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ORIGINAL PAPER

# Synthesis and antiproliferative evaluation of novel biheterocycles based on coumarin and 2-aminoselenophene-3-carbonitrile unit

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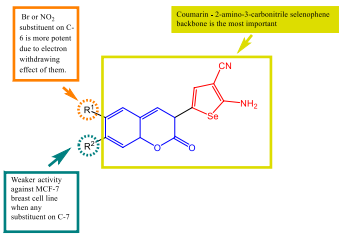
## Abstract

A series of novel coumarins with 2-amino-3-cyanoselenophen-5-yl unit on C-3 have been synthesized. These compounds prepared easily at room temperature, in a short time and in high yield. The importance of biheterocyclic units as dominant structural motif of coumarin derivatives has been well recognized. Anti-cancer activity screening on MCF-7 cell line allowed identification of 2-amino-5-(6-bromo-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile with the highest level of cytotoxic activity with mean $IC_{50}$ and *c*Log*P* (partition co-efficient) values 10.84 µM and 3.18, respectively. The most radical scavenging compound was also recognized.

### Graphic abstract




**Keywords** Coumarin · Selenophene · Antitumor agents · Heterocycles · Antioxidant activity

## Introduction

Cancer is the second deadliest form of disease worldwide. About 10 million people died in 2018 due to cancer. According to the World Health Organization (WHO) report cancer is one of the prominent cause of death in the world and based on, more than 13 million cancers death will happen in 2030 [1]. It was also estimated that one of five people before age 75 will suffer from cancer [2]. For treatment of cancer diseases many efforts have been carried out and although very important progress has been made some of cancer patients do not respond to therapy or recurrence subsequent initial response. Nevertheless, chemotherapy is a basic approach for the treatment of cancer diseases and then new drug designs and synthesis is still necessary.

Biheterocycles are an important class of organic derivatives due to their widespread application in organic synthesis, advanced materials, and pharmaceuticals [3, 4]. Both natural and synthetic biheterocyclic compounds play vital role in drug development. The most efficient approaches are chemical modification of biologically active naturally found molecules. Coumarins (1,2-benzopyrones) are naturally found molecules and widely distributed in plants. Nowadays, to discover and expand the chemical properties of coumarins, many synthetic procedures are developing. They exhibit a wide range of biological activities and applications

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due to the ability to exert noncovalent interactions with many enzymes and receptors in living organisms. Hence, application of coumarins as anti-neurodegenerative, anti-cancer, anticoagulant, anti-inflammatory, antioxidant, antiviral, anti-diabetics, antibacterial, human monoamine oxidase inhibitory, antichloine esterase, and antifungal agents are widely appeared in the literature [5–9]. Coumarin derivatives are also commercially significant groups of organic fluorescent materials [10–12].

Selenophene is one of the important heterocyclic compounds and some selenophene compounds have been found to possess anti-cancer activity [13, 14]. In addition, these compounds are very useful synthetic intermediates and they can function as suitable building blocks to synthesize other biologically active compounds, such as natural products.

The hybrid compound, formed by the coupling of two different effects and the independent compound with a single covalent bond, has a novel composite structure which has a greater pharmacological effect than the sum of each component with the synergies of these moieties having independent effects [15]. It is known that coumarin derivatives show antiproliferative activity in MCF-7 cell line [16]. On the other hand, organoselenium compounds have attracted much attention due to antiviral, antimicrobial, antioxidant and antiproliferative activity [16–18]. Anti-cancer mechanisms of selenium derivatives have been linked to apoptosis and estrogen receptor (ER) stress signal mediators. Selenophenes are also potential esterogen receptor agonists which increase binding affinity to estrogen receptors. A number of 2,5-substituted selenophene compounds displayed enhanced agonist potency and antiproliferative activity [13].

Therefore, the new hybrid compounds that will be formed by combining coumarin and selenophene compounds are expected to exhibit greater biological activity. Coumarin–selenophene hybrid compounds are rare in the literature. The compounds obtained in a limited number of studies showed significant biological activity and these studies will lead to further studies. Arsenyan et al. In 2019 [19], they synthesized selenopheno[2,3-*f*]coumarin compounds. These new compounds synthesized showed antimetastatic activity against melanoma and breast cancer. In another study conducted in 2015 [20], selenopheno[2,3-*c*]coumarin compounds were synthesized. The cytotoxic activity of these compounds was investigated in angiogenesis inhibitory activity and antioxidant effect.

In view of our interest in developing novel coumarin derivatives, we synthesized new biheterocycles which include both coumarin and selenophene unit in one frame. Despite huge synthetic efforts dedicated to the coumarin scaffold, little work has been devoted to modifying the lactone function. A series of novel coumarin–2-aminoselenophene-3-carbonitrile derivatives were synthesized and biological evaluation of these derivatives were investigated (Fig. 1). This is the first report of synthesis of coumarin–2-aminoselenophene-3-carbonitrile derivatives and substantial antiproliferative potency in breast cancer MCF-7 cell lines.

## Results and discussion

### Synthesis of coumarin–2-aminoselenophene-3-carbonitrile biheterocycles 3a–3h

In this study, new biheterocyclic coumarin derivatives with modified 2-aminoselenophene-3-carbonitrile were designed and synthesized. Scheme 1 shows the synthetic routes of eight novel coumarin and 2-aminoselenophene-3-carbonitrile based biheterocyclic compounds.

These new biheterocyclic coumarin derivatives were prepared in three steps. At first step, 3-acetylcoumarin derivatives **1a**–**1h** were prepared, later condensation reaction of **1a**–**1h** with malononitrile in the presence of diethylamine gave key intermediates arylidene malononitriles **2a**–**2h**, in the last stage reaction of arylidene malononitriles **2a**–**2h** with selenium gave new biheterocyclic compounds **3a**–**3h**. To prepare these novel biheteroacyclic compounds, Gewald method was modified. Starting compounds 3-acetylcoumarin derivatives **1a**–**1h** were easily obtained with excellent yields (80–99%) by reacting commercially available corresponding salisylaldehyde and ethyl acetoacetate in the presence of catalytic amount of diethylamine at room temperature. Following the optimized procedure, the key synthetic precursors, 2-[1-(2-oxo-2*H*-chromen-3-yl)ethylidene]malononitriles **2a**–**2h** were synthesized according to Knoevenagel reaction. The reaction of compounds **1a**–**1h** and malononitrile with catalytic amount of diethylamine was completed easily with good to excellent yield at room temperature (69–98%). Compounds **2a**–**2h** were further applied with Se in ethanol and catalyzed with diethylamine. Reactions were performed at room temperature and completed in 3–7 h with moderate yields (50–81%, Table 1). All new

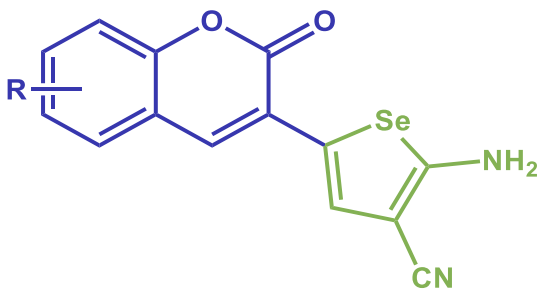



**Fig. 1** 2-Aminoselenophene-3-carbonitrile based coumarin derivatives

**Scheme 1**

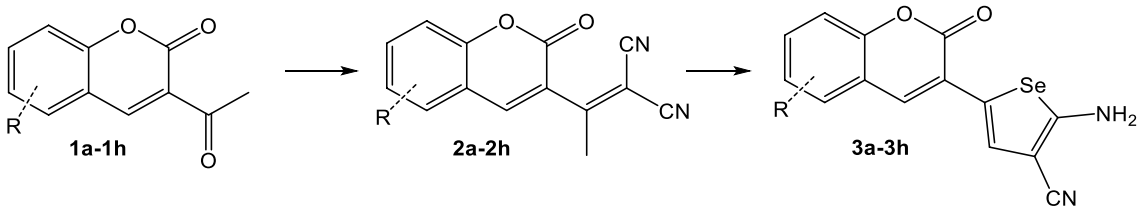
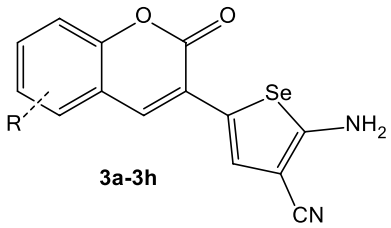
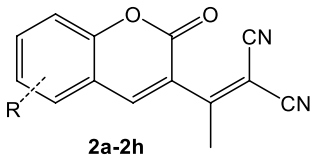



**Table 1** New coumarin–2-aminoselenophene-3-carbonitrile compounds synthesized in diethylamine catalyst




| Entry | Compound | R | Time/h | Yield/% | M.p./°C |
|---|---|---|---|---|---|
| 1 | **3a** | H | 5 | 50 | 244–246 |
| 2 | **3b** | 7-$OCH_3$ | 5 | 68 | 187–189 |
| 3 | **3c** | 6-Br | 5 | 81 | 212–214 |
| 4 | **3d** | 7-OH | 5 | 72 | > 250 |
| 5 | **3e** | 6-$NO_2$ | 6 | 51 | 129–131 |
| 6 | **3f** | 6,8-$Br_2$ | 3 | 59 | 225–227 |
| 7 | **3g** | 6-Cl | 5 | 55 | > 250 |
| 8 | **3h** | 7-$NEt_2$ | 7 | 50 | 148–150 |

**Table 2** Malononitrile compounds synthesized in diethylamine catalyst




| Entry | Compound | R | Time/h | Yield/% | M.p./°C |
|---|---|---|---|---|---|
| 1 | **2a** | H | 2 | 93 (57 [25]) | 163–165 (163 [25]) |
| 2 | **2b** | 7-$OCH_3$ | 3 | 78 | 170–172 |
| 3 | **2c** | 6-Br | 1 | 98 (60 [25]) | 202–204 [25] |
| 4 | **2d** | 7-OH | 2.5 | 80 | 238–240 |
| 5 | **2e** | 6-$NO_2$ | 4.5 | 69 | 139–141 |
| 6 | **2f** | 6,8-$Br_2$ | 3 | 72 | 198–200 |
| 7 | **2g** | 6-Cl | 2 | 79 | 185–187 |
| 8 | **2h** | 7-$NEt_2$ | 4 | 89 (88 [26]) | 164–166 (166–168 [26]) |

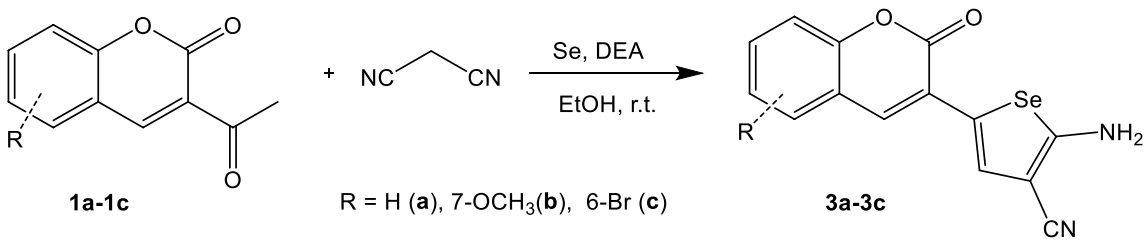
compounds were individually characterized and their identity confirmed by $^{1}$H NMR and $^{13}$C NMR. Among these compounds, 2-[1-(2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (**2a**), 2-[1-(6-bromo-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (**2c**), and 2-[1-[7-(*N*,*N*-diethylamino)-2-oxo-2*H*-chromen-3-yl]ethylidene]malononitrile (**2h**) were reported in the literature. However, the yield of these compounds is higher with our method (Table 2). Novel coumarin–selenophene-based biheteroacyclic derivatives namely, 2-amino-5-(2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitriles **3a**–**3h**, for the first time, were synthesized in this study.

Attempts to one-pot synthesis of **3a**–**3c** via reaction of **1a**–**1c** with malononitrile and selenium in ethyl alcohol at room temperature (Table 3) were also successful and gave the highest yields when the molar ratio of **1a**–**1c**: malonitrile: Se is 0.75:1.0:1.0 (Table 3, entries 3, 7, and 11). Adjustment of the molar ratio of **1a**–**1c** from 1.0 to 0.75 increased the yield of corresponding coumarin–selenophenes to 65, 72, and 48%, respectively. Nevertheless, decreasing the molar ratio of **1a**–**1c** to 0.5 was not successful, giving the corresponding coumarin–selenophenes in 46, 56, and 33%, respectively (Table 3, entries 4, 8, and 12).

During the optimization studies, synthesis of main precursors **2a**–**2c** and target molecules **3a**–**3c** was tested with different bases diethylamine, morpholine, and saturated $NaHCO_3$. The results are summarized in Table 4.

It is obviously seen that reactions with diethylamine were completed rapidly and with better results than those of reactions with morpholine. The yield of **3a**–**3c** is 50, 68, and 81%, respectively. Saturated $NaHCO_3$ was found unsatisfactory for the synthesis of **2a**–**2c** and **3a**–**3c**. A brief survey of base catalysts revealed that diethylamine has an influence in the outcome of the reaction. To find best combination of diethylamine with solvent, a number of solvents which less or more polar than ethanol were tested. The screening of solvents revealed that ethanol is the most effective solvent (Table 5, entries 1, 7, and 13).

**Table 3** Optimization studies of one-pot synthesis of **3a**–**3c**




| Entry | Compound | Mol ratio (3:malononitrile) | Yield/% |
|---|---|---|---|
| 1 | **3a** | 1.0:1.0 | 50 |
| 2 | **3a** | 0.9:1.0 | 53 |
| 3 | **3a** | 0.75:1.0 | 65 |
| 4 | **3a** | 05:1.0 | 46 |
| 5 | **3b** | 1.0:1.0 | 58 |
| 6 | **3b** | 0.9:1.0 | 60 |
| 7 | **3b** | 0.75:1.0 | 72 |
| 8 | **3b** | 05:1.0 | 56 |
| 9 | **3c** | 1.0:1.0 | 41 |
| 10 | **3c** | 0.9:1.0 | 43 |
| 11 | **3c** | 0.75:1.0 | 48 |
| 12 | **3c** | 05:1.0 | 33 |

**Table 4** Optimization studies of the synthesis of **3a**–**3c** with coumarin-malononitrile derivatives **2a**–**2c** with different bases in EtOH

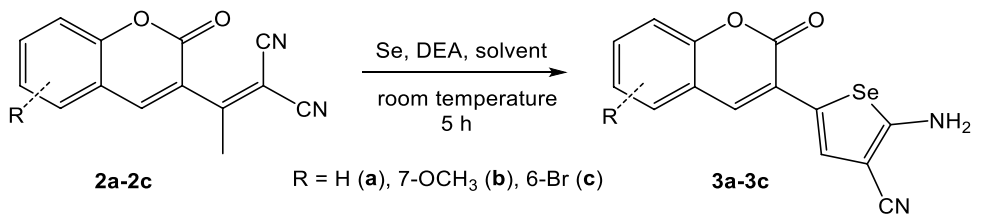
| Entry | Compound | Catalyst | Time/h | Yield/% |
|---|---|---|---|---|
| 1 | **3a** | DEA | 5 | 50 |
| 2 | **3a** | Morpholine | 5 | 38 |
| 3 | **3a** | Saturated $NaHCO_3$ | 5 | None |
| 4 | **3b** | DEA | 5 | 68 |
| 5 | **3b** | Morpholine | 5 | 52 |
| 6 | **3b** | Saturated $NaHCO_3$ | 5 | None |
| 7 | **3c** | DEA | 5 | 81 |
| 8 | **3c** | Morpholine | 5 | 70 |
| 9 | **3c** | Saturated $NaHCO_3$ | 5 | Trace |
| 10 | **2a** | DEA | 2 | 93 |
| 11 | **2a** | Morpholine | 4 | 80 |
| 12 | **2a** | Saturated $NaHCO_3$ | 8 | 20 |
| 13 | **2b** | DEA | 3 | 78 |
| 14 | **2b** | Morpholine | 3 | 72 |
| 15 | **2b** | Saturated $NaHCO_3$ | 8 | 15 |
| 16 | **2c** | DEA | 1 | 98 |
| 17 | **2c** | Morpholine | 1.5 | 88 |
| 18 | **2c** | Saturated $NaHCO_3$ | 8 | 23 |

## Antiproliferative activity

The principal interest of this study is synthesis and biological evaluation of coumarin derivatives with and without selenophene unit on lactone moiety of coumarin molecules. In this respect, eight novel coumarin–2-aminoselenophene-3-carbonitrile derivatives and eight their corresponding coumarins were investigated to determine their potency against to MCF-7 breast cancer cell line and to measure antioxidant activity. To investigate the antiproliferative activity of these novel coumarin–2-aminoselenophene-3-carbonitrile derivatives, all compounds were screened against MCF-7 breast cancer cell line in comparison with the activity of the known anti-cancer reference drug 5-flourouracil (5-FU), and the results are summarized in Table 6, Figs. 2 and 3.

This cell line was selected as many clinical trials showing the activity of selenium compounds in the reduction of hormone dependent cancer [21, 22]. Doses were chosen from the results of previous studies [16]. These compounds were applied for a period 0–48 h. At the end of incubation, antiproliferative activity was measured with xCELLigence system. Control cell, not containing compounds. In Figs. 4 and 5, given values show the mean and standard deviation from three independent experiments carried out in triplicate. The number of surviving cells decreased as the incubation

**Table 5** Optimization studies of the synthesis of **3a**–**3c** with coumarin-malononitrile derivatives **2a**–**2c** in different solvents




| Entry | Compound | Solvent | Catalyst | Yield/% |
|---|---|---|---|---|
| 1 | **3a** | EtOH | DEA | 50 |
| 2 | **3a** | MeOH | DEA | 33 |
| 3 | **3a** | Ethylene glycol | DEA | 10 |
| 4 | **3a** | Toluene | DEA | None |
| 5 | **3a** | 2-Propanol | DEA | None |
| 6 | **3a** | DCM | DEA | None |
| 7 | **3b** | EtOH | DEA | 68 |
| 8 | **3b** | MeOH | DEA | 47 |
| 9 | **3b** | Ethylene glycol | DEA | 18 |
| 10 | **3b** | Toluene | DEA | None |
| 11 | **3b** | 2-Propanol | DEA | None |
| 12 | **3b** | DCM | DEA | None |
| 13 | **3c** | EtOH | DEA | 81 |
| 14 | **3c** | MeOH | DEA | 60 |
| 15 | **3c** | Ethylene glycol | DEA | 29 |
| 16 | **3c** | Toluene | DEA | None |
| 17 | **3c** | 2-Propanol | DEA | None |
| 18 | **3c** | DCM | DEA | None |

**Table 6** In vitro cytotoxic activities of coumarins **1a**–**1h** and their corresponding coumarin-selenophene derivatives **3a**–**3h** against to MCF-7 breast cancer cell line after 48 h treatment

| Coumarin-selenophenes | $IC_{50}$/μM | *c*Log*P*[a] | Coumarins | $IC_{50}$/μM | *c*Log*P*[a] |
|---|---|---|---|---|---|
| **3a** | 11.73 ± 0.41 | 2.32 | **1a** | 85.45 ± 1.91 | 1.15 |
| **3b** | 41.42 ± 1.1 | 2.58 | **1b** | 87.02 ± 1.32 | 1.24 |
| **3c** | 10.83 ± 0.53 | 3.18 | **1c** | 43.91 ± 0.82 | 2.02 |
| **3d** | 46.31 ± 0.76 | 2.46 | **1d** | 93.05 ± 0.88 | 1.14 |
| **3e** | 12.21 ± 0.80 | 2.06 | **1e** | 65.74 ± 0.99 | 0.91 |
| **3f** | 15.18 ± 0.65 | 4.05 | **1f** | 25.20 ± 0.49 | 2.89 |
| **3g** | 40.21 ± 0.48 | 3.03 | **1g** | 94.15 ± 1.68 | 1.87 |
| **3h** | 34.68 ± 1.34 | 3.98 | **1h** | 65.56 ± 0.70 | 2.64 |

Values are the mean ± SD. All experimentes were performed three times

[a] *c*Log*P* value of the synthesized compounds (calculated from ChemBioDrawUltra 12.0.3)

time increased for coumarins **1a**–**1h** and **3a**–**3h**. It is also clear that cell viability rate is lower for **3a**–**3h**.

The cytotoxic activities of tested compounds coumarin **1a**–**1h** and coumarin–selenophenes **3a**–**3h** were expressed as $IC_{50}$. In general, all novel coumarin–2-aminoselenophene-3-carbonitrile derivatives **3a**–**3h** were effective in inhibiting the MCF-7 breast cancer cells with $IC_{50}$ values ranging from 10.84 to 46.32 μM. Among them, **3c**, **3a**, and **3e** exhibited potent antiproliferative activity with values of $IC_{50}$ (10.84, 11.74, and 12.21 μM, respectively) better than that of 5-FU ($IC_{50}$ = 13.5 μM) in breast cancer MCF-7 cells (Fig. 4).

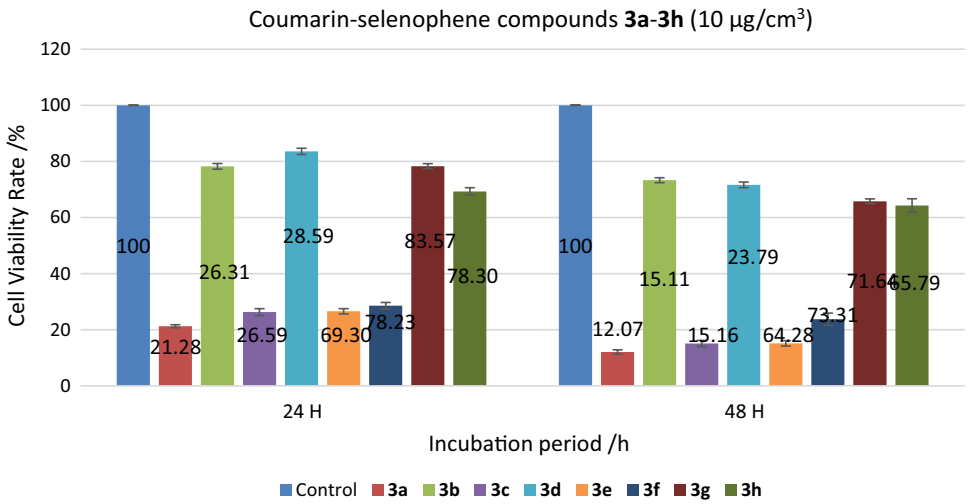



**Fig. 2** Anti-cancer activity of coumarin–2-aminoselenophene-3-carbonitrile derivatives in comparison with control

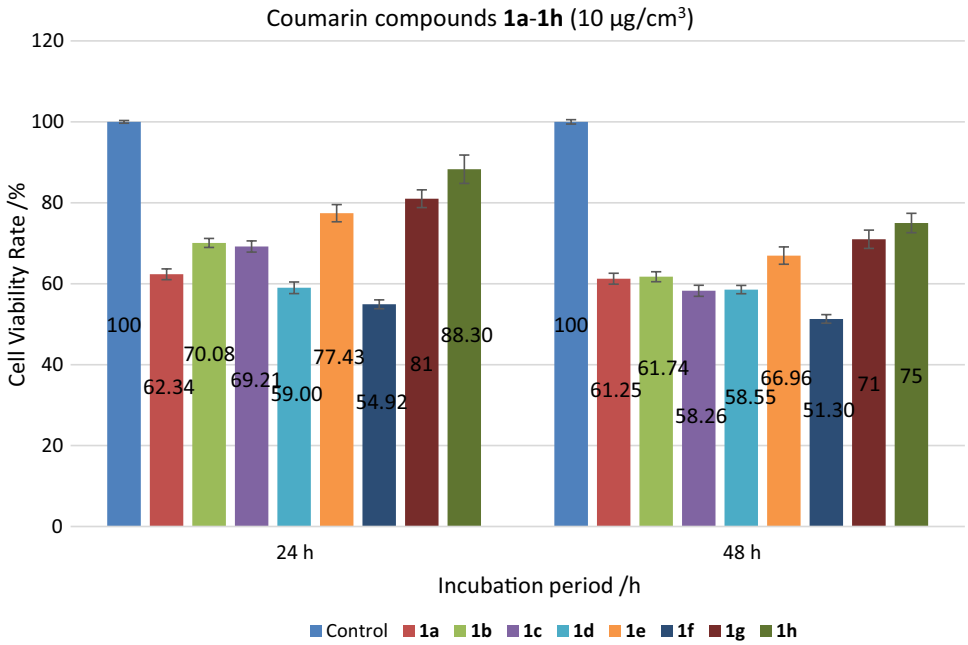
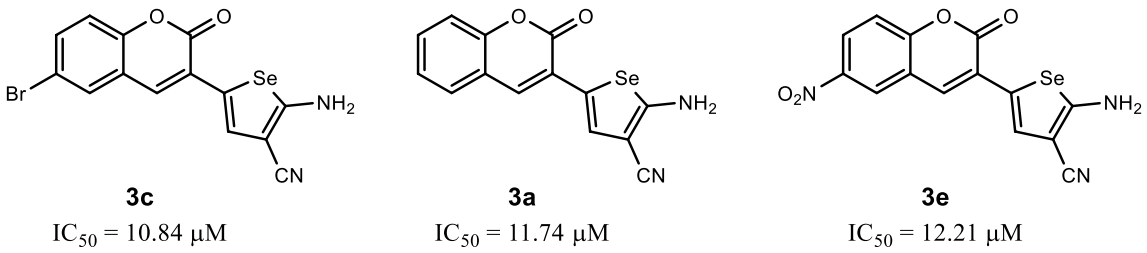



**Fig. 3** Anti-cancer activity of coumarin derivatives in comparison with control




**3c** $IC_{50}$ = 10.84 µM

**3a** $IC_{50}$ = 11.74 µM

**3e** $IC_{50}$ = 12.21 µM

**Fig. 4** The most potent coumarin–selenophene compounds to MCF-7 breast cancer cell line

Regarding the activity of coumarins **1a**–**1h** against MCF-7 breast cancer cell line, all of the tested molecules showed a slight antitumor activity with $IC_{50}$ values ranging from 25.20 to 94.15 µM. The results in Table 6 showed that only **1f** possessed slightly cytotoxicity with $IC_{50}$ = 25.20 µM. Antitumor activity of all tested coumarins **1a**–**1h** was lower than that of 5-FU ($IC_{50}$ = 13.5 µM) in breast cancer MCF-7 cells. The activity of the tested coumarin derivatives **1a**–**1h**

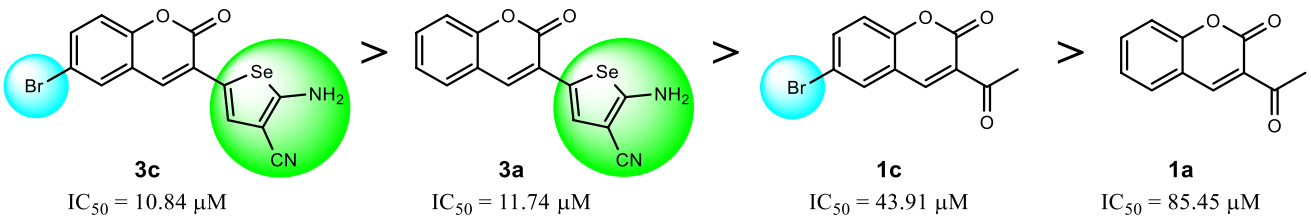



**Fig. 5** Comparing the activity of two most potent coumarin–selenophene compounds with their corresponding coumarins against resistant MCF-7 breast cancer cell line

against to MCF-7 breast cancer cell line had following decreasing order: **1f > 1c > 1 h > 1e > 1a > 1b > 1d > 1g**.

When coumarin derivatives **1a–1h** were compared with their corresponding coumarin–selenophenes, coumarin–selenophenes are the most potent candidate to suppress cancer cells proliferation in vitro (Fig. 5).

In previous studies, it was reported that coumarin derivatives show strong activity in the presence of electron withdrawing groups at C-6 of coumarin moiety. To develop potent anti-cancer agents, Nasr et al. synthesized sixteen coumarin derivatives and evaluated them against three different human carcinoma cell lines and found out that 6-brominated coumarin derivatives have significant cytotoxicity against all tested cells [23]. In addition, 6-nitro substituted coumarins show potent activity to MCF-7 breast cancer cell line [24]. It is also reported that substituents at position C-3, C-4, or C-7 of the coumarin core enhance biological activities, and they are recognized to bring apoptosis in leukemic cells [25]. In our study, the SAR (structure–activity relationship) result showed that 2-amino-3-cyanoselenophen-5-yl substituent on C-3 of coumarin unit is also more effective to resist to MCF-7 breast cancer cell line (Fig. 6).

It is also interesting that the most optimal compound against to breast-cancer cell lines belong to the **3c** which have Br on C-6 and 2-amino-3-cyanoselenophen-5-yl substituent on C-3 has four times better activity to MCF-7 breast cancer cell line than its corresponding coumarin **1c**. This clearly indicates the importance of 2-amino-3-cyanoselenophen-5-yl substituent on C-3 on coumarin moiety. On the other hand, the introduction of *N*,*N*-diethyl, –OH, $–OCH_3$ on C-7 did not increase antiproliferative activity against MCF-7 cell line (Table 6).

## Antioxidant activity

Antioxidant compounds which scavenge free radicals have an important role in human life. Hence, we investigated antioxidant activity of sixteen novel biheterocyclic coumarins along with antiproliferative activity. DPPH (1,1-diphenyl-2-picrylhydrazyl) method was used to test

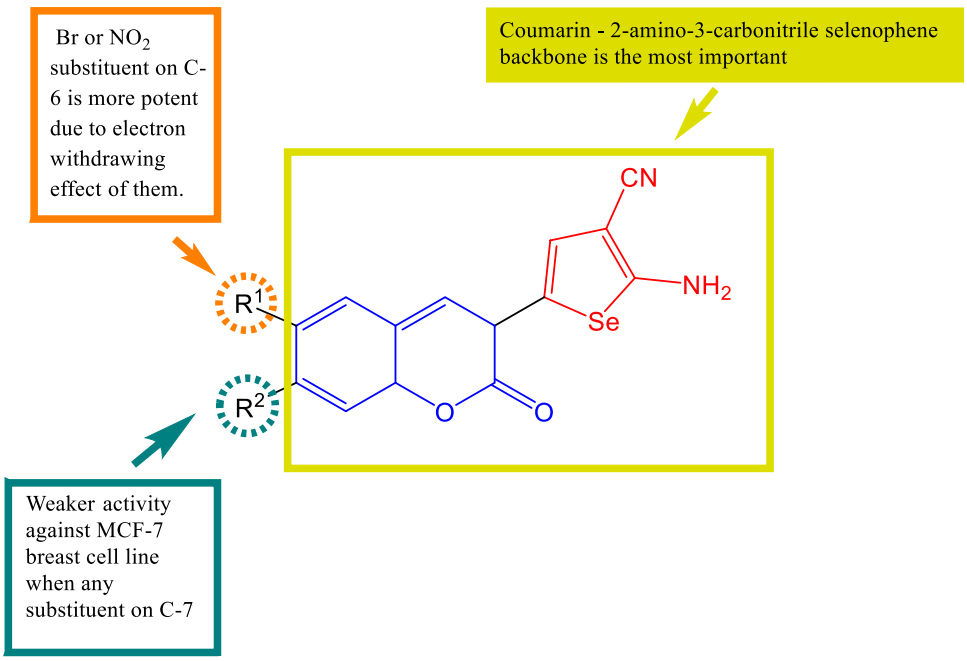



**Fig. 6** SAR of coumarin–2-aminoselenophene-3-carbonitrile derivatives

the compounds. The method measures antioxidant activity by using stable free radical $\alpha$,$\alpha$-diphenyl-$\beta$-picrylhydrazyl (DPPH) [26]. Comparation of the scavenging capacity of coumarin–selenophenes **3a**–**3h** and coumarins **1a**–**1h** was carried out against ascorbic acid, as a standard material. Reduction of stable DPPH radical by of coumarin–selenophenes **3a**–**3h** and coumarins **1a**–**1h** was observed changing the purple-colored solution into yellow-colored diphenylpicrylhydrazine. In the presence of hydrogen-donating antioxidant compounds, radical DPPH was reduced to non-radical DPPH-H form. The results are given Table 7.

Generally all coumarin–selenophenes **3a**–**3h** and coumarins **1a**–**1h** showed good to moderate antioxidant activity. While there was poor correlation between the antioxidant activity and the antiproliferative activity, **3a** is still the most active one among all the tested compounds. It was too clear that coumarin–2-aminoselenophene-3-carbonitrile backbone is very important for biological activity (Table 7). When looking at the results of antioxidant activity, coumarin–selenophene compounds showed inhibition in the range of 75.82–91.28%, while the compound of coumarins showed inhibition in the range of 61.11–89.14%. The compounds with the highest inhibitory effect in coumarin–selenophene compounds were **3a** (91.28%) and **3d** (90.58%), while coumarin compounds were **1e** (89.14%) and **1h** (86.94%).

## Conclusion

In conclusion, all synthesized coumarin–selenophenes had antitumor activity against breast cancer MCF-7 cells. It can be suggested that the coumarin–2-aminoselenophene-3-carbonitrile backbone may be an interesting antitumor pharmaphore, moreover some coumarin–selenophenes were even more potent than the standard drug 5-FU. The most potent compounds in this study were **3c**, **3a**, and **3e**.

**Table 7** Antioxidant activities of coumarins **1a**–**1h** and their corresponding coumarin-selenophene derivatives **3a**–**3h**

| Coumarin-selenophenes | Inhibition/% | Coumarins | Inhibition/% |
|---|---|---|---|
| **3a** | 91.28 | **1a** | 64.45 |
| **3b** | 82.28 | **1b** | 61.11 |
| **3c** | 82.52 | **1c** | 64.86 |
| **3d** | 90.58 | **1d** | 80.00 |
| **3e** | 85.47 | **1e** | 89.14 |
| **3f** | 84.87 | **1f** | 86.39 |
| **3g** | 87.44 | **1g** | 78.51 |
| **3h** | 75.82 | **1h** | 86.94 |

## Experimental

All the reagents were obtained from different commercial sources. Unless noted otherwise, all of compounds were used as provided without further purification. Ethyl acetoacetate (≥ 99%), salicylaldehyde (≥ 98%), diethylamine (≥ 99.5%), dicyanomethane (≥ 99%), morpholine (≥ 99%), selenium powder (− 100 mesh 99.99% trace metals basis), $NaHCO_3$ (≥ 99.7%) 5-bromosalicylaldehyde (98%), 4-methoxysalicylaldehyde (98%), 5-nitrosalicylaldehyde (98%), 5-chlorosalicylaldehyde (98%), 3,5-dibromosalicylaldehyde (98%), 4-(*N*,*N*-diethylamino)salicylaldehyde (98%) were purchased from Sigma Aldrich. Ethanol (absolute), methanol (anhydrous, ≥ 99.8%), ethylene glycol (99.8%), toluene (anhydrous, 99.8%), 2-propanol (anhydrous, 99.5%), dichloromethane (anhydrous, ≥ 99.8%), hexane (anhydrous, 95%), ethyl acetate (anhydrous, 99.8%) were purchased from Merck. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60, F254, Merck, Darmstadt, Germany) using hexane/ethyl acetate (4:1, v/v) and the spots were detected by exposure to UV lamp at $\lambda = 254$ nm for few seconds. Melting points were determined using an Electrothermal 9100 instrument (United Kingdom) in open capillary tubes. IR spectra were recorded on a Perkin-Elmer 55148 spectrometer (USA) using KBr pellets. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ using the solvent peak as internal reference (DMSO-$d_6$: $\delta_H = 2.50$ ppm, $\delta_C = 39.51$ ppm; $CDCl_3$ at 7.27 ppm for $^1$H and 77.0 ppm for $^{13}$C) on a Bruker 300 MHz Ultrashield TM spectrometer (Germany) operating at 300 MHz and 75 MHz, respectively or a Bruker Avance III 400 MHz spectrometer (Germany) operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), br s (broad singlet). Elemental analyses were measured on a Thermo Flash 2000 Organic Elemental Analyzer (USA).

### Synthesis of 3-acetylcoumarin derivatives 1a–1h

A round-bottom flask equipped with a magnetic stirrer was charged with salicylaldehyde derivative (10 mmol), ethylacetoacetate (10 mmol), and diethylamine (10% w/w). After the solid formation, the mixture was washed with dilute HCl to neutralization of waste of base then ethanol was added. Synthesized 3-acetylcoumarin derivative was crystallized

from ethanol. The product was identified using FT-IR and NMR spectroscopy.

**3-Acetyl-6,8-dibromo-2*H*-chromen-2-one (1f, $C_{11}H_6Br_2O_3$)** Red solid; yield 2.802 g (81%); m.p.: 163–165 °C; $R_f$: 0.35 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu}$ = 3061, 3045 (C–H, aromatic), 2995 (C–H, aliphatic), 1725 (C=O), 1681 (C=O), 1599, 1539 (C=C, aromatic), 1204 (C–O), 554 (C–Br) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.36 (s, 1H, =CH), 7.99 (s, 1H, Ar–H), 7.27 (s, 1H, Ar–H), 2.73 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 194.42, 158.00, 145.62, 139.55, 134.20, 131.41, 130.14, 125.89, 121.38, 118.66, 30.45 ppm.

## Synthesis of coumarinyl malononitrile compounds 2a–2h

A mixture of 3-acetylcoumarin derivatives (10 mmol), malononitrile (10 mmol), catalytic amount of diethylamine and 25 $cm^3$ ethanol were stirred at RT for 1–4.5 h. The reaction was monitored by TLC. After completion of the reaction, as shown by disappearance of 3-acetylcoumarin derivative, the mixture was poured into 20 $cm^3$ ice-cold water. The separated solid was filtered, washed with water (3 × 10 $cm^3$), and dried. The crude product was recrystallized from ethanol. The product was identified using FT-IR and NMR spectroscopy.

**2-[1-(7-Methoxy-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (2b, $C_{15}H_{10}N_2O_3$)** Yellow solid; yield 2.077 g (78%); m.p.: 170–172 °C; $R_f$: 0.57 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu}$ = 3042 (C–H, aromatic), 2995 (C–H, aliphatic), 2226 (CN), 1719 (C=O), 1604, 1577 (C=C, aromatic), 1285 (C–N), 1237 (C–O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 8.46 (s, 1H, =CH), 7.76 (d, $J$ = 11.6 Hz, 1H, Ar–H), 7.11 (d, $J$ = 3.2 Hz, 1H, Ar–H), 7.06–7.03 (m, 1H, Ar–H), 3.91 (s, 3H, $OCH_3$), 2.59 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 172.77, 165.03, 157.45, 156.55, 132.63, 131.56, 120.22, 114.12, 113.04, 112.82, 111.87, 101.16, 86.73, 56.78, 23.45 ppm.

**2-[1-(7-Hydroxy-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (2d, $C_{14}H_8N_2O_3$)** Yellow solid; yield 2.018 g (80%); m.p.: 238–240 °C; $R_f$: 0.52 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu}$ = 3308 (OH), 3090 (C–H, aromatic), 2986 (C–H, aliphatic), 2202 (CN), 1693 (C=O), 1613, 1562 (C=C, aromatic), 1256 (C–N), 1192 (C–O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 8.24 (s, 1H, =CH)), 7.88 (d, $J$ = 11.6 Hz, 1H, Ar–H), 7.65 (d, $J$ = 11.6. Hz, 1H, Ar–H), 6.81–6.70 (m, 1H, Ar–H), 4.52 (br s, 1H), 2.51 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 170.96, 162.85, 162.17, 156.77, 138.63, 131.75, 126.17, 111.32, 108.84, 102.28, 102.10, 75.51, 11.73 ppm.

**2-[1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (2e, $C_{14}H_7N_3O_4$)** Orange solid; yield 1.940 g (69%); m.p.: 139–141 °C; $R_f$: 0.33 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu}$ = 3016 (C–H, aromatic), 2995 (C–H, aliphatic), 2197 (CN), 1702 (C=O), 1602, 1523 (C=C, aromatic), 1276 (C–N), 1201 (C–O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 8.23 (d, $J$ = 7.6 Hz, 1H, Ar–H), 8.11 (s, 1H, =CH), 7.99 (d, $J$ = 7.6 Hz, 1H, Ar–H), 7.12 (s, 1H, Ar–H), 2.51 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 177.32, 158.10, 142.21, 132.80, 127.85, 125.66, 125.11, 120.92, 109.67, 86.68, 10.98 ppm.

**2-[1-(6,8-Dibromo-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (2f, $C_{14}H_6Br_2N_2O_2$)** Red solid; yield 2.837 g (72%); m.p.: 198–200 °C; $R_f$: 0.30 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu}$ = 3061 (C-H, aromatic), 2998, 2966 (C–H, aliphatic), 2194 (CN), 1727 (C=O), 1601, 1539 (C=C, aromatic), 1238 (C–N), 1206 (C–O), 557 (C–Br) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 8.58 (s, 1H, =CH), 8.26 (s, 1H, Ar–H), 7.63 (s, 1H, Ar–H), 2.59 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 176.62, 157.29, 150.44, 138.36, 132.17, 130.40, 125.99, 121.04, 116.37, 110.03, 88.30, 11.00 ppm.

**2-[1-(6-Chloro-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (2g, $C_{14}H_7ClN_2O_2$)** Yellow solid; yield 2.138 g (79%); m.p.: 185–187 °C; $R_f$: 0.46 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu}$ = 3041 (C–H, aromatic), 2995 (C–H, aliphatic), 2190 (CN), 1737 (C=O), 1593, 1549 (C=C, aromatic), 1230 (C–N), 1200 (C–O), 565 (C–Cl) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 8.21 (s, 1H, =CH), 7.54 (s, 1H, Ar–H), 7.32 (d, $J$ = 7.6 Hz, 1H, Ar–H), 7.08 (d, $J$ = 7.6 Hz, 1H, Ar–H), 2.51 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 177.18, 161.73, 154.09, 132.45, 131.89, 129.51, 128.00, 127.08, 118.99, 116.28, 77.87, 11.08 ppm.

## Synthesis of coumarin–2-aminoselenophene-3-carbonitrile derivatives 3a-3 h

A mixture of arylidene malononitrile (5 mmol), selenium (5 mmol), 15 $cm^3$ ethanol, and catalytic amount of diethylamine was stirred at RT for 3–7 h. The reaction was monitored by TLC. After completion of reaction, as shown by disappearance of arylidene malononitrile, unreacted selenium was filtered and the mixture was poured into 40 $cm^3$ ice-cold water. The separated solid was filtered, washed with water (3 × 20 $cm^3$), and dried. The crude product was recrystallized from ethanol. The product was identified using FT-IR and NMR spectroscopy.

## One pot synthesis of coumarin–2-aminoselenophene-3-carbonitrile derivatives 3a–3h

A mixture of 3-acetylcoumarin derivative (5 mmol), malononitrile (5 mmol), selenium (5 mmol), 15 $cm^3$ ethanol, and catalytic amount of diethylamine was stirred at RT for 7 h. The reaction was monitored by TLC. After completion of reaction, unreacted selenium was filtered and 15 $cm^3$ ethyl acetate was added, and the reaction mixture was washed with water ($3 \times 15$ $cm^3$). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness, the crude product was recrystallized from ethanol. The pure products were identified using FT-IR and NMR spectroscopy.

**2-Amino-5-(2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile (3a, $C_{14}H_8N_2O_2Se$)** Brown solid; yield 0.788 g (50%); m.p.: 244–246 °C; $R_f$: 0.41 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu} = 3201$ ($NH_2$), 3071 (C–H, aromatic), 2988 (C–H, aliphatic), 2178 (CN), 1702 (C=O), 1605, 1456 (C=C, aromatic), 1215 (C–N), 1198 (C–O) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.35$ (s, 2H, $NH_2$), 7.98 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.69 (t, $J = 8.4$ Hz, 1H, Ar–H), 7.45 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.40 (s, 1H, =CH), 7.14 (t, $J = 7.6$ Hz, 1H, Ar–H), 7.05 (s, 1H, Ar–H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 160.41$, 156.95, 152.71, 152.63, 140.59, 132.43, 130.11, 129.40, 129.06, 124.90, 118.46, 116.41, 115.87, 113.96, 86.16 ppm.

**2-Amino-5-(7-methoxy-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile (3b, $C_{15}H_{10}N_2O_3Se$)** Brown solid; yield 1.001 g (68%); m.p.: 187–189 °C; $R_f$: 0.52 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu} = 3214$ ($NH_2$), 3015 (C–H, aromatic), 2995 (C–H, aliphatic), 2197 (CN), 1702 (C=O), 1654, 1513 (C=C, aromatic), 1276 (C–N), 1201 (C–O) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.47$ (s, 2H, $NH_2$), 7.86 (s, 1H, Ar–H), 7.78 (s, 1H, Ar–H), 7.76 (s, 1H, =CH), 7.12 (d, $J = 3.2$ Hz, 1H, Ar–H), 7.07 (d, $J = 3.6$ Hz, 1H, Ar–H), 7.05 (t, $J = 4.4$ Hz, 1H, Ar–H), 3.91 (s, 3H, $OCH_3$) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 165.04$, 157.46, 156.55, 146.06, 131.57, 120.81, 120.23, 114.13, 113.05, 112.82, 111.88, 101.18, 86.72, 56.80 ppm.

**2-Amino-5-(6-bromo-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile (3c, $C_{14}H_7BrN_2O_2Se$)** Brown solid; yield 0.808 g (81%); m.p.: 212–214 °C; $R_f$: 0.29 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu} = 3210$ ($NH_2$), 3056 (C–H, aromatic), 2991 (C–H, aliphatic), 2196 (CN), 1728 (C=O), 1598, 1553 (C=C, aromatic), 1234 (C–N), 1181 (C–O), 1069, 663 (C–Br) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.61$ (s, 2H, $NH_2$), 8.15 (s, 1H, Ar–H), 7.59 (s, 1H, Ar–H), 7.51 (s, 1H, =CH), 7.46 (d, $J = 4.8$ Hz, 1H, Ar–H), 7.43 (d, $J = 4.8$ Hz, 1H, Ar–H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 160.13$, 152.81, 140.67, 137.20, 133.00, 131.28, 128.42, 120.53, 119.17, 118.87, 116.82, 90.37 ppm.

**2-Amino-5-(7-hydroxy-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile (3d, $C_{14}H_8N_2O_3Se$)** Black solid; yield 0.878 g (72%); m.p.: > 250 °C; $R_f$: 0.45 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu} = 3349$ (OH), 3152 ($NH_2$), 3075 (C–H, aromatic), 2980 (C–H, aliphatic), 2166 (CN), 1729 (C=O), 1601, 1472 (C=C, aromatic), 1232 (C–N), 1153 (C–O) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.55$ (s, 2H, $NH_2$), 7.71–7.66 (m, 2H, Ar–H), 7.18 (d, $J = 6.0$ Hz, 1H, Ar–H), 6.95 (s, 1H, =CH)), 6.49 (s, 1H, Ar–H), 5.14 (br s, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 159.93$, 158.50, 158.06, 148.96, 145.09, 132.89, 131.91, 127.89, 115.28, 113.96, 112.68, 112.45, 103.77, 91.91 ppm.

**2-Amino-5-(6-nitro-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile (3e, $C_{14}H_7N_3O_4Se$)** Brown solid; yield 0.522 g (51%); m.p.: 129–131 °C; $R_f$: 0.27 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu} = 3204$ ($NH_2$), 3013 (C–H, aromatic), 2998 (C–H, aliphatic), 2195 (CN), 1701 (C=O), 1614, 1513 (C=C, aromatic), 1246 (C–N), 1221 (C–O) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.29$ (s, 2H, $NH_2$), 7.89 (d, $J = 7.2$ Hz, 1H, Ar–H), 7.72 (dd, $J = 10.8$ Hz, 2.4 Hz, 1H, Ar–H), 7.23 (s, 1H, =CH)), 7.18 (s, 1H, Ar–H), 6.98 (s, 1H, Ar–H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 161.83$, 158.47, 153.05, 143.11, 140.48, 129.65, 124.64, 124.58, 123.55, 122.06, 118.13, 116.84, 114.10, 94.38 ppm.

**2-Amino-5-(6,8-dibromo-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile (3f, $C_{14}H_6Br_2N_2O_2Se$)** Brown solid; yield 0.828 g (59%); m.p.: 225–227 °C; $R_f$: 0.25 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu} = 3205$ ($NH_2$), 3022 (C–H, aromatic), 2992 (C–H, aliphatic), 2193 (CN), 1706 (C=O), 1625, 1523 (C=C, aromatic), 1276 (C–N), 1198 (C–O), 535 (C–Br) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.22$ (s, 2H, $NH_2$), 8.08 (s, 1H, Ar–H), 7.58 (s, 1H, =CH), 6.75 (s, 1H, Ar–H), 6.12 (s, 1H, Ar–H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 158.94$, 152.00, 145.27, 142.92, 137.99, 131.09, 126.28, 125.42, 125.34, 120.22, 117.69, 114.42, 114.07, 90.42 ppm.

**2-Amino-5-(6-chloro-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile (3g, $C_{14}H_7ClN_2O_2Se$)** Yellow solid; yield 0.682 g (55%); m.p.: > 250 °C; $R_f$: 0.41 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu} = 3201$ ($NH_2$), 3020 (C=C, aromatic), 2994 (C–H, aliphatic), 2191 (CN), 1700 (C=O), 1610, 1508 (C=C, aromatic), 1270 (C–N), 1202 (C–O), 593 (C–Cl) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.58$ (s, 2H, $NH_2$), 8.23 (s, 1H, Ar–H), 8.06 (s, 1H, Ar–H), 7.68 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.39 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.11 (s, 1H, =CH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$):

$\delta$ = 157.55, 155.45, 151.63, 142.17, 133.70, 126.31, 125.26, 122.66, 118.65, 117.35, 115.64, 94.21 ppm.

**2-Amino-5-[7-(*N*,*N*-diethylamino)-2-oxo-2*H*-chromen-3-yl]selenophene-3-carbonitrile (3h, $C_{18}H_{17}N_3O_2Se$)** Black solid; yield 0.637 g (50%); m.p.: 148–150 °C; $R_f$: 0.46 (hexane/ethyl acetate 4:1 v/v); FT-IR (KBr): $\overline{\nu}$ = 3223 ($NH_2$), 3056 (C–H, aromatic), 2995, 2888 (C–H, aliphatic), 2199 (CN), 1702 (C=O), 1628, 1505 (C=C, aromatic), 1286 (C–N), 1209 (C–O) $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.48 (s, 2H, $NH_2$), 8.68 (s, 1H, Ar–H), 7.27 (d, $J$ = 7.2 Hz, 1H, Ar–H), 6.48 (s, 1H, =CH), 6.21 (dd, $J$ = 11.2 Hz, 2.4 Hz, 1H, Ar–H), 6.07 (s, 1H, Ar–H), 3.40 (q, $J$ = 7.2 Hz, 4H, 2 $CH_2$), 1.21 (t, $J$ = 7.2 Hz, 6H, 2 $CH_3$) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.40, 154.26, 148.82, 147.87, 135.38, 131.90, 131.32, 123.40, 117.48, 111.43, 110.04, 104.40, 96.70, 44.81, 12.57 ppm.

## Antiproliferative activity

Human breast cancer cell line MCF-7 was obtained from HUKUK WDCM756: Culture Collection of Animal Cells, Foot and Mouth Disease Institute (ANKARA-TURKEY). Cells were routinely cultivated in RPMI 1640 supplemented with 10% fetal bovine serum, penicillin (100 U/$cm^3$) and streptomycin (100 mg/$cm^3$) at 37 °C and 5% $CO_2$ [5]. In current study, xCELLigence system (ACEA) (USA) used to monitor cytotoxicity, using electronic cell sensor array technology.

5-Fluorouracil (5-Fu) was purchased from Sigma-Aldrich. 5-FU as the positive control was dissolved in RPMI culture medium and further concentrations of 15, 4.5, 1.35, 0.4, 0.12 µg/$cm^3$ were prepared. Tested were dissolved in DMSO at 1 mg/$cm^3$ immediately before using and diluted to the appropriate volume just before adding to the cell culture. xCELLigence E-plates were filled with 0.1 $cm^3$ RPMI medium/well and the background signal was determined. Then, 0.1 $cm^3$ of cell suspension was added in to each well (3 × 104 cells/well). Thereafter, positive control and tested cytostatics according to selected concentration ranges (0, 5, 10, 15, 20, 50 µg/$cm^3$) were added to cultivation media and cell index was recorded for next 48 h. $IC_{50}$ values were determined for each cytostatic after 48 h of treatment [18].

## DPPH radical scavenging activity

The DPPH radical scavenging activities of the **3a**–**3h** and coumarins **1a**–**1h** were evaluated according to Blois method [26]. Initially, 0.1 $cm^3$ of the samples at concentration of 250, 500, 750, and 1000 µg/$cm^3$ was mixed with 1 $cm^3$ of 0.2 mM DPPH that was dissolved in methanol. The reaction mixture was incubated in the dark for 20 min at 28 °C. The control contained all reagents without the sample while methanol was used as blank. The DPPH radical scavenging activity was determined by measuring the absorbance at 517 nm using the UV–Vis spectrophotometer (Thermo scientific-USA). The DPPH radical scavenging activity of ascorbic acid was also assayed for comparison. The percentage of DPPH radical scavenger was calculated using Eq. (1):

$$\text{Radical scavenging activity } (\%) = \left[\left(A_0 - A_1/A_0\right) \times 100\right] \quad (1)$$

where $A_0$ is the absorbance of the control reaction and $A_1$ is the absorbance in the presence of the samples or standards.

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