilent 6510 Q-TOF LC/MS instrument. The UV (absorption) spectra were recorded using Jasco V-550 spectrophotometer. Fluorescence measurements were carried out with a Horiba Jobin Yvon Fluorolog-3 Spectrofluorimeter. The absorption and fluorescence spectra of 2*H*-chromenylpyrazolecarboxylates carried out in dichloromethane solvent at 1×10^{-5} M concentration.

7.2. General procedure for the preparation of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde derivatives (**5**)

7.2.1. Synthesis of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde (**5a**)

$POCl_3$ (2.8 g, 1.69 mL, 18 mmol) was added drop wise at −10 °C to a stirred solution of 4-hydroxy-2*H*-chromen-2-one **4a** (1 g, 6 mmol) in dry DMF (4.5 g, 4.74 mL, 60 mmol) over a period of 15 min and the reaction was continued for 1 h at the same temperature. Then the reaction mixture was brought to 60 °C and stirred for another 1 h. After completion of reaction (TLC), the reaction mixture was poured in to crushed ice (50 g) with constant stirring. The compound was extracted with chloroform, and layers were separated, the organic layer was washed with water and brine solution and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by column chromatography afforded 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **5a** as pale yellow color solid in 75% yield; m.p: 120–122 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 10.32 (s, 1H, CHO), 8.13 (d, 1H, J = 8.12 Hz, aromatic), 7.79 (t, 1H, J = 8.30 Hz, aromatic), 7.44 (d, 1H, J = 7.55 Hz, aromatic), 7.40 (d, 1H, J = 7.55 Hz, aromatic); EI-MS (m/z): 209, 211 $[M + H]^+$.

7.2.2. 4-Chloro-6-methyl-2-oxo-2H-chromene-3-carbaldehyde (**5b**)

Yield: 80%; pale yellow color solid; m.p: 101–103 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 10.31 (s, 1H, CHO), 7.88 (s, 1H, aromatic), 7.49 (d, 1H, J = 8.54 Hz, aromatic), 7.28 (d, 1H, J = 8.54 Hz, aromatic), 2.49 (s, 3H, CH_3); EI-MS (m/z): 225, 227 $[M + H]^+$.

7.3. General procedure for the preparation of substituted (E)-4-chloro-3-((2-phenylhydrazono)methyl)-2H-chromen-2-ones (**7**)

7.3.1. Synthesis of (E)-4-chloro-3-((2-phenylhydrazono)methyl)-2H-chromen-2-one (**7a**)

Phenylhydrazine hydrochloride **6a** (0.160 g, 1.1 mmol) in mixture of H_2O and AcOH was added to a stirred solution of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **5a** (0.208 g, 1.0 mmol) in methanol at 60 °C and the reaction was continued for another 30 min at same temperature. The reaction was monitored by TLC and an orange–red precipitate formation was observed. After completion of the reaction, the reaction mixture was cooled to room temperature, precipitate was filtered off, and the resulted precipitate was dissolved in ethyl acetate and washed with cold water to remove the acetic acid. The organic layer was separated and dried over Na_2SO_4, solvent was removed under reduced pressure afforded (*E*)-4-chloro-3-((2-phenylhydrazono)methyl)-2*H*-chromen-2-one (**7a**, 0.275 g) as orange color sold in 92% yield; m.p: 181–183 °C; IR (KBr): 3284, 2921, 2851, 1696, 1596, 1521, 1488, 1447, 1280, 1253, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (bs, 1H, NH), 8.02 (d, 1H, J = 7.66 Hz, aromatic), 7.98 (s, 1H, imine), 7.55 (t, 1H, J = 7.66 Hz, aromatic), 7.32–7.36 (m, 2H, aromatic), 7.27–7.29 (m, 2H, aromatic), 7.12 (d, 2H, J = 7.66 Hz, aromatic), 6.98 (t, 1H, J = 7.66 Hz, aromatic); EI-MS (m/z): 299, 301 $[M + H]^+$.

Similarly other 2*H*-chromenylphenylhydrazones were synthesized and are summarized below.

7.3.2. (E)-4-Chloro-3-((2-m-tolylhydrazono)methyl)-2H-chromen-2-one (**7b**)

Yield: 90%; orange color solid; m.p: 178–179 °C; IR (KBr): 3415, 3278, 2924, 2854, 1695, 1597, 1567, 1524, 1450, 1324, 1287, 1259, 1189, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, 1H, J = 6.04 Hz, aromatic), 7.96 (s, 1H, imine), 7.54 (dt, 1H, J = 1.51 and 7.55 Hz, aromatic), 7.36 (t, 2H, J = 7.55 Hz, aromatic), 7.13 (t, 1H, J = 7.55 Hz, aromatic), 6.98–6.91 (m, 2H, aromatic), 6.72 (d, 1H, J = 7.55 Hz, aromatic), 2.36 (s, 3H, CH_3); EI-MS (m/z): 313, 315 $[M + H]^+$.

7.3.3. (E)-4-Chloro-3-((2-(3-chlorophenyl)hydrazono)methyl)-2H-chromen-2-one (**7d**)

Yield: 86%; orange red color solid; m.p: 224–226 °C; IR (KBr): 3372, 3293, 3077, 2925, 1700, 1598, 1567, 1521, 1325, 1284, 1124, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.74 (s, 1H, NH), 8.10 (s, 1H, imine), 8.00 (d, 1H, J = 8.00 Hz, aromatic), 7.58 (t, 1H, J = 7.00 Hz, aromatic), 7.39 (t, 1H, J = 7.00 Hz, aromatic), 7.34 (d, 1H, J = 8.00 Hz, aromatic), 7.16 (d, 1H, J = 8.00 Hz, aromatic), 7.13 (s, 1H, aromatic), 7.00 (d, 1H, J = 8.00 Hz, aromatic), 6.74 (d, 1H, J = 8.00 Hz, aromatic); EI-MS (m/z): 333, 335 $[M + H]^+$.

7.3.4. (E)-3-((2-(4-Bromophenyl)hydrazono)methyl)-4-chloro-2H-chromen-2-one (**7e**)

Yield: 82%; orange red color solid; m.p: 201–203 °C; IR (KBr): 3447, 3280, 2923, 1703, 1569, 1562, 1527, 1481, 1290, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 10.64 (s, 1H, NH), 8.08 (s, 1H, imine), 8.00 (d, 1H, J = 7.08 Hz, aromatic), 7.56 (t, 1H, J = 7.08 Hz, aromatic),7.38 (t, 1H, J = 8.09 Hz, aromatic), 7.34 (d, 1H, J = 8.09 Hz, aromatic), 7.30 (d, 1H, J = 9.11 Hz, aromatic), 7.04 (d, 2H, J = 8.09 Hz, aromatic).

7.3.5. (E)-4-Chloro-6-methyl-3-((2-m-tolylhydrazono)methyl)-2H-chromen-2-one (**7g**)

Yield: 88%; orange red color solid; m.p: 187–189 °C; IR (KBr): 3427, 3274, 2923, 2854, 1685, 1599, 1565, 1530, 1480, 1290, 1244, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H, imine), 7.78 (s, 1H, aromatic), 7.32 (dd, 1H, J = 8.30, 2.26 Hz, aromatic), 7.22 (d, 1H, J = 8.30 Hz, aromatic), 7.14 (t, 1H, J = 7.55 Hz, aromatic), 6.88–6.92 (m, 2H, aromatic), 6.70 (d, 1H, J = 7.55 Hz, aromatic), 2.50 (s, 3H, CH_3), 2.35 (s, 3H, CH_3).

7.3.6. (E)-4-Chloro-3-((2-(3-chlorophenyl)hydrazono)methyl)-6-methyl-2H-chromen-2-one (**7h**)

Yield: 83%; orange red color solid; m.p: 216–218 °C; IR (KBr): 3442, 3278, 2920, 1685, 1601, 1567, 1527, 1487, 1297, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 7.76 (s, 1H, NH), 8.04 (s, 1H, imine), 7.78 (s, 1H, aromatic), 7.36 (d, 1H, J = 8.37 Hz, aromatic), 7.22 (d, 1H, J = 8.37 Hz, aromatic), 7.17 (d, 1H, J = 8.37 Hz, aromatic), 7.12 (s, 1H, aromatic), 6.98 (d, 1H, J = 8.37 Hz, aromatic), 6.75 (d, 1H, J = 8.37 Hz, aromatic), 2.44 (s, 3H, CH_3).

7.4. General procedure for the synthesis of substituted 2-oxo-2H-chromenylpyrazolecarboxylates (**8**)

7.4.1. Synthesis of diethyl-3-(4-chloro-2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**8a**)

The compound (*E*)-4-chloro-3-((2-phenylhydrazono)methyl)-2*H*-chromen-2-one (**7a**, 0.3 g, 1 mmol) and diethyl but-2-ynedioate (0.187 g, 1.1 mmol) were heated to 130 °C for 10 h. After completion of reaction (TLC), the reaction was cooled to room temperature and extracted with ethyl acetate (2 × 30 mL), washed with water and brine solution. The organic layer was separated and dried over

Na_2SO_4, the solvent was removed under reduced pressure, the crude product was purified by column chromatography afforded diethyl-3-(4-chloro-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate **8a** as pale yellow color solid in 62% yield; m.p: 118–120 °C; IR (KBr): 2924, 2856, 1722, 1604, 1543, 1476, 1372, 1301, 1255, 1209, 1099, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, 1H, J = 7.93 Hz, aromatic), 7.68–7.33 (m, 8H, aromatic), 4.34 (q, 2H, J = 7.17 Hz, OCH_2), 4.21 (q, 2H, J = 7.17 Hz, OCH_2), 1.27 (t, 3H, J = 7.17 Hz, CH_3), 1.19 (t, 3H, J = 7.17 Hz, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): 161.02, 160.33, 158.42, 159.29, 148.65, 145.13, 138.67, 137.72, 133.30, 129.24, 129.14, 126.18, 124.87, 123.99, 119.57, 118.08, 116.77, 114.88, 62.78, 60.81, 13.83, 13.70; EI-MS (m/z): 467 $[M+H]^+$, 489 $[M+Na]^+$; HRMS-ESI calcd for $C_{24}H_{20}ClN_2O_6$ $[M+H]^+$ 481.1161; found 481.1151.

Similarly other substituted 2-oxo-2*H*-chromenylpyrazolecarboxylates were synthesized and are summarized below.

*7.4.2. Diethyl-3-(4-chloro-2-oxo-2H-chromen-3-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**8b**)*

Yield: 66%; pale yellow solid; m.p: 97–99 °C; IR (KBr): 2925, 2856, 1722, 1604, 1534, 1491, 1445, 1379, 1301, 1268, 1224, 1159, 1103, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 1H, J = 7.91 Hz, aromatic), 7.61 (t, 1H, J = 6.92 Hz, aromatic), 7.43–7.32 (m, 5H, aromatic), 7.24–7.20 (m, 1H, aromatic), 4.33 (q, 2H, J = 6.92 Hz, OCH_2), 4.21 (q, 2H, J = 6.92 Hz, OCH_2), 2.43 (s, 3H, CH_3), 1.26 (t, 3H, J = 6.92 Hz, CH_3), 1.19 (t, 3H, J = 6.92 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 160.96, 160.38, 152.47, 151.85, 148.39, 145.08, 139.46, 128.76, 133.18, 129.88, 128.99, 126.25, 124.74, 120.95, 119.91, 118.22, 116.84, 62.63, 60.74, 21.32, 13.96, 13.81; EI-MS (m/z): 481 $[M+H]$, 503 $[M+Na]$; HRMS-ESI calcd for $C_{25}H_{22}N_2O_6Cl$ $[M+H]^+$ 481.1161; found 481.1151.

*7.4.3. Diethyl-3-(4-chloro-2-oxo-2H-chromen-3-yl)-1-(4-methoxyphenyl)-1H-pyrazole-4,5-dicarboxylate (**8c**)*

Yield: 69%; pale yellow solid; m.p: 131–132 °C; IR (KBr): 2967, 2932, 2839, 1724, 1609, 1546, 1514, 1475, 1305, 1251, 1208, 1165, 1100, 1025, 979 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 1H, J = 7.99 Hz, aromatic), 7.61 (t, 1H, J = 7.99 Hz, aromatic), 7.47 (d, 2H, J = 8.99 Hz, aromatic), 7.40 (d, 1H, J = 7.99 Hz, aromatic), 7.36 (t, 1H, J = 7.99 Hz, aromatic), 6.95 (d, 2H, J = 8.99 Hz, aromatic), 4.32 (q, 2H, J = 6.99 Hz, OCH_2), 4.20 (q, 2H, J = 6.99 Hz, OCH_2), 3.85 (s, 3H, OCH_3), 1.28 (t, 3H, J = 6.99 Hz, CH_3), 1.18 (t, 3H, J = 6.99 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 160.15, 159.97, 157.73, 152.58, 147.75, 144.76, 132.92, 126.28, 125.67, 124.57, 120.26, 118.40, 116.88, 114.18, 62.37, 60.54, 55.33, 14.07, 13.98; EI-MS (m/z): 497 $[M+H]^+$, 519 $[M+Na]^+$; HRMS-ESI calcd for $C_{25}H_{21}N_2O_7Cl$ $[M+H]^+$ 497.1115; found 497.1098.

*7.4.4. Diethyl-3-(4-chloro-2-oxo-2H-chromen-3-yl)-1-(3-chlorophenyl)-1H-pyrazole-4,5-dicarboxylate (**8d**)*

Yield: 60%; pale yellow solid; m.p: 119–121 °C; IR (KBr): 2927, 1711, 1593, 1540, 1479, 1447, 1300, 1256, 1208, 1162, 1106, 1041, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 1H, J = 7.93 Hz, aromatic), 7.67–7.59 (m, 2H, aromatic), 7.52–7.33 (m, 5H, aromatic), 4.38 (q, 2H, J = 7.17 Hz, OCH_2), 4.22 (q, 2H, J = 7.17 Hz, OCH_2), 1.33 (t, 3H, J = 7.17 Hz, CH_3), 1.19 (t, 3H, J = 7.17 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 152.50, 145.45, 139.74, 137.59, 135.03, 133.14, 130.15, 129.12, 126.25, 124.73, 124.33, 121.97, 118.20, 116.88, 115.52, 62.80, 60.79, 13.96, 13.87; EI-MS (m/z): 501 $[M+H]^+$, 523 $[M+Na]^+$.

*7.4.5. Diethyl-1-(4-bromophenyl)-3-(4-chloro-2-oxo-2H-chromen-3-yl)-1H-pyrazole-4,5-dicarboxylate (**8e**)*

Yield: 58%; pale yellow solid; m.p: 140–142 °C; IR (KBr): 3098, 2924, 2856, 1727, 1609, 1542, 1483, 1396, 1308, 1273, 1210, 1102, 1007, 978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, 1H, J = 7.93 Hz, aromatic), 7.67–7.57 (m, 3H, aromatic), 7.51–7.33 (m, 4H, aromatic), 4.35 (q, 2H, J = 7.17 Hz, OCH_2), 4.21 (q, 2H, J = 7.17 Hz, OCH_2), 1.32 (t, 3H, J = 7.17 Hz, CH_3), 1.19 (t, 3H, J = 7.17 Hz, CH_3); EI-MS (m/z): 546 $[M+H]^+$; HRMS-ESI calcd for $C_{24}H_{19}BrClN_2O_6$ $[M+H]^+$ 545.011; found 545.012.

*7.4.6. Diethyl-3-(4-chloro-6-methyl-2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**8f**)*

Yield: 60%; pale yellow solid; m.p: 168–169 °C; IR (KBr): 2923, 2856, 1722, 1610, 1580, 1532, 1493, 1369, 1263, 1229, 1198, 1165, 1099, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (s, 1H, aromatic), 7.60–7.54 (m, 2H, aromatic), 7.50–7.38 (m, 4H, aromatic), 7.29 (d, 1H, J = 8.24 Hz, aromatic), 4.33 (q, 2H, J = 6.99 Hz, OCH_2), 4.20 (q, 2H, J = 6.99 Hz, OCH_2), 2.47 (s, 3H, CH_3), 1.27 (t, 3H, J = 6.99 Hz, CH_3), 1.18 (t, 3H, J = 6.99 Hz, CH_3); EI-MS (m/z): 481 $[M+1]^+$, 503 $[M+Na]^+$.

*7.4.7. Diethyl-3-(4-chloro-6-methyl-2-oxo-2H-chromen-3-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**8g**)*

Yield: 64%; pale yellow solid; m.p: 118–120 °C; IR (KBr): 3063, 2924, 2856, 1719, 1612, 1583, 1469, 1376, 1272, 1234, 1197, 1166, 1098, 1009, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (s, 1H, aromatic), 7.45–7.39 (m, 2H, aromatic), 7.38–7.29 (m, 3H, aromatic), 7.22 (d, 1H, J = 8.22 Hz, aromatic), 4.34 (q, 2H, J = 7.00 Hz, OCH_2), 4.20 (q, 2H, J = 7.00 Hz, OCH_2), 2.48 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 1.28 (t, 3H, J = 7.00 Hz, CH_3), 1.18 (t, 3H, J = 7.00 Hz, CH_3); EI-MS (m/z): 495 $[M+H]^+$, 517 $[M+Na]^+$; HRMS-ESI calcd for $C_{26}H_{23}N_2O_6NaCl$ $[M+Na]^+$ 517.1142; found 517.1149.

*7.4.8. Diethyl-3-(4-chloro-6-methyl-2-oxo-2H-chromen-3-yl)-1-(3-chlorophenyl)-1H-pyrazole-4,5-dicarboxylate (**8h**)*

Yield: 56%; pale yellow solid; m.p: 130–131 °C; IR (KBr): 2926, 1716, 1586, 1536, 1472, 1377, 1263, 1227, 1106, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (s, 1H, aromatic), 7.62 (s, 1H, aromatic), 7.52–7.40 (m, 4H, aromatic), 7.31 (d, 1H, J = 8.30 Hz, aromatic), 4.38 (q, 2H, J = 7.55 Hz, OCH_2), 4.21 (q, 2H, J = 7.55 Hz, OCH_2), 2.48 (s, 3H, CH_3), 1.33 (t, 3H, J = 7.55 Hz, CH_3), 1.19 (t, 3H, J = 7.55 Hz, CH_3); EI-MS (m/z): 515 $[M+H]^+$, 537 $[M+Na]^+$; HRMS-ESI calcd for $C_{25}H_{20}N_2O_6NaCl_2$ $[M+Na]^+$ 537.0596; found 537.0601.

*7.5. General procedure for the preparation of substituted 3-acetylchromenones (**10**)*

*7.5.1. Synthesis of 3-acetyl-2H-chromen-2-one (**10a**)*

Piperidine (5 mol %) was added to a stirred solution of salicylaldehyde **9a** (0.244 g, 1 mmol) and ethyl 3-oxobutanoate (0.286 g, 1.1 mmol) in dichoromethane/acetonitrile (4 mL) at room temperature. The contents were stirred for 4 h at the same temperature. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by column chromatography using silica gel (60–120) afforded 3-acetyl-2*H*-chromen-2-one **10a** in 90% yield as pale yellow solid; m.p: 121–123 °C. IR (KBr): 1741, 1679, 1614, 1558, 1455, 1367, 1211 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.60 (s, 1H, aromatic), 7.30–7.80 (m, 4H, aromatic), 2.80 (s, 3H, CH_3). EI-MS (m/z): 189 $[M+H]^+$.

Similarly other 3-acetyl-2*H*-chromen-2-ones were synthesized and are summarized below.

*7.5.2. 3-Acetyl-6-methoxy-2H-chromen-2-one (**10b**)*

Yield: 83%; pale yellow solid; m.p: 131–133 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.41 (s, 1H, aromatic), 7.29 (d, 1H, J = 9.06 Hz, aromatic), 7.20 (dd, 1H, J = 9.06, 2.64 Hz, aromatic), 7.01 (d, 1H, J = 2.64 Hz, aromatic), 3.85 (s, 3H, OCH_3), 2.70 (s, 3H, $COCH_3$); EI-MS (m/z): 219 $[M+H]^+$.

*7.5.3. 3-Acetyl-7-methoxy-2H-chromen-2-one (**10c**)*

Yield: 88%; pale yellow solid; m.p: 126–128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H, aromatic), 7.52 (d, 1H, J = 8.30 Hz, aromatic), 6.86 (dd, 1H, J = 8.30, 2.26 Hz, aromatic), 6.81 (d, 1H, J = 2.26 Hz, aromatic), 3.92 (s, 3H, OCH_3), 2.67 (s, 3H, $COCH_3$); EI-MS (m/z): 219 $[M + H]^+$.

*7.5.4. 7-(3-Methylbut-2-enyloxy)-3-acetyl-2H-chromen-2-one (**10d**)*

Yield: 84%; pale yellow solid; m.p: 108–110 °C; IR (KBr): 2927, 1724, 1676, 1613, 1545, 1499, 1292, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H, aromatic), 7.50 (d, 1H, J = 8.30 Hz, aromatic), 6.84 (dd, 1H, J = 8.30, 2.26 Hz, aromatic), 6.78 (d, 1H, J = 2.26 Hz, aromatic), 5.48–5.41 (m, 1H, CH), 4.60 (d, 2H, J = 8.30 Hz, OCH_2), 2.67 (s, 3H, $COCH_3$), 1.82 (s, 3H, CH_3), 1.78 (s, 3H, CH_3); EI-MS (m/z): 273 [M + H], 295 $[M + Na]^+$.

*7.5.5. 2-Acetyl-3H-benzo[f]chromen-3-one (**10e**)*

Yield: 78%, pale yellow solid, m.p: 186–189 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.28 (s, 1H, aromatic), 8.40 (d, 1H, J = 8.20 Hz, aromatic), 8.08 (d, 1H, J = 8.20 Hz, aromatic), 7.92 (d, 1H, J = 8.02 Hz, aromatic), 7.75 (t, 2H, J = 8.10 Hz, aromatic), 7.60 (t, 2H, J = 8.10 Hz, aromatic), 7.48 (d, 1H, J = 8.20 Hz, aromatic), 2.75 (s, 3H, $COCH_3$). Mass (ESI-MS): m/z 239 $[M + H]^+$.

*7.5.6. 3-Acetyl-8,8-dimethyl-7,8-dihydro-2H,6H-pyrano[3,2-g] chromen-2-one (**10f**)*

Yield: 90%; pale yellow solid; m.p: 158–160 °C; IR (KBr): 2924, 2853, 1720, 1681, 1621, 1552, 1430, 1225, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.40 (s, 1H, aromatic), 7.35 (s, 1H, aromatic), 6.70 (s, 1H, aromatic), 2.88 (t, 2H, J = 6.79 Hz, CH_2), 2.70 (s, 3H, $COCH_3$), 1.88 (t, 2H, J = 6.79 Hz, CH_2), 1.45 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); EI-MS (m/z): 273 [M + H], 295 $[M + Na]^+$.

*7.6. General procedure for the preparation of 3-{1-[(E)-2-phenylhydrazono]ethyl}-2H-chromen-2-one (**11**)*

These compounds were prepared as per the procedure mentioned in Section 7.3.

*7.6.1. 3-{1-[(E)-2-Phenylhydrazono]ethyl}-2H-chromen-2-one (**11a**)*

Yield: 78%; orange yellow color solid; m.p: 185–187 °C; IR (KBr): 3427, 3298, 3052, 2929, 1719, 1600, 1551, 1490, 1447, 1256, 1232, 1157, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (s, 1H, aromatic), 7.54–7.60 (m, 2H, aromatic), 7.50 (dd, 1H, J = 7.55 and 1.51 Hz, aromatic), 7.34 (d, 1H, J = 8.30 Hz, aromatic), 7.30 (t, 2H, J = 7.55 Hz, aromatic), 7.16 (d, 2H, J = 7.55 Hz, aromatic), 6.92 (t, 1H, J = 7.55 Hz, aromatic), 2.30 (s, 3H, CH_3); EI-MS (m/z): 279 [M + H], 301 $[M + Na]^+$.

*7.6.2. 3-{1-[(E)-2-(3,4-Dimethylphenyl)hydrazono]ethyl}-2H-chromen-2-one (**11c**)*

Yield: 82%; orange yellow color solid; m.p: 168–170 °C; IR (KBr): 3320, 2920, 2852, 1714, 1613, 1580, 1515, 1449, 1303, 1172, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.55 (d, 1H, J = 8.20 Hz, aromatic), 7.48 (t, 1H, J = 8.02 Hz, aromatic), 7.48 (s, 1H, aromatic), 7.32 (d, 1H, J = 8.20 Hz, aromatic), 6.98 (d, 1H, J = 8.02 Hz, aromatic), 6.90 (s, 1H, aromatic), 6.81 (d, 1H, J = 8.20 Hz, aromatic), 2.28 (s, 6H, $2CH_3$); EI-MS (m/z): 329 $[M + Na]^+$.

*7.6.3. 3-{1-[(E)-2-(3-Chlorophenyl)hydrazono]ethyl}-2H-chromen-2-one (**11e**)*

Yield: 74%; orange yellow color solid; m.p: 171–173 °C; IR (KBr): 3430, 3292, 2927, 1698, 1486, 1424, 1259, 1156, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, aromatic), 7.48–7.60 (m, 3H, aromatic), 7.36 (t, 1H, J = 8.30 Hz, aromatic), 7.18 (s, 1H, aromatic), 7.14 (d, 1H, J = 7.74 Hz, aromatic), 6.92 (d, 1H, J = 8.12 Hz, aromatic), 6.84 (d, 1H, J = 7.55 Hz, aromatic), 2.30 (s, 3H, CH_3).

*7.6.4. 3-{1-[(E)-2-(3-Fluorophenyl)hydrazono]ethyl}-2H-chromen-2-one (**11f**)*

Yield: 75%; orange yellow color solid; m.p: 200–201 °C; IR (KBr): 3295, 1711, 1613, 1525, 1487, 1448, 1265, 1168, 1130 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.50–7.58 (m, 3H, aromatic), 7.34 (d, 1H, J = 8.30 Hz, aromatic), 7.28 (d, 1H, J = 7.55 Hz, aromatic), 7.16 (q, 1H, J = 8.30 Hz, aromatic), 6.92 (dt, 1H, J = 11.33 and 2.26 Hz, aromatic), 6.77 (d, 1H, J = 7.55 Hz, aromatic), 6.56 (td, 1H, J = 8.3 and 2.26 Hz, aromatic), 2.30 (s, 3H, CH_3); EI-MS (m/z): 319 $[M + Na]^+$.

*7.6.5. 3-{1-[(E)-2-(4-Chlorophenyl)hydrazono]ethyl}-2H-chromen-2-one (**11g**)*

Yield: 72%, orange yellow color solid; m.p: 199–201 °C; IR (KBr): 3444, 3290, 2924, 1736, 1607, 1512, 1486, 1451, 1204, 1155, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.44–7.56 (m, 3H, aromatic), 7.34 (d, 1H, J = 8.49 Hz, aromatic), 7.20 (d, 2H, J = 8.49 Hz, aromatic), 7.04 (d, 2H, J = 8.68 Hz, aromatic), 2.30 (s, 3H, CH_3); EI-MS (m/z): 315 $[M + Na]^+$.

*7.6.6. 3-{1-[(E)-2-(4-Bromophenyl)hydrazono]ethyl}-2H-chromen-2-one (**11h**)*

Yield: 71%; orange yellow color solid; m.p: 156–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.57 (d, 1H, J = 8.05 Hz, aromatic), 7.48–7.52 (m, 2H, aromatic), 7.36 (d, 3H, J = 8.79 Hz, aromatic), 7.29 (d, 1H, J = 7.32 Hz, aromatic), 7.02 (d, 2H, J = 8.79 Hz, aromatic), 2.30 (s, 3H, CH_3).

*7.6.7. 3-{1-[(E)-2-(3-Chlorophenyl)hydrazono]ethyl}6-methoxy-2H-chromen-2-one (**11k**)*

Yield: 73%; orange yellow color solid; m.p: 184–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.50 (s, 1H, aromatic), 7.18 (s, 1H, aromatic), 7.14 (d, 1H, J = 8.12 Hz, aromatic), 7.07 (dd, 3H, J = 8.87 and 1.88 Hz, aromatic), 6.99 (d, 1H, J = 1.88 Hz, aromatic), 6.92 (d, 1H, J = 7.93 Hz, aromatic), 6.84 (d, 1H, J = 7.55 Hz, aromatic), 3.88 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); EI-MS (m/z): 343 $[M + H]^+$.

*7.6.8. 7-Methoxy-3-{1-[(E)-2-phenylhydrazono]ethyl}-2H-chromen-2-one (**11l**)*

Yield: 78%; orange yellow color solid; m.p: 173–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (s, 1H, aromatic), 8.00 (s, 1H, aromatic), 7.52 (d, 1H, J = 8.30 Hz, aromatic), 7.44 (d, 1H, J = 8.12 Hz, aromatic), 7.21 (d, 1H, J = 8.00 Hz, aromatic), 7.10 (d, 2H, J = 8.30 Hz, aromatic), 6.82–6.86 (m, 2H, aromatic), 3.90 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3).

*7.6.9. 7-[(3-Methyl-2-butenyl)oxy]-3-{1-[(E)-2-phenylhydrazono] ethyl}-2H-chromen-2-one (**11o**)*

Yield: 66%; orange yellow color solid; m.p: 204–206 °C; IR (KBr): 3321, 2920, 1697, 1609, 1497, 1440, 1366, 1253, 1215, 1151, 1011 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.50 (s, 1H, aromatic), 7.48 (d, 1H, J = 9.25 Hz, aromatic), 7.30 (t, 1H, J = 8.32 Hz, aromatic), 7.16 (d, 2H, J = 8.32 Hz, aromatic), 6.90 (d, 1H, J = 7.40 Hz, aromatic), 6.86 (dd, 1H, J = 8.32, 1.85 Hz, aromatic), 6.83 (d, 1H, J = 1.85 Hz, aromatic), 5.50 (t, 1H, J = 6.47 Hz, CH), 4.60 (d, 2H, OCH_2), 2.30 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.80 (s, 3H, CH_3).

*7.6.10. (E)-2-(1-(2-Phenylhydrazono)ethyl)-3H-benzo[f]chromen-3-one (**11r**)*

Yield: 82%; orange red color solid; m.p: 197–199 °C; IR (KBr): 3317, 3054, 1712, 1602, 1532, 1248, 1159 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H, aromatic), 8.36 (d, 1H, J = 7.72 Hz, aromatic),

7.98 (d, 1H, $J = 8.83$ Hz, aromatic), 7.92 (d, 1H, $J = 7.72$ Hz, aromatic), 7.71 (t, 1H, $J = 7.72$ Hz, aromatic), 7.58 (t, 1H, $J = 7.72$ Hz, aromatic), 7.48 (d, 1H, $J = 8.83$ Hz, aromatic), 7.32 (t, 2H, $J = 7.72$ Hz, aromatic), 7.22 (d, 2H, $J = 7.72$ Hz, aromatic), 6.94 (t, 1H, $J = 7.72$ Hz, aromatic), 2.28 (s, 3H, CH_3); EI-MS (m/z): 329 $[M + H]^+$.

*7.6.11. (E)-2-(1-(2-m-Tolylhydrazono)ethyl)-3H-benzo[f]chromen-3-one (**11s**)*

Yield: 78%; orange red color solid; m.p: 163–165 °C; IR (KBr): 3294, 3035, 2927, 1713, 1676, 1599, 1551, 1516, 1211, 1159, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H, aromatic), 8.40 (t, 2H, $J = 8.12$ Hz, aromatic), 8.04 (d, 1H, $J = 9.06$ Hz, aromatic), 7.96 (t, 2H, $J = 7.74$ Hz, aromatic), 7.72–7.78 (m, 1H, $J = 7.72$ Hz, aromatic), 7.48 (t, 2H, $J = 6.79$ Hz, aromatic), 7.08–7.12 (m, 2H, aromatic), 2.78 (s, 3H, CH_3), 2.32 (s, 3H, CH_3).

*7.6.12. (E)-2-(1-(2-(3-Chlorophenyl)hydrazono)ethyl)-3H-benzo[f]chromen-3-one (**11t**)*

Yield: 72%; orange red color solid; m.p: 193–195 °C; IR (KBr): 3425, 3299, 3061, 1733, 1710, 1675, 1597, 1555, 1512, 1465, 1240, 1210, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H, aromatic), 8.41 (d, 1H, $J = 8.30$ Hz, aromatic), 8.10 (d, 1H, $J = 9.06$ Hz, aromatic), 7.98 (d, 1H, $J = 9.06$ Hz, aromatic), 7.88–7.92 (m, 2H, aromatic), 7.56–7.62 (m, 2H, aromatic), 7.48 (t, 2H, $J = 9.06$ Hz, aromatic), 2.34 (s, 3H, CH_3); EI-MS (m/z): 363 $[M + H]^+$.

*7.7. General procedure for the preparation of diethyl-3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**12**)*

These compounds were prepared as per the procedure mentioned in Section 7.4.

*7.7.1. Diethyl-3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**12a**)*

Yield: 82%; pale yellow solid; m.p: 125–126 °C; IR (KBr): 2924, 2855, 1728, 1640, 1597, 1465, 1319, 1273, 1237, 1163, 1104, 986, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, aromatic), 7.58–7.40 (m, 7H, aromatic), 7.38 (d, 1H, $J = 8.10$ Hz, aromatic), 7.30 (m, 1H, aromatic), 4.28 (q, 4H, $J = 7.17$ Hz, $2OCH_2$), 1.25 (t, 6H, $J = 6.9$ Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 161.95, 159.71, 159.58, 153.98, 146.53, 142.05, 138.87, 136.84, 132.04, 129.18, 128.29, 128.02, 127.56, 124.55, 120.66, 118.89, 116.60, 62.46, 61.13, 13.94, 13.67; EI-MS (m/z): 433 $[M + H]$, 455 $[M + Na]$; HRMS-ESI calcd for $C_{29}H_{29}N_2O_7$ $[M + H]^+$ 517.1974; found 517.1970.

*7.7.2. Dimethyl-3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**12b**)*

Yield: 80%; colorless solid; m.p: 169–170 °C; IR (KBr): 2950, 2923, 2845, 1725, 1608, 1500, 1446, 1312, 1281, 1234, 1168, 1097, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.04 (s, 1H, aromatic), 7.64 (d, 2H, $J = 8.89$ Hz, aromatic), 7.59–7.52 (m, 3H, aromatic), 7.45–7.37 (m, 3H, aromatic), 7.30 (t, 1H, $J = 6.69$ Hz, aromatic), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 162.42, 160.16, 159.48, 154.00, 146.48, 142.11, 138.80, 136.44, 132.08, 129.23, 128.31, 124.57, 124.42, 118.90, 116.63, 53.12, 52.15; EI-MS (m/z): 405 $[M + H]^+$.

*7.7.3. Diethyl-3-(2-oxo-2H-chromen-3-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**12c**)*

Yield: 86%; pale yellow solid; m.p: 141–143 °C; IR (KBr): 2925, 2854, 1730, 1608, 1501, 1443, 1279, 1260, 1225, 1170, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, aromatic), 7.52 (d, 2H, $J = 8.40$ Hz, aromatic), 7.40–7.20 (m, 6H, aromatic), 4.28 (q, 4H, $J = 7.17$ Hz, $2OCH_2$), 2.44 (s, 3H, CH_3), 1.25 (m, 6H, $2CH_3$); EI-MS (m/z): 447, 469 $[M + H]^+$, $[M + Na]^+$.

*7.7.4. Dimethyl-3-(2-oxo-2H-chromen-3-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**12d**)*

Yield: 84%; pale yellow solid; m.p: 168–170 °C; IR (KBr): 2924, 2853, 1727, 1598, 1541, 1478, 1447, 1314, 1242, 1100, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H, aromatic), 7.52 (d, 2H, $J = 7.55$ Hz, aromatic), 7.40–7.31 (m, 3H, aromatic), 7.30–7.22 (m, 3H, aromatic), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 162.49, 160.30, 159.57, 154.04, 146.43, 142.17, 139.63, 138.72, 132.12, 130.10, 129.01, 128.35, 125.08, 124.61, 121.33, 120.55, 118.95, 116.72, 53.19, 52.23, 21.32; EI-MS (m/z): 429 $[M + H]^+$; HRMS-ESI calcd for $C_{25}H_{23}N_2O_6$ $[M + H]^+$ 447.1556; found 447.1546.

*7.7.5. Diethyl-1-(3,4-dimethylphenyl)-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12e**)*

Yield: 89%; pale yellow solid; m.p: 109–110 °C; IR (KBr): 2969, 2925, 1725, 1609, 1546, 1502, 1461, 1317, 1219, 1175, 1097, 1016, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.57–7.47 (m, 2H, aromatic), 7.37 (d, 1H, $J = 8.30$ Hz, aromatic), 7.33–7.17 (m, 4H, aromatic), 4.28 (q, 4H, $J = 7.17$ Hz, $2OCH_2$), 2.33 (s, 6H, $2CH_3$), 1.28 (t, 6H, $J = 6.9$ Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 161.54, 159.68, 158.81, 154.18, 146.21, 141.32, 137.43, 136.84, 136.64, 131.64, 130.01, 128.17, 125.56, 124.25, 121.63, 121.28, 119.10, 116.48, 115.84, 62.08, 60.77, 19.84, 19.57, 14.10, 13.87; EI-MS (m/z): 461 $[M + H]^+$, 483 $[M + Na]^+$.

*7.7.6. Diethyl-1-(4-methoxyphenyl)-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12f**)*

Yield: 85%; pale yellow solid; m.p: 134–135 °C; IR (KBr): 2981, 1733, 1705, 1638, 1607, 1514, 1464, 1306, 1249, 1218, 1176, 1097, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.52 (d, 2H, $J = 7.55$ Hz, aromatic), 7.45–7.34 (m, 3H, aromatic), 7.28–7.22 (m, 1H, aromatic), 6.95 (d, 2H, $J = 8.87$ Hz, aromatic), 4.28 (q, 4H, $J = 7.17$ Hz, $2OCH_2$), 3.85 (s, 3H, OCH_3), 1.28 (t, 6H, $J = 6.9$ Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 161.67, 160.01, 159.59, 158.88, 154.29, 146.15, 141.34, 136.75, 132.23, 131.72, 128.26, 126.14, 124.33, 121.35, 119.22, 116.80, 114.16, 62.14, 60.89, 55.37, 14.23, 14.00; EI-MS (m/z): 463 $[M + H]^+$, 485 $[M + Na]^+$.

*7.7.7. Diethyl-1-(3-chlorophenyl)-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12g**)*

Yield: 76%; pale yellow solid; m.p: 214–216 °C; IR (KBr): 2924, 2855, 1735, 1604, 1550, 1459, 1374, 1309, 1220, 1170, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, aromatic), 7.59–7.49 (m, 3H, aromatic), 7.49–7.34 (m, 4H, aromatic), 7.29 (d, 1H, $J = 7.36$ Hz, aromatic), 4.30 (q, 4H, $J = 7.17$ Hz, $2OCH_2$), 1.30 (t, 6H, $J = 6.9$ Hz, $2CH_3$); EI-MS (m/z): 467,469 $[M + H]^+$, 489 $[M + Na]^+$.

*7.7.8. Dimethyl-1-(3-chlorophenyl)-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12h**)*

Yield: 73%; pale yellow solid; m.p: 201–203 °C. IR (KBr): 3064, 2924, 1728, 1595, 1554, 1465, 1319, 1273, 1236, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H, aromatic), 7.60–7.50 (m, 3H, aromatic), 7.48–7.35 (m, 4H, aromatic), 7.30 (d, 1H, $J = 7.17$, aromatic), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); EI-MS (m/z): 439, 441 $[M + H]^+$, 461, 463 $[M + Na]^+$; HRMS-ESI calcd for $C_{22}H_{15}N_2O_6Cl$ $[M + H]^+$ 439.0696; found 439.0681.

*7.7.9. Diethyl-1-(3-fluorophenyl)-3-(2-oxo-2H-chromene-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12i**)*

Yield: 74%; pale yellow solid; m.p: 151–152 °C; IR (KBr): 2971, 2926, 1716, 1654, 1608, 1535, 1584, 1446, 1385, 1302, 1232, 1162, 1092, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, aromatic), 7.59–7.24 (m, 7H, aromatic), 7.21–7.11 (m, 1H, aromatic), 4.30 (q, 4H, $J = 7.17$ Hz, $2OCH_2$), 1.28 (t, 6H, $J = 7.17$, $2CH_3$); ^{13}C NMR

(75 MHz, $CDCl_3$): 164.24, 161.55, 160.94, 159.48, 154.24, 146.86, 141.74, 136.74, 132.01, 130.44, 130.33, 128.34, 124.50, 120.85, 120.07, 119.03, 116.82, 116.26, 115.59, 112.55, 112.22, 62.53, 61.13, 14.14, 13.89; EI-MS (*m*/*z*): 451, 473 $[M + H]^+$, $[M + Na]^+$.

*7.7.10. Dimethyl-1-(3-fluorophenyl)-3-(2-oxo-2H-chromene-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12j**)*

Yield: 70%; pale yellow solid; m.p: 202–203 °C; IR (KBr): 2949, 1728, 1606, 1554, 1473, 1444, 1323, 1244, 1162, 1102, 987 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.04 (s, 1H aromatic), 7.59–7.27 (m, 7H, aromatic), 7.21–7.12 (m, 1H, aromatic), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); EI-MS (*m*/*z*): 423 $[M + H]^+$, 445 $[M + Na]^+$.

*7.7.11. Diethyl-1-(4-chlorophenyl)-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12k**)*

Yield: 74%; pale yellow solid; m.p: 110–112 °C; IR (KBr): 2924, 2856, 1737, 1603, 1547, 1494, 1456, 1373, 1308, 1249, 1217, 1173, 1094, 954 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.52 (d, 2H, *J* = 8.75 Hz, aromatic), 7.50–7.42 (m, 4H, aromatic), 7.37 (d, 1H, *J* = 8.75 Hz, aromatic), 7.28 (d, 1H, *J* = 7.77 Hz, aromatic), 4.30 (q, 4H, *J* = 7.17 Hz, $2OCH_2$), 1.28 (t, 6H, *J* = 6.80 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 161.50, 159.40, 158.80, 154.33, 146.74, 141.50, 137.67, 136.57, 135.11, 131.89, 129.33, 128.32, 125.94, 124.41, 121.04, 119.13, 116.84, 62.39, 61.04, 14.20, 13.97; EI-MS (*m*/*z*): 467 $[M + H]^+$, 489 $[M + Na]^+$.

*7.7.12. Diethyl-1-(4-bromophenyl)-3-(2-oxo-2H-chromene-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12l**)*

Yield: 75%; pale yellow solid; m.p: 142–144 °C; IR (KBr): 2922, 2855, 1734, 1604, 1542, 1491, 1450, 1367, 1311, 1262, 1218, 1166, 1096, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.61 (d, 2H, *J* = 8.89 Hz, aromatic), 7.57–7.51 (m, 2H, aromatic), 7.41 (d, 2H, *J* = 8.89 Hz, aromatic), 7.38 (d, 1H, *J* = 8.89 Hz, aromatic), 7.27 (t, 1H, *J* = 7.91 Hz, aromatic), 4.30 (q, 4H, *J* = 7.17 Hz, $2OCH_2$), 1.30 (t, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 159.54, 153.98, 142.14, 137.86, 136.55, 132.35, 132.16, 128.32, 126.11, 124.59, 123.17, 118.84, 116.65, 62.63, 61.23, 13.93, 13.73; EI-MS (*m*/*z*): 330 $[M + H]^+$, 331 $[M+2H]^+$.

*7.7.13. Dimethyl-1-(4-bromophenyl)-3-(2-oxo-2H-chromene-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12m**)*

Yield: 72%; pale yellow solid; m.p: 215–217 °C; IR (KBr): 2923, 2855, 1739, 1712, 1612, 1542, 1490, 1446, 1378, 1254, 1095, 974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H, aromatic), 7.65 (d, 2H, *J* = 8.89 Hz, aromatic), 7.58–7.52 (m, 2H, aromatic), 7.43–7.36 (m, 3H, aromatic), 7.30 (t, 1H, *J* = 8.2 Hz, aromatic), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); EI-MS (*m*/*z*): 483, 485 $[M + H]^+$, 505, 507 $[M + Na]^+$.

*7.7.14. Diethyl-3-(6-methoxy-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**12n**)*

Yield: 76%; pale yellow solid; m.p: 102–104 °C; IR (KBr): 2976, 2929, 1730, 1617, 1548, 1502, 1464, 1363, 1308, 1229, 1091, 1020, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H, aromatic), 7.53–7.44 (m, 5H, aromatic), 7.30 (d, 1H, *J* = 9.06 Hz, aromatic), 7.10 (dd, 1H, *J* = 9.06, 3.02 Hz, aromatic), 6.92 (d, 1H, *J* = 3.02, Hz, aromatic), 4.30 (q, 4H, *J* = 7.17 Hz, $2OCH_2$), 3.83 (s, 3H, OCH_3), 1.26 (t, 6H, *J* = 6.9 Hz, $2CH_3$); EI-MS (*m*/*z*): 463 $[M + H]^+$, 485 $[M + Na]^+$.

*7.7.15. Diethyl-3-(6-methoxy-2-oxo-2H-chromene-3-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**12o**)*

Yield: 80%; pale yellow solid; m.p: 107–109 °C; IR (KBr): 2924, 2855, 1713, 1585, 1546, 1497, 1459, 1377, 1269, 1223, 1160, 1105, 1016, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H, aromatic), 7.38–7.22 (m, 5H, aromatic), 7.09 (dd, 1H, *J* = 2.64, 8.87 Hz, aromatic), 6.92 (d, 1H, *J* = 2.64 Hz, aromatic), 4.28 (q, 4H, *J* = 7.17 Hz, $2OCH_2$), 3.83 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 1.28 (t, 6H, *J* = 6.9 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 161.80, 159.74, 159.38, 156.14, 148.65, 146.53, 141.54, 139.28, 139.02, 129.86, 128.92, 125.24, 121.54, 121.36, 119.71, 119.37, 117.74, 110.17, 62.30, 61.01, 55.68, 21.42, 14.13, 13.88; EI-MS (*m*/*z*): 477 $[M + H]^+$, 499 $[M + Na]^+$.

*7.7.16. Diethyl-1-(3-chlorophenyl)-3-(6-methoxy-2-oxo-2H-chromene-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12p**)*

Yield: 74%; pale yellow solid; m.p: 152–154 °C; IR (KBr): 2926, 1713, 1586, 1548, 1492, 1455, 1269, 1216, 1166, 1106, 1015, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H, aromatic), 7.56 (s, 1H, aromatic), 7.45–7.39 (m, 3H, aromatic), 7.20 (d, 1H, *J* = 8.75, aromatic), 7.10 (dd, 1H, *J* = 8.75, 2.18 Hz, aromatic), 6.93 (d, 1H, *J* = 2.18 Hz, aromatic), 4.28 (q, 4H, *J* = 7.17 Hz, $2OCH_2$), 3.84 (s, 3H, OCH_3), 1.30 (t, 6H, *J* = 6.9 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 161.46, 159.30, 159.00, 156.13, 146.88, 141.41, 140.04, 136.49, 134.92, 129.98, 129.08, 124.94, 122.59, 121.10, 119.80, 119.30, 117.73, 110.13, 62.38, 61.02, 55.59, 14.13, 13.93; EI-MS (*m*/*z*): 497 $[M + H]^+$, 519 $[M + Na]^+$.

*7.7.17. Diethyl-3-(7-methoxy-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**12q**)*

Yield: 72%; pale yellow solid; m.p: 136–138 °C; IR (KBr): 2975, 2931, 1729, 1617, 1548, 1502, 1466, 1359, 1309, 1229, 1181, 1092, 1022, 939 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H, aromatic), 7.53–7.45 (m, 5H, aromatic), 7.40 (d, 1H, *J* = 8.49 Hz, aromatic), 6.85–6.80 (m, 2H, aromatic), 4.28 (q, 4H, *J* = 7.17 Hz, $2OCH_2$), 3.90 (s, 3H, OCH_3), 1.30 (t, 6H, *J* = 6.9 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 163.09, 159.71, 159.55, 156.12, 146.83, 141.88, 139.19, 129.24, 129.16, 129.05, 124.70, 117.37, 112.98, 112.73, 100.58, 62.30, 61.02, 55.71, 14.17, 13.88; EI-MS (*m*/*z*): 473 $[M + H]^+$.

*7.7.18. Diethyl-3-(7-methoxy-2-oxo-2H-chromene-3-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**12r**)*

Yield: 79%; pale yellow solid; m.p: 162–164 °C; IR (KBr): 2978, 2925, 2852, 1729, 1613, 1460, 1267, 1232, 1151, 1096, 1025, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, aromatic), 7.43–7.20 (m, 5H, aromatic), 6.86–6.80 (m, 2H, aromatic), 4.28 (2q, 4H, *J* = 7.17 Hz, $2OCH_3$), 3.89 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 1.28 (2t, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): 163.02, 161.79, 159.75, 159.39, 156.08, 146.72, 141.75, 139.18, 139.06, 136.73, 129.72, 129.18, 128.85, 125.22, 121.52, 117.45, 115.96, 112.85, 112.69, 100.56, 62.18, 60.88, 55.64, 21.37, 14.12, 13.85; EI-MS (*m*/*z*): 477 $[M + H]^+$, 499 $[M + Na]^+$; HRMS-ESI calcd for $C_{26}H_{24}N_2O_7Na$ $[M + Na]^+$ 499.1481; found 499.1462.

*7.7.19. Diethyl-1-(3-chlorophenyl)-3-(7-methoxy-2-oxo-2H-chromene-3-yl)-1H-pyrazole-4,5-dicarboxylate (**12s**)*

Yield: 69%; pale yellow solid; m.p: 143–145 °C; IR (KBr): 2976, 2931, 2191, 1726, 1618, 1549, 1463, 1360, 1317, 1285, 1231, 1117, 1094, 1024, 949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, aromatic), 7.55 (s, 1H, aromatic), 7.47–7.38 (m, 4H, aromatic), 6.86–6.80 (m, 2H, aromatic), 4.30 (q, 4H, *J* = 7.17 Hz, $2OCH_2$), 3.90 (s, 3H, OCH_3), 1.30 (t, 6H, *J* = 6.9 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 163.14, 161.71, 159.41, 156.07, 147.11, 141.96, 139.96, 134.90, 130.04, 129.24, 129.10, 124.92, 122.59, 116.93, 116.65, 112.96, 112.55, 100.54, 62.45, 61.06, 55.68, 14.07, 13.84; EI-MS (*m*/*z*): 497 $[M + H]^+$.

*7.7.20. Diethyl-3-(7-(3-methylbut-2-enyloxy-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**12t**)*

Yield: 68%; pale yellow solid; m.p: 109–110 °C; IR (KBr): 2925, 2860, 1726, 1610, 1618, 1550, 1502, 1456, 1359, 1305, 1226, 1169, 1092, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, aromatic), 7.56–7.34 (m, 6H, aromatic), 6.88–6.76 (m, 2H, aromatic), 5.45 (t, 1H, *J* = 6.23 Hz, CH), 4.58 (d, 2H, CH_2), 4.28 (q, 4H, *J* = 7.17 Hz,

2OCH$_3$), 1.82 (s, 3H, CH$_3$), 1.78 (s, 3H, CH$_3$), 1.28 (t, 6H, J = 6.9 Hz, 2CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): 162.41, 162.00, 159.73, 156.04, 142.01, 139.18, 138.97, 129.16, 129.07, 124.71, 118.89, 117.10, 113.58, 112.58, 101.29, 65.40, 62.31, 61.05, 25.92, 18.40, 14.15, 13.85; EI-MS (m/z): 517 [M + H]$^+$, 538 [M + Na]$^+$.

*7.7.21. Diethyl-3-(7-(3-methylbut-2-enyloxy-2-oxo-2H-chromene-3-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**12u**)*

Yield: 71%; pale yellow solid; m.p: 138–140 °C; IR (KBr): 2925, 1732, 1615, 1551, 1465, 1358, 1284, 1230, 1173, 1090, 1018 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.94 (s, 1H, aromatic), 7.41–7.20 (m, 5H, aromatic), 6.84–6.78 (m, 2H, aromatic), 5.45 (t, 1H, J = 6.23 Hz, CH), 4.57 (d, 2H, J = 6.61 Hz, CH$_2$), 4.28 (q, 4H, J = 7.17 Hz, 2OCH$_2$), 2.43 (s, 3H, CH$_3$), 1.81 (s, 3H, CH$_3$), 1.77 (s, 3H, CH$_3$), 1.28 (t, 6H, J = 6.9 Hz, 2CH$_3$). EI-MS (m/z): 531 [M + H]$^+$, 553 [M + Na]$^+$.

*7.7.22. Diethyl-3-(7-(3-methylbut-2-enyloxy-2-oxo-2H-chromene-3-yl)-1-(3-chlorophenyl)-1H-pyrazole-4,5-dicarboxylate (**12v**)*

Yield: 66%; pale yellow solid; m.p: 130–132 °C; IR (KBr): 2972, 2925, 1727, 1612, 1549, 1463, 1358, 1314, 1285, 1228, 1172, 1103, 1013, 951 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.95 (s, 1H, aromatic), 7.55 (s, 1H, aromatic), 7.46–7.37 (m, 4H, aromatic), 6.87–6.78 (m, 2H, aromatic), 5.47 (t, 1H, J = 6.04 Hz, CH), 4.58 (d, 2H, J = 6.79 Hz, CH$_2$), 4.32 (q, 4H, J = 7.17 Hz, 2OCH$_2$), 1.82 (s, 3H, CH$_3$), 1.78 (s, 3H, CH$_3$), 1.30 (t, 6H, J = 6.9 Hz, 2CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): 162.46, 161.61, 159.41, 159.25, 156.19, 147.21, 141.80, 140.18, 138.65, 136.48, 134.97, 129.99, 129.19, 129.05, 125.06, 122.67, 119.15, 117.05, 116.91, 113.60, 112.56, 101.30, 65.38, 62.38, 61.02, 25.97, 18.47, 14.23, 13.99; EI-MS (m/z): 551 [M + H]$^+$, 573 [M + Na]$^+$.

*7.7.23. Diethyl-3-(3-oxo-3H-benzo(f)chromene-2-yl)-1-phenyl-1H-pyrazole-4,5-dicarboxylate (**12w**)*

Yield: 76%; pale yellow solid; m.p: 155–157 °C; IR (KBr): 3072, 2971, 2929, 1746, 1710, 1629, 1571, 1548, 1501, 1467, 1368, 1304, 1258, 1220, 1175, 1096, 955 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.81 (s, 1H, aromatic), 8.29 (d, 1H, J = 8.00 Hz, aromatic), 7.98 (d, 1H, J = 9.00 Hz, aromatic), 7.88 (d, 1H, J = 8.00 Hz, aromatic), 7.62 (t, 1H, J = 8.00 Hz, aromatic), 7.57–7.43 (m, 7H, aromatic), 4.32 (q, 4H, J = 7.17 Hz, 2OCH$_2$), 1.29 (t, 3H, J = 7.00 Hz, CH$_3$), 1.25 (t, 3H, J = 7.00 Hz, CH$_3$); EI-MS (m/z): 483 [M + H]$^+$, 505 [M + Na]$^+$; HRMS-ESI calcd for C$_{28}$H$_{22}$N$_2$O$_6$ [M + H]$^+$ 483.1556; found 483.1544.

*7.7.24. Diethyl-3-(3-oxo-3H-benzo(f)chromene-2-yl)-1-m-tolyl-1H-pyrazole-4,5-dicarboxylate (**12x**)*

Yield: 79%; pale yellow solid; m.p: 148–150 °C; IR (KBr): 2973, 2924, 1719, 1623, 1549, 1504, 1453, 1368, 1306, 1269, 1216, 1173, 1095, 962 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.81 (s, 1H, aromatic), 8.30 (d, 1H, J = 8.49 Hz, aromatic), 7.99 (d, 1H, J = 9.06 Hz, aromatic), 7.89 (d, 1H, J = 7.93 Hz, aromatic), 7.67–7.60 (m, 1H, aromatic), 7.57–7.48 (m, 2H, aromatic), 7.40–7.23 (m, 4H, aromatic), 4.26 (q, 4H, J = 7.17 Hz, 2OCH$_2$), 2.43 (s, 3H, CH$_3$), 1.24 (t, 6H, J = 6.9 Hz, 2CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): 161.74, 154.12, 139.25, 139.19, 137.38, 133.11, 130.42, 129.80, 129.53, 129.02, 128.91, 128.20, 126.00, 125.47, 121.88, 121.75, 120.19, 117.05, 113.36, 62.18, 60.97, 21.51, 14.25, 13.97; EI-MS (m/z): 497 [M + H]$^+$, 519 [M + Na]$^+$; HRMS-ESI calcd for C$_{29}$H$_{24}$N$_2$O$_6$Na [M + Na]$^+$ 519.1532; found 519.1520.

*7.7.25. Diethyl-1-(3-chlorophenyl)-3-(3-oxo-3H-benzo(f)chromen-2yl)-1H-pyazole-4,5-dicarboxylate (**12y**)*

Yield: 68%; pale yellow solid; m.p: 157–158 °C; IR (KBr): 2978, 2924, 2851, 1727, 1591, 1574, 1484, 1303, 1253, 1219, 1095 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.80 (s, 1H, aromatic), 8.28 (d, 1H, J = 8.30 Hz, aromatic), 7.98 (d, 1H, J = 9.06 Hz, aromatic), 7.88 (d, 1H, J = 7.93 Hz, aromatic), 7.67–7.58 (m, 2H, aromatic), 7.55 (d, 1H, J = 7.36 Hz, aromatic), 7.49 (d, 1H, J = 9.06 Hz, aromatic), 7.46–7.41 (m, 3H, aromatic), 4.32 (q, 4H, J = 7.17 Hz, 2OCH$_2$), 1.30 (t, 6H, J = 6.9 Hz, 2CH$_3$); EI-MS (m/z): 517 [M + H]$^+$, 539 [M + Na]$^+$.

*7.7.26. Diethyl-3-(8,8-dimethyl-2-oxo-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-3-yl)-1-pheny-1H-4,5-pyrazoledicarboxylate (**12z**)*

Yield: 78%; pale yellow solid; m.p: 207–209 °C; IR (KBr): 2925, 2855, 1720, 1624, 1565, 1497, 1441, 1470, 1360, 1296, 1251, 1217, 1147, 1088, 1013, 954 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.87 (s, 1H, aromatic), 7.52–7.40 (m, 5H, aromatic), 7.16 (s, 1H, aromatic), 6.73 (s, 1H, aromatic), 4.30 (q, 4H, J = 7.17 Hz, 2OCH$_2$), 2.82 (t, 2H, J = 6.00 Hz, CH$_2$), 1.85 (t, 2H, J = 6.00 Hz, CH$_2$), 1.37 (s, 6H, CH$_3$), 1.28 (t, 3H, J = 7.00 Hz, CH$_3$), 1.23 (t, 3H, J = 7.00 Hz, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): 161.91, 159.73, 158.04, 154.31, 147.06, 141.74, 139.31, 136.68, 129.10, 128.93, 128.65, 124.73, 118.31, 117.12, 116.34, 112.45, 104.62, 75.70, 62.20, 60.94, 32.61, 27.09, 22.05, 14.17, 13.88; EI-MS (m/z): 517 [M + H]$^+$, 539 [M + Na]$^+$.

*7.7.27. Diethyl-3-(8,8-dimethyl-2-oxo-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-3-yl)-1-(3-methylphenyl)-1H-4,5-pyrazoledicarboxylate (**12za**)*

Yield: 81%; pale yellow solid; m.p: 180–182 °C; IR (KBr): 2980, 2930, 1723, 1623, 1567, 1496, 1440, 1242, 1148, 1095, 1038, 848 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.87 (s, 1H, aromatic), 7.37–7.19 (m, 4H, aromatic), 7.16 (s, 1H, aromatic), 6.72 (s, 1H, aromatic), 4.28 (q, 4H, J = 7.17 Hz, 2OCH$_2$), 2.82 (t, 2H, J = 6.79 Hz, CH$_2$), 2.43 (s, 3H, CH$_3$), 1.84 (t, 2H, J = 6.79 Hz, CH$_2$), 1.37 (s, 3H, CH$_3$), 1.28 (t, 6H, J = 6.9 Hz, 2CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): 161.71, 159.75, 159.44, 157.90, 154.29, 146.94, 141.53, 139.20, 139.04, 136.68, 129.58, 128.81, 128.58, 125.26, 121.55, 118.13, 117.27, 116.13, 112.44, 104.58, 75.57, 62.07, 60.78, 32.60, 27.09, 22.02, 21.44, 14.19, 13.92; EI-MS (m/z): 531 [M + H]$^+$.

*7.7.28. Diethyl-1-(3-chlorophenyl)-3-(8,8-dimethyl-2-oxo-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-3-yl)-1H-4,5-pyrazoledicarboxylate (**12zb**)*

Yield: 73%; pale yellow solid; m.p: 188–190 °C; IR (KBr): 2978, 2932, 1722, 1627, 1572, 1541, 1489, 1352, 1277, 1223, 1147, 1118, 1092, 1042, 970 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.87 (s, 1H, aromatic), 7.55 (s, 1H, aromatic), 7.43–7.38 (m, 3H, aromatic), 7.17 (s, 1H, aromatic), 6.72 (s, 1H, aromatic), 4.26 (q, 2H, J = 7.17 Hz, OCH$_2$), 4.23 (q, 2H, J = 7.17 Hz, OCH$_2$), 2.82 (t, 2H, J = 6.66 Hz, CH$_2$), 1.85 (t, 2H, J = 6.66 Hz, CH$_2$), 1.37 (s, 3H, CH$_3$), 1.24 (t, 6H, J = 6.9 Hz, 2CH$_3$). EI-MS (m/z): 551 [M + H]$^+$.

*7.8. General procedure for the preparation of substituted phenylchromeno[4,3-c]pyrazol-4(1H)-ones (**13**)*

These compounds were obtained in minor quantity during the preparation of compounds **12a**–**zb** as per the procedure depicted in Section 7.7.

*7.8.1. 3-Methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-one (**13a**)*

Yield: 24%; colorless solid; m.p: 186–188 °C; IR (KBr): 2926, 1716, 1586, 1536, 1472, 1377, 1263, 1227, 1106, 1011 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.65–7.50 (m, 5H, aromatic), 7.45–7.39 (m, 2H, aromatic), 7.08 (d, 1H, J = 7.93 Hz, aromatic), 7.03–6.96 (m, 1H, aromatic), 2.67 (s, 3H, CH$_3$); EI-MS (m/z): 339 [M + H]$^+$, 361 [M + Na]$^+$.

*7.8.2. 3-Methyl-1-m-tolylchromeno[4,3-c]pyrazol-4(1H)-one (**13b**)*

Yield: 28%; colorless solid; m.p: 181–183 °C; IR (KBr): 2926, 1716, 1586, 1536, 1472, 1377, 1263, 1227, 1106, 1011 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.48–7.28 (m, 6H, aromatic), 7.11 (d, 1H,

J = 7.55 Hz, aromatic), 7.04–6.97 (m, 1H, aromatic), 2.67 (s, 3H, CH_3), 2.49 (s, 3H, CH3); EI-MS (m/z): 291 $[M + H]^+$, 313 $[M + Na]^+$.

*7.8.3. 1-(4-Methoxyphenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (**13c**)*

Yield: 24%; pale yellow solid; m.p: 179–181 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.35 (m, 4H, aromatic), 7.10–6.97 (m, 4H, aromatic), 3.92 (s, 3H, OCH_3), 2.65 (s, 3H, CH_3); EI-MS (m/z): 307 $[M + H]^+$, 329 $[M + Na]^+$.

*7.8.4. 1-(3-Chlorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (**13d**)*

Yield: 26%; pale yellow solid; m.p: 196–197 °C; IR (KBr): 2926, 1716, 1586, 1536, 1472, 1377, 1263, 1227, 1106, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65–7.40 (m, 6H, aromatic), 7.15 (d, 1H, J = 7.77 Hz, aromatic), 7.06 (t, 1H, J = 7.77 Hz, aromatic), 2.66 (s, 3H, CH_3); EI-MS (m/z): 311, 313 $[M + H]^+$, 333, 335 $[M + Na]^+$.

*7.8.5. 1-(4-Chlorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (**13e**)*

Yield: 29%; pale yellow solid; m.p: 195–197 °C; IR (KBr): 2926, 1716, 1586, 1536, 1472, 1377, 1263, 1227, 1106, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, 2H, J = 8.49 Hz, aromatic), 7.50 (d, 2H, J = 8.68 Hz, aromatic), 7.47–7.38 (m, 2H, aromatic), 7.14 (d, 1H, J = 7.93 Hz, aromatic), 7.09–7.01 (m, 1H, aromatic), 2.65 (s, 3H, CH_3); EI-MS (m/z): 311 $[M + H]^+$.

*7.8.6. 1-(3-Fluorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (**13f**)*

Yield: 22%; pale yellow solid; m.p: 183–185 °C; IR (KBr): 3078, 2925, 2855, 1744, 1602, 1520, 1456, 1254, 1201, 1166, 1018, 975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64–7.54 (m, 1H, aromatic), 7.50–7.28 (m, 5H, aromatic), 7.16 (d, 1H, J = 7.55 Hz, aromatic), 7.05 (t, 1H, J = 8.30, 15.10 Hz, aromatic), 2.65 (s, 3H, CH_3); EI-MS (m/z): 295 $[M + H]^+$, 317 $[M + Na]^+$; HRMS-ESI calcd for $C_{17}H_{11}N_2O_2F$ $[M + H]^+$ 295.0882; found 295.0893.

*7.8.7. 1-(4-Bromophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (**13g**)*

Yield: 30%; colorless solid; m.p: 201–203 °C; IR (KBr): 2924, 2853, 1734, 1614, 1517, 1483, 1451, 1396, 1205, 1144, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, J = 8.30 Hz, aromatic), 7.49–7.38 (m, 4H, aromatic), 7.15 (d, 1H, J = 8.30 Hz, aromatic), 7.09–7.02 (m, 1H, aromatic), 2.64 (s, 3H, CH_3); EI-MS (m/z): 355, 357 $[M + H]^+$, 377, 379 $[M + Na]^+$.

*7.8.8. 8-Methoxy-3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-one (**13h**)*

Yield: 10%; pale yellow solid; m.p: 171–173 °C; IR (KBr): 2925, 2855, 1736, 1595, 1523, 1461, 1377, 1243, 1207, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (s, 1H, aromatic), 7.68–7.42 (m, 6H, aromatic), 7.22 (d, 1H J = 7.96 Hz, aromatic), 3.83 (s, 3H, OCH_3), 2.65 (s, 3H, CH_3); EI-MS (m/z): 295 $[M + H]^+$, 317 $[M + Na]^+$.

*7.9. General procedure for the synthesis of substituted phenylchromeno[4,3-c]pyrazol-4(1H)-ones (**13**)*

*7.9.1. Synthesis of 1-phenylchromeno[4,3-c]pyrazol-4(1H)-one (**13i**)*

Catalytic amount of piperidine was added to a stirred solution of 4-chloro-3-((2-phenylhydrazono)methyl)-2*H*-chromen-2-one **7i** (0.298 g, 1 mmol) in pyridine (4 mL), and contents were heated at 100 °C for 2 h. After completion of the reaction (TLC, formed dark red color), reaction mixture was cooled to room temperature and diluted with water (3 mL). Dilute HCl was added to the crude reaction mixture, to quench the excess pyridine. The brown color solid was filtered, washed with water and purified over silica gel (60–120) afforded compound **13i** as pale yellow color solid in 78% yield, m.p: 220–222 °C; IR (KBr): 2926, 1716, 1586, 1536, 1472, 1377, 1263, 1227, 1106, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (s, 1H, aromatic), 7.62 (s, 1H, aromatic), 7.52–7.40 (m, 4H, aromatic), 7.31 (d, 1H, J = 8.30 Hz, aromatic), 4.38 (q, 2H, J = 7.55 Hz, OCH_2), 4.21 (q, 2H, J = 7.55 Hz, OCH_2), 2.48 (s, 3H, CH_3), 1.33 (t, 3H, J = 7.55 Hz, CH_3), 1.19 (t, 3H, J = 7.55 Hz, CH_3); EI-MS (m/z): 515 $[M + H]^+$, 537 $[M + Na]^+$.

*7.9.2. 1-m-Tolylchromeno[4,3-c]pyrazol-4(1H)-one (**13j**)*

Yield: 74%; pale yellow solid; m.p: 216–218 °C; IR (KBr): 2922, 2854, 1724, 1660, 1555, 1464, 1328, 1236, 1149, 1101, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.29 (s, 1H, imine), 7.53–7.31 (m, 6H, aromatic), 7.13 (d, 1H, J = 7.55 Hz, aromatic), 7.07–7.01 (m, 1H, aromatic), 2.50 (s, 3H, CH_3); EI-MS (m/z): 277 $[M + H]^+$, 299 $[M + Na]^+$.

*7.9.3. 1-(3-Chlorophenyl)chromeno[4,3-c]pyrazol-4(1H)-one (**13k**)*

Yield: 71%; pale yellow solid; m.p: 230–231 °C; IR (KBr): 3075, 2925, 1744, 1616, 1585, 1525, 1483, 1451, 1393, 1275, 1192, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (s, 1H, imine), 7.65–7.43 (m, 6H, aromatic), 7.21–7.16 (m, 1H, aromatic), 7.13–7.06 (m, 1H, aromatic), 7.05 (t, 1H, J = 8.30 Hz, aromatic); EI-MS (m/z): 297 $[M + H]^+$, 319 $[M + Na]^+$.

*7.9.4. 8-Methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-one (**13l**)*

Yield: 73%; colorless solid; m.p: 228–230 °C; IR (KBr): 2926, 1716, 1586, 1536, 1472, 1377, 1263, 1227, 1106, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H, imine), 7.66–7.53 (m, 5H, aromatic), 7.33 (d, 1H, J = 8.49 Hz, aromatic), 6.86 (s, 1H, aromatic), 2.18 (s, 3H, CH_3); EI-MS (m/z): 277 $[M + H]^+$, 299 $[M + Na]^+$.

*7.9.5. 8-Methyl-1-m-tolylchromeno[4,3-c]pyrazol-4(1H)-one (**13m**)*

Yield: 68%; pale yellow solid; m.p: 213–215 °C; IR (KBr): 2922, 1745, 1613, 1527, 1494, 1459, 1378, 1279, 1225, 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, imine), 7.54–7.21 (m, 6H, aromatic), 6.90 (d, 1H, J = 1.51 Hz, aromatic), 2.50 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); EI-MS (m/z): 291 $[M + H]^+$, 313 $[M + Na]^+$.

*7.9.6. 1-(3-Chlorophenyl)-8-methylchromeno[4,3-c]pyrazol-4(1H)-one (**13n**)*

Yield: 66%; pale yellow solid; m.p: 231–233 °C; IR (KBr): 3105, 2921, 1752, 1583, 1522, 1452, 1271, 1193, 1155, 1088, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.29 (s, 1H, imine), 7.65–7.46 (m, 4H, aromatic), 7.32 (t, 2H, J = 8.49 Hz, aromatic), 6.95 (s, 1H, aromatic), 2.24 (s, 3H, CH_3); EI-MS (m/z): 311 $[M + H]^+$, 333 $[M + Na]^+$.

7.10. X-ray crystallography

X-ray data were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71073 Å) with ω-scan method [28]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from 5918 reflections for **8a**. Integration and scaling of intensity data were accomplished using SAINT program [28]. The structures were solved by direct methods using SHELXS97 [21] and refinement was carried out by full-matrix least-squares technique using SHELXL97 [21]. Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms [C–H = 0.93–0.97 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H or $1.2U_{eq}(c)$ for other H atoms]. The methyl groups were allowed to rotate but not to tip.

*7.10.1. Crystal data for compound **8a***

$C_{24}H_{19}ClN_2O_6$, M = 466.86, colorless block, 0.15 × 0.12 × 0.06 mm^3, monoclinic, space group $P2_1/n$ (No. 14), a = 11.4178(10), b = 9.1724(8), c = 21.0665(17) Å, β = 102.213(1)°, V = 2156.3(3) $Å^3$, Z = 4, D_c = 1.438 g/cm^3, F_{000} = 968, CCD Area Detector, MoKα radiation, λ = 0.71073 Å, T = 294(2) K, $2\theta_{max}$ = 50.0°, 20,035 reflections collected, 3791 unique (R_{int} = 0.0192). Final *GooF* = 1.030, *R*1 = 0.0428, *wR*2 = 0.1162, *R* indices based on 3458 reflections with $I > 2(I)$ (refinement on F^2), 300 parameters, 0 restraints, μ = 0.223 mm^{-1}. CCDC 879720 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

7.11. Biology activity

7.11.1. Cell proliferation assay using MTT

This assay is a quantitative colorimetric method for determination of cell cytotoxicity [16,22]. The assessed parameter is the metabolic activity of viable cells. Metabolically active cells reduce pale yellow tetrazolium salt (MTT) to a dark blue water-insoluble formazan, which can be directly quantified after solubilization with DMSO. The absorbance of the formazan directly correlates with the number of viable cells. The cells were plated in 96-well plates at a density of 2.0 × 10^4 in 100 μL of medium per well of 96-well plate. Cultures were incubated with the test compounds (10 μM) and incubated for 48 h. The medium was replaced with fresh medium containing 100 μg/mL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) for 2–3 h. The supernatant was aspirated and MTT-formazan crystals were dissolved in 100 μL DMSO; OD measured at λ540 nm (reference wavelength, λ 620 nm) on ELISA reader cell cytotoxicity% was calculated by comparing the absorbance of treated versus untreated cells.

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Appendix A. Supplementary data

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