Iraqi Journal of Pharmacy 20(Supp-01) (2023) 236-242

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage : https://iphr.mosuljournals.com

Research Article:

Thermosonication-Catalyzed Synthesis of New 3-Esterified Coumarins as Biocompatible Antitumor Candidates

Sawsan Hasan Hammoodi [1]

[1] *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.*

Article Information

Article history:

Received on: 26 October 2023
Revised on: 21 November 2023
Accepted on: 25 November 2023
Published on: 30 December 2023

Keywords:

Knoevenagel reaction;
Esterification;
Coumarin;
Antitumor;
Biocompatibility.

Abstract

Background: Coumarin chemical moiety and its-based molecules attracted a lot of research attention by chemists of natural products and organic synthesis. This attention works in two directions: synthetic approaches and biological activities. **Methods:** In this work, salicylaldehyde was condensed via a thermosonication-catalyzed Knoevenagel reaction with malonic acid, giving coumarin-3-carboxylic acid. The latter was esterified through its carboxylic acid with various 2-functionalized phenols under a thermosonication-promoted $SOCl_2$-catalized esterification reaction. The four 3-esterified coumarins (**SY1**–**SY4**) were characterized by different spectrophotometer analyzers, including FTIR, ^{1}H-NMR, and ^{13}C-NMR. Four cell lines of malignant type and one of normal class were used to specify the antitumor activity and biocompatibility of the synthetic **SY1**-**SY4**, respectively, by employing the MTT-probing methodology. **Results:** The outcomes indicated the accuracy of the proposed molecular structures, and the synthetic compounds have poor, with the exception of **SY1**, antitumor activity. Also, the antiproliferative effect of the three compounds (**SY2**-**SY4**) is roughly similar against malignant and normal cells. On the other hand, the compound **SY1** demonstrated good antitumor activity against the malignant cells used but a poor inhibitory effect toward normal cells. **Conclusion:** The author concluded from these findings that the molecular structure of **SY1** can offer a promising template to synthesize more potent and biocompatible antitumor agents with a coumarin chemical nucleus.

1. Introduction

Cancer is an ongoing threat to human health and ranks as the second most significant cause of mortality around the world, following cardiovascular disease. According to annual projections from the American Cancer Society, there would be 609,820 cancer deaths and 1,958,310 new cases of cancer in the United States at the end of 2023 (1). Cancer is able to invade or extend to nearly all body departments when abnormal cells develop out of control (2). Although a multitude of chemotherapeutic drugs have been developed to suppress uncontrollable cell division processes for the management of a variety of tumors (3–5), serious adverse reactions to these drugs remain a significant drawback (6). Multi-drug resistance is an additional major concern in the management of cancer (7). As a result of challenges including cytotoxicity and resistance to drugs, numerous studies are being carried out in an effort to identify and manufacture efficient anticancer medications (8). Based on their sources, approximately 80% of the marketed anticancer drugs are extracted from natural substances (9).

Coumarins are a class of naturally occurring compounds belonging to the benzopyrone family; their name comes from the *Coumarouna odorata* (Aubl.) species, from which they were initially discovered (10). Coumarin, with a molecular framework illustrated in **Figure 1**, is a common secondary metabolite found widely in different plant families, such as Rutaceae, Umbelliferae, Leguminosae, Compositae, and Lamiaceae (11). In addition to the naturally isolated coumarins (12), many synthetic derivatives have been produced as a result of several substitution sites in the chemical structure, resulting in a broader spectrum of

***Corresponding author:** *Sawsan Hasan Hammoodi, Department of pharmaceutical chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.*

Email: sawsan.hasan@uomosul.edu.iq

How to cite:

Hammoodi,, S., H., (2023). Thermosonication-Catalyzed Synthesis of New 3-Esterified Coumarins as Biocompatible Antitumor Candidates. Iraqi J. Pharm. 20(Supp-01), 236-242.

DOI: **https://doi.org/10.33899/iphr.2023.144182.1066**

coumarin derivatives with a greater range of applications (13). Some examples of these applications include antibacterial (14), antifungal (15), anti-inflammatory (16), antioxidant (17), anticoagulant (18), anticancer (19), and others(20).

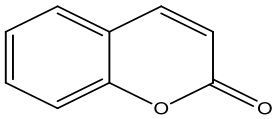
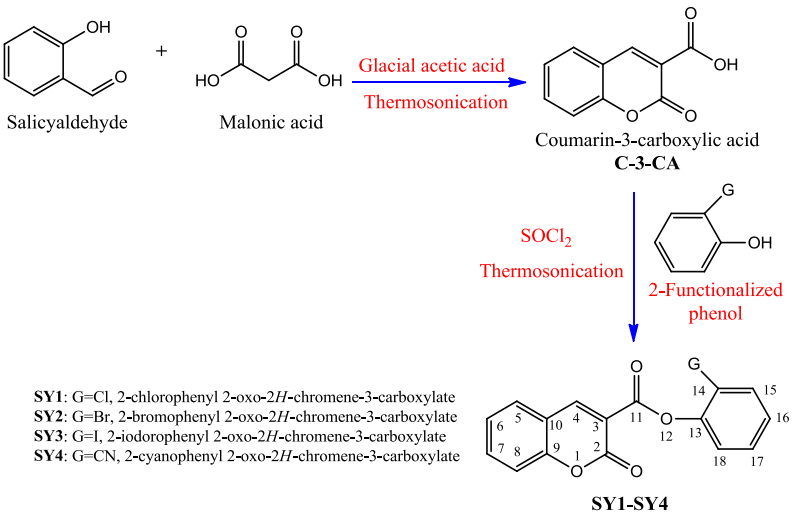


Figure 1. The molecular framework of coumarin chemical backbone

In recent years, natural and synthetic coumarin derivatives have demonstrated an extraordinarily broad and inestimable promise in the field of cancer treatment (21). Coumarin derivatives are widely distributed in nature and easily bind non-covalently with a wide range of receptors and enzymes, such as kinase, sulfatase, aromatase, telomerase, carbonic anhydrase, and monocarboxylate transporters (22,23). In addition, they possess excellent bioavailability, exceptional biocompatibility, and high metabolite resistance. As a result, the coumarin moiety offers an excellent template for the creation of new anticancer drugs (24,25).

This work aimed to create four molecules of coumarin functionalized at position 3 with various 2-substituted aromatics, as illustrated in **Scheme 1**. The antitumor activity of the synthetic **SY1**-**SY4** was quantified using the MTT-probing technique against four malignant cell lines. These were AMN3, MCF7, HeLa, and SKG. The same visual probing technique was also employed to specify the biocompatibility of these compounds in a normal cell line named MCF-A10.



Scheme 1. Synthesis of 3-esterified coumarins (**SY1–SY4**)

2. Experimental work

2.1 Chemicals and instruments

All chemicals, solvents, and reagents used for the production of 3-esterified coumarins (**SY1–SY4**) as well as the tumorous cell lines were ordered from documented international resources and utilized directly without any additional purification. The melting points (Mp) of the synthesized 3-esterified coumarins were determined based on the open-capillary technique utilizing a digital electro-thermal device (CIA9300). Thin-layer chromatography (TLC) comprises conventional aluminum-based silica gel sheets, and a blend of acetone and chloroform (1:4) was utilized to monitor the entire synthesis's progress and to demonstrate the purity of the generated coumarins. UV-1600PC UV-Vis, Bruker-ATR-FT-IR, and Bruker Avance DRX-400 MHz spectrophotometers were utilized as the instruments to scan the UV, FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra of the manufactured compounds.

2.2 Synthesis of coumarin-3-carboxylic acid (C-3-CA)

Mild heating was used to prepare the reaction mixture by assessing the dissolve of malonic acid (1.04 g, 10 mmol, 1, 04 g) in an excess of freshly-distilled salicylaldehyde (15 ml) with vortexing. To glacial acetic acid (5 ml) preserved in an ice bath, the prepared solution was slowly added from a separatory funnel where the working blend temperature was

kept under 10 °C. The blend was kept stirred for 20 min at that place, thermosonicated for 30 min at 40 °C in a thermo-heated sonicator, and poured into an aqueous ice cube. The separated solid was filtered, washed with cold water, dissolved in 5% NaOH (20 ml), acidified by 10% HCl, and purified by recrystallization from aqueous ethanol (97%). The practical melting temperature is 191-193 °C, while the documented one is 190-192 °C. Moreover, the reaction productivity is 1.67 g (88.12%) (22).

2.3 Synthesis of 3-esterified coumarins (SY1–SY4)

In an ice bath, a closable conical flask containing a solution of **C-3-CA** (5 mmol, 0.95 g) in an excess of freshly distilled $SOCl_2$ was magnetically stirred for 30 min. The working blend was then thermosonicated at 50 °C for 40 min, evaporated, and the solid was treated with a solution of 5 mmol of 2-substituted phenol in 20 ml of dry ether. The esterification mixture was then thermosonicated at 50 °C for 150 min, extracted with water, and the ether layer collected and vaporized. The crude was purified by recrystallization from ethyl acetate (26,27). **Table 1** shows the physical and chemical characteristics of the 3-esterified coumarins (**SY1**–**SY4**), while **Table 2** records the values of different peaks observed from the FTIR spectrophotometer. On the other hand, **Table 3** lists the number, coupling style, and chemical shifts of the protons depending on the interpretation of the ^{1}H-NMR spectrophotometer. Finally, the chemical shifts of the carbons revealed in the ^{13}C-NMR spectrophotometer are displayed in **Table 4**.

Table 1. The physical and chemical characteristics of the synthetic **SY1**–**SY4** coumarins

Symbol	Appearance	Melting point (°C)	Percentage and amount of yield	R_f (acetone: chloroform) (1:4)	λ_{max} (methanol) nm
SY1	Pale yellow powder	164-166	88.22% 1.32 g	0.38	426
SY2	Pale yellow powder	148-150	70.14% 1.21 g	0.45	426
SY3	Pale yellow powder	138-141	68.23% 1.34 g	0.58	422
SY4	Pale yellow powder	177-179	56.01% 0.81 g	0.27	424

Table 2. The peak values observed in the FTIR spectra of the synthetic **SY1**–**SY4** coumarins

Symbol	Cyclic =C-H Weak peak	Cyclic ester C=O Strong peak	Aliphatic ester C=O Strong peak	Lactone-*Z*-alkene C=C Strong peak	Aromatic C=C Medium peak	Aromatic C-G Variable peak
SY1	3034	1733	1712	1592	1551	913
SY2	3030	1733	1710	1590	1551	838
SY3	3036	1732	1711	1588	1552	731
SY4	3022	1734	1709	1589	1550	2243

The scores recorded in the cm^{-1} unit

Table 3. The data acquired from interpreting the ^{1}H-NMR spectra of the synthetic **SY1**–**SY4** coumarins

Symbol	Position 4	Aromatic positions 5-8	Aromatic positions 15-18
SY1	8.87 Singlet	7.71-7.91 Multiplet	7.30-7.56 Multiplet
SY2	8.86 Singlet	7.70-7.90 Multiplet	7.25-7.67 Multiplet
SY3	8.85 Singlet	7.75-7.92 Multiplet	7.16-7.57 Multiplet
SY4	8.87 Singlet	7.73-7.90 Multiplet	7.46-7.63 Multiplet

The results represent the δ (chemical shift) measured in ppm using a frequency of 400 MHz and DMSO-d6 as a solvent.

Table 4. The data acquired from interpreting the ^{13}C-NMR spectra of the synthetic **SY1**–**SY4** coumarins

Symbol	2	3	4	5	6	7	8	9
SY1	158.7	114.4	122.3	128.0	125.9	129.8	117.4	154.7
	10	11	13	14	15	16	17	18
	119.0	164.2	148.8	128.9	133.6	128.2	127.4	125.1
SY2	2	3	4	5	6	7	8	9
	158.6	114.4	122.3	128.1	125.9	129.8	117.5	154.7
	10	11	13	14	15	16	17	18
	119.1	164.2	150.2	118.3	135.2	129.0	128.9	124.8
SY3	2	3	4	5	6	7	8	9
	158.7	114.4	122.4	128.0	125.9	129.8	117.4	154.6

	10	11	13	14	15	16	17	18
	119.0	164.1	153.1	92.7	141.2	128.9	128.2	124.2
SY4	2	3	4	5	6	7	8	9
	158.7	114.4	122.2	128.0	125.8	129.8	117.4	154.7
	10	11	13	14	15	16	17	18
	119.4	164.2	153.2	108.3	134.6	127.5	133.6	123.9

The results represent the δ (chemical shift) measured in ppm using a frequency of 100 MHz and DMSO-d6 as a solvent. The numbers in the gray quarters represent the atom's numbers based on the structure drawn in Scheme 1. The chemical shift of the CN group of ***SY4*** *coumarin is 116.2 ppm.*

2.4 MTT-probing methodology

The investigated malignant or normal cells grew for 24 hours in a broadening atmosphere in a 96-pit container at a population density of 10^4 per pit. An individual study dilution was used to investigate each pit. The selected concentrations were produced employing DMSO as a dilute creator from the parent liquor (1 mg/ml) and ranged from 6.25 µg/ml to 400 µg/ml for each incident. The growth-promoted residue was tossed away after 72 hours, and the MTT probe was incorporated after this interdisciplinary dismissiveness. The staining solution (28 µl, 3.27×10^3 M) was employed as a cell responsiveness cursor. The visible absorbance for every pit was assessed using a microplate reader with the wavelength set to 492 nm following a 1.5-hour period of gestation at 37°C. The proliferation restriction percent (PR%), which served as the foundation for calculating the antiproliferative effect, was calculated by starting with the input form of math (Aw- At)/Aw x 100. The figures for Aw and At, respectively, constituted the absorbance assessments of pits without treatment and treated pits. By plotting PR% numbers against exponential concentration scores, an inductive mathematical approach was used to determine the IC_{50} classification (28,29).

3. Results and discussion

3.1 Designing the synthetic pathway

As illustrated in **Scheme 1**, the synthesis of 3-esterified coumarins (**SY1–SY4**) involved two steps. Firstly, salicylaldehyde was condensed with malonic acid via a thermosonication-catalyzed Knoevenagel reaction in the presence of glacial acetic acid, yielding the intermediate compound named coumarin-3-carboxylic acid (**C-3-CA**). Second, the resulted product **C-3-CA** was esterified with different 2-substituted phenols under a thermosonication-promoted $SOCl_2$-catalized esterification reaction to produce the desired 3-esterified coumarins (**SY1–SY4**).

3.2 Valuation of the neoplastic inhibitory effect

The conventional MTT-probing technique was used to evaluate the neoplastic inhibitory effect of the generated 3-esterified coumarins *in vitro* on four malignant cell lines. These cells included AMN3 (CVCL-M395, the murine mammary adenocarcinoma), MCF-7 (86012803, the Caucasian breast adenocarcinoma), HeLa (93021013, the epithelioid cervix carcinoma), and SKG (C27676, the human papillomavirus-related cervical squamous carcinoma cell). In addition, one normal cell line called MCF-A10 (non-malignant breast epithelial cells) was used to assess the biocompatibility of these compounds. In this approach, 5-fluorouracil (**5-FU**) and DMSO were employed as the positive and negative dominions, respectively (30).

According to the outcomes of the study, which are indicated in **Table 5**, the prepared 3-esterified coumarins have a poor neoplastic inhibitory effect, with the exception of **SY1,** on the examined malignant cell lines. Also, the prepared three compounds (**SY2**-**SY4**) possess approximately similar antiproliferative effects against both cancerous and normal cells. In comparison to other prepared candidates, **SY1** showed superior tumor-inhibiting efficacy against the examined malignant cell lines, especially AMN3 and SKG cells, with IC_{50} values of 68.12±0.93 µg/ml and 66.01±1.02 µg/ml, respectively. The author credited this noticeable effect to the presence of the chloro group, an electron-withdrawing group, which improves the physicochemical properties of compounds by enhancing their aqueous solubility, cellular uptake, and cytotoxic activity (31–33). Additionally, the introduction of chlorine is reported to boost the stability and specificity of the binding site since it may fit in a deep and narrow hydrophobic pocket of the biological target (34,35).

On the other hand, the synthesized coumarin candidates were evaluated *in vitro* for their cytotoxicity effects on a normal cell line (MCF-A10). In comparison to **5-FU**, the inspected candidates (**SY1**-**SY4**) have less cytotoxic impact against the tested MCF-A10 normal cell, with IC50 values ranging between 117.83±0.92 µg/ml and 226.38±0.89 µg/ml. From the findings listed in Table 5, compound **SY1** showed the lowest degree of cytotoxicity and the greatest safety profile towards MCF-A10, followed by **SY4, SY3**, and **SY2** candidates (36–38)**.**

Table 5. The outcomes represented as IC_{50} (µg/ml)±SD(n=3) gathered from the MTT-probing methodology concerning synthetic **SY1**–**SY4** coumarins

Cell line titles	Codes of the reference anticancer drug and synthetic **SY1**–**SY4** coumarins				
	SY1	**SY2**	**SY3**	**SY4**	**5-FU**
AMN3	68.12±0.93	276.24±0.89	290.11±0.92	290.28±0.91	25.23±1.01
MCF7	62.34±0.97	270.48±0.99	292.67±0.90	289.24±0.95	13.45±0.92
HeLa	65.38±1.01	274.01±0.90	287.11±1.09	282.22±0.98	14.17±1.01
SKG	66.01±1.02	273.89±0.90	283.44±0.91	292.87±0.94	23.37±0.94
MCF-A10	226.38±0.89	117.83±0.92	156.17±0.96	159.22±1.10	40.55±0.92

4. Conclusion

The creation and structural elucidation of four new 3-esterified coumarins were demonstrated in this research. Besides, the safety of the prepared candidates against a normal cell line (MCF-A10) was evaluated. The research outcomes highlighted that the generated coumarin candidates had a negligible neoplastic inhibitory impact, with the exception of the **SY1** compound, on the four examined cancerous cell lines. Additionally, the synthesized coumarin candidates had a poor inhibitory effect on the examined normal cell line when compared to the standard (**5-FU**), and **SY1** showed the highest level of safety profile. As a result, **SY1** can be considered a promising template to create more powerful and biocompatible antitumor agents.

5. References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians* 2023;73(1):17–48.

2. Javed M, Saade A, Jasim A, Zeedan T, Dmitry T, Bokov O, et al. Anticancer Drug-Loading Capacity of Green Synthesized Porous Magnetic Iron Nanocarrier and Cytotoxic Effects Against Human Cancer Cell Line. *Journal of Cluster Science* 2022;4:44–7.

3. Mustafa YF. Chemotherapeutic applications of folate prodrugs: A review. *NeuroQuantology* 2021;19(8):99–112.

4. Mustafa YF, Abdulaziza NT, Jasim MH. 4-Methylumbelliferone and its derived compounds: A brief review of their cytotoxicity. *Egyptian Journal of Chemistry* 2021;64(4):1807–16.

5. Bashir MK, Mustafa YF, Oglah MK. Antitumor, antioxidant, and antibacterial activities of glycosyl-conjugated compounds: A review. *Systematic Reviews in Pharmacy* 2020;11(4):175–87.

6. Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes and Diseases* 2023;10(4):1367–401.

7. Emran T Bin, Shahriar A, Mahmud AR, Rahman T, Abir MH, Siddiquee MFR, et al. Multidrug Resistance in Cancer: Understanding Molecular Mechanisms, Immunoprevention and Therapeutic Approaches. *Frontiers in Oncology* 2022;12(6):1–38.

8. Mustafa YF, Mohammed NA alwahab. A promising oral 5-fluorouracil prodrug for lung tumor: Synthesis, characterization and releas. *Biochemical and Cellular Archives* 2021;21(Supp 1):1991–9.

9. Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W, et al. Natural Products as Anticancer Agents: Current Status and Future Perspectives. Vol. 27, Molecules. 2022. 1–64 p.

10. Mustafa YF, Bashir MK, Oglah MK, Khalil RR, Mohammed ET. Bioactivity of some natural and semisynthetic coumarin derived compounds. *NeuroQuantology* 2021;19(6):129–38.

11. Mustafa YF, Bashir MK, Oglah MK. Original and innovative advances in the synthetic schemes of coumarin-based derivatives: A review. *Systematic Reviews in Pharmacy* 2020;11(6):598–612.

12. Jebir RM, Mustafa YF. Watermelon Allsweet: A promising natural source of bioactive products. *Journal of Medicinal and Chemical Sciences* 2022;5(5):652–66.

13. Flores-Morales V, Villasana-Ruíz AP, Garza-Veloz I, González-Delgado S, Martinez-Fierro ML. Therapeutic Effects of Coumarins with Different Substitution Patterns. *Molecules* 2023;28(5).

14. Roomi AB, Widjaja G, Savitri D, Jalil AT, Mustafa YF, Thangavelu L, et al. SnO2:Au/Carbon Quantum Dots Nanocomposites: Synthesis, Characterization, and Antibacterial Activity. *Journal of Nanostructures* 2021;11(3):514–23.

15. Waheed SA, Mustafaa YF. Novel naphthalene-derived coumarin composites: synthesis, antibacterial, and antifungal activity assessments. *Eurasian Chemical*

Communications 2022;4(8):709–24.

16. Bouasla S, Amaro-Gahete J, Esquivel D, López MI, Jiménez-Sanchidrián C, Teguiche M, et al. Coumarin derivatives solvent-free synthesis under microwave irradiation over heterogeneous solid catalysts. *Molecules* 2017;22(12).

17. Waheed SA, Mustafa YF. Synthesis and evaluation of new coumarins as antitumor and antioxidant applicants. *Journal of Medicinal and Chemical Sciences* 2022;5(5):808–19.

18. Mustafa YF, Mohammed ET, Khalil RR. Synthesis, characterization, and anticoagulant activity of new functionalized biscoumarins. *Egyptian Journal of Chemistry* 2021;64(8):4461–8.

19. Atia YA, Bokov DO, Zinnatullovich KR, Kadhim MM, Suksatan W, Abdelbasset WK, et al. The role of amino acid functionalization for improvement of adsorption Thioguanine anticancer drugs on the boron nitride nanotubes for drug delivery. *Materials Chemistry and Physics* 2022;278(10):125664.

20. Mustafa Y, Waheed S, Jasim S, Jebir R, Ismael R, Qutachi O. A Narrative Review of Benzo-Fused Coumarins, Shedding Light on Their Medicinal Activities. *Iraqi Journal of Pharmacy* 2023;20(1):7–16.

21. Jasim SF, Mustafa YF. New fused-coumarin composites: Synthesis, anticancer and antioxidant potentials evaluation. *Eurasian Chemical Communications* 2022;4(7):607–19.

22. Abdulaziz NT, Mustafa YF. Antibacterial and Antitumor Potentials of Some Novel Coumarins. *International Journal of Drug Delivery Technology* 2022;12(1):239–47.

23. Jeon YJ, Jang JY, Shim JH, Myung PK, Chae JI. Esculetin, a Coumarin Derivative, Exhibits Anti-proliferative and Pro-apoptotic Activity in G361 Human Malignant Melanoma. *Journal of Cancer Prevention* 2015;20(2):106–12.

24. Mustafa YF, Bashir MK, Oglah MK. Synthesis, antioxidant and antitumor activities of new coumarins grafted to 5-fluorouracil. 2022;20(2):359–65.

25. Zhang L, Xu Z. Coumarin-containing hybrids and their anticancer activities. Vol. 181, European Journal of Medicinal Chemistry. Elsevier Masson SAS; 2019. p. 111587.

26. Kasim SM, Abdulaziz NT, Mustafa YF. Synthesis and biomedical activities of coumarins derived from natural phenolic acids. *Journal of Medicinal and Chemical Sciences* 2022;5(4):546–60.

27. Mahmood AAJ, Mustafa YF, Abdulstaar M. New coumarinic azo-derivatives of metoclopramide and diphenhydramine: Synthesis and in vitro testing for cholinesterase inhibitory effect and protection ability against chlorpyrifos. *International Medical Journal Malaysia* 2014;13(1):3–12.

28. Mustafa YF, Khalil RR, Mohammed ET, Bashir MK, Oglah MK. Effects of structural manipulation on the bioactivity of some coumarin-based products. *Archives of Razi Institute* 2021;76(5):1297–305.

29. Bashir MK, Mustafa YF, Oglah MK. Synthesis and antitumor activity of new multifunctional coumarins. *Periodico Tche Quimica* 2020;17(36):871–83.

30. Truong D hien, Nguyen DH, Thuy N, Ta A, Bui AV, Do TH. Evaluation of the Use of Different Solvents for Phytochemical Constituents, Antioxidants, and In Vitro Anti-Inflammatory Activities of Severinia buxifolia. *Journal of Food Quality* 2019;2019.

31. Mustafa YF, Khalil RR, Mohammed ET. Synthesis and antitumor potential of new 7-halocoumarin-4-acetic acid derivatives. *Egyptian Journal of Chemistry* 2021;64(7):3711–6.

32. Oglah MK, Bashir MK, Mustafa YF, Mohammed ET, Khalil RR. Synthesis and biological activities of 3,5-disubstituted-4-hydroxycinnamic acids linked to a functionalized coumarin. *Systematic Reviews in Pharmacy* 2020;11(6):717–25.

33. Mai CW, Yaeghoobi M, Abd-Rahman N, Kang YB, Pichika MR. Chalcones with electron-withdrawing and electron-donating substituents: Anticancer activity against TRAIL resistant cancer cells, structure-activity relationship analysis and regulation of apoptotic proteins. *European Journal of Medicinal Chemistry* 2014;77:378–87.

34. Kadayat TM, Park S, Jun KY, Magar TBT, Bist G, Shrestha A, et al. Effect of chlorine substituent on cytotoxic activities: Design and synthesis of systematically modified 2,4-diphenyl-5H-indeno[1,2-b]pyridines. *Bioorganic and Medicinal Chemistry Letters* 2016;26(7):1726–31.

35. Jumintono J, Alkubaisy S, Yánez Silva D, Singh K, Turki Jalil A, Mutia Syarifah S, et al. Effect of cystamine on sperm and antioxidant parameters of ram semen stored at 4 °C for 50 hours. *Archives of Razi Institute* 2021;76(4):981–9.

36. Mustafa YF, Oglah MK, Bashir MK, Mohammed ET, Khalil RR. Mutual prodrug of 5-ethynyluracil and 5-fluorouracil : Synthesis and pharmacokinetic profile. *Clinical Schizophrenia and Related Psychoses* 2021;15(5):1–6.

37. Firoozeh Abolhasani Zadeh, Bokov DO, Salahdin OD, Abdelbasset WK, Jawad MA, Kadhi MM, et al. Cytotoxicity evaluation of environmentally friendly synthesis Copper/Zinc bimetallic nanoparticles on MCF- 7 cancer cells. *Rendiconti Lincei Scienze Fisiche e Naturali* 2022;

38. Raya I, Chupradit S, Mustafa YF, H. Oudaha K, M. Kadhim M, Turki Jalil A, et al. Carboxymethyl Chitosan Nano-Fibers for Controlled Releasing 5-Fluorouracil Anticancer Drug. *Journal of Nanostructures* 2021;12(1):136–43.

التصنيع المحفز بالحرارة لأسترات الكومارين كمرشحين متوافقين حيويا ومضادين للأورام

الخلاصة:جذبت المادة الكيميائية للكومارين والجزيئات القائمة عليه الكثير من الاهتمام البحثي من قبل الكيميائيين للمنتجات الطبيعية والتخليق العضوي. هذا الاهتمام يعمل في اتجاهين: الأساليب الاصطناعية والأنشطة البيولوجية. **الطريقة:** في هذا العمل، تم تكثيف ساليسيل-ألدهايد عن طريق تفاعل كنوفيناجل المحفز بالحراره مع حمض المالونيك، مما يعطي حمض الكربوكسيل-3-كومارين. تفاعل الأخير من خلال حمض الكربوكسيل الخاص به مع مختلف الفينولات ثنائية الوظيفة تحت تفاعل الأسترة المحفزب$SOCl_2$ المعززبالحرارة .تميزت الكومارينات الاربعة (SY1 – SY4) بمحللات طيفية مختلفة، بما في ذلك FTIR و^{1}H-NMR و^{13}C-NMR. تم استخدام أربعة خطوط من الخلايا من النوع الخبيث وواحد من الفئة العادية لتحديد النشاط المضاد للأورام والتوافق الحيوي للمركبات (SY1 – SY4)على التوالي، من خلال استخدام فحص MTT. **النتائج**: : أشارت النتائج إلى دقة التركيب الجزيئي المقترح، وكانت المركبات الاصطناعية ذات نشاط مضاد للاورام ضعيف ، باستثناء SY1 كما أن التأثير المضاد للتكاثر للمركبات الثلاثة -SY2) (SY4 متشابه تقريبًا ضد الخلايا الخبيثة والعادية. من ناحية أخرى، أظهر المركب SY1 نشاطًا جيدًا مضادًا للأورام ضد الخلايا الخبيثة المستخدمة ولكن تأثيره المثبط ضعيف تجاه الخلايا الطبيعية. **الاستنتاج:** استنتج المؤلف من هذه النتائج أن التركيب الجزيئي لـ SY1 يمكن أن يقدم نموذجًا واعدًا لتصنيع مركبات مضادة للأورام أكثر فعالية وتوافق حيوي من الكومارين.

الكلمات الافتتاحية: تفاعل كنوفيناجل،الأسترة، الكومارين، مضاد للاورام، التوافق الحيوي.