Cukurova University
Journal of
Natural & Applied Sciences

Original Paper

In vitro Cytogenotoxic Effects of a Coumarin-Selenophene Hybrid Compound

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Cite this article as: Ila H.B. (2024). In vitro Cytogenotoxic Effects of a Coumarin-Selenophene Hybrid Compound. Cukurova University Journal of Natural & Applied Sciences 3(1): 11-18

Abstract

This study was carried out to reveal the *in vitro* cytogenotoxic effect of 2-amino-5-(6-bromo-2-oxo-2H-chromen-3-yl) selenophene-3-carbonitrile (6-BrCoumSel or CoumSel), a newly synthesized coumarin-selenophene hybrid compound. Coumarin (2H-chromen-2-one), one of the main components of the test substance hybrid molecule (CoumSel), is an aromatic organic chemical compound with the formula $C_9H_6O_2$. Pharmacologically, coumarin belongs to the flavonoid group of chemicals. The other component, selenophene, has the formula C_4H_4Se and is an unsaturated organic compound containing a five-membered ring containing selenium in its structure. It is a colorless liquid and is one of the most common selenium heterocycles. It was found that in human lymphocytes cultured in vitro, the hybrid CoumSel compound increased the frequency of chromosome abnormalities (CA) and micronuclei (MN), especially at high concentrations, compared to the untreated group (0 µg/ml). However, the increase in MN in the 200 µg/ml 48-hour treatment was statistically significant. The notable cytotoxic effects were detected at high concentrations. The potential of CoumSel as an antiproliferative drug with its current properties should not be ignored.

Keywords: Coumarin-selenophene hybrid compound, *in vitro* human lymphocyte, chromosome aberration, micronucleus, cytotoxicity.

1. Introduction

Found in many plants, including some edible plants, coumarin is a pleasant-smelling natural flavoring substance. It has extensive use in the pharmaceutical and cosmetics industry but is partially toxic to the liver and kidneys. LD_{50} rat: 293 mg/kg (Figure 1) [1].

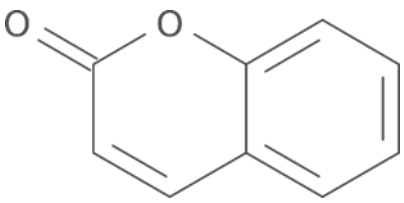

Figure 1. Coumarin (benzo- α -pyrone)

Although slightly dangerous to humans, coumarin is hepatotoxic in rats, but this toxicity has been reported to be less in mice. Metabolism in rodents converts coumarin into a more dangerous and unstable byproduct, causing liver cancer in rats and lung tumors in mice [2,3]. Although coumarin is a negative mutagen in *in vivo* studies, it has been demonstrated that it has both promutagenic properties and can increase the effects of some promutagens by increasing micronucleus stimulation in *in vitro* cells stimulated with S9 [4,5]. While some coumarin derivatives showed significant cytotoxic effects due to apoptosis in cancer cell lines like MCF-7, HeLa, etc., they did not show cytotoxic effects in the healthy cell line (HEK-293). It has been stated that these

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Received: Feb 14, 2024
Accepted: Mar 8, 2024

compounds are promising antimicrobial agents against pathogenic strains of *Pseudomonas aeruginosa* and *Candida albicans*, which were examined to evaluate their antimicrobial effects [6–8]. Coumarin and its derivatives are an anticoagulant drug prescribed to reduce the risk of blood clotting, venous thrombosis, and pulmonary embolism by inhibiting vitamin K synthesis [9]. Vitamin K is an activator of coagulation factors II, VII, IX, and X, so as the amount of vitamin K decreases, the synthesis of these factors also decreases. Coumarin is an oral anticoagulant that inhibits Vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K (What are Coumarins, n.d.). Coumarin and its derivatives are preferred in the pharmaceutical industry because they show antioxidant, antitumor, and anti-inflammatory activity. Some coumarin derivatives constitute the active ingredient of insecticides. Cause of its pleasant smell is also used in foodstuffs, soaps, perfumes, and other cleaning products. Moreover, coumarin is utilized as an optical brightening in the structure of laser and fluorescence dyes [11].

The other component of the test substance (CoumSel) is selenophene, which has the formula C4H4Se. Selenophene is an unsaturated organic compound containing a five-membered ring carrying selenium. The selenophene molecule is straight and aromatic and is subject to electrophilic substitution reactions at the -2 or -2.5 positions. This structure may have brought some properties to selenophene. These reactions are slower than furan but faster than thiophene. The first confirmed production of selenophene was achieved by Mazza and Solazzo in 1927 by heating acetylene and selenium together at approximately 300°C [12,13]

Selenophene is a biologically active compound with hepatoprotective, antinociceptive (pain relieving), anticonvulsant [14], antihypertensive [15], and antitumoral [16] properties. Compounds containing selenophene are extremely useful synthetic intermediates (Figure 2). They can serve as suitable building blocks to synthesize other biologically active compounds.

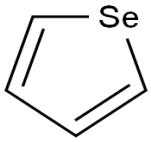


Figure 2. Selenophene [17]

Some of the selenophene-derived compounds showed anticancer [18,19], antiradical/antioxidant [20–22], and antiestrogenic activity [23,24]. Some selenophene-derived compounds exhibit potent cytotoxic/apoptotic properties with broad-spectrum antitumor activity [25–28]. An enhanced activity of the selenophene analog molecule against DNA gyrase has been documented [29]. Again, tert-butyl benzo[b]tellurophen-2-ylmethylcarbamate, a selenophene derivative, caused inhibition of histone H3 lysine 9 demethylase (KDM4) in HeLa cells but did not show such an effect in healthy cells [30].

The selenium contained in the selenophene compound participates in the structure of different compounds in soil, plants, and water. It is vital for organisms. It is a structural element of many enzymes, notably glutathione peroxidase, which protects cell membranes from oxidative damage. The chemical form of selenium, the selenium level of the organism, and the number of elements that interfere with selenium metabolism or increase the requirement in the diet, such as sulfur, vitamin E, lipids, amino acids, proteins, cadmium, mercury, copper and arsenic, determine the need for selenium. Selenium deficiency can cause different abnormalities in humans. However, excessive selenium intake can also cause poisoning [31].

This study was conducted to reveal the genotoxic and cytotoxic label of the newly synthesized coumarin-selenophene derivative molecule (CoumSel), which has the potential to be used for different purposes in many industrial fields and whose biological effect potential has not yet been adequately evaluated. The studies were conducted with peripheral blood cultures obtained from healthy volunteers under *in vitro* conditions. The genotoxicity and cytotoxicity findings detected provided significant results regarding this chemical. Considering the potential of the existing chemical to be used in many industrial areas, the results of the scientific study will provide an analytic perspective for the future projection of CoumSel.

2. Material and Method

2.1. Test Substance (6-Br- CoumSel or CoumSel)

The test substance in the study, the coumarin-selenophene hybrid compound, 6-bromo salicylaldehyde (6-Br-CoumSel) molecule, was synthesized in the organic chemistry laboratory of Cukurova University Arts and Science Faculty Department of Chemistry as follows: Initially, coumarin compounds were synthesized by Pechmann and Knoevenagel methods. Then, the 2-amino

selenophene-3-carbonitrile molecule was synthesized by the Gewald method, and coumarin-selenophene hybrid derivatives were prepared [11].

The test concentrations were determined by conducting preliminary experiments under *in vitro* conditions with this newly synthesized derivative chemical. In the study, we tried to reveal an insight related to the genotoxic potential of the test chemical by investigating *in vitro* chromosome aberration (CA) and micronucleus (MN) induction in peripheral lymphocytes. The cytotoxic effect of the test substance by mitotic index (MI) and nuclear division index (NDI) data were analyzed.

Chemical name: 2-amino-5-(6-bromo-2-oxo-2H-chromen-3-yl) selenophene-3-carbonitrile

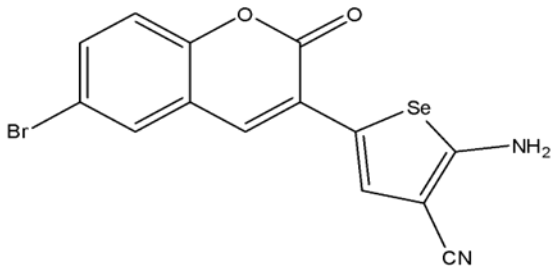
Chemical formula: C14H7BrN2O2Se

Nickname: CoumSel (Figure 3)

Molecular weight: 394.08 g/mol

Solubility: Dimethyl sulfoxide (DMSO)

Physical appearance: Solid, brown



2-amino-5-(6-bromo-2-oxo-2*H*-chromen-3-yl)selenophene-3-carbonitrile

Figure 3. Coumsel

2.2. Chemicals

Colchicine (CAS No: 64–86–8), cytochalasin B (CAS 14930–96–2), Mitomycin C (MMC) (CAS 50–07–7), and DMSO (CAS 67-68-5) were purchased from Sigma-Aldrich Company (Steinheim, Germany).

2.3. Experimental Design and Statistical Analysis

To perform this work, the permits were obtained from the Cukurova University Ethics Committee (06 March 2020/97, Decision No: 16). Human peripheral blood was taken from nonsmokers four healthy volunteers (two males and two females [ages: 21 and 24]) with an intravenous needle. Human blood culture was treated with CoumSel at 0, 50, 100, or 200 μg/mL concentrations for one or two cell cycle periods (24 h or 48 h). The highest concentration was determined with OECD TG 473 and TG 489 protocols. According to this protocol, the recommended highest concentration should show 55 ± 5% cytotoxicity. Dimethyl sulfoxide (DMSO) as the solvent control and mitomycin C (MMC) as well as the positive control were used in the experiments. All values were reported as means ± standard error (SE); we analyzed the data using the One-Way Analysis of Variance (ANOVA) LSD post hoc test and SPSS software (IBM SPSS Statistics 25). The concentration-response effects we determined using the Pearson correlation. In group comparisons, the standard level of significance is $P \leq 0.05$.

2.4. Chromosome Abnormality (CA) Test

To examine the cytogenetic effects of 6-bromo-CoumSel, used as the test substance, we applied four different concentrations (0, 50, 100, and 200 μg/mL) to the healthy peripheral blood culture for 24 or 48 hours. Since the test substance did not dissolve homogeneously in distilled water, we dissolved it in DMSO, an organic solvent. To block mitosis in the metaphase stage, 0.06 µg/mL of the colchicine solution was added to each tube at the 70th hour of the culture period, and the tubes were mixed by

gently shaking. We pretreated cells with colchicine for 2 hours at 37°C. At the end of the 72nd hour, we harvested and stained the cells from culture tubes, as stated by Arslan et al. [32].

The 100 well-distributed c-metaphases in homogeneously stained preparations were examined to detect chromosomal abnormalities (CA) in each variant. To determine the mitotic index (MI), we calculated the percentage of dividing cells at 3000 cells.

$$MI(\%) = \frac{number\ of\ cells\ in\ mitosis}{total\ number\ of\ cells} x100 \quad (1)$$

2.5. Micronucleus (MN) Test

The cultured human peripheral lymphocytes were treated with four concentrations of the chemical 6-bromo-CoumSel for 24 or 48 hours. At the end of the culture period, we prepared micronucleus slides for each variant according to the method of Arslan et al. [32].

To detect micronucleated cells in prepared preparations, we examined 1000 binucleated cells. To calculate the nucleus division index (NDI), we determined the cells with 1, 2, 3, and 4 nuclei among 1000 cells and applied the following formula.

$$NDI=\frac{[(1\ x\ M1) + (2\ x\ M2) + (3\ x\ M3) + (4\ x\ m4)]}{N\ (total\ number\ of\ cells)} \quad (2)$$

3. Results

3.1. Chromosome Abnormality (CA) Findings

It was found that the CA values caused by the test substance (CoumSel) were at the level of the DMSO and 0 µg/ml groups. Slight rises in CA findings related to enhanced CoumSel concentration were not meaningful and were within confidence limits. Moreover, we could not observe a safe number of metaphases in the 48-hour treatment of the highest concentration (200 µg/mL) due to the possible toxic effect on the culture, so we did not include it in the statistical analysis. Abnormality levels per cell (CA/cell) showed similarities to CA% values (Table 3.1). As with CA%, there were no notable differences in CA/cell (P>0.05). On the other hand, we confirmed the cytotoxic effect potential of the test substance. In particular, the increase in CoumSel concentration caused significant cytotoxic effects at both treatment periods (24 and 48 hours). The highest concentration of CoumSel (200 µg/ml) showed a cytotoxic effect compared to the negative (0 µg/mL) control in the 24-hour application (P<0.001). It was statistically confirmed that this cytotoxic effect occurs at the MMC level. Again, 100 µg/mL CoumSel exhibited significant cytotoxic potential compared to both the DMSO control and 0 µg/ml groups in the 48-hour treatment (P<0.001) (Table 1)

Table 1. Chromosome aberrations percentage (CA%), CA/cell ratio, and mitotic index (MI) in human-cultured lymphocytes treated with CoumSel

Test Substance	Treatment		*CA%±SE	CA/cell ±SE	**MI±SE
	Time (hour)	Cons. (µg/mL)			
MMC	24	0,25 µL/mL	35.25 ± 1.25	0.525 ± 0.018	2.57 ± 0.26 a3
DMSO	24	10 µL	1.00 ± 0.00	0.010 ± 0.000	6.22 ± 0.23 a3
CoumSel	24	0	1.25 ± 0.25 a3	0.012 ± 0.002 a3	7.39 ± 0.47 a3 b2
CoumSel	24	50	1.50 ± 0.28 a3	0.015 ± 0.003 a3	6.69 ± 0.13 a3
CoumSel	24	100	1.50 ± 0.28 a3	0.015 ± 0.003 a3	7.00 ± 0.11 a3
CoumSel	24	200	1.75 ± 0.25 a3	0.017 ± 0.002 a3	3.28 ± 0.12 c3
MMC	48	0,25 µL/mL	62.00 ± 2.19	2.250 ± 0.237	1.15 ± 0.16
DMSO	48	10 µL	0.50 ± 0.28	0.005 ± 0.003	7.24 ± 0.29
CoumSel	48	0	1.25 ± 0.25 a3	0.012 ± 0.002 a3	7.39 ± 0.47 a3
CoumSel	48	50	1.75 ± 0.47 a3	0.017 ± 0.005 a3	7.60 ± 0.11 a3
CoumSel	48	100	2.00 ± 0.40 a3	0.020 ± 0.004 a3	5.00 ± 0.3 a3b3c3
CoumSel	48	†200	-	-	-

3.2. Micronucleus (MN) Findings

In the study, 200 µg/mL, 48-hour CoumSel application significantly increased the MN‰ rate compared to the negative control (0 µg/mL) group (P<0.001). The MN per binuclear cell (MN/binuclear cell) ratio caused by the test substance shows a similar trend to the MN‰ ratio. Nuclear division indices (NDI) are negatively related to the test substance concentration, but the dose-effect correlation is not statistically significant. The highest cytotoxic effects occurred at 100 µg/mL and 200 µg/mL. CoumSel in these concentrations significantly reduced the NDI value in both treatment periods (24 or 48 hours) compared to both the solvent (DMSO) control and the negative control group (P<0.001) (Table 2)

Table 2. Effect of CoumSel on the ratios of micronucleus (MN), MN/binuclear cell, and nuclear division index (NDI) in human-cultured lymphocytes

Test substance	Treatment		*MN‰±SE	MN/Binuclear cell ±SE	NDI±SE
	Time (hour)	Cons. (µg/ml)			
MMC	24	0,25 µL/mL	23.50 ± 1.041	0.228 ± 0.014	1.245 ± 0.051
DMSO	24	10 µL	6.00 ± 0.408	0.006 ± 0.000	1.483 ± 0.029
CoumSel	24	0	3.25 ± 0.479 a3	0.003 ± 0.000 a3	1.367 ± 0.030 a2b2
CoumSel	24	50	4.00 ± 0.408 a3	0.004 ± 0.000 a3	1.433 ± 0.009 a3
CoumSel	24	100	3.50 ± 0.289 a3	0.004 ± 0.000 a3	1.309 ± 0.016 b3
CoumSel	24	200	5.75 ± 1.031 a3	0.006 ± 0.001 a3	1.185 ± 0.023 b3c3
MMC	48	0,25 µL/mL	130.75 ± 4.990	0.109 ± 0.000	1.095 ± 0.015
DMSO	48	10 µL	2.75 ± 0.250	0.003 ± 0.000	1.338 ± 0.052
CoumSel	48	0	3.25 ± 0.479 a3	0.003 ± 0.000 a3	1.367 ± 0.030 a3
CoumSel	48	50	3.50 ± 0.289 a3	0.004 ± 0.000 a3	1.309 ± 0.016 a3
CoumSel	48	100	2.50 ± 0.289 a3	0.003 ± 0.000 a3	1.196 ± 0.014 a1b3c3
CoumSel	48	†200	13.00 ± 0.577 a3b3c3	0.013 ± 0.014 a3	1.126 ± 0.004 b3c3

*: Examined 1000 cells in each donor, 4000 cells in total. †: Calculated from a total of 3000 cells. a: The difference is significant compared to the positive (MMC) control. b: The difference is significant compared to the solvent (DMSO) control. c: The difference is significant compared to the untreated (0 µg/ml) control. a1b1c1≤ 0.05, a2b2c2≤ 0.01, a3b3c3≤ 0.001

4. Discussion and Conclusion

The in vitro cytogenotoxic effect hypothesis of the coumarin-selenophene hybrid compound (CoumSel) was tested with in vitro human peripheral lymphocytes. Experiments revealed that chromosome aberration (CA) and micronucleus (MN) frequencies increased, especially in cells where high concentrations were applied, but only the MN increase at 200 µg/mL concentration was significant. There are many effects underlying the emergence of this result. These may be oxidative activity on DNA or microtubule (mitotic spindle) structure, covalent binding affinity to the DNA backbone, or topoisomerase enzyme inhibition effect. In addition, the various agents on enzymes or auxiliary factors involved in DNA replication or repair or nucleotide monomers may cause genotoxicity. According to the results of an old study confirming this idea, monofunctional and bifunctional pyrroles increased sister chromatid exchange (SCE), which is an indicator of genotoxicity in human lymphocytes, and especially bifunctional pyrroles were more effective in increasing SCE [33]. A different study reported similar results. According to the results of this study, two of the three commercially available partially photo-treated pyrrole-derived intermediates (1H-pyrrole-2-carboxaldehyde and 6-chloro-2-pyridinecarboxylic acid) are genotoxic even at low concentrations, while 2-pyridinecarbonitrile is only cytotoxic [34].

The tautomeric conformation of any biomolecule is determined by the combination and distribution of electrical charges of the atoms that make up that molecule. Any proton or electron shifts in the molecule may unpredictably affect its standard stability, causing it to transform into a different conformational form. This situation can directly or indirectly affect the molecule and prevent its optimized function. Unstable oxygen species (ROS), described as reactive in aerobic respiring cells, attack all biomolecules, including nucleic acids, and can disrupt their characteristic electrical dynamics. This phenomenon, called oxidative stress, can result in the molecule's unique function being restricted or completely blocked. It has long been known that the primary origin

of oxidizing products is electron leaks in the mitochondrial respiratory chain (ETS). Many studies investigating the effects of oxidative interactions on genome stability released significant outputs. These findings include genomic instability of the cell and activation or inactivation of various biochemical mechanisms. DNA lesions or molecular dysfunctions resulting from reactive attack may cause cell cycle arrest and apoptotic cell death. Briefly, it is undeniable that the multicomponent mitotic machinery that ensures cell division is de facto affected by oxidative stress [35–42]. Test substance CoumSel may have had cytotoxic effects through different mechanisms. Erşatır et al. stated that Coumsel, a coumarin and 2-aminoselenophene-3-carbonitrile derivative, showed significant cytotoxic and antiproliferative effects on the MCF-7 cell line. The same researchers found that contrary to popular belief, these coumarin derivatives have a radical scavenging (antioxidative) effect, not an oxidative one [43]. It could not find any reliable study on the direct oxidative effect of coumarin selenophene derivative compounds.

According to the mitotic index (MI) and nuclear division index (NDI) data I determined in my study, CoumSel showed cytotoxic effects, especially at high concentrations. This observed effect may be due to genotoxicity because they share a similar underlying pattern. However, there are also minor variational differences in our findings. Although no definite clastogenic effect is observed, the increase in MN frequency highlights the aneugenic effect of the test substance. I suggest oxidative or nonoxidative impacts on the cell division apparatus (mitotic spindle, centromere, etc.) as the reason for this. The cytotoxicity in our study may have arisen from confusion in the spindle apparatus. It is known that tubulin-binding molecules interfere with the dynamic balance of microtubules, destroying microtubule reorganization in the M phase and forming abnormal spindles. This causes cell cycle arrest, leading to apoptotic cell death [44].

In summary, the genotoxic and cytotoxic effects of CoumSel at high concentrations are remarkable. With this anti-mitotic feature, it may provide new insight into the solution to the problem of uncontrolled cell proliferation. Additionally, focusing on different experiments that will reveal the metabolic action of the test chemical will expand the scientific perspective.

Acknowledgments

I thank CUBAP for this support. Moreover, I especially thank Büşra Boz for evaluating the experimental data and the other researchers who contributed to our project (Dr. Giray and Dr. Erşatır).

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