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Synthesis, antioxidant and antitumor activities of new coumarins grafted to 5-fluorouracil

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ABSTRACT

Compounds with chemical systems depend on the coumarin architecture have sparked a lot of interest in the scientific community, not only because of their different morphological characteristics, but also because of their wide range of biological properties. In this study, four 7-halomethylcoumarin-4-acetic acid derivatives tagged as YMa-YMd were synthesized by coupling various 3-halomethyl phenols with 3-oxoglutaric acid that prepared *in situ* from the interaction of citretten and concentrated H_2SO_4. The acquired coumarin derived compounds were grafted to 5-fluorouracil through amide bond using dichlorosulfoxide as a coupling reagent. The chemical frames of the final conjugated coumarins, named YM1-YM4, were identified and established by analyzing their spectral data gathered from various analytical spectrophotometers, involving FTIR, ^{1}HNMR, and ^{13}CNMR. The potential of the conjugated coumarins to act as antioxidants was investigated by monitoring their ability to trap the free radicals of DPPH. Besides, the chemotherapeutic potential was assessed against two standard tumor-cell lines, named HeLa and MCF 7, using a well-validated technique based on the MTT as a visual indication. The outcomes acquired from these assessments indicated that the synthesized conjugated coumarins have less impact as antioxidizing and cytotoxic agents comparing with the utilized standard drugs. Furthermore, these coumarins showed essentially the same pattern of action against the two cell lines examined, with MCF-7 acquired the most inhibitory effect. Additionally, conjugated coumarin YM1 showed valuable activities as antioxidant and chemotherapeutic agent compared to the other synthesized derivatives. As a result, the authors concluded that the synthesized conjugated coumarins might be used as antioxidant and anticancer agents, with conjugated coumarin YM1 being the most promising. Moreover, the synthesized core might serve as a beneficial framework for developing medicines with potent antioxidant and anticancer properties.

Keywords: Antioxidant, Antitumor, Conjugated coumarins, 5-Fluorouracil.
Article type: Research Article.

INTRODUCTION

Despite the ongoing improvements in chemotherapeutic agents research, cancer continues to be a major problem for modern medicinal chemistry (Bray *et al.* 2018), necessitating increased global efforts to find more potential anticancer medicines with fewer side effects to treat this illness (Oglah *et al.* 2020b, Mustafa 2021a; Mustafa *et al.* 2021b). Classical antimetabolite 5-fluorouracil (5-FU) causes cytotoxicity by inhibiting cellular thymidylate synthase and misinserting into DNA and/or RNA, disrupting the essential functions of these oligonucleotides (Mustafa *et al.* 2020d). Since its discovery in 1957, 5-FU was used to treat a variety of malignancies, including gastrointestinal, gastric, pancreas, brain, and chest tumors as a stand-alone treatment or as a member of multiple regimens (Mustafa & Mohammed 2021). Nevertheless, 5-FU has a number of disadvantages that restrict its therapeutic usage, including harmful effects, a brief plasma half-life due to the dihydropyrimidine-dehydrogenase, anomalous uptake with fluctuating plasma levels after oral therapy, and susceptibility to cancer cells' resistance

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mechanisms (Moath Kahtan Bashir *et al.* 2020; Mustafa & Abdulaziz 2021). Considerable efforts have been made and reviewed throughout the years to deal with these challenges (Chakraborty & Dastidar 2019). The integration of 5-FU into various forms of prodrugs, which are meant whether to address cancerous cells or escape specific breakdown cellular metabolism, is among the most relevant approaches (Giret *et al.* 2013). Vogel originally identified the mother natural coumarin molecule from tonka beans, *Dipteryx odorata* around two centuries ago (Mustafa *et al.* 2021b). Coumarins are an unique series of biologically active compounds belonging to the benzo-α-pyrone class. Coumarin-derived compounds have a major place in medicinal chemistry due to their flexible and distinctive oxygen-containing heterocyclic architecture (Mustafa & Abdulaziz 2020). Since of their high metabolite resistance, excellent biocompatibility, and exceptional bioavailability, coumarins are being researched as therapeutic possibilities with significant bioactivity (Aldewachi *et al.* 2020). The coumarin scaffold may bind non-covalently with various receptor genotypes because of its basic structure, leading in a broad array of pharmacological activities (Kummerle *et al.* 2018). The anticancer effect is one of them, and it has been thoroughly studied with promising findings (Fang & Ji 2020). Coumarins can thus be used as templates for developing potential cytotoxic agents (Zhang *et al.* 2018). Notwithstanding the discovery of many techniques for synthesizing coumarin-based derivatives (Mustafa *et al.* 2020a), Hans von Pechmann's condensation method, with its newer enhancements, seems to be the most commonly used approach. Due to the simplicity, low-cost launching ingredients and excellent outputs of different synthesized coumarins, this reaction must pique attention (Calcio Gaudino *et al.* 2016). The aim of this study is to synthesize four various 7-halomethylcoumarins conjugated at 4-position with 5-FU via an amide linker. The precursor coumarins were prepared via Pechmann-phenotype reaction by condensing various 3-halomethyl phenols with 3-oxoglutaric acid. The latter was produced *in situ* by reacting citretten with concentrated sulfuric acid. The capacity of the conjugated coumarins to quench DPPH free radical was investigated. Also, their potential to act as chemotherapeutic agents was assessed by MTT-aided technique versus two common tumor cell lines, including HeLa (Epitheloid Cervix Carcinoma) and MCF-7 (Caucasian Breast Adenocarcinoma).

MATERIALS AND METHODS

The carcinoma lines and their implantation cultures, as well as the reagents, chemicals, and solvents needed to conduct the production and evaluate the anticancer and antioxidant potentials, were purchased from Scharlau, Sigma-Aldrich, Bioworld, Labcorp, Chem-Lab, and Haihang. Upon that basis of an open-capillary technique, the melting temperatures (mp) of the synthesized coumarin-depended compounds were reported using the electrothermal's IA9300 digital melting temperature equipment. Thin-layer chromatography (TLC) was used to track the progress of the total synthesis and to show the purity of the produced singlet and conjugated coumarins. Membrane filter Sigma TM TLC-Silica Gel 60 (F254) and a diethylether: MeOH (4:1) blend were employed as the movable and static phases in this method, respectively. The ^{1}HNMR, ^{13}CNMR, IR, and λ_{max} scopes of the produced compounds were determined using reagent-grade spectrometers; the Bruker Avance 3 HD 400 and 100 MHz (DMSO-d_6), Bruker FTIR-alpha ATR, and Cary 300 UV-Vis Bio, respectively.

Total chemical synthesis

The chemical schematic steps for synthesizing the intermediate compounds (**YMa-YMd**) as well as their corresponding 5-FU conjugates (**YM1-YM4**) are depicted in Fig. 1.

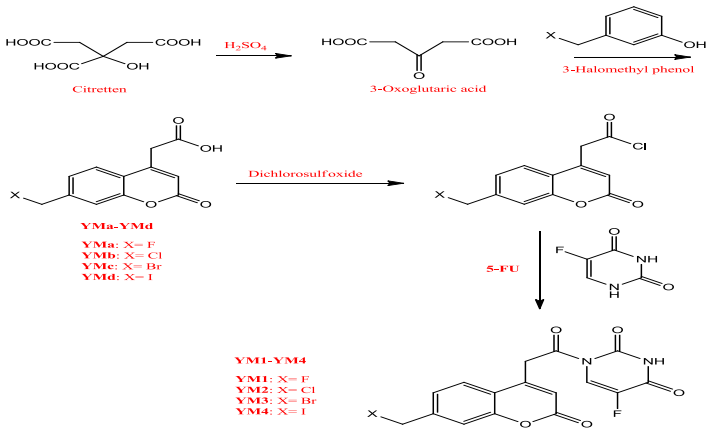

Fig.1. Synthesis of the intermediate and conjugated compounds.

General method for synthesizing the intermediate compounds (YMa-YMd)

Ten mL of concentrated H_2SO_4 in a bottom flask was chilled to 0°C in a salt-ice bath. Citretten (0.96 g, 5 mmol) was gently introduced to this chilly acid, with the frequency determined by the reaction temperature, which should be held below 5 °C. The reaction mixture was left to be agitated at 25 °C for 0.5 h before being gently increased to 70 °C. The pace of warming was regulated by the production of froth and bubbling. As a clear solution develops, the reaction mixture was put in a salt-ice bath. On the condition that the reaction temperature be kept below 10 °C, concentrated H_2SO_4 (5 mL) and 3-halomethyl phenol (5 mmol) were supplied to the agitated mixture. The reaction mass was frozen for 36 h before being put into an ice-water combination and filtered. By recrystallizing from ethyl acetic ester, the raw was cleaned from contaminants (Y. Mustafa *et al.* 2021).

General method for synthesizing the conjugated coumarins (YM1-YM4)

A two-nick shaped flask containing the corresponding intermediate compound (5 mmol) in 25 mL replenished dichlorosulfoxide was submerged in a salt-ice bath. A stopper containing blue litmus paper was used to surround the shoulder, while a condenser was used to confine the middle nick. The combination was gently agitated for 30 min in dry conditions, then for the same amount of time at room temperature before being refluxed for 3 h. The color shift of the litmus-paper, that replaced every 30 min, was used to determine the reaction's progress. As the color of the blue litmus-paper no longer changed, the excess of dichlorosulfoxide was distilled-off. The acyl-chloride congener of the intermediate compound was indicated by the white solid substance that persisted in the flask's bottom (Mustafa *et al.* 2021c,d).

A solution of 3-halomethyl phenol (4.8 mmol) and pyridine (1 mL) in 50 mL dry diethyl ether was introduced through one part at ambient temperature to the same flask containing the powdery residue, and agitated under dry conditions for 0.5 h. The reaction mass was refluxed for a period of time, as indicated by the litmus-paper changing color as mentioned above. After the reaction was completed, the organic layer was isolated, dried, and evaporated following the addition of 50 ml of H_2O to the liquid. Recrystallization of a combination of propanone: CH_2Cl_2 yielded the target conjugate (Mustafa 2021b; Oglah *et al.* 2020a).

Assessment of the DPPH radical Quenching capacity

The ability of the synthesized coumarin conjugates (**YM1-YM4**) to quench the DPPH (2,2-diphenyl-1-picrylhydrazine) radical-phenotype was investigated using cevitamic acid as a primary potent antioxidant reagent (Oglah and Mustafa, 2020a,b). In a summary, six methanolic double-diluted concentrations of each studied coumarin conjugate were produced from an ambient methanolic solution (1 μM), starting at 400 μM and ending with 6.25 μM. Using the incoming criterion for absorbance, the antiradical magnitude was expressed as a percentage: Quenching percentage (Q%) = $(A_{\text{cevitamic acid}} - A_{\text{sample}}/A_{\text{cevitamic acid}}) \times 100$. The metric Q_{50} was developed using non-linear analysis by displaying the association between Q% and logarithmic concentrations. This value reflects the optimum dose for quenching 50% of the DPPH radicals (Khalil & Mustafa 2020; Mustafa *et al.* 2020c). Simply, combine 1.5 mL of the studied coumarin conjugate with 0.5 mL of 0.1 mM methanolic DPPH reagent to make the screening combination. The latter was allowed to stand in opaque and inoculated at 25 °C for 0.5 h. The examined conjugate's ability to change the violet color of the screening combination was measured colorimetrically at 515 nm. This assay's negative criteria consisted of 1.5 ml MeOH and 0.5 mL methanolic DPPH solution (Mohammed & Mustafa 2020; Mustafa *et al.* 2020b).

Assessment of the in vitro cytotoxicity

The particular cancer cell line was dispersed to a total of 10^4 cells per well in a 96-well plate. Following the detected time, each well was treated with a particular concentration of the tested conjugated coumarin. The concentrations used (400, 200, 100, 50, 25, 12.5, 6.25 μg mL^{-1}) were derived from a 1 mM in DMSO sample solution. By ejecting the growth media, placing the MTT solution (29 μL, 3.32 mM), and then incubating the treated cells at 37 °C for 1.5 h, the test was carried out repeatedly in the following 24 hr and then in the next 72 h after treatment. A microplate reader calibrated to 492 nm was used to verify the absorbances of the untreated (UW) and treated (TW) wells. The growth reduction percent (GR%) was calculated using the following numerical equation: $\mathbf{GR\% = (A_{UW} - A_{TW})/A_{UW} \times 100}$. $\mathbf{A_{UW}}$ and $\mathbf{A_{TW}}$ represent the absorbances of the untreated and treated wells, respectively (Moath Khtan Bashir *et al.* 2020; Mustafa 2019).

RESULTS AND DISCUSSION

Constructing the chemical synthetic pathway

Under the impact of concentrated sulfuric acid, citretten was oxidatively decarboxylated forming the chemical compound named 3-oxoglutaric acid. This dicarboxylic containing compound was coupled with various 3-halomethyl phenols through Pechmann-phenotype reaction yielding the intermediate derivatives YMa-YMd. The resulted 7-halomethylcoumarin-4-acetic acids were conjugated with 5-FU via the creation of an amide bond utilizing dichlorosulfoxide as a condensing agent affording the target conjugated coumarins YM1-YM2.

Analysis of the acquired structural data

Table 1 depicts the measured structural properties of the intermediate derivatives YMa-YMd. These properties included mp, λ_{max}, yield (%), and the functional groups identified from the FTIR spectra.

Table 1. The detected structural-related parameters of the intermediate derivatives.

Symbol	mp (°C)	λ_{max} EtOH, nm	yield (%)	IR					
				C-H alkene	O-H acid	C-H alkane	C = O ester	C = O acid	C-X
YMa	174-176	272	62	3034	3001	2912	1730	1704	1012
YMb	161-163	271	65	3036	2998	2904	1732	1700	802
YMc	156-158	271	60	3040	3000	2906	1736	1709	715
YMd	163-166	275	58	3039	2999	2905	1735	1704	622

The structural characteristics of the target conjugated coumarins YM1-YM4 are presented in Table 2. The mp, λ_{max}, yield (%), and functional groups found from the FTIR spectra were among these characteristics.

Table 2. The detected structural-related parameters of the target conjugated coumarins.

Symbol	mp (°C)	λ_{max} EtOH, nm	yield (%)	IR					
				N-H amide	C-H alkene	C=O ester	C=O amide	C-F	C-X
YM1	156-158	280	74	3156	3033	1728	1678	1080	1011
YM2	143-145	283	75	3160	3037	1730	1672	1078	803
YM3	138-140	281	70	3158	3042	1731	1682	1078	717
YM4	146-149	281	72	3161	3040	1732	1680	1082	625

The chemical shifts, expressed in ppm, of the various protons and carbons reported in the NMR spectra concerning the target conjugated coumarins are represented in Tables 3 and 4, respectively.

Table 3. The chemical shifts of various protons that detected in the ^{1}HNMR spectra concerning the target conjugated coumarins YM1-YM4.

Symbol	H-14	H-17	H-5	H-6	H-8	H-3	H-7'	H-11
YM1	11.80 s, 1H	8.01 s, 1H	7.62 d, 1H *J* = 4 Hz	7.01 d, 1H *J* = 4 Hz	6.78 s, 1H	6.40 s, 1H	5.38 s, 2H	2.95 s, 2H
YM2	11.76 s, 1H	8.03 s, 1H	7.60 d, 1H *J* = 4 Hz	7.03 d, 1H *J* = 4 Hz	6.78 s, 1H	6.38 s, 1H	4.69 s, 2H	2.90 s, 2H
YM3	11.72 s, 1H	7.98 s, 1H	7.58 d, 1H *J* = 4 Hz	7.06 d, 1H *J* = 4 Hz	6.78 s, 1H	6.41 s, 1H	4.51 s, 2H	2.91 s, 2H
YM4	11.78 s, 1H	7.95 s, 1H	7.64 d, 1H *J* = 4 Hz	7.04 d, 1H *J* = 4 Hz	6.79 s, 1H	6.40 s, 1H	2.21 s, 2H	2.88 s, 2H

Note: The symbols s, d, and *J* represent the NMR terms named singlet, duplet, and coupling constant, respectively.

Free radical trapping effect

Due to the obvious potential that various antioxidants can manage many human disorders such as Alzheimer's disease, diabetes, and cancer, significant research attention is now focused on investigating compounds with powerful free-radical quenching effects. In this context, publications on the involvement of numerous natural and synthesized coumarins as antioxidant molecules abound in the literature (Fierascu *et al.* 2019; Nejres *et al.* 2020).

The property of the synthesized conjugated coumarins to represent antioxidants was assessed by monitoring their capacity to trap the DPPH radicals. In this context, Table 5 shows that the synthesized conjugated coumarins have a lower activity to trap the DPPH radicals than cevitamic acid. Also, these conjugates revealed good-to-excellent activity with Q_{50} ranged between 50.16 μM and 59.46 μM, with the highest activity attributed to conjugated coumarin YM1. The authors proposed that this superiority may be contributed to the presence of the fluoromethyl group at position 7 of the coumarin backbone (Bai *et al.* 2016; Mustafa 2018).

Table 4. The chemical shifts of various carbons that detected in the ^{13}CNMR spectra concerning the target conjugated coumarins YM1-YM4.

Symbol	C-12	C-2	C-15	C-9	C-4	C-16	C-7	C-5
	168.6	162.3	160.2	157.4	156.1	143.8	138.2	128.5
	C	C	C	C	C	C	C	CH
YM1	C-6	C-10	C-8	C-3	C-17	C-7'	C-11	
	126.3	124.4	118.6	114.1	109.7	85.5	42.8	
	CH	C	CH	CH	CH	CH_2	CH_2	
	C-12	C-2	C-15	C-9	C-4	C-16	C-7	C-5
	168.5	162.2	160.1	155.6	156.2	143.7	139.1	130.2
YM2	C	C	C	C	C	C	C	CH
	C-6	C-10	C-8	C-3	C-17	C-7'	C-11	
	128.2	126.1	120.4	114.0	109.9	48.5	42.8	
	CH	C	CH	CH	CH	CH_2	CH_2	
	C-12	C-2	C-15	C-9	C-4	C-16	C-7	C-5
	168.4	162.1	160.0	157.1	156.3	143.6	138.3	129.4
YM3	C	C	C	C	C	C	C	CH
	C-6	C-10	C-8	C-3	C-17	C-7'	C-11	
	127.7	123.1	118.8	114.3	109.6	36.9	42.8	
	CH	C	CH	CH	CH	CH_2	CH_2	
	C-12	C-2	C-15	C-9	C-4	C-16	C-7	C-5
	168.1	162.0	160.6	157.8	156.9	143.8	137.4	127.9
YM4	C	C	C	C	C	C	C	CH
	C-6	C-10	C-8	C-3	C-17	C-7'	C-11	
	126.3	124.5	118.7	114.1	109.4	18.4	42.8	
	CH	C	CH	CH	CH	CH_2	CH_2	

The structural data displayed in Tables 1-4 reported that the synthetic steps were successful and efficient. Also, the chemical structures of the designed conjugated coumarins are sufficiently confirmed.

Cytotoxic effect

The exploratory ability of the created conjugates to function as effective anticancer agents was evaluated using the conventional MTT-dye test technique. In which, six serial diluted-strengths of each conjugate were used, as well as 5-FU as an accredited anticancer drug and DMSO as a negative predictor. HeLa and MCF-7 were the two neoplastic cell lines used in this experiment. Table 5 presents four intriguing facts about the cytotoxic impact of the created coumarins. the standard medicine, 5-FU, the synthesized conjugates were less effective as antineoplastic agents.

Table 5. The results gathered from the assessments of the free-radicals trapping and cytotoxic effects concerning the synthesized conjugated coumarins.

Investigated activity	Reference drug	YM1	YM2	YM3	YM4
DPPH-free radical trapping	Q_{50}= 46.45 ± 0.72 μM	Q_{50}= 50.16±1.04 μM	Q_{50}= 53.76±1.12 μM	Q_{50}= 59.46±0.98 μM	Q_{50}= 58.15±0.98 μM
Cytotoxicity versus HeLa	IC_{50}= 13.08 ±1.05 μM	IC_{50}= 28.24 ±1.10 μM	IC_{50}= 32.96 ±1.00 μM	IC_{50}= 40.21 ±1.15 μM	IC_{50}= 36.56 ±0.97 μM
Cytotoxicity versus MCF-7	IC_{50}= 12.23 ±0.90 μM	IC_{50}= 20.18 ±0.95 μM	IC_{50}= 22.38 ±0.98 μM	IC_{50}= 32.14 ±0.95 μM	IC_{50}= 30.01 ±1.04 μM

Note: The findings were expressed in terms of mean ± SD. For triple-separated trials, the SD (standard deviation) values were considered.

To begin, the compounds exhibit the same trend of effect when compared to the cell lines studied, and this pattern is analogous to that of antioxidant activity. As a result, the authors ascribed the cytotoxicity mechanism to the capacity of the produced compounds to retain the harmful radicals (Mustafa *et al.* 2018; Pérez-Cruz *et al.* 2018). Second, their antiproliferative effect is higher against MCF-7 than against HeLa. Third, of the examined drugs, conjugate YM1 had the most potent anticancer effect against the cell lines studied. Finally, when compared to

CONCLUSION

The creation and molecular characterization of four derivatives of conjugated coumarin framework were presented in this paper. The researchers discovered that the synthesized conjugates revealed good-to-excellent antioxidant activity in comparison to the standard drug, with the highest activity attributed to conjugated coumarin YM1. The anticancer evaluation revealed that the synthesized coumarin conjugates with a predominance of activity attributed to YM1 had a good-to-excellent impact against the test tumor-cell lines with essentially the same mode of action. Furthermore, the synthesized compounds demonstrated a preferential impact against MCF-7 cell line.

REFERENCES

Aldewachi, H, Mustafa, YF, Najm, R & Ammar, F 2020, Adulteration of slimming products and its detection methods. *Systematic Reviews in Pharmacy*, 11: 289-296.

Bai, Y, Li, D, Zhou, T, Qin, N, Li, Z, Yu, Z & Hua, H 2016, Coumarins from the roots of angelica dahurica with antioxidant and antiproliferative activities. *Journal of Functional Foods* 20: 453-462.

Bashir, MK, Mustafa, YF & Oglah, MK 2020, Antitumor, antioxidant, and antibacterial activities of glycosyl-conjugated compounds: A review. *Systematic Reviews in Pharmacy*, 11: 175-187.

Bashir, MK, Mustafa, YF & Oglah, MK 2020, Synthesis and antitumor activity of new multifunctional coumarins. *Periodico Tche Quimica*, 17: 871-883.

Bray, F, Ferlay, J, Soerjomataram, I, Siegel, RL, Torre, LA & Jemal, A 2018, Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68: 394-424.

Calcio Gaudino, E, Tagliapietra, S, Martina, K, Palmisano, G & Cravotto, G 2016, Recent advances and perspectives in the synthesis of bioactive coumarins. *RSC Advances*, 6: 46394-46405.

Chakraborty, P & Dastidar, P 2019, An easy access to topical gels of an anti-cancer prodrug (5-fluorouracil acetic acid) for self-drug-delivery applications. *Chemical Communications*, 55: 7683-7686.

Fang, H & Ji, H 2020, Furanocoumarin a: a novel anticancer agent on human lung cancer a549 cells from fructus liquidambaris. *Anti-Cancer Agents in Medicinal Chemistry*, 19: 2091-2096.

Fierascu, RC, Fierascu, I, Avramescu, SM & Sieniawska, E 2019. Recovery of natural antioxidants from agro-industrial side streams through advanced extraction techniques. *Molecules* (*Basel, Switzerland*).

Giret, S, Théron, C, Gallud, A, Maynadier, M, Gary Bobo, M, Garcia, M, Wonga Chia Man, M & Carcel, C 2013, A designed 5-fluorouracil-based bridged silsesquioxane as an autonomous acid-triggered drug-delivery system. *Chemistry - A European Journal*, 19: 12806-12814.

Khalil, RR & Mustafa, YF 2020, Phytochemical, antioxidant and antitumor studies of coumarins extracted from Granny Smith apple seeds by different methods. *Systematic Reviews in Pharmacy*, 11: 57-63.

Kummerle, AE, Vitorio, F, Franco, DP & Pereira, TM 2018, Coumarin compounds in medicinal chemistry: some important examples from the last year. *Current Topics in Medicinal Chemistry*, 18.

Mohammed, ET & Mustafa, YF 2020, Coumarins from red delicious apple seeds: extraction, phytochemical analysis, and evaluation as antimicrobial agents. *Systematic Reviews in Pharmacy*, 11: 64-70.

Mustafa, Y, Khalil, R & Mohammed, E 2021, Synthesis and antitumor potential of new 7-halocoumarin-4-acetic acid derivatives. *Egyptian Journal of Chemistry*, 64: 3711-3716.

Mustafa, YF & Abdulaziz, NT 2020, Biological potentials of hymecromone-based derivatives: A systematic review. *Systematic Reviews in Pharmacy*, 11: 438-452.

Mustafa, YF & Abdulaziz, NT 2021, Hymecromone and its products as cytotoxic candidates for brain cancer: A brief review. *NeuroQuantology*, 19: 175-186.

Mustafa, YF & Mohammed, NA, 2021, A promising oral 5-fluorouracil prodrug for lung tumor: Synthesis, characterization and releas. *Biochemical and Cellular Archives*, 21: 1991-1999.

Mustafa, YF 2018, Synthesis, characterization and antibacterial activity of novel heterocycle, coumacine, and two of its derivatives. *Saudi pharmaceutical journal*, 26: 870-875.

Mustafa, YF 2019, Synthesis, characterization and preliminary cytotoxic study of sinapic acid and its analogues. *Journal of Global Pharma Technology*, 11: 1-10.

Mustafa, YF 2021a, Chemotherapeutic applications of folate prodrugs: a review. *NeuroQuantology*, 19: 99-112.

Mustafa, YF 2021b, Synthesis, characterization, and biomedical assessment of novel bisimidazole - coumarin conjugates. *Applied Nanoscience*.

Mustafa, YF, Abdulaziza, NT & Jasima, MH 2021a, 4-Methylumbelliferone and its derived compounds: A brief review of their cytotoxicity. *Egyptian Journal of Chemistry*, 64: 1807-1816.

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

Mustafa, YF, Bashir, MK, Oglah, MK, Khalil, RR & Mohammed, ET 2021b, Bioactivity of some natural and semisynthetic coumarin derived compounds. *NeuroQuantology*, 19: 129-138.

Mustafa, YF, Kasim, SM, Al Dabbagh, BM & Al Shakarchi, W 2021c, Synthesis, characterization and biological evaluation of new azo-coumarinic derivatives. *Applied Nanoscience (Switzerland)*.

Mustafa, YF, Khalil, RR & Mohammed, ET, 2020b, Antimicrobial activity of aqueous extracts acquired from the seeds of two apples' cultivars. *Systematic Reviews in Pharmacy*, 11: 382-387.

Mustafa, YF, Mohammed, ET & Khalil, RR 2020c, Antioxidant and antitumor activities of methanolic extracts obtained from Red Delicious and Granny Smith apples' seeds. *Systematic Reviews in Pharmacy*, 1: 570-576.

Mustafa, YF, Mohammed, ET & Khalil, RR 2021d, Synthesis, characterization, and anticoagulant activity of new functionalized biscoumarins. *Egyptian Journal of Chemistry*, 64: 4461- 4468.

Mustafa, YF, Najem, MA & Tawffiq, ZS 2018, Coumarins from Creston apple seeds: Isolation, chemical modification, and cytotoxicity study. *Journal of Applied Pharmaceutical Science*, 8: 049-056.

Mustafa, YF, Oglah, MK & Bashir, MK 2020d, Conjugation of sinapic acid analogues with 5- Fluorouracil: Synthesis, preliminary cytotoxicity, and release study. *Systematic Reviews in Pharmacy*, 11: 482-489.

Nejres, AM, Ali, HK, Behnam, SP & Mustafa, YF 2020, Potential effect of ammonium chloride on the optical physical properties of polyvinyl alcohol. *Systematic Reviews in Pharmacy*, 11: 726-732.

Oglah, MK & Mustafa, YF 2020a, Synthesis, antioxidant, and preliminary antitumor activities of new curcumin analogues. *Journal of Global Pharma Technology*, 12: 854-862.

Oglah, MK & Mustafa, YF 2020b, Curcumin analogs: synthesis and biological activities. *Medicinal Chemistry Research*, 29: 479-486.

Oglah, MK, Bashir, MK, Mustafa, YF, Mohammed, ET & Riyadh, R 2020a, Synthesis and biological activities of 3,5-disubstituted- 4-hydroxycinnamic acids linked to a functionalized coumarin. *Systematic Reviews in Pharmacy*, 11: 717-725.

Oglah, MK, Mustafa, YF, Bashir, MK & Jasim, MH, 2020b, Curcumin and its derivatives: A review of their biological activities. *Systematic Reviews in Pharmacy*, 11: 472-481.

Pérez Cruz, K, Moncada Basualto, M, Morales Valenzuela, J, Barriga González, G, Navarrete Encina, P, Núñez Vergara, L, Squella, JA & Olea Azar, C 2018, Synthesis and antioxidant study of new polyphenolic hybrid-coumarins. *Arabian Journal of Chemistry*, 11: 525-537.

Zhang, Z, Bai, ZW, Ling, Y, He, LQ, Huang, P, Gu, HX & Hu, RF 2018, Design, synthesis and biological evaluation of novel furoxan-based coumarin derivatives as antitumor agents. *Medicinal Chemistry Research*, 27: 1198-1205.

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