Novel Coumarin-Selenophene Hybrids as Potential Antiproliferative Agents: Synthesis and Biological Evaluation

Mehmet Erşatır[a], Metin Yıldırım[b], Elife Sultan Giray[a], Serap Yalın[b]

[a]*Department of Chemistry, Arts and Science Faculty, Cukurova University, Adana, Turkey*

[b]*Department of Biochemistry, Faculty of Pharmacy, Mersin University, Mersin, Turkey*

mehmetersatir8@gmail.com

Abstract A series of new coumarin-selenophene compounds containing selenophene rings on C-3 were synthesized at room temperature, in a short time and with high yields. Hybrid compounds containing the coumarin ring are known to exhibit significant biological activities. Anticancer activity analyzes of the compounds in the MCF-7 cell line were performed. It can be seen from IC50 values that the COUMSEL c compound has a high level of cytotoxic effect. At the same time, COUMSEL a compound was the most radical scavenging compound.

Keywords*: *coumarin, selenophene, hybrid compounds, antiproliferative activity

Introduction 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 [1].

The groups forming the hybrid compound having these novel functions may be large structures such as polypeptides, nucleic acids or small organic molecules. In particular, hybrid compounds formed by combining coumarin compounds known to exhibit biological activity in laboratory-scale organic synthesis with small heterocyclic compounds are common.

Coumarin compounds are found naturally in the roots, stems, leaves, flowers and fruit parts of plants and having a large number of biological activities such as anticoagulant, anticancer, anticonvulsant, antioxidant, antiinflammatory and so on [1]. They are isolated from plants and further synthesized and synthesized and converted into hybrid compounds with other compounds. The most common reactions for coumarin synthesis are Knoevenagel and Pechman reactions. There are many studies on coumarin synthesis in the literature. There are syntheses using different methods such as ultrasonic bath and microwave as well as studies using different solvents and catalysts in this field [2].

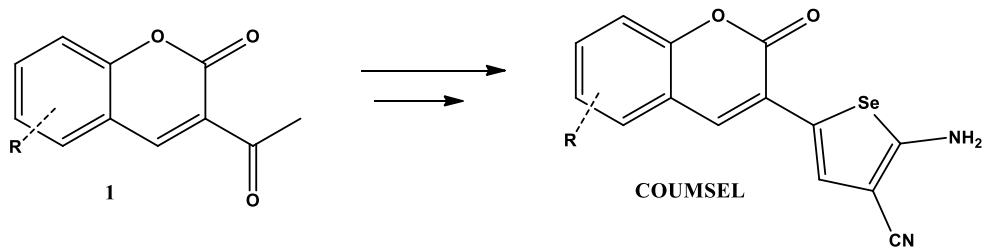
The synthesis of selenium-containing compounds has accelerated in the last two decades with the adoption of selenium-containing amino acids as amino acids of the 21st century. Although the synthesis of selenophene was known in the previous years, the studies carried out by the German chemist Gewald in the 1960s come to the forefront. In a study conducted by Gewald in 1966, 2-aminothiophene compounds were formed as a result of the condensation reaction of aldehydes and ketones with α-cyanoesters. When selenium is used instead of sulfur in this reaction, 2-aminoselenophene compounds can be synthesized [3].

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 [4], 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 [5], selenopheno [2,3, c] coumarin compounds were synthesized. The cytotoxic activity of these compounds was investigated in angiogenesis inhibitory activity and antioxidant effect. In 2017, Domracheva et al. The anticancer activity of selenophenocoumarin compounds synthesized in this study was investigated [6]. As can be seen in these studies, synthesis of different types of coumarin-selenophene compounds is needed in the literature. The novel hybrid compounds to be synthesized may lead to important studies, especially in anticancer studies.

In the light of all this, different 3-acetylcoumarin compounds were synthesized by Knoevenagel reaction and converted to malononitrile derivatives by modified Gewald reaction. Subsequently, 8 new 3-substituted coumarin selenophene compounds were synthesized by reaction with selenium. Then DPPH antioxidant activity tests and MCF-7 anticancer activity tests of the synthesized 3-acetylcoumarin-selenophene derivative compounds and the results were compared with the starting compounds coumarins.

Results and Discussion

Synthesis of COUMSELs



R: H (a), 6-Br (c), 6-NO_2 (e), 6-Cl (f)

In this study, anti-proliferative effects of coumarin compounds with and without selenophene rings on C-3 on MCF-7 cell line were examined and the results are given in Table 1.

Table 1. Anti-proliferative activities of coumarins and their corresponding COUMSEL's coumpunds against MCF-7 cell line

COUMSELs	IC_{50} value (µM)	cLogP*	Coumarins	IC_{50} value (µM)	cLogP*
COUMSEL a	11.73±0.41	2.32	**1 a**	85.45±1.91	1.15
COUMSEL c	10.83 ±0.53	3.18	**1 c**	43.91±0.82	2.02
COUMSEL e	12.21±0.80	2.06	**1e**	65.74±0.99	0.91
COUMSEL f	15.18±0.65	4.05	**1 f**	25.20±0.49	2.89

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

**cLog P* value of the synthesized compounds (calculated from ChemBioDrawUltra 12.0.3)

When the effects of MCF-7 on breast cancer cells are examined, it can be seen from IC50 values that the coumarins containing selenophene have very good antiproliferative effects compared to coumarins, which are the starting compounds. In particular, the compounds IC50 values of COUMSEL c, COUMSEL a and COUMSEL e found to be better than the IC50 value (10.84; 11.74 and 12.21 µM, respectively) of 5-fluorouracil (IC_{50}= 13,5µM), the reference substance (Table 1).

The free radical scavenging activities of the compounds were also examined by DPPH method. The results are given in Table 2.

Table 2. Antioxidant activities of coumarins and COUMSELs

COUMSEL's	Inhibition %	Coumarins	Inhibition %
COUMSEL a	91.28	**1 a**	64.45
COUMSEL c	82.52	**1 c**	64.86
COUMSEL e	85.47	**1e**	89.14
COUMSEL f	84.87	**1 f**	86.39

When looking at the results of antioxidant activity, the compounds containing selenophene and the coumarins, which are the starting compounds, also showed very good antioxidant activity. In these results, it is seen that the compounds containing selenophene have a slightly better effect (Table 2).

Conclusion

In conclusion, all synthesized coumarin-selenophene compounds showed a good anti-proliferative effect. The coumarin compounds known to be biologically active have been proven to show better biological activity when they carry a selenophene ring on C-3. In particular, the 3 synthesized compounds had better effect on the MCF-7 cell line than the 5-fluorouracil shown as a reference. These compounds can also be used as reference materials in future studies.

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