PHARMACIA

Pharmacia 70(4): 1487–1492
DOI 10.3897/pharmacia.70.e108670

Research Article

Design, synthesis and molecular docking study of coumarin pyrazoline derivatives against MCF-7 breast cancer cell line

Wafaa Yusuf Khalaf[1], Rita Sabah Elias[1], Leaqaa Abdulredha Raheem[1]

1 *Department of Pharmaceutical Chemistry, Collage of Pharmacy, University of Basrah, Basrah, Iraq*

Corresponding author: Leaqaa Abdulredha Raheem (Leaqaa.raheem@uobasrah.edu.iq)

Received 26 June 2023 ♦ **Accepted** 18 July 2023 ♦ **Published** 8 December 2023

Citation: Khalaf WY, Elias RS, Raheem LA (2023) Design, synthesis and molecular docking study of coumarin pyrazoline derivatives against MCF-7 breast cancer cell line. Pharmacia 70(4): 1487–1492. https://doi.org/10.3897/pharmacia.70.e108670

Abstract

A new eight series of 3-(2-oxo-2H-chromen-3-yl)-5-(substituted phenyl)-1H-pyrazole-1-carbaldehyde derivatives (9–16) were designed and created from coumarin-chalcone derivatives (1–8). The structures of the derivatives were established by using melting point, mass spectrum, IR, ^{1}HNMR, and ^{13}C NMR spectroscopic methods. In vitro antiproliferative activities were evaluated against MCF-7 breast cancer cell line using Microculture Tetrazolium (MTT) assay. The results showed that the compounds 9, 12- 14 has a moderate activity against MCF-7 breast cancer cell line with IC_{50} 61.44, 70.11, 22.6 and 25.99 µg/mL respectively, while the compounds 10,11, 15 and 16 were found to be inactive against studied cell line within IC_{50} > 100 µg/mL. The possible binding interaction between studied compounds (9–16) and human ER-α (PDB ID: 1ERR) were studied by molecular docking. The results revealed that only the compounds 11 and 16 form π -H interaction with ER-α (PDB ID: 1ERR) within the highest negative values of binding affinity -7.04260 and -7.17308 kcal.mol^{-1} respectively than the other compounds, while Raloxifene used here as a positive control form a strong ionic bonding with Asp 351 within the binding affinity -9.61928 kcal/mol which is more negative value than the studied compounds.

Keywords

coumarin, pyrazoline, molecular docking, MCF-7, MTT assay

Introduction

Breast cancer is the most common cancer in women following melanoma as well as the 2nd largest source of cancer deaths in women before lung cancer (Patel et al. 2012). According to the World Health Organization's tumor database for 2021 at website: (https://www.who.int/cancer), more than two million women are diagnosed with breast cancer yearly (Amernic 2013). Since many anticancer drugs have been developed for treating a wide variety of the malignancies, including Cisplatin, Vinblastine and Mercaptopurine, they all have severe side effects on the hematopoietic system, bone marrow, gastro-intestinal epithelium, and hair follicles. Moreover, multi-drug resistance (MDR) is a serious issue with chemotherapeutic agents (Akkol et al. 2020).

In recent times, coumarin, Fig. 1 has shown promising use in treating cancer, it may help mitigate the adverse reactions of radiation (Sandhu et al. 2014). Incorporating coumarin into hybridization structures leads to

significant cancer treatment because of the compound's capacity to destroy tumor cells, as shown in several studies (Nepali et al. 2014 ; Al-Awad et al. 2020) Hence the need for the creation of healthy, powerful, highly tissue-selective anti-tumor drugs with a unique spectrum of activity because of the emergence of treatment resistance, the appearance of adverse reactions, the remission and return of tumors. The combined drug-like action of molecular hybrids has made them especially successful with scientists and researchers. In the past ten to fifteen years, several molecular hybridization-based anti-cancer medicines have now been identified (Pasricha and Gahlot 2020).

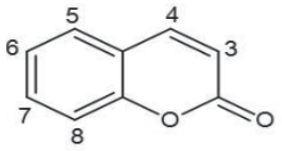

Figure 1. Chemical structure of coumarin.

The coumarin scaffold was hybridized with nitrogen -containing heteroatom molecule known as pyrazoline, Fig. 2 to increase its biological activity, and it demonstrated a wide range of activity (Kovvuri et al. 2018). Moreover, researchers studied showed that coumarin and pyrazoline were tested for their ability to block telomerase; the results showed that their compound was useful for various types of breast cancer (Thakur et al. 2015). Thus, the molecular hybridization technique is crucial in the discovery of new medicines for treating a wide range of multifactorial disorders (Sandhu et al. 2014).

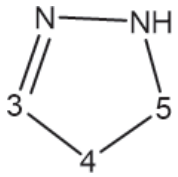

Figure 2. Chemical structure of pyrazoline.

The work includes the synthesis of eight coumarin pyrazoline derivatives. Synthetic compounds were established for their anti-cancer activity against MCF 7 assay method.

Experimental

Materials and methods

3,4-Dimethoxybenzaldehyde,4-Chlorobenz-aldehyde, Ethyl acetoacetate, 4-Hydroxy- benzaldehyde were purchased from MERCK.4-Acetamidobenzaldehyde,4-Dimethylaminobenzaldehyde, 4-Methoxy- benzaldehyde, Dimethylamine taken from BDH.Benzaldehyde and Petroleum ether were obtained from APC pure. All chemicals were used as provided without more purification.

Chemical synthesis

Synthesis of 3-acetyl coumarin

3-acetylcoumarin was synthesized according to the following procedure (Kumar et al. 2017) as shown in (Suppl. material 1: scheme 1):

In a 50-mL round bottom flask containing ethyl aceto acetate(3 mL, 3.06 g) and salicylaldehyde (3 mL, 3.5 g), dimethyl amine (15 drops) was added as a catalyst drop by drop with continued stirring at room temperature for 20 minutes. Yellow precipitation formatted. Re-crystallization with ethanol to form a fine needle with pale-yellow color.

Synthesis of coumarin chalcone derivatives (1–8)

The compounds (1–8) were prepared according to the literature (Savita et al. 2019), as shown in (Suppl. material 1: scheme 2).

In a 50 mL round-bottom flask, (1.9 g, 0.001 mol) of 3-Acetylcoumarin and (0.001 mol) of the corresponding aromatic aldehyde were dissolved in 3 mL of ethanol and refluxed for 2–12 hours with piperidine (7 drops) as catalyst. The end point of the reaction was detected by using a TLC plate. The reaction mixture was filtered off after cooling.The precipitated solid was collected, washed with water, recrystallized from appropriate solvents, and dried for 24 hours at room temperature.

Synthesis of Coumarin-Pyrazoline derivatives (9 to 16)

The compounds were synthesized according to the literature (Ahmed et al. 2019), as shown in (Suppl. material 1: scheme 3).

In a 50 mL round-bottom flask equipped with a magnetic stirrer, (0.01mol.) of appropriate coumarin-chalcone derivatives, (20 mL) of formic acid, and 0.02 mol. hydrazine hydrate were refluxed for 2–8 hours. The end point of the reaction was detected by using a TLC plate. The reaction mixture was filtered off after cooling. The precipitated solid was formed, washed with water, recrystallized from suitable solvents, and dried at room temperature for 24 hours.

Physical measurements

The Stuart SMP apparatus was employed to measure the melting point. Fourier transform infrared spectroscopy (FTIR) studies were completed by Schimadzu FTIR spectrometer (Japan) using potassium bromide (KBr) pellets for solid samples. ^{1}H-Nuclear magnetic resonance (NMR) and ^{13}C-NMRspectra were recorded by a Bruker instrument (Brucker, Switzerland). $CDCl_3$ and DMSO-$_{d6}$ were employed as the solvent; however, tetramethyl silane served as the internal standard. Coupling constant (*J*) values were reported in hertz (Hz). A 5973 Agilent Mass spectrometer equipped with electron impact 70 eV(electron volt) was employed to obtain mass spectral measurements.

Preliminary cytotoxicity screening (Mustafa et al. 2021, Mustafa et al. 2023)

MCF-7 breast cell line was preserved in PRMI-1640 (Gibco-The National Cell Bank of Iran provided the human breast cancer cell line MCF7) complemented with 10% fetal bovine, 100 units/mL penicillin and 100 µg/mL streptomycin. Cells were reseeded at a 50% confluence twice a week using Trypsin/EDTA (Gibco) and incubation at 37 °C and 5% CO_2. The MTT cell viability assay was performed on 96-well plates to determine the cytotoxic effect. The MCF-7 cell line was seeded at around $1^{*}10^{4}$ cells/well. After 24 hours or the formation of a confluent monolayer, the cells were treated with the produced substance at the final concentration (1000 g/mL). After 72 hours, cell viability was assessed by extracting the medium by applying 28 µL of 2 mg/ mL of MTT solution. Upon removal of the MTT solution, the crystal remaining in the well were solubilized by adding 100 µL of DMSO followed by an incubation at 37 °C for 15 minutes with shaking.

The absorbency was assessed on a microplate reader (Model WAVE XS2, Bio Tek, USA) at test wavelength 570 nm, the test was initiated at triplicate. The percentages of viable and killed cells were then calculated according to Eq. 1 and 2 respectively:

$$\text{Proliferation Rate (PR) \%} = B / A * 100 \qquad \text{Eq (1).}$$

$$\text{Inhibition Rate (IR) \%} = 100 - PR \qquad \text{Eq (2).}$$

Were:

A: is the mean optical density of untreated wells

B: is the optical density of treated wells.

Molecular docking studies

The human ER-α ligand binding site with Raloxifene as nonsteroidal antagonist was used as a target protein. The crystal structure of human estrogenic receptor-α (PDB ID: 1ERR) was downloaded from protein data bank (www.rcsb.org). The water molecules were removed from protein PDB file (1ERR), then the side chain missing and residues were repaired and the energies of protein were minimized with the MMFF94s force field by applying MOE (Molecular Operating System) program 2015. The studied compounds were draw and their energies were minimized using the same force filed. A molecular docking study was undertaken between the resulted structure of the studied compounds and the crystal structure of the hER-α (1ERR) by using the MOE 2015.

Physicochemical Properties and Lipinski's Rule of Five (RO5)

Lipinski's Rule of Five (Lipinski 2004) indicates a chemical compound's potential as a medication with a specific biological activity that is intended for oral delivery (Chen et al. 2020). According to (RO5), a drug-like compound must have a molecular weight less than 500 g/mol, a log p value less than 5, representing its hydrophobicity, a number of hydrogen bond donors less than 5, and a number of hydrogen bond acceptors less than 10 (Chagas et al. 2018). Additional investigation has added two additional requirements: a polar surface area (PSA) less than 140 $Å^2$ which is associated with permeability, and the number of rotatable bonds less than 10, which is associated with flexibility.

Results and discussion

Chemistry

The synthesis of coumarin-pyrazoline derivatives (9–16), was accomplished via the cyclocondensation reaction of appropriate coumarin-chalcone derivatives (1–8) with hydrazine hydrate in presence of formic acid, as shown in (Suppl. material 1: scheme 3).

Identification

The structures of coumarin-pyrazoline derivatives(9–16), were established by numerous significant spectral changes, such as MS, IR, ^{1}H NMR and ^{13}C NMR.

The molecular weight of synthesis compound detected by mass spectrum, and most derivatives determined by appearance as molecular ion ($M^{+\cdot}$) peaks equal to molecular weight for each derivative, as noticed in (Suppl. material 3: table S1).

The synthesis compounds were established by the FT-IR spectra and showed a strong band at 1724–1732 cm^{-1} attributed to carbonyl groups of coumarin part, while the absorption band at 1649–1674 cm^{-1} related to aldehyde groups at pyrazoline ring (Singh et al. 2010; Ahmed et al. 2019). All synthetic compounds with Pyrazoline derivatives show the absorption bands in the regions 1608–1618 cm^{-1} corresponding to the C═N stretching bands of pyrazoline ring (Ahmed et al. 2019). In addition, the absorption bands at regions around 1415–1481 cm^{-1} were attributed to the (N–N) stretch vibrations, which also confirm the formation of the desired pyrazoline ring in all the derivatives (Celik et al. 2020), as shown in (Suppl. material 3: table S2).

The ^{1}H-NMR spectrum of coumarin- pyrazoline derivatives (9–16) showed singlet signal within the chemical shift about 8.9 ppm refers to the aldehyde (–CHO) proton that presence at pyrazoline ring (Ahmed et al. 2019). The methylene group (CH_2) of pyrazoline ring has two nonequivalent protons (Ha and Hb) appeared as pair of doublets of doublets signals. The Ha proton appeared at chemical shift 3.23–3.27 ppm with coupling constant about 18 Hz and 4.8 Hz, as geminal and vicinal coupling with Hb and Hc protons respectively, while the Hb proton appeared at chemical shift 3.89–3.98 ppm with coupling constant about 18 Hz and 11.8 Hz as geminal and vicinal coupling with Ha and Hc protons respectively. The doublet of doublets signal at chemical shift 5.39–5.54 ppm with

coupling constants about 11.8 Hz and 4.8 Hz as a result of vicinal coupling with nonequivalent protons, Ha and Hb respectively. This signal refers to Hc proton of methine group (CH) of the pyrazoline ring (Patel 2019; Patel et al. 2021).Other chemical shift and their interpretation shown in (Suppl. material 3: table S3).

The ^{13}C-NMR spectra of synthesis coumarin pyrazoline derivatives 9–16 showed two signals around 44 ppm and 59 ppm, referred to (-CH_2) and (-CH) of pyrazoline ring, that demonstrate the formation of the carbon skeleton of pyrazolines (Singh et al. 2010), a signal at about 153 ppm, refers to the C=N group as a part of the pyrazoline ring (Saroja et al. 2021).

The signal appears at 160 ppm, indicated the formation of an aldehyde group on the pyrazoline ring (Singh et al. 2010). While other aromatic carbons appeared between 116.5–158.6 ppm (Patel et al. 2021) as noticed in (Suppl. material 3: table S4).

In vitro-In silico studies

All the synthesize coumarin pyrazoline compounds were studied using Lipinski's Rule of Five. It indicates a chemical compound's potential as a medication with a specific biological activity that is intended for oral delivery (Chen et al. 2020). The result shows that the calculated molecular weight of all compounds in the range 318.33–378.38 g/mol; the calculated number of hydrogen bond acceptors in the range 4–6; the calculated number of Hydrogen bonds donor in range 0–1; the calculated number of rotatable bonds in the range 3–5; the lipid–water partition coefficient was between 1.74 and 2.79; the calculated polar surface area in range 62.88–92.34. A substance's pharmacokinetic characteristics and bioavailability throughout an organism's metabolic process will be improved by complies with the five principles (Patel et al. 2021; Saroja et al. 2021), as shown in (Suppl. material 3: table S5).

Cytoxicity effect

The half maximal Inhibitory Concentration (IC_{50}) was considered depended on the dose-response curve created after finding the percent of the Cell death at several concentrations of the Composites as shown in Suppl. material 1: fig. S1. All the synthesized compounds displayed cytotoxicity and IC_{50} estimated in a range of 22.6–318.32 μg/mL as shown in (Suppl. material 3: table S6).

The coumarin pyrazoline derivatives 9–16 revealed little inhibition over the MCF-7 cell line as compared to Raloxifene (IC_{50} = 7.29). Two of the all pyrazoline compounds, 4-hydroxy-3-methoxyphenyl substituted pyrazoline (cpd.13) and 4-chlorophenyl substituted pyrazoline (cpd.14), showed remarkable activity than other compounds with IC_{50} = 22.6 μg/mL, and 25.99 μg/mL respectively against MCF-7 cell line.

Compound 9 without substituted showed moderate activity against MCF-7 cell line with IC_{50} = 61.44 μg/mL. Compounds 12 (4-$NHCOCH_3$ substituted pyrazoline), showed moderate activity against MCF-7 at IC_{50} = 70.11 μg/mL. The rest of the coumarin pyrazoline derivatives represented inactive compounds on the MCF-7 cell line.

Molecular docking

The molecular docking study was made to understand in what manner coumarin- pyrazolines derivatives cooperate with the receptor.

The estrogen receptor (ER) was selected in this study since the majority of common kinds of breast cancer are determined by the expression of the ER-positive type, so to investigate the interaction of compounds 9–16 with the targeted proteins (ER-α), a molecular docking study was used.

To describe the better possible binding modes between studied compounds (9–16) and ER-α. The human ER-α ligand binding site with Raloxifene as nonsteroidal antagonist was used as a target protein. The crystal structure of human estrogenic receptor-α (PDB ID: 1ERR) was downloaded from protein data bank (www.rcsb.org). Before docking chain B and molecules of water were removed from PDB file of protein (ID: 1ERR). While the side chains missing and residues were corrected and the energy of protein were minimized using the force field MMFF94s. The studied compounds were draw and their energies were minimized with the same force field (MMFF94s) by applying MOE (Molecular Operating System) program 2015. The resulted structures of the studied compounds were used for docking analysis with the crystal structure of ER-α (1ERR) in MOE 2015 program.

Docking analysis provided several conformations that were scored to determine favorable binding modes with estrogenic receptor. The highest docking score for studied compounds and native ligand are summarized in (Suppl. material 3: table S7) in addition to the measured root mean square deviation (RMSD).

The docking studies of studied compounds were performed into the binding pocket of hER-α (PDB: 1ERR) protein (Met 343, Leu 346, Thr 347, Lue 349, Ala 350, Asp 351, Glu 353, Leu 354, Trp 363, Leu 384, Leu 387, Met 388, Leu 391, Arg 394, Phe 404, Met 421, Ile 424, Leu 428, Gly 521, His 524, Leu 525, Leu 536, Leu 539).

The results of docking studied revealed the following findings. The studied compounds were fitted in the active site of the native ligand (Raloxifene) in the hER-α (ID: 1ERR) as seen from the Suppl. material 2: figs S2–S10). But the binding energies of the studied compound were observed between -7.17308 to -6.71756 kcal.mol^{-1}, with a maximum score achieved by compounds 11 and 16 with-7.04260 and -7.17308 kcal.mol^{-1} respectively, indicating the potency of these compounds as estrogenic receptor inhibitor (Savita et al. 2019). But, when these values were comparable to the binding energy obtained for Raloxifene co crystallized with the hER-α (1ERR), used here as a positive control (-9.61928 kcal/mol), and the comparison of the binding of studied compounds and Raloxifene with

estrogenic receptor (1ERR), indicated that compound 11 form two π -H interactions, one between substituted aromatic ring and Ala350, but the other interaction was observed between the pyrone ring and Thr 347, while compound 16 form one π -H interaction between substituted aromatic ring and Leu525. Raloxifene form a strong ionic bonding with Asp 351 (Savita et al. 2019), which is absent in compounds 11 and 16, which means that a strong binding interaction with Asp 351 is important for activity. Furthermore, depending on the binding energy and binding mode of Raloxifene with the estrogenic receptor- α (1ERR), we can clearly see that all the studied compounds are less active than raloxifene as an estrogenic receptor inhibitor.

Conclusion

In this study, coumarin pyrazoline derivatives were synthesis and characterized by mass spectrum, FT-IR, ^{1}H NMR and ^{13}CNM spectrum. The cytotoxic activity of the compounds was estimated against MCF-7 anticancer cell line. All compounds had moderated anticancer activity. Molecular docking of compounds shown this fact.

Acknowledgments

Special thanks to University of Basrah-Pharmacy Collage for their support in this study.

References

Ahmed MH, El-Hashash MA, Marzouk MI, El-Naggar AM (2019) Design, synthesis, and biological evaluation of novel pyrazole, oxazole, and pyridine derivatives as potential anticancer agents using mixed chalcone. Journal of Heterocyclic Chemistry 56(1): 114–123. https://doi.org/10.1002/jhet.3380

Al-Awad SM, Raheem LA, Jaccob AA (2020) Synthesis and pharmacological evaluation of novel coumarin derivatives. International Journal of Research in Pharmaceutical Sciences 11(1): 865–874. https://doi.org/10.26452/ijrps.v11i1.1908

Akkol EK, Genç Y, Karpuz B, Sobarzo-Sánchez E, Capasso R (2020) Coumarins and coumarin-related compounds in pharmacotherapy of cancer. Cancers 12(7): 1–25. https://doi.org/10.3390/cancers12071959

Amernic J (2013) Perspectives on the role of metaphor. Routledge Companion to Account Commun, 76–93. https://doi.org/10.4324/9780203593493

Çelik G, Arslan T, Şentürk M, Ekinci D (2020) Synthesis and characterization of some new pyrazolines and their inhibitory potencies against carbonic anhydrases. Archiv der Pharmazie (Weinheim) 353(3): 4–9. https://doi.org/10.1002/ardp.201900292

Chagas CM, Moss S, Alisaraie L (2018) Drug metabolites and their effects on the development of adverse reactions: Revisiting Lipinski's Rule of Five. International Journal of Pharmaceutics [Internet] 49(1–2): 133–149. https://doi.org/10.1016/j.ijpharm.2018.07.046

Chen X, Li H, Tian L, Li Q, Luo J, Zhang Y (2020) Analysis of the physicochemical properties of acaricides based on Lipinski's Rule of Five. Journal of Computational Biology 27(9): 1397–4106. https://doi.org/10.1089/cmb.2019.0323

Kovvuri J, Nagaraju B, Ganesh KC, Sirrisha K,Sirisha K, Chandrasekhar C, Alarifi A (2018) Catalyst-free synthesis of pyrazole-aniline linked coumarin derivatives and their antimicrobial evaluation. Journal of Saudi Chemical Society 22(6): 665–677. https://doi.org/10.1016/j.jscs.2017.12.002

Kumar N, Bhatnagar A, Dudhe R (2017) Synthesis of 3-(4, 5-dihydro-1-phenyl-5-substituted phenyl-^{1}H-pyrazol-3-yl)-2H- chromen-2-one derivatives and evaluation of their anticancer activity. Arabian Journal of Chemistry 10: S2443–S2452. https://doi.org/10.1016/j.arabjc.2013.09.008

Lipinski CA (2004) Lead-and-drug-like compounds: The rule-of-five revolution. Drug Discovery Today: Technologies 1(4): 337–341. https://doi.org/10.1016/j.ddtec.2004.11.007

Mustafa YF, Riyadh Khalil R, Mohammed ET, Bashir MK, Oglah MK (2021) Effects of structural manipulation on the bioactivity of some coumarin-based products. Archives of Razi Institute 76(5): 1297–1305.

Mustafa YF, Zain Al-Abdeen SH, Khalil RR,Mohammed ET (2023) Novel functionalized phenyl acetate derivatives of benzo[e]-bispyrone fused hybrids: Synthesis and biological activities. Results in Chemistry 5(April): 100942. https://doi.org/10.1016/j.rechem.2023.100942

Nepali K, Sharma S, Sharma M, Bedi PMS, Dhar KL (2014) Rational approaches, design strategies, structure activity relationship and mechanistic insights for anticancer hybrids. European Journal of Medicinal Chemistry 77: 422–487. https://doi.org/10.1016/j.ejmech.2014.03.018

Pasricha S, Gahlot P (2020) Synthetic strategies and biological potential of coumarin-chalcone hybrids: A new dimension to drug design. Current Organic Chemistry 24(4): 402–438. https://doi.org/10.2174/1385272824666200219091830

Patel J (2019) Microwave assisted synthesis, characterization and antimicrobial evaluation of pyrazolyl and pyrazoline. International Journal of Research and Analytical Reviews 6(1): 385–404. www.ijrar.org [E-ISSN2348-1269, P- ISSN2349-5138]

Patel K, Karthikeyan C, Raja SV, S. Hari Narayana Moorthy N, Lee H, Sahu K (2012) Synthesis of some coumarinyl chalcones and their antiproliferative activity against breast cancer cell lines. Letters in Drug Design & Discovery 8(4): 308–311. https://doi.org/10.2174/157018011794839475

Patel M, Pandey N, Timaniya J, Parikh P, Chauhan A, Jain N (2021) Coumarin-carbazole based functionalized pyrazolines: Synthesis, characterization, anticancer investigation and molecular docking. RSC Advances 11(44): 27627–27644. https://doi.org/10.1039/D1RA03970A

Sandhu S, Bansal Y, Silakari O, Bansal G (2014) Coumarin hybrids as novel therapeutic agents. Bioorganic & Medicinal Chemistry 22(15): 3806–3814. https://doi.org/10.1016/j.bmc.2014.05.032

Saroja T, Ezhilarasi RM, Selvamani V, Mahalakshmi S (2021) Synthesis, characterization and in-silico analysis of new 2-pyrazolines. Journal of Scientific Research 13(1): 183–194. https://doi.org/10.3329/jsr.v13i1.46995

Savita P, Shivani R, Sudha H, Sarita I (2019) Synthesis of coumarin-Chalcone Derivatives. IOSR Journal 12(7): 46–51.

Thakur A, Singla R, Jaitak V (2015) Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. European Journal of Medicinal Chemistry 101: 476–495. https://doi.org/10.1016/j.ejmech.2015.07.010

Supplementary material 1

Synthesis compounds

Author: Leaqaa Abdulredha Raheem

Data type: docx

Explanation note: Scheme of synthesis 3-acetyl coumarin as starting material and others, scheme of synthesis of chalcon and then pyrazoline derivatives.

Link: https://doi.org/10.3897/pharmacia.70.e108670.suppl1

Supplementary material 2

Docking study

Author: Leaqaa Abdulredha Raheem

Data type: docx

Explanation note: It includes studying the molecular docking and the nature of the bonding of the synthesized compounds to the protien part.

Link: https://doi.org/10.3897/pharmacia.70.e108670.suppl2

Supplementary material 3

Data synthesis compounds, physico-chemical properties and identification of synthesis compound

Author: Leaqaa Abdulredha Raheem

Data type: docx

Explanation note: Table of data synthesis compounds, physico-chemical properties, identification of synthesis compound by 1H-NMR and 13CNMR Data and Mass spectrometry data.

Link: https://doi.org/10.3897/pharmacia.70.e108670.suppl3