Green Chemistry Letters and Reviews

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tgcl20

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**To cite this article:** Anhar Abdel-Aziem, Huda Refaat Mahmoud Rashdan, Entesar Mohamed Ahmed & Sara N. Shabaan (2019) Synthesis and cytotoxic activity of some novel benzocoumarin derivatives under solvent free conditions, Green Chemistry Letters and Reviews, 12:1, 9-18, DOI: 10.1080/17518253.2018.1556743

**To link to this article:** https://doi.org/10.1080/17518253.2018.1556743



Published online: 18 Dec 2018.

GREEN CHEMISTRY LETTERS AND REVIEWS
2019, VOL. 12, NO. 1, 9–18
https://doi.org/10.1080/17518253.2018.1556743

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# Synthesis and cytotoxic activity of some novel benzocoumarin derivatives under solvent free conditions

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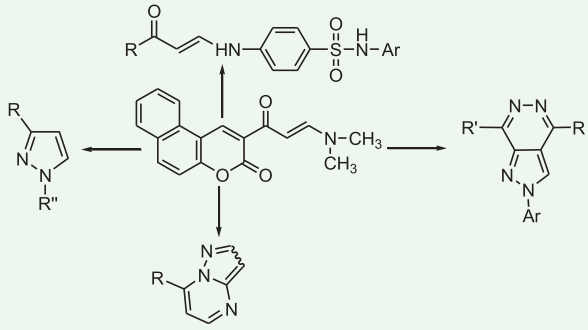
**ABSTRACT**

In the present study, a rapid, less expensive, clean and environmental friendly route to synthesis new pyrazoles, pyrazolopyridazines and condensed pyrimidines was developed *via* grinding of 2-(3-(dimethylamino)acryloyl)-3*H*-benzo[*f*]chromen-3-one (**1**) with different reagents. All the new compounds were characterized and established using elemental analysis and spectral data. Eight compounds were selected for in *vitro* antiproliferative against different human cancer cell lines entitled melanoma, cancers of the lung, leukemia, breast, brain, colon, prostate, ovary and kidney by the USA NCI.



**ARTICLE HISTORY**
Received 15 August 2018
Accepted 4 December 2018

**KEYWORDS**
Green chemistry; coumarins; hydrazonoyl halides; pyrazolo[3,4-*d*]pyridazines; sulphadrugs; cytotoxicity

## Introduction

The organic solvents are volatile and harmful, causing risks to peoples who inhale them as well as the environment. Thus, development of less hazardous synthetic methods for organic reactions is one of our objectives in current research. The grinding method is one of green chemistry techniques as it is carried out in the absence of solvent (*1–4*). Moreover, the solvent-free reactions have numerous advantages: reduced pollution, low costs, high yields and purities of products (*5, 6*). Otherwise, many compounds which contain coumarin nucleus exhibit antimicrobial (*7*), analgesic (*8*), ulcerogenic (*9*), anticoagulant (*10*), antiviral (*11*) and antimalarial (*12*), anti-inflammatory (*13, 14*) anti-leishmanial (*15*) as well as antioxidant (*16, 17*) activities. The antitumor activity of coumarins received a considerable interest owing to their cytotoxic activity against various types of cancer cells, including gastric cancer, liver cancer, colon cancer, breast cancer, prostate cancer, Periodontal Ligament, fibroblast, nasopharyngeal carcinoma, and normal fibroblast cell lines (*18–22*). In addition, coumarin derivatives can inhibit growth in human cancer cell lines (*23*) such as renal (ACHN), lung (A549, H727), leukemia (HL-60), breast (MCF7) and renal cell carcinoma (*24*). Coumarin and its derivatives are important components among the molecules in the drug industry. Warfarin, acenocoumarol and phenprocoumon are a derivatives of coumarin used as anticoagulant drugs. These are vitamin K antagonist which inhibits the coagulation *via* blocking of the coagulation factors [I, VII, IX and X] (*25–27*). Moreover, warfarin reduced metastases from intestinal cancer to a wide extent (*28*) and is also used beside the surgical treatment of cancer masses (*29*) (Figure 1).

In addition, scopoletin (*30, 31*) and esculatin (*32*) were found in nature and they have antiproliferative, antiarthritic, antioxidant, and anti-inflammatory activities. Ensaculin (KA-672) is a drug belong to coumarin family

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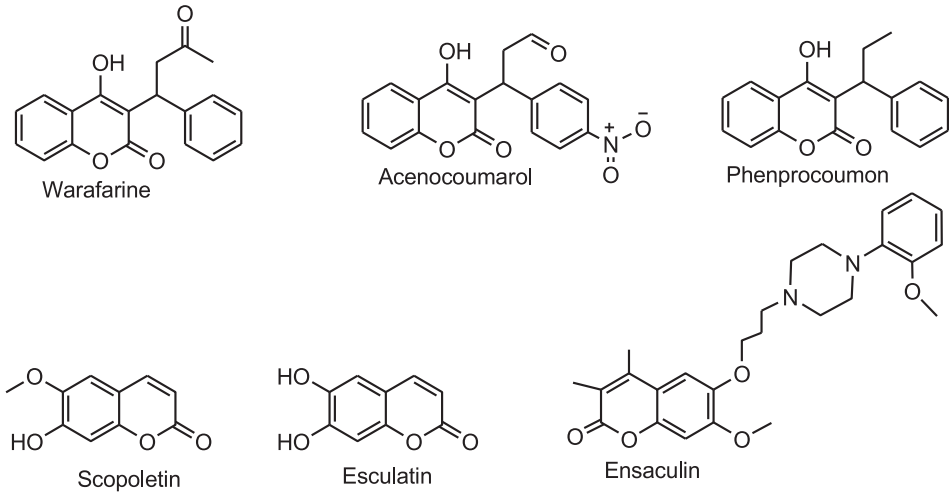



**Figure 1.** Naturally and synthetic coumarins used as drugs.

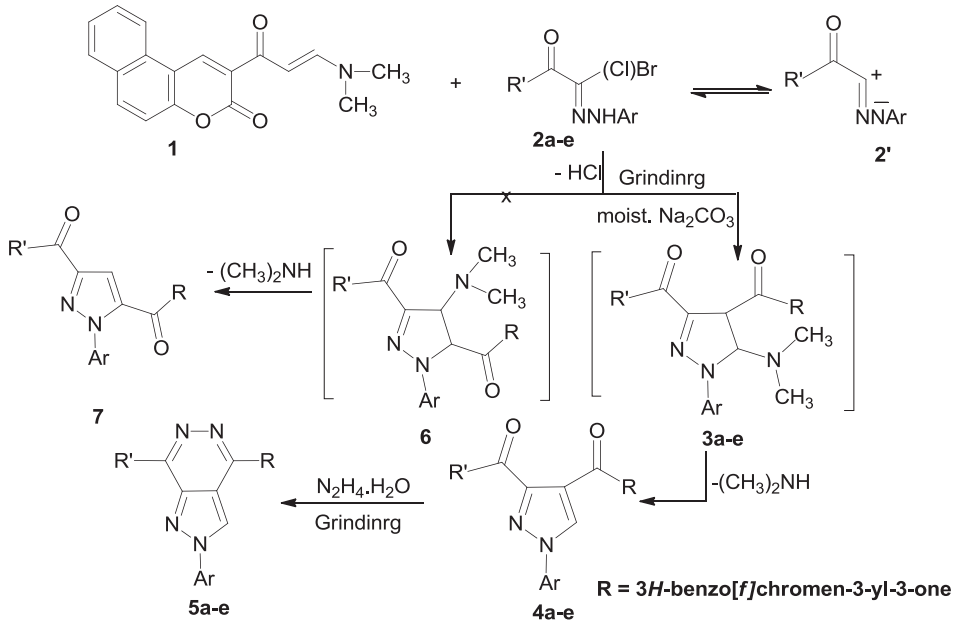
and acts on a number of receptor systems, being both a weak NMDA antagonist and a $5HT_{1A}$ agonist (*33*, *34*) (Figure 1). Furthermore, combining coumarins with different bioactive molecules like: pyrazole, pyrazolo[1,5 *a*]pyrimidine (*35*), have recently been reported to exhibit significant anticancer activities. In continuation of our previous studies on solvent free condition (*36*, *37*), we report here in a facial, eco-friendly, high yielding approach to synthesis new coumarin derivatives containing different bioactive moieties by grinding and evaluate their anticancer activity.

## Results and discussion

Due to the pharmaceutical importance of coumarins, pyrazoles and pyrazolopyridazines, we are interested in this part of the work to integrate these biologically active molecules. Thus, grinding of 2-(3-(dimethylamino)acryloyl)-3*H*-benzo[*f*]chromen-3-one **(1)** with the appropriate of hydrazonoyl halides **2a-e** in moist sodium carbonate afforded pyrazoles **4a-e,** respectively. In grindstone technique, the grinding process is performed at room temperature and the reaction occurs due to heat generated by frictions between substrate and reagent. Products **4a-e** were assumed to formed through 1,3-dipolar cycloaddition reaction of the nitrilimines **2′** (synthesized in situ from reaction of **2a-e** with triethylamine) to the activated double bond in compound **1** affording cyclo adduct **3a-e** which undergoes loss of dimethylamine molecule furnishing the final product (rout A). Another route (B), producing **7** does not operate based on spectral data. In $^1$H NMR spectrum of **4a** as an example, the ester group was resonated as triplet and quartet signals at δ 1.28 and 4.31 ppm, respectively and methyl protons was observed at δ 2.42 ppm. The H-5 of pyrazole and H-4 of coumarin were appeared as two singlet signals at δ 8.45 and 9.21 ppm, respectively. Other signals owing to aromatic protons was observed at δ 7.27–8.39 ppm (Scheme 1). $^{13}$C NMR showed signals at 13.5 ppm due to $-CH_3$ of ester group and at 24.2 ppm for $-CH_3$ of p-tolyl, 63.5 ppm for $-OCH_2$ of ester beside that signals appeared at 104.6–152.5 ppm for Ar-C. Finally, three signals related to 3 C=O at δ 159.3, 160.5, 165.2 ppm. The mass spectrum of all products **4a-e** exhibited a molecular ion peak for the respective compound (see Experimental).

Formation of products **4a-e** rather than product **7** were further confirmed chemically by grinding pyrazoles **4a-e** with hydrazine hydrate affording pyrazolo[3,4-*d*]pyridazines **5a-e** in a good yield (Scheme 1). Based on the above results, we exclude pyrazoles **7** and indicated that the isolable products are pyrazoles **4a-e**. Structure **5a-e** is well supported by spectral data as well as elemental analyses. IR spectrum of **5a** lacked the absorption band of ester group and revealed the presence of broad absorption band at 3425 $cm^{-1}$ corresponding to OH group. Whereas, $^1$H NMR spectrum showed singlet signal at δ 2.46 ppm attributed to the protons of the methyl group in addition to two singlet signals at δ 8.97 and 9.88 ppm attributed to H-4 proton of the coumarin ring and hydroxyl group, respectively. Aromatic protons appeared in the region of δ 7.02–8.81 ppm.

However, the activity of enaminone **1** towards some selected nitrogen nucleophiles was investigated. Thus, grinding of enaminone **1** with *N*-nucleophiles such as hydrazine hydrate and thiocarbohydrazide afforded pyrazoles **9** and **10**, respectively. The structure of these products was substantiated by spectral data and elemental analyses. IR spectrum of **10** showed a characteristic band at *v* 3424, 3304 $cm^{-1}$ related to –NH and $-NH_2$ groups, 1689 for carbonyl group, and C=N and C=S groups was shown at 1621 and 1265 $cm^{-1}$, respectively.




| No.Comp | R' | Ar |
|---|---|---|
| **(2, 4)a, 5a** | $OC_2H_5$, OH | p-$CH_3$-$C_6H_4$ |
| **(2, 4)b, 5b** | $CH_3$, $CH_3$ | p-$NO_2$-$C_6H_4$ |
| **(2, 4)c, 5c** | $CH_3$, $CH_3$ | p-$CH_3$-$C_6H_4$ |
| **(2, 4)d, 5d** | benzofuran-2-yl, benzofuran-2-yl | p-$CH_3$-$C_6H_4$ |
| **(2, 4)e, 5e** | benzofuran-2-yl, benzofuran-2-yl | H |

**Scheme 1.** Synthesis of pyrazoles 4a-e and pyrazolo[3,4-d]pyridazines 5a-e.

The $^1$H NMR spectrum for **10** as an example, displayed signals at δ 7.32–9.18 ppm assigned to nine aromatic protons, and two singlet signals at δ 10.76, 11.12 ppm corresponding for -NH and –$NH_2$ groups which were exchangeable by $D_2O$. Compound **9** was assumed to be formed *via* nucleophilic addition of hydrazine hydrate to β-carbon atom of enaminone **1** followed by elimination of dimethylamine yielded intermediate **8** which undergoes cyclocondensation affording **9** as outlined in Scheme 2.

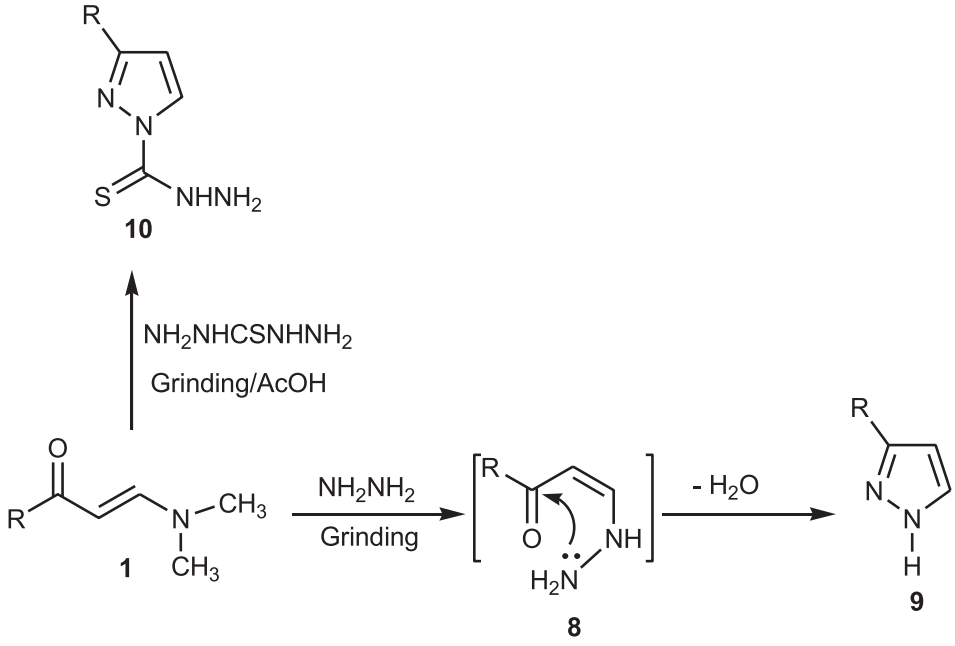
Besides, the reaction of enaminone **1** with some heterocyclic amine was also examined. Thus, condensation of enaminone **1** with 2-amino thiazole by grinding with few drops of acetic acid afforded thiazole derivative **11**. Analogously, grinding of enaminone **1** with the appropriate of 3-amino-4-cyanopyrazole (**12a**), 3-amino-4-phenylpyrazole (**12b**), 3-aminotriazole (**12c**), 2-aminobenzimidazole (**12d**) or 4,6-dimethyl-1*H*-pyrazolo [3,4-*b*]pyridin-3-amine (**12e**) yielded condensed pyrimidine derivatives **15a-e**, respectively (Scheme 3). Compounds **15a-e** may be formed *via* Michael addition of the exo-amino group of amine to the double bond of enaminone **1** followed by elimination of dimethylamine molecule to yield the non-isolable intermediate **13** which undergoes intramolecular cyclization *via* loss of water molecule affording compound **15** (Scheme 3).

Moreover, our present study was extended to investigate the chemical behavior of enaminone **1** towards some sulphadrugs. Thus, condensation of enaminone **1** with sulphadrugs, namely: [sulphadiazine, sulphademidine, sulphadimethoxazine or sulphisoxazole] **16a-d** by grinding with few drops of acetic acid afforded benzene sulphonamide derivatives **17a-d**, respectively in a good yield (Scheme 4). Chemical structure of compounds **17a-d** assigned on the basis of the elemental analysis and spectra. IR spectrum of **17b** showed a broad band at 3410 $cm^{-1}$ corresponds to 2NH groups and at 1724 $cm^{-1}$, 1665 $cm^{-1}$ due to 2 C=O functional groups. $^1$H NMR spectrum revealed singlet signal at δ 2.27 ppm attributed to two methyl groups, beside that of aromatic protons at δ 6.60–9.25 ppm and two singlet signals at δ 10.60 and 11.28 ppm assignable to two NH protons exchangeable by $D_2O$.

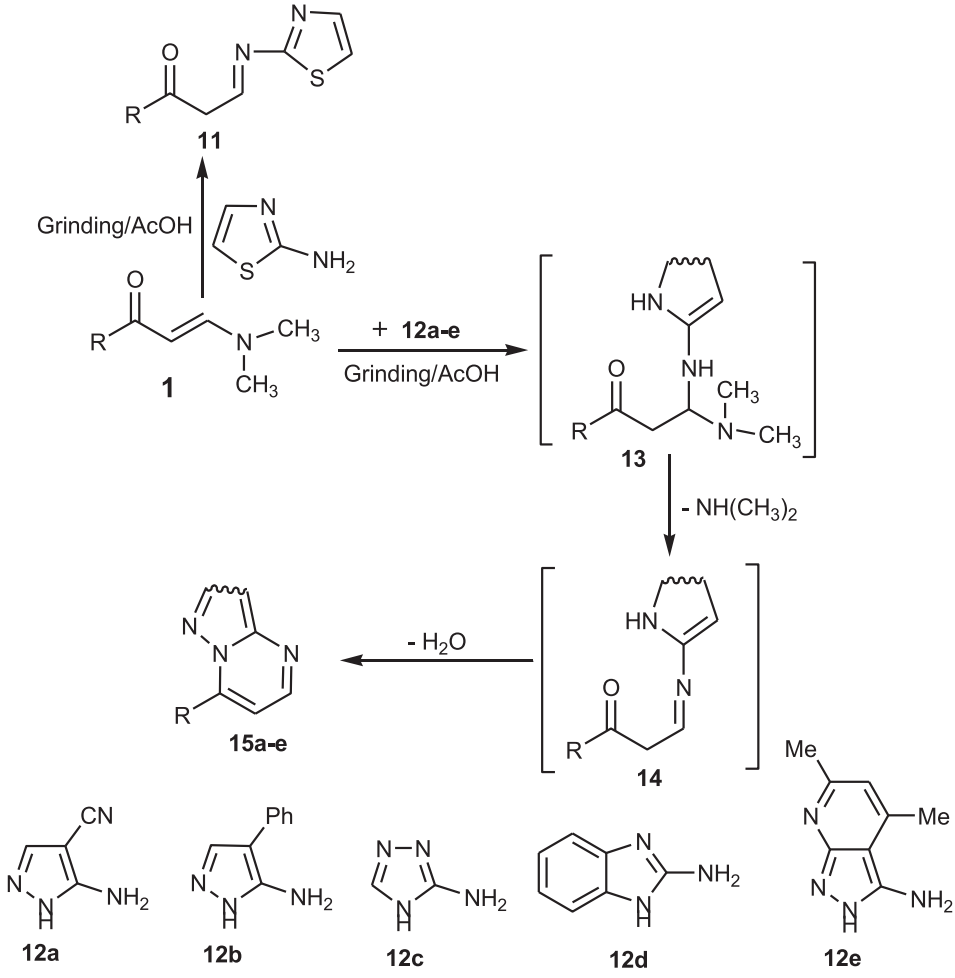
## Pharmacological screening

### *In vitro cytotoxic assay*

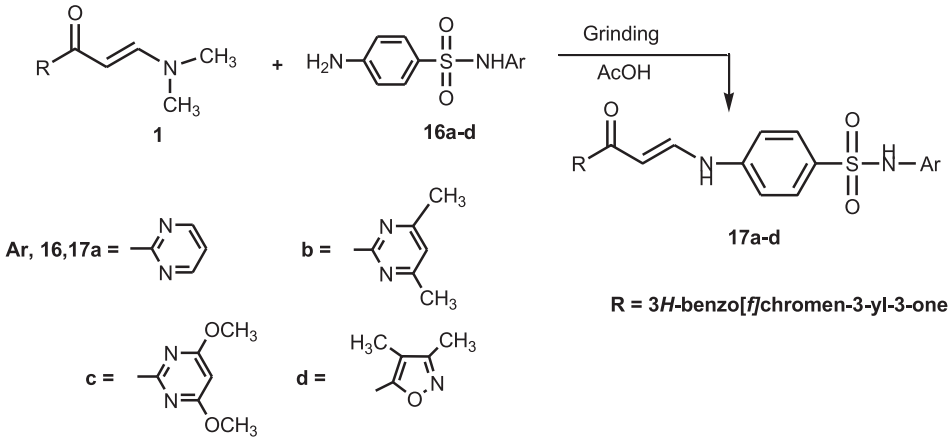
The cytotoxic activity of eight compounds was determined by USA National Cancer Institute against different human cancer cell lines, using Adriamycin and 5-Florouracil as positive controls. The results are cited




**Scheme 2.** Synthesis of pyrazoles 9 and 10.




**Scheme 3.** Synthesis of thiazole 13 and pyrimidines 15a-e.




**Scheme 4.** Synthesis of sulphonamides 17a-d.

**Table 1.** The delta values and growth inhibition percent of the selected compounds against some subpanel cell lines.

| Cpd. No | NSC. NO. | Delta | Panel and subpanel cell lines (growth inhibition percent) |
|---|---|---|---|
| **4a** | 795392 | 30.00 | **Non-Small Cell Lung Cancer**: HOP-92 (30.46), NCI-H522 (27.47). **Melanoma**: LOX IMVI (23.27), UACC-62 (33.19). **Renal Cancer**: UO-31 (36.39). **Breast Cancer**: MCF7 (39.65), MDA-MB-231/ATCC (28.67), T-47D (28.69). |
| **4c** | 795409 | 29.39 | **CNS Cancer**: SNB-75 (33.60). **Renal Cancer**: UO-31 (34.81). **Breast Cancer**: MDA-MB-231/ATCC (29.95). |
| **4e** | 795393 | 35.16 | **Leukemia**: K-562 (48.45). **Non-Small Cell Lung Cancer**: HOP-92 (27.44), NCI-H522 (39.44). **Colon Cancer**: KM12 (26.42). **CNS Cancer**: SNB-75 (30.85). **Melanoma**: MDA-MB-435 (47.79), UACC-62 (32.42). **Ovarian Cancer**: GROV1 (30.61). **Renal Cancer**: UO-31(40.70). **Breast Cancer**: MCF7 (35.10). |
| **5a** | 795389 | 28.14 | **Leukemia**: CCRF-CEM (40.52), MOLT-4 (27.88), SR (26.83). **CNS Cancer**: SNB-75 (35.43). **Melanoma**: LOX IMVI (28.29). **Renal Cancer**: UO-31 (38.49). **Breast Cancer**: MCF-7 (28.18), MDA-MB-231/ATCC (39.19), T-47D (32.65). |
| **5c** | 795408 | 32.63 | **Leukemia**: CCRF-CEM (49.40), MOLT-4 (38.57), SR (46.91). **Colon Cancer**: HCT-15 (40.08). **CNS Cancer**: SF-268 (28.01), SNB-75 (37.36), U251 (27.25). **Melanoma**: LOX IMVI (37.44). **Ovarian Cancer**: GROV1 (37.36), OVCAR-3 (31.19), OVCAR-4 (40.02), **Renal Cancer**: UO-31(47.97). **Breast Cancer**: MCF7 (32.76), MDA-MB-231/ATCC (50.53), T-47D (35.17). |
| **5d** | 795400 | 45.85 | **Leukemia**: CCRF-CEM (52.87), HL-60(TB) (37.76), K-562 (65.42), MOLT-4 (44.29), RPMI-8226 (34.46), SR (75.26). **Non-Small Cell Lung Cancer**: HOP-92 (52.71), NCI-H522 (76.17). **Colon Cancer**: HCT-116 (54.04), HCT-15 (35.24), KM12 (34.9). **CNS Cancer**: SF-268 (37.42), SF-295 (39.17), SNB-75 (40.39). **Melanoma**: LOX IMVI (42.81), M14 (47.4), MDA-MB-435 (67.65), UACC-62 (40.51). **Ovarian Cancer**: GROV1 (48.41), OVCAR-3 (54.06), OVCAR-4 (30.19), NCI/ADR-RES (33.83). **Renal Cancer**: UO-31(53.78). **Prostate Cancer**: PC-3 (46.56). **Breast Cancer**: MCF7 (64.38), MDA-MB-231/ATCC (40.68), T-47D (36.41). |
| **5e** | 795390 | 39.98 | **Leukemia**: CCRF-CEM (33.71), K-562 (62.22), MOLT-4 (30.19), RPMI-8226 (27.33), SR (64.48). **Non-Small Cell Lung Cancer**: HOP-92 (38.94), NCI-H522 (62.84). **Colon Cancer**: HCT-116 (28.02), HCT-15 (28.48), KM12 (28.34), **CNS Cancer**: SF-268 (34.92), SF-295 (32.83), SNB-75 (42.58), U251 (30.54). **Melanoma**: LOX IMVI (37.99), M14 (47.4), MDA-MB-435 (35.15), SK6MEL-2 (60.45), UACC-62 (39.30). **Ovarian Cancer**: GROV1 (41.66), OVCAR-3 (39.91), OVCAR-4 (33.25). **Renal Cancer**: UO-31(47.03). **Prostate Cancer**: PC-3 (32.37). **Breast Cancer**: MCF7 (53.04), MDA-MB-231/ATCC (38.84), T-47D (35.61). |
| **9** | 795395 | 30.55 | **Leukemia**: SR (34.25). **Non-Small Cell Lung Cancer**: NCI-H460 (34.96), **Renal Cancer**: UO-31 (37.82). **Breast Cancer**: MCF7 (37.46), T-47D (30.15). |

in Table 1 and revealed that pyrazole **4e** exhibited powerful growth inhibition activity against Leukemia K-562 (48.45%), Melanoma MDA-MB-435 (47.79%) as well as Renal Cancer UO-31(40.70%). On the other hand, compounds **5a** and **5c** showed promising anticancer potency against Renal Cancer UO-31, Leukemia CCRF-CEM and Breast Cancer cell lines. However, compound **5d** showed remarkable growth inhibitory activity against all of Leukemia cell lines specially K-562 (65.42%) and SR (75.26%). In addition to a pronounced anticancer activity towards Non-Small Cell Lung Cancer NCI-H522 (76.17%), Melanoma MDA-MB-435 (67.65%) and Breast Cancer MCF7 (64.38%). Moreover, compound **5e** exhibited promising growth inhibition activities against several cancer cell lines including Leukemia K-562 (62.22%), SR (64.48%), Non-Small Cell Lung Cancer NCI-H522 (62.84%) as well as Melanoma SK6MEL-2 (60.45%). Furthermore, it showed potent anticancer activity against Renal Cancer UO-31 and Breast Cancer MCF by 47.03% and 53.04%, respectively. Moreover, pyrazole **9** showed moderate activity against Breast Cancer MCF7, Renal Cancer UO-31, Leukemia SR, Non-Small Cell Lung Cancer NCI-H460 and T-47D by 37.46%, 37.82%, 34.25%, 34.96% and 30.15%, respectively.

## Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. $^{1}$H and $^{13}$CNMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz and JNM-LA 400 FT-NMR system spectrometer and chemical shifts are expressed in ppm units using

TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Anticancer activity was performed at Development Therapeutic Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), Bethesda, Maryland, USA. Enaminone **1** (*38*), Hydrazonoyl halides **2a**–**e** (*39–44*) were prepared as reported in the literature.

## Synthesis of pyrazoles 4a-e

A mixture of enaminone **1** (0.293 g, 1 mmol), the appropriate hydrazonoyl halides **2a-e** (1 mmol each) and moist sodium carbonate (0.2 g, 2 mmol) was thoroughly ground with a pestle in an open mortar at room temperature until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3–10 min. After completion of the reaction as monitored by TLC, the mixture was diluted with water, filtered and recrystallized from a DMF/EtOH affording **4a-e**, respectively.

**2-(3-Ethoxycarbonyl-1-p-tolyl-1*H*-pyrazol-4-yl)-carbonyl-3*H*-benzo[*f*]chromen-3-one (4a)**

Yellow crystals; yield: 90%; m.p. 180–181°C; FT-IR (KBr, $cm^{-1}$): *v* 3059, 2921 (CH), 1727, 1634 (C=O), 1594 (C=N), 1563 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.28 (t, 3H, *J* = 7 Hz, $CH_2\mathbf{CH_3}$), 2.42 (s, 3H, Ar-$CH_3$), 4.31 (q, 2H, *J* = 7 Hz, $\mathbf{CH_2}CH_3$), 7.27–7.32 (m, 2H), 7.49 (d, 1H, *J* = 8 Hz), 7.62–7.76 (m, 4H), 7.93 (d, 1H, *J* = 8 Hz), 8.09 (d, 1H, *J* = 8 Hz), 8.39 (d, 1H, *J* = 8 Hz), 8.45 (s,1H), 9.21 (s,1H); $^{13}$C NMR (300 MHz, $CDCl_3$, δ, ppm): 13.5 ($CH_3$), 24.2 ($CH_3$), 63.5 ($OCH_2$),104.6–152.5 (Ar-C), 159.3, 160.5, 165.2 (3C=O); MS (m/z): 452 ($M^+$). Anal. calcd. for $C_{27}H_{20}N_2O_5$ (452.46): C, 71.67; H, 4.46; N, 6.19%; found: C, 71.56; H, 4.55; N, 6.27%.

**2-(3-Acetyl-1-p-nitrophenyl-1*H*-pyrazol-4-yl)-carbonyl-3*H*-benzo[*f*]chromen-3-one (4b)**

Black powder; yield: 86%; m.p.: 270–271°C; FT-IR (KBr, $cm^{-1}$): *v* 3089, 2920 (CH) 1725, 1702, 1642 (C=O), 1593 (C=N), 1555 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.56 (s, 3H, $COCH_3$), 7.23–7.30 (m, 3H), 7.46 (d, 1H, *J* = 8 Hz), 7.62–7.77 (m, 3H,), 7.90 (d, 1H, *J* = 8 Hz,), 8.06 (d, 1H, *J* = 8 Hz), 8.42 (d, 1H, *J* = 8 Hz), 8.46 (s,1H), 9.22 (s,1H); $^{13}$C NMR (300 MHz, $CDCl_3$, δ, ppm): 25.8 ($CH_3$), 107.1–145.7 (Ar-C), 159.8, 162.7, 164.2 (3C=O). Anal. calcd. for $C_{25}H_{15}N_3O_6$ (453.4): C, 66.23; H, 3.33; N, 9.27%; found: C, 66.30; H, 3.40; N, 9.36%.

**2-(3-Acetyl-1-p-tolyl-1*H*-pyrazol-4-yl)-carbonyl-3*H*-benzo[*f*]chromen-3-one (4c)** Black crystals; yield: 87%; m.p. 180–182°C; FT-IR (KBr, $cm^{-1}$): *v* 3059, 2922 (CH), 1706, 1680 (C=O), 1594 (C=N), 1492 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.44 (s, 3H, $CH_3$), 2.68 (s, 3H, $COCH_3$), 7.26–7.34 (m, 3H), 7.48 (d, 1H, *J* = 8 Hz), 7.59–7.78 (m, 3H), 7.92 (d, 1H, *J* = 8 Hz), 8.07 (d, 1H, *J* = 8 Hz,), 8.40 (d, 1H, *J* = 8 Hz), 8.45 (s,1H), 9.20 (s,1H); $^{13}$C NMR (300 MHz, $CDCl_3$, δ, ppm): 23.5 ($CH_3$), 27.1 ($CH_3$), 110.3–148.1 (Ar-C), 158.8, 160.7, 165.1 (3C=O). Anal. calcd. for $C_{26}H_{18}N_2O_4$ (422.43): C, 73.92; H, 4.29; N, 6.63%; found: C, 74.05; H, 4.38; N, 6.76%.

**2-(3-Benzofuran-2-yl-carbonyl)-1-p-tolyl-1*H*-pyrazol-4-yl)-carbonyl-3*H*-benzo [*f*]chromen-3-one (4d)**

Yellow powder; yield: 86%; m.p.: 284–285°C; FT-IR (KBr, $cm^{-1}$): *v* 3135, 3056, 2924 (CH), 1725, 1640 (C=O), 1601 (C=N), 1553 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.43 (s, 3H, $CH_3$), 7.28–7.79 (m, 12H, ArH's), 7.90 (d, 1H, *J* = 8 Hz, ArH), 8.12 (d, 1H, *J* = 8 Hz, ArH), 8.34 (d, 1H, *J* = 8 Hz, ArH), 8.45 (s,1H, ArH), 9.24 (s,1H, ArH); MS (m/z): 523 ($M^+$-1). Anal. calcd. for $C_{33}H_{20}N_2O_5$ (524.52): C, 75.56; H, 3.84; N, 5.34%; found: C, 75.67; H, 3.78; N, 5.22%.

**2-(3-Benzofuran-2-yl-carbonyl)-1-phenyl-1*H*-pyrazol-4-yl)-carbonyl-3*H*-benzo [*f*]chromen-3-one (4e)**

Red powder; yield: 70%; m.p. 290–292°C; FT-IR (KBr, $cm^{-1}$): *v* 3036, 2923 (CH), 1722, 1650 (C=O), 1613 (C=N), 1513 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.35–7.71 (m, 13H), 7.88 (d, 1H, *J* = 8 Hz), 8.09 (d, 1H, *J* = 8 Hz), 8.12 (d, 1H, *J* = 8 Hz), 8.50 (s,1H), 9.24 (s,1H). Anal. calcd. for $C_{32}H_{18}N_2O_5$ (510.5): C, 75.29; H, 3.55; N, 5.49%; found: C, 75.19; H, 3.47; N, 5.60%.

## General method for synthesis of pyrazolo[3,4-d]pyridazines 5a-e

A mixture of pyrazoles **4a-e** (1 mmol each) and hydrazine hydrate (0.1 mL, 2 mmol) was ground with a pestle in a mortar at room temperature for 10–15 min. (monitored by TLC). The reaction mixture was poured into water and the solid product was collected by filtration washed with ethanol, dried and recrystallized from ethanol affording pyrazolo[3,4-*d*]pyridazines **5a-e**, respectively.

**2-(7-Hydroxy-2-p-tolyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-3*H*-benzo[*f*] chromen-3-one (5a)**

Brown crystals; yield: 90%; m.p. 145–146°C; FT-IR (KBr, $cm^{-1}$): *v* 3425 (OH), 3060, 2925 (CH), 1715 (C=O), 1606 (C=N), 1532 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ ppm): 2.46 (s, 3H, $CH_3$), 7.02 (d, 1H, *J* = 8 Hz), 7.07–7.49 (m, 4H, A), 7.61 (d, 1H, *J* = 8 Hz), 7.71–7.88 (m, 2H), 7.98 (d, 1H, *J* = 8 Hz), 8.06 (d, 1H, *J* = 8 Hz), 8.81 (d, 1H, *J* = 8 Hz), 8.97 (s,1H), 9.88 (s,1H, OH); $^{13}$C NMR (300 MHz, DMSO-$d_6$, δ, ppm): 24.6 ($CH_3$),106.1–152.5 (Ar-C), 160.3

(C=O). Anal. calcd. for $C_{25}H_{16}N_4O_3$ (420.42): C, 71.42; H, 3.84; N, 13.33%; found: C, 71.51; H, 3.76; N, 13.26%.

**2-(7-Methyl-2-(4-nitrophenyl)-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-3*H*-benzo[*f*] chromen-3-one (5b)**

Brown crystals; yield: 85%; m.p. 120–122°C; FT-IR (KBr, $cm^{-1}$): *v* 3087, 2921 (CH), 1722, 1688 (C=O), 1605 (C=N), 1530 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.40 (s, 3H, $CH_3$), 7.23–7.30 (m, 3H), 7.46 (d, 1H, *J* = 8 Hz), 7.62–7.77 (m, 3H), 7.90 (d, 1H, *J* = 8 Hz), 8.06 (d, 1H, *J* = 8 Hz), 8.42 (d, 1H, *J* = 8 Hz), 8.46 (s,1H), 9.22 (s,1H); $^{13}$C NMR (300 MHz, $CDCl_3$, δ, ppm): 20.8 ($CH_3$), 104.7–152.7 (Ar-C), 162.4 (C=O); MS (m/z): 499 ($M^+$). Anal. calcd. for $C_{25}H_{15}N_5O_4$ (449.42): C, 66.81; H, 3.36; N, 15.58%; found: C, 66.73; H, 3.29; N, 15.49%.

**2-(7-Methyl-2-p-tolyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-3*H*-benzo[*f*]chromen-3-one (5c)**

Brown powder; yield: 88%; m.p. 230–232°C; FT-IR (KBr, $cm^{-1}$): *v* 3102, 2922 (CH), 1725, 1692, 1636 (C=O), 1619 (C=N), 1512 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.35 (s, 3H, $CH_3$), 2.42 (s, 3H, $CH_3$), 7.25–7.32 (m, 3H), 7.45 (d, 1H, *J* = 8 Hz), 7.57–7.76 (m, 3H), 7.94 (d, 1H, *J* = 8 Hz), 8.09 (d, 1H, *J* = 8 Hz), 8.42 (d, 1H, *J* = 8 Hz), 8.46 (s,1H), 9.21 (s,1H); $^{13}$C NMR (300 MHz, $CDCl_3$, δ, ppm): 21.3 ($CH_3$), 25.2 ($CH_3$), 107.2–150.1 (Ar-C), 161.7 (C=O); MS (m/z): 418 ($M^+$). Anal. calcd. for $C_{26}H_{18}N_4O_2$ (418.45): C, 74.63; H, 4.34; N, 13.38%; found: C, 74.52; H, 4.26; N, 13.45%.

**2-(7-(benzofuran-2-yl)-2-p-tolyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-3*H*-benzo [*f*]chromen-3-one (5d)**

Brown powder; yield: 89%; m.p. 130–132°C; FT-IR (KBr, $cm^{-1}$): *v* 3130, 3060, 2920 (CH), 1722 (C=O), 1602 (C=N), 1525 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.40 (s, 3H, $CH_3$), 7.28–7.79 (m, 12H), 7.90 (d, 1H, *J* = 8 Hz), 8.12 (d, 1H, *J* = 8 Hz), 8.34 (d, 1H, *J* = 8 Hz), 8.45 (s,1H), 9.24 (s,1H); MS (m/z): 520 ($M^+$). Anal. calcd. for $C_{33}H_{20}N_4O_3$ (520.54): C, 76.14; H, 3.87; N, 10.76%; found: C, 76.04; H, 3.95; N, 10.68%.

**2-(7-(benzofuran-2-yl)-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-3*H*-benzo [*f*]chromen-3-one (5e)**

Brown powder; yield: 91%; m.p. 184–186°C; FT-IR (KBr, $cm^{-1}$); *v* 3070, 2924 (CH), 1720 (C=O), 1600 (C=N), 1530 (C=C); $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.21–7.75 (m, 13H), 7.85 (d, 1H, *J* = 8 Hz), 8.03 (d, 1H, *J* = 8 Hz), 8.10 (d, 1H, *J* = 8 Hz), 8.55 (s,1H), 9.22 (s,1H). Anal. calcd. for $C_{32}H_{18}N_4O_3$ (506.51): C, 75.88; H, 3.58; N, 11.06%; found: C, 75.79; H, 3.70; N, 11.17%.

**Synthesis of 2-(1*H*-pyrazol-3-yl)-3*H*-benzo[*f*]chromen-3-one (9)**

A mixture of enaminone **1** (0.293 g, 1 mmol) and hydrazine hydrate (0.1 mL, 2 mmol) was ground with a pestle in a mortar at room temperature. After few seconds the mixture became sticky, the grinding process was continued for 10–15 min. (monitored by TLC). The formed product was washed with ethanol, filtered and recrystallized from ethanol to give the desired product **9**.

Off-white powder; yield: 89%; m.p. 260–261°C; FT-IR (KBr, $cm^{-1}$): *v* 3284 (NH), 3052 (CH), 1721 (C=O), 1619 (C=N), 1597 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.27–7.90 (m, 4H), 8.03 (d, 1H, *J* = 8 Hz), 8.20 (d,1H, *J* = 8 Hz), 8.29 (d,1H, *J* = 8 Hz), 8.58 (d,1H, *J* = 8 Hz), 9.20 (s,1H), 10.89 (s, 1H, NH-$D_2O$ exchangeable); MS (m/z): 262. Anal. calcd. for $C_{16}H_{10}N_2O_2$ (262.26): C, 73.27; H, 3.84; N, 10.68%; found: C, 73.39; H, 3.72; N, 10.80%.

**Synthesis of 3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-1*H*-pyrazole-1-carbothiohydrazide (10)**

A mixture of enaminone **1** (0.293 g, 1 mmol), thiocarbohydrazide (0.106 gm, 1 mmol) and few drops of acetic acid was ground with a pestle in a mortar at room temperature with for 5–10 min. (monitored by TLC). The formed product was washed with ethanol, filtered and recrystallized from ethanol affording pyrazole **10**.

Red powder; yield: 89%; m.p. 320–322°C; FT-IR (KBr, $cm^{-1}$): *v* 3424, 3304 ($NH_2$, NH), 3059, 3051, 2920 (CH), 1689 (C=O), 1621 (C=N), 1565 (C=C), 1265 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.32–7.96 (m, 4H), 8.06 (d, 1H, *J* = 8 Hz), 8.22 (d,1H, *J* = 8 Hz), 8.36 (d,1H, *J* = 8 Hz), 8.63 (d,1H, *J* = 8 Hz), 9.18 (s,1H), 10.76 (s, 1H, NH-$D_2O$ exchangeable), 11.12 (s, 2H, $NH_2$-$D_2O$ exchangeable); MS (m/z): 336 ($M^+$). Anal. calcd. for $C_{17}H_{12}N_4O_2S$ (336.37): C, 60.70; H, 3.60; N, 16.66; S, 9.53%; found: C, 60.82; H, 3.48; N, 16.54; S, 9.41%.

**Synthesis of thiazole derivative 11 and pyrimidines 15a-e**

To a mixture of enaminone **1** (0.293 g, 1 mmol) and 2-aminothiazole, 3-amino-4-cyanopyrazole (**12a**), 3-amino-4-phenylpyrazole (**12b**), 3-aminotriazole (**12c**), 2-aminbenzimidazole (**12d**) or 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**12e**) (1 mmol each), few drops of acetic acid was added and the mixture was ground with a pestle in a mortar at room temperature for 5–10 min. until the mixture turned into a melt, during which time a color change occurred (the change is colorless to yellow). After completion of the reaction as indicated by TLC, the reaction mixture was poured into water, the solid product was filtered, washed with ethanol, dried and recrystallized from ethanol affording the desired products **11** and **15a-e**, respectively.

**2-(*E*)-3-(thiazol-2-ylimino)propanoyl)-3*H*-benzo[*f*]chromen-3-one (11)**

Brown powder; yield: 90%; m.p. 270–272°C; FT-IR (KBr, $cm^{-1}$): *v* 3424 (NH), 3067, 2920 (CH), 1726, 1659 (C=O), 1617 (C=N), 1561 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.12–7.60 (m, 4H), 7.68–8.49 (m, 5H, ArH's + NH), 8.65 (d,1H, *J* = 8 Hz), 8.89 (d,1H, *J* = 8 Hz), 9.70 (s,1H); MS (m/z): 349 [$M^+$+1]. Anal. calcd. for $C_{19}H_{12}N_2O_3S$ (348.38): C, 65.51; H, 3.47; N, 8.04; S, 9.20%; found: C, 65.63; H, 3.60; N, 8.14; S, 9.32%.

**7-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (15a)**

Yellow crystals; yield 90%; m.p. 348–349°C (lit. m.p. 350°C (*45*)).

**2-(3-Phenylpyrazolo[1,5-*a*]pyrimidin-7-yl)-3*H*-benzo[*f*]chromen-3-one (15b)**

Red crystals; yield: 91%; m.p. 311–312°C (lit. m.p. 310°C (*45*)).

**2-([1,2,4]triazolo[4,3-*a*]pyrimidin-5-yl)-3*H*-benzo[*f*]chromen-3-one (15c)**

Brown crystals; yield: 90%; m.p. 232–234°C (lit. m.p. 232°C (*45*)).

**2-Benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-yl-benzo[*f*]chromen-3-one (15d)**

Brown crystals; yield: 90%; m.p. 280–282°C (lit. m.p. 280°C (*45*)).

**2-(8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4-yl)--3*H*-benzo[*f*] chromen-3-one (15e)**

Orange powder; yield: 91%; m.p. >360°C; FT-IR (KBr, $cm^{-1}$): *v* 3078, 2922 (CH), 1724, 1665 (C=O), 1613 (C=N), 1550 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 2.31(s, 3H, $CH_3$), 2.61 (s, 3H, $CH_3$), 6.66 (d,1H, *J* = 8 Hz), 7.08 (s,1H), 7.56–7.68 (m, 3H), 7.70–8.57 (m, 3H), 8.89 (d,1H, *J* = 8 Hz), 9.70 (s,1H). Anal. calcd. for $C_{24}H_{16}N_4O_2$ (392.410): C, 73.46; H, 4.11; N, 14.28%; found: C, 73.58; H, 4.23; N, 14.16%.

## Reaction of enaminone 1 with sulphadruges

A mixture of enaminone **1** (0.293 g, 1 mmol), sulphadrugs **16a-d** (1 mmol each), and few drops of acetic acid was ground with a pestle in a mortar at room temperature for 5–10 min. until the mixture turned into a melt, during which time a color change occurred (the change is colorless to yellow to orange). After completion of the reaction as monitored by TLC. The mixture was poured into water and the solid product was filtered, washed with ethanol, dried and recrystallized from DMF affording the desired products **17a-d**, respectively.

**4-[3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-propenylamino]-*N*-pyrimidin-2-yl-benzenesulfonamide (17a)**

Orange crystals; yield: 92%; m.p. >360°C; FT-IR (KBr, $cm^{-1}$); 3427 broad (2NH), 3076, 2925 (CH), 1724, 1681 (C=O), 1604 (C=N), 1525 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 6.69 (d, 1H, *J* = 8 Hz), 7.20 (d, 1H, *J* = 8 Hz), 7.49 (d, 1H, *J* = 8 Hz), 7.65–8.07 (m, 4H), 8.12 (d, 1H, *J* = 8 Hz), 8.20–8.34 (m, 5H), 8.53 (d, 1H, *J* = 8 Hz), 9.24 (s,1H), 9.36 (s,1H), 10.71 (s,1H, NH-$D_2O$ exchangeable), 11.57 (s,1H, NH-$D_2O$ exchangeable); MS (m/z): 498 ($M^+$).. Anal. calcd. for $C_{26}H_{18}N_4O_5S$ (498.51): C, 62.64; H, 3.64; N, 11.24; S, 6.43%; found: C, 62.52; H, 3.76; N, 11.12; S, 6.31%.

***N*-(4,6-Dimethyl-pyrimidin-2-yl)-4-[3-oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-propenylamino]-benzenesulfonamide (17b)**

Orange crystals; yield: 91%; m.p. 290–291°C; FT-IR (KBr, $cm^{-1}$): 3410 broad (2NH), 3078, 2956, 2920 (CH), 1724, 1665 (C=O), 1580 (C=N), 1541 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 2.27 (s, 6H, $2CH_3$), 6.60 (d, 1H, *J* = 8 Hz), 6.74 (d, 1H, *J* = 8 Hz), 7.30 (d, 1H, *J* = 8 Hz), 7.52 (d, 1H, *J* = 8 Hz), 7.61–8.03 (m, 4H), 8.18 (d, 1H, *J* = 8 Hz), 8.22–8.32 (m, 2H), 8.57 (d, 1H, *J* = 8 Hz), 9.25 (s,1H), 9.39 (s,1H), 10.60 (s,1H, NH-$D_2O$ exchangeable), 11.28 (s,1H, NH-$D_2O$ exchangeable); MS (m/z): 526 ($M^+$). Anal. calcd. for $C_{28}H_{22}N_4O_5S$ (526.56): C, 63.87; H, 4.21; N, 10.64; S, 6.09%; found: C, 63.75; H, 4.33; N, 10.76; S, 6.20%.

***N*-(2,6-Dimethoxy-pyrimidin-4-yl)-4-[3-oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-propenylamino]-benzenesulfonamide (17c)**

Orange crystals; yield: 92%; m.p. 260–261°C; FT-IR (KBr, $cm^{-1}$); 3438 broad (2NH), 3058, 2966, 2922 (CH), 1726, 1659 (C=O), 1598 (C=N), 1551 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 3.60 (s, 6H, $2OCH_3$), 6.58 (d, 1H, *J* = 8 Hz), 6.74 (d, 1H, *J* = 8 Hz), 7.27 (d, 1H, *J* = 8 Hz), 7.47 (d, 1H, *J* = 8 Hz), 7.60–7.81 (m, 4H), 7.88 (d, 1H, *J* = 8 Hz), 7.94–8.32 (m, 2H), 8.57 (d, 1H, *J* = 8 Hz), 9.25 (s,1H), 9.38 (s,1H), 10.55 (s,1H, NH-$D_2O$ exchangeable), 12.08 (s,1H, NH-$D_2O$ exchangeable); MS (m/z): 558. Anal. calcd. for $C_{28}H_{22}N_4O_7S$ (558.56): C, 60.21; H, 3.97; N, 10.03; S, 5.74%; found: C, 60. 10; H, 3.86; N, 10.15; S, 5.86%.

***N*-(3,4-Dimethyl-isoxazole-5-yl)-4-[3-oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-propenylamino]-benzenesulfonamide (17d)**

Orange crystals; yield: 92%; m.p. >360 °C; FT-IR (KBr, $cm^{-1}$); 3434 broad (2NH), 3062, 2966, 2924 (CH), 1725,

1659 (C=O), 1617 (C=N), 1551 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 1.59 (s, 3H, $CH_3$), 1.97 (s, 3H, $CH_3$), 7.60–7.93 (m, 15H, Ar-H + 2NH); MS (m/z): 515 ($M^+$). Anal. calcd. for $C_{27}H_{21}N_3O_6S$ (515.54): C, 62.90; H, 4.11; N, 8.15; S, 6.22%; found: C, 62.78; H, 4.23; N, 8.28; S, 6.34%.

## Cytotoxic screening

### *NCI-60 screening methodology*

The cytotoxicity against cancer cell lines were conducted at USA National Cancer Institute according to reported standard procedure (Sulphorhodamine B assay) (*46–48*).

## Conclusions

In this research, benzo[*f*]chromen-3-one moiety is introduced as new class in antitumor agent against different cancer cell lines. Briefly, target compounds were prepared *via* reactions of 2-(3-(dimethylamino)acryloyl)-3*H*-benzo[*f*]chromen-3-one with hydrazonoyl halides, *N*-nucleophiles and sulphadrugs by grinding reactants together at room temperature. The anticancer activity was performed at USA National Cancer Institute (NCI) against different human tumor cell lines called melanoma, leukemia and cancers of the brain, lung, colon, ovary, prostate, breast and kidney. The results displayed that pyrazole **4e** and pyrazolo[3,4-*d*]pyridazines **5a**, **5c**-**5e** exhibited powerful anticancer activity against most cell lines.

## Acknowledgements

The authors would like to thank members of USA National Cancer Institute (NCI), for cytotoxicity evaluations of the newly synthesized compounds.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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