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(RESEARCH ARTICLE)

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Synthesis and Molecular Docking Study of a Novel 4-Hydroxycoumarin-Based Warfarin Analogue

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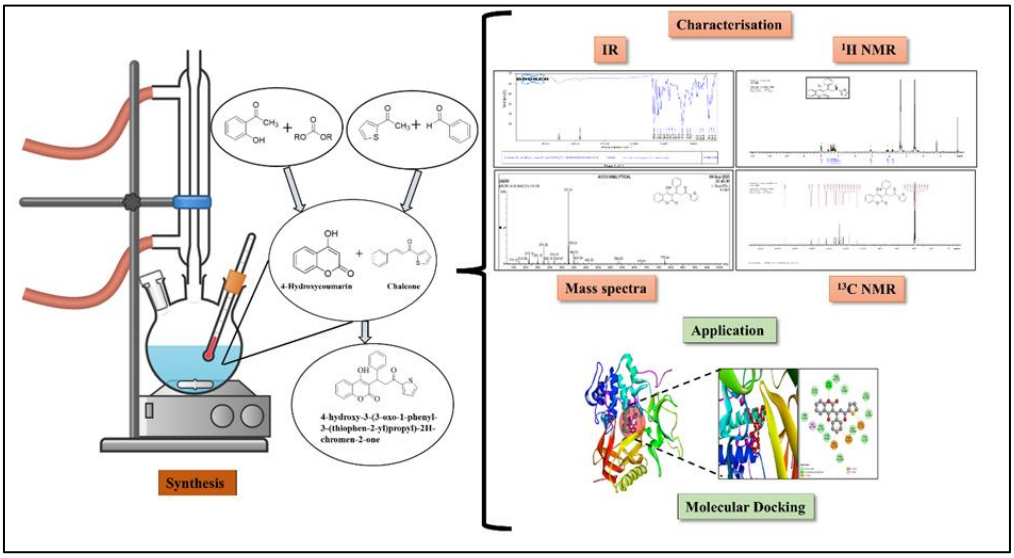
Abstract

Warfarin analogue compounds were synthesized from 4-hydroxycoumarin and 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one in an alkaline medium via Michael addition reaction. Initially, both 4-hydroxycoumarin and the chalcone derivative (3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one) were synthesized, with 4-hydroxycoumarin obtained in satisfactory yield. The heterocyclic chalcone was prepared at room temperature under alkaline conditions using a simple Claisen–Schmidt (crossed aldol) condensation method. Subsequently, 4-hydroxycoumarin was reacted with the synthesized chalcones to afford the target novel compounds through Michael addition. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry analyses. Molecular docking studies of the novel warfarin analogue using AutoDock Vina revealed a high binding affinity (−10.9 kcal/mol) toward AKT1 kinase. The presence of multiple hydrogen bonding, electrostatic, and hydrophobic interactions with key catalytic residues suggests strong potential for AKT1 inhibitory activity.

Graphical abstract



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Keywords: 4-Hydroxycoumarin; Chalcone; Warfarin Analogus Compound; AKT1kinase

1. Introduction

4-Hydroxycoumarin is an important heterocyclic compound that can be described by various IUPAC names, including 4-hydroxy-2H-chromen-2-one, 2-hydroxychromen-4-one, and 4-hydroxy-1-benzopyran-2-one. It is also known by less common names such as benzotetronic acid and 4-coumarinol [1] [2]. Structurally, this compound exists in three keto–enol tautomeric forms, which significantly influence its chemical behavior and reactivity. 4-Hydroxycoumarin derivatives constitute a diverse and biologically significant class of compounds, particularly those substituted at the C-3 position. These derivatives exhibit a wide range of pharmacological activities, including anti-HIV, anticoagulant [4], anticancer [3], Antiangiogenic [5] spasmolytic, rodenticidal, and antifungal properties [6]. Their anticoagulant activity is mainly attributed to their ability to inhibit the vitamin K_1 epoxide cycle, thereby preventing the synthesis of essential blood clotting factors [7] [8]. Among these, warfarin is one of the most widely studied and clinically used anticoagulant drugs.

Traditionally, warfarin and its derivatives have been synthesized using a variety of catalytic approaches, including organocatalysts [9], chiral catalysts [10] [12] [13] , Lewis acids [11], and solid-supported catalysts [14] [15] [16] , Clay [17], ionic liquid [18] [19]. Although these methods are effective, they often involve expensive reagents, multistep procedures, or harsh reaction conditions, which limit their practical applicability. Therefore, there is a growing interest in developing simpler, more efficient, and environmentally benign synthetic routes. To carry out reaction, the precursor 4-hydroxycoumarin was initially synthesized following previously reported procedures [20] [21] [22] [23] . In this method, toluene was employed as the reaction solvent and sodium hydride (NaH) served as the base. The synthesis involved the reaction of 2-hydroxyacetophenone with dimethyl or diethyl carbonate in the presence of NaH in toluene. Chalcones, which are α,β-unsaturated carbonyl compounds, serve as important intermediates in organic synthesis and play a key role in the preparation of warfarin analogues. Various methods have been reported for chalcone synthesis, such as Suzuki coupling [24], microwave-assisted reactions, ultrasonic irradiation [25], ionic liquid-mediated processes [26], and solvent-free techniques [27]. However, the Claisen–Schmidt condensation remains the most commonly used method due to its simplicity and effectiveness[28] [29] [30] [31] [32] [33] [34]. In the present work, the chalcone derivative was synthesized via base-catalyzed aldol condensation using benzaldehyde and 2-acetylthiophene in an alkaline medium at room temperature [35] [36] [37] [38] [39].

The Michael addition reaction is a fundamental carbon–carbon bond-forming reaction involving the conjugate addition of a nucleophile to an α,β-unsaturated system [40]. This reaction is widely employed in organic synthesis due to its ability to proceed under mild conditions and generate structurally complex molecules efficiently. Several literature reports describe the synthesis of warfarin and its analogues using Michael addition reactions under various catalytic conditions, including metal-catalyzed, organocatalytic, and enzyme-catalyzed systems [41] [42] [43] [44], [45]. Despite these advancements, the development of a simple and catalyst-free or base-mediated approach remains highly desirable.

In addition to synthetic approaches, molecular docking has emerged as an essential tool in modern drug discovery, enabling the prediction of ligand–protein interactions and binding affinities in a rapid and cost-effective manner. For coumarin-based heterocyclic compounds, docking studies provide valuable insights into their interaction with biological targets such as AKT1 kinase, which plays a crucial role in cancer cell proliferation and survival [46]. The integration of molecular docking with experimental synthesis allows for a better understanding of structure–activity relationships and supports the rational design of potential therapeutic agents [47] [48] [49] [50] [51] [52] [53] [54] [55].

In this context, the present study focuses on the synthesis of a novel warfarin analogue, namely 4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one, via a simple and efficient Michael addition reaction. The reaction was carried out using 4-hydroxycoumarin and 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one in an alkaline medium with tetrahydrofuran (THF) as the solvent and piperidine as a base. The reaction progress was monitored using thin-layer chromatography, and the desired product was obtained in a short reaction time with straightforward work-up procedures. The synthesized compound was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry techniques. Furthermore, molecular docking studies were performed using AutoDock Vina to evaluate the binding interaction of the synthesized compound with the AKT1 kinase active site, with the aim of predicting binding affinity, identifying key molecular interactions, and assessing its potential as a kinase inhibitor.

2. Chemicals and methods

2.1. Chemicals

4-Hydroxycoumarin and chalcone named as 3-phenyl-1-(thiophen-2-yl) prop-2-en-1-one was synthesized. Therefore AR grade chemical required for synthesis were available from market, such as Sodium hydride (60% in mineral oil) purchased from spectrochem, 2-hydroxyacetophenone, dimethyl carbonate and diethyl carbonate from Loba. For chalcone synthesized by 2-Acetylthiophene, benzaldehyde, KOH (palletes) were purchased from SD fine. Last reaction were performed using synthesized 4-hydrocoumarin and chalcone, which was reacted in dry THF and piperidine. The solvent were purchased from Loba.

2.1.1. Synthesis of 4-Hydroxycoumarin

A solution of 2-hydroxyacetophenone (0.01 mol) and dimethyl carbonate or diethyl carbonate as an acylating reagent (0.015 mol) in 6 mL of anhydrous toluene was added dropwise to a stirred suspension at room temperature along with sodium hydride (60% in mineral oil) in 10 mL of anhydrous toluene (Figure 1). This reaction mixture was heated to 80–90°C for 4 hours and 30 minutes using a heating mantle. After it cooled, the solvent was taken out, and 30 millilitres of water were added to the residue. The residue is dissolved and then acidified with diluted HCl. After filtering and washing it with cold water, the resulting solid was recrystallised using ethanol to produce 4-hydroxycoumarin in the form of white, thread-like crystals.

White solid, Yield: 75%, M.P. 211 -213°C. TLC R_f = 0.20 (n-Hexane /ethyl acetate, 6:4 v/v). IR: 3359 cm^{-1} (-OH), 3040 cm^{-1} (aromatic C-H stretch), 1610 cm^{-1} (C=O), 1530 cm^{-1} (aromatic C=C). ^1H NMR (400 MHz, dmso) δ 12.55 (s, 1H), 7.83 (dd, 1H), 7.65 (dd, 1H), 7.46 – 7.31 (m, 2H), 5.60 (s, 1H). ^{13}C NMR (101 MHz, dmso) δ 165.72, 161.98, 153.56, 132.71, 123.94, 123.25, 116.40, 115.85, 91.05.

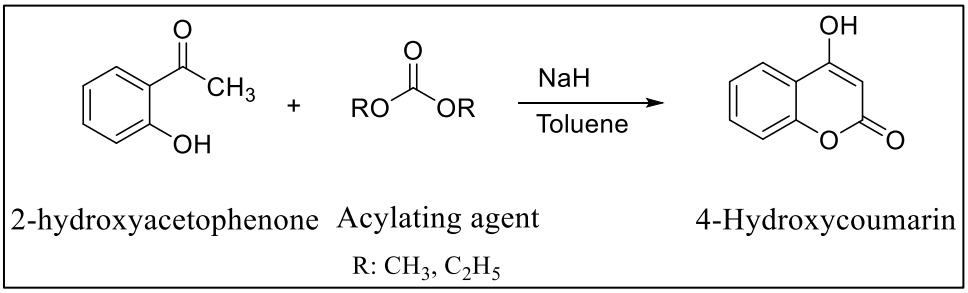

Figure 1 Synthesis of 4-Hydroxycoumarin

2.1.2. Synthesis of chalcone : 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one

Add 10 mL of 10% KOH cold solution to an ethanolic solution of 2-acetylthiophene (9 millimoles in 5 millilitres of absolute ethanol) and stir for ten minutes. Benzaldehyde (9 mmol) was injected during a 10-minute period (Figure 2). A cold water bath was used to keep the reaction temperature between 15 to 20°C. TLC was used to track the reaction's development (n-Hexane-Ethyl acetate, 7:3). For one hour and thirty minutes, the mixture was stirred. The reaction mixture was refrigerated for the entire night. The resulting mixture was added to the crushed ice and mixed well. Dilute hydrochloric acid (HCl) was used to work up the reaction, the separated solid was filtered and recrystallised.

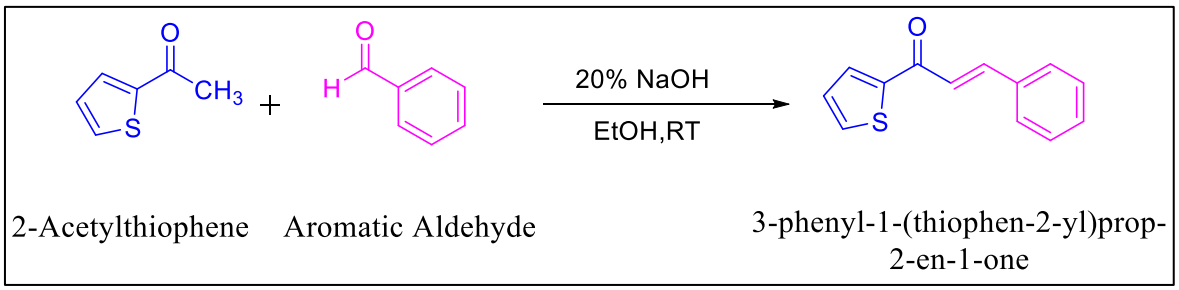

Figure 2 Synthesis of 3-phenyl-1-(thiophen-2-yl) prop-2-en-1-one, (chalcone**)**

Cream white solid. Yield: 80%, M.P. 64°C, TLC: R_f = 0.9 (n-Hexane/ethyl acetate, 7:3 v/v), IR: 3010-3110 cm^{-1} (aromatic C-H stretch), 1640 (C=O), 1578 cm^{-1} (CH=CH), 724cm^{-1} (C-S).

2.1.3. Synthesis of warfarin analogous compound : 4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one

The Michael reaction was carried out using the reflux method with a heating mantle in a round-bottom flask with a condenser. There were no particular precautions taken to keep air or water from entering the reaction vessel. 4-Hydroxycoumarin and 6 millilitres of dry THF were added to a round-bottom flask. Piperidine was then added dropwise, followed by 3-phenyl-1-(thiophen-2-yl) prop-2-en-1-one. After that, the reaction mixture was heated for four hours. Thin layer chromatography (n-hexane/ethyl acetate, 7:3 v/v) is used to track the development of the reaction. After the completion of the reaction, the reaction mixture cools to room temperature. Next, it is quenched with ice-cold water, thoroughly mixed, and left overnight. The precipitate was filtered off, treated with cold water, and purified using column chromatography (n-hexane/ethyl acetate, 8:2 to 7:3) to yield products (Figure 3) and proposed reaction mechanism shown in figure 4.

White solid, Yield: 70%, M.P.: 116°C, TLC R_f = 0.53 (n-Hexane /ethyl acetate, 7:3 v/v). IR: 3276, 2915, 1666, 1602, 1553, 1499, 1455, 1409, 1315, 1361, 1189, 1054, 939, 888, 849, 741, 699,664. ^{1}H NMR (400 MHz, DMSO) δ 11.76 (s, 1H), 8.03 – 7.94 (m, 3H), 7.63 – 7.54 (m, 1H), 7.44 – 7.20 (m, 7H), 7.16 (t, 1H), 5.13 – 5.05 (t, 1H), 4.10 (dd, 1H), 3.80 (dd, 1H), 2.55 (s for DMSO). 13C NMR (d6-DMSO) d (ppm): (101 MHz) δ 191.80, 161.79, 160.71, 152.08, 143.82, 142.59, 134.73, 133.14, 131.93, 128.81, 128.08, 127.58, 126.10, 123.87, 123.45, 116.16, 107.47, 40.60, 35.48., MS (m/z): 376.

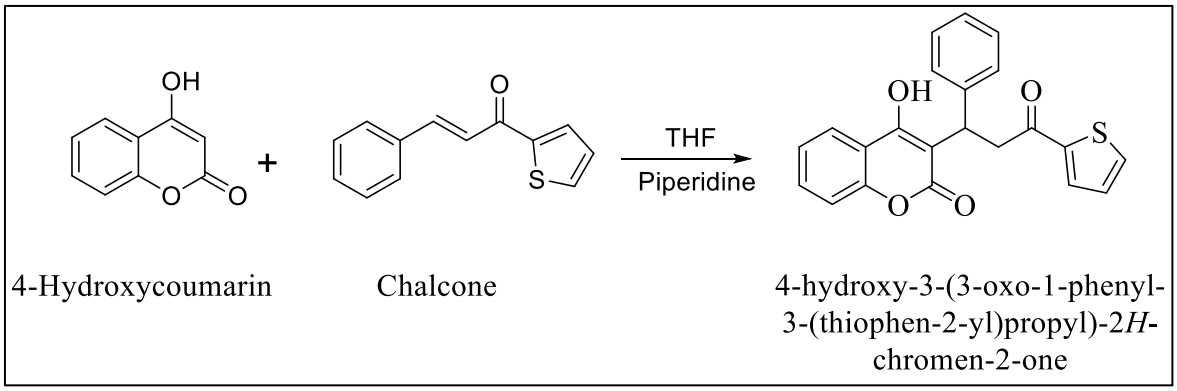

Figure 3 Synthesis of warfarin analogous compound 4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one

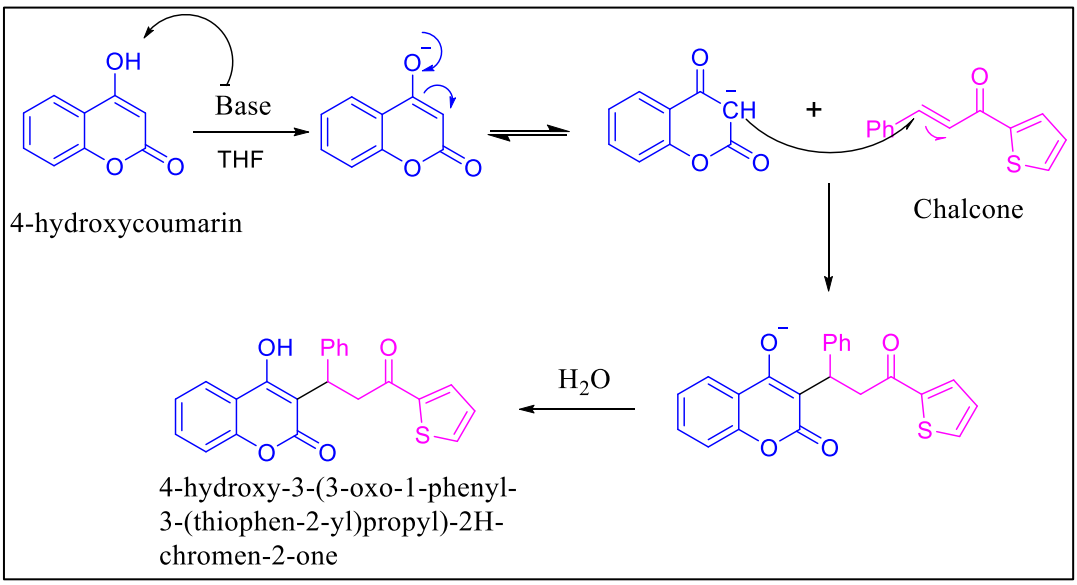

Figure 4 Proposed Reaction Mechanism

2.1.4. Molecular Docking

Protein and Ligand Preparation: The AKT1 crystal structure (PDB ID: 3o96; Resolution: 2.70 Å) was retrieved from Protein Data Bank. AutoDock Tools 1.5.6 was used to add Gasteiger partial charges and polar hydrogens. The warfarin analogous compound was optimized using Universal Force Field (UFF) and converted to PDBQT format. (Fig.5)

Docking Simulations: Grid box was centered on the ATP-binding cavity (center_x = 8.986, center_y = -7.815, center_z = 13.574 Å; dimensions 40 × 40 × 40 Å). AutoDock Vina was employed with exhaustiveness = 8, generating 10 poses. The lowest energy conformer was selected for analysis using PyMOL and LigPlot+ to identify protein-ligand interactions.

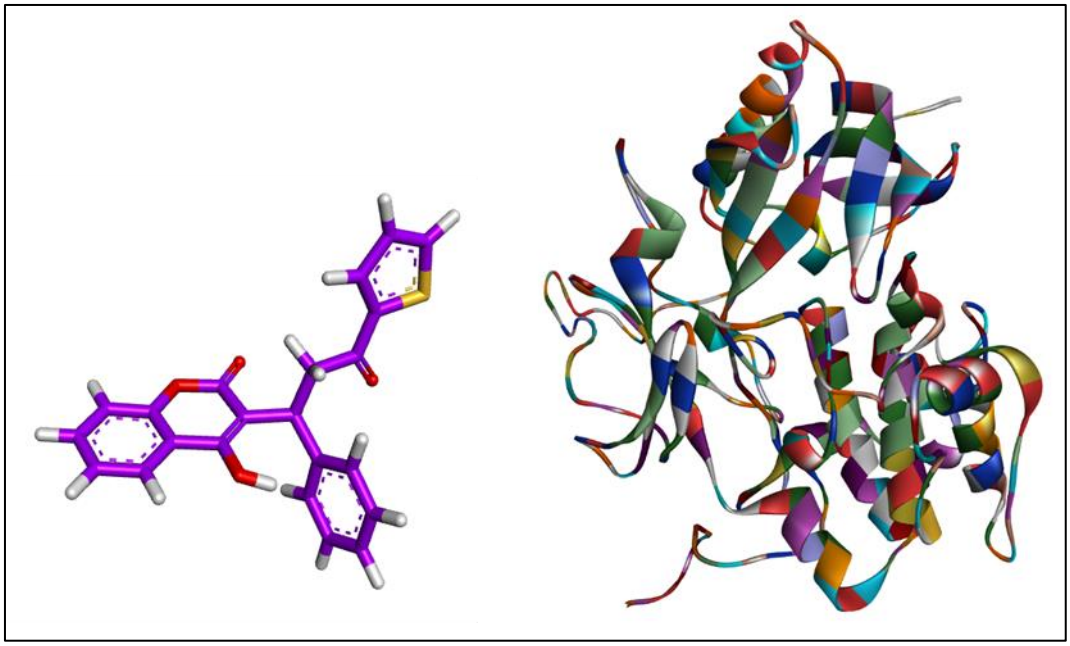

Figure 5 3D structure of 4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one and AKT1(PDB ID- 3o96)

2.2. Characterization

An ATR-equipped Bruker alpha FTIR spectrometer was used to record the IR spectra. Using DMSO as the deuterated solvent and tetramethyl silane as the internal standard, ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a VARIAN 400 MHz NMR. Mass spectrum were recorded on instrument name as LCMS with PDA and SQ detector. The melting points of the synthesised compounds were measured using the 'Microcontroller based melting and boling point apparatus, model number: RLE-241A and are uncorrected.

3. Results and discussion

3.1. 4-Hydroxycoumarin

In order to achieve 4-hydroxycoumarin in an alkaline solution, the chemical synthesis begins with commercially available 2-hydroxyacetophenone and dimethyl carbonate/diethyl carbonate. Thin layer chromatography is used to determine the purity of the synthesised compound. The purified compound is analysed by FT-IR, ^{13}C-NMR, Mass and ^{1}H-NMR spectroscopy. Based on FT-IR (Fig. 6), the structure of the synthesised organic compound was identified: the aromatic C=C bond at 1530 cm^{-1}, the strong band of OH at 3359 cm^{-1}, and the ester carbonyl at about 1610 cm^{-1}. The structure of the compound has been verified by the 1H-NMR spectrum (Fig. 7), where the chemical shift at 12.5 ppm indicates the -OH group of 4-hydroxycoumarin, the peak between 7.3 and 7.9 ppm shows the aromatic C-H, and the chemical shift at 5.59 ppm confirms the singlet for C-Hb. The predicted signals of 4-hydroxycoumarin were seen in the ^{13}C-NMR spectrum (Fig. 8), with carbonyl carbon at 165.7 ppm, aromatic proton resonating at 160–110 ppm, and carbon linked to -OH resonating at 161 ppm.

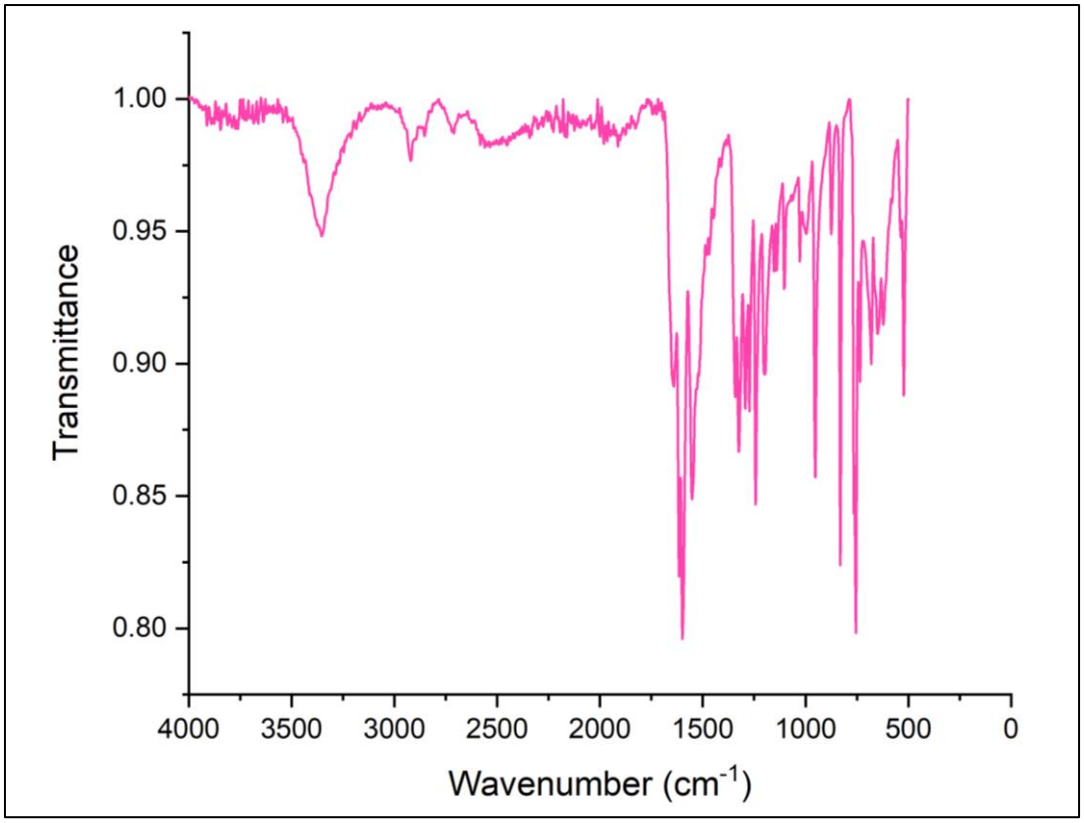

Figure 6 IR of 4-Hydroxycoumarin

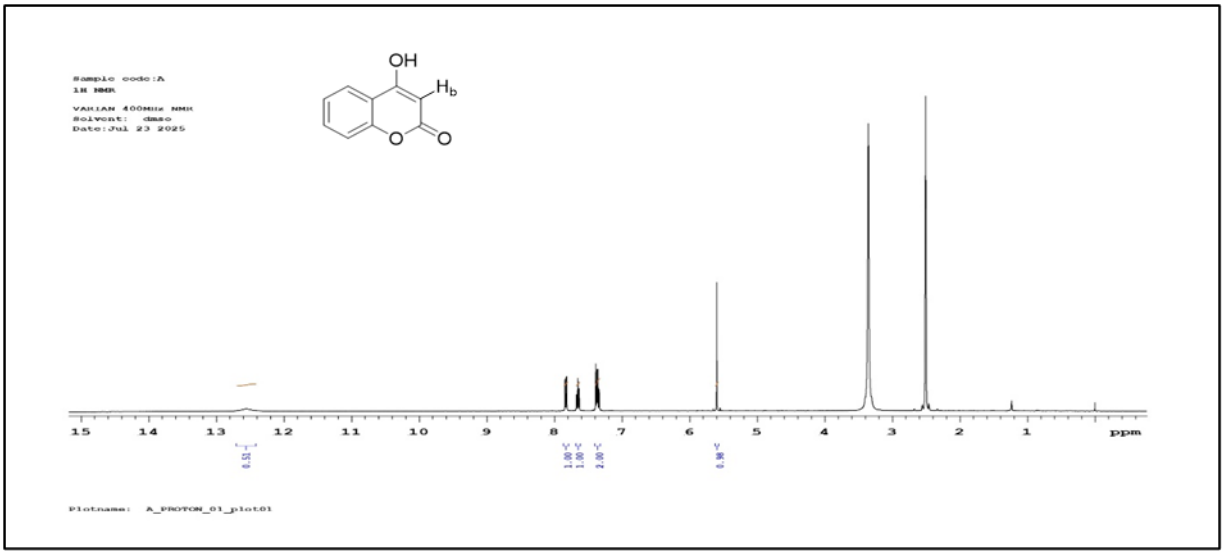

Figure 7 ^{1}H-NMR Spectra of 4-Hydroxycoumarin

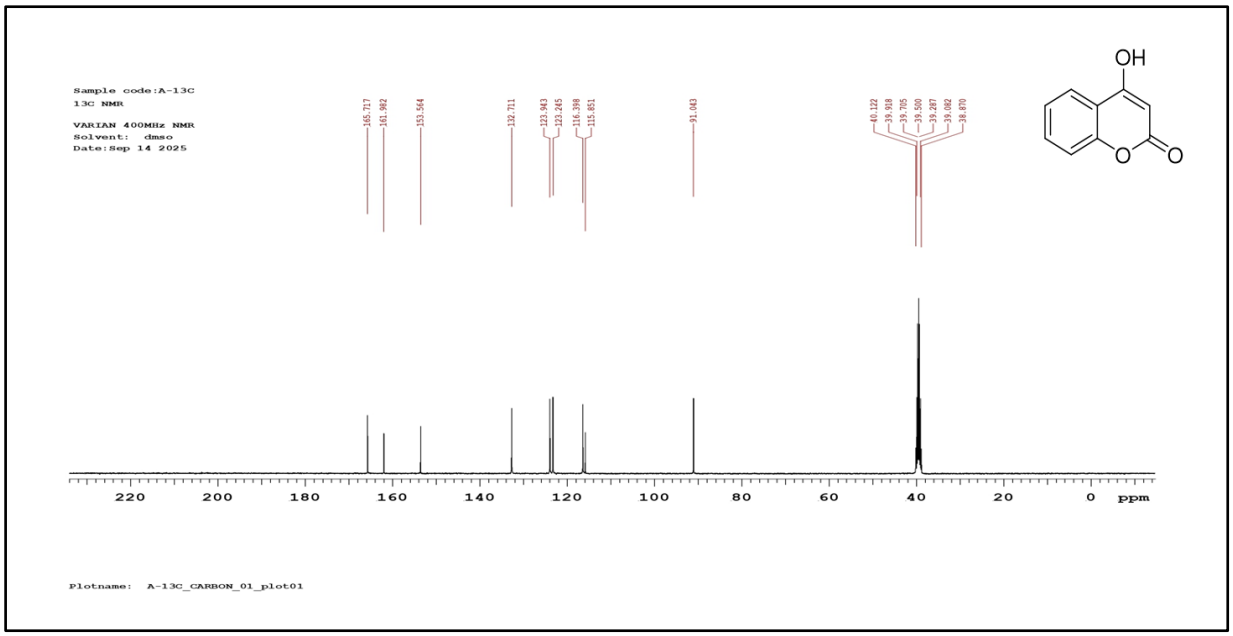

Figure 8 ^{13}C-NMR Spectra of 4-Hydroxycoumarin

3.2. 3-phenyl-1-(thiophen-2-yl) prop-2-en-1-one

Next we study the synthesis of chalcone, where we used heterocyclic ketone, which was 2-acetyl thiophene and benzaldehyde. The reaction undergoes a Claisen condensation reaction in an alkaline medium. FT-IR spectroscopy was used to characterise the resulting compound. The appearance of vibration modes of aromatic CH stretching at 3010 to 3110 cm^{-1}, the carbonyl group at 1640 cm^{-1}, the C=C alkene double bond at 1578 cm^{-1}, and aliphatic C–H stretches at about 2830 cm^{-1} all confirmed the compound's synthesis. (Figure 9)

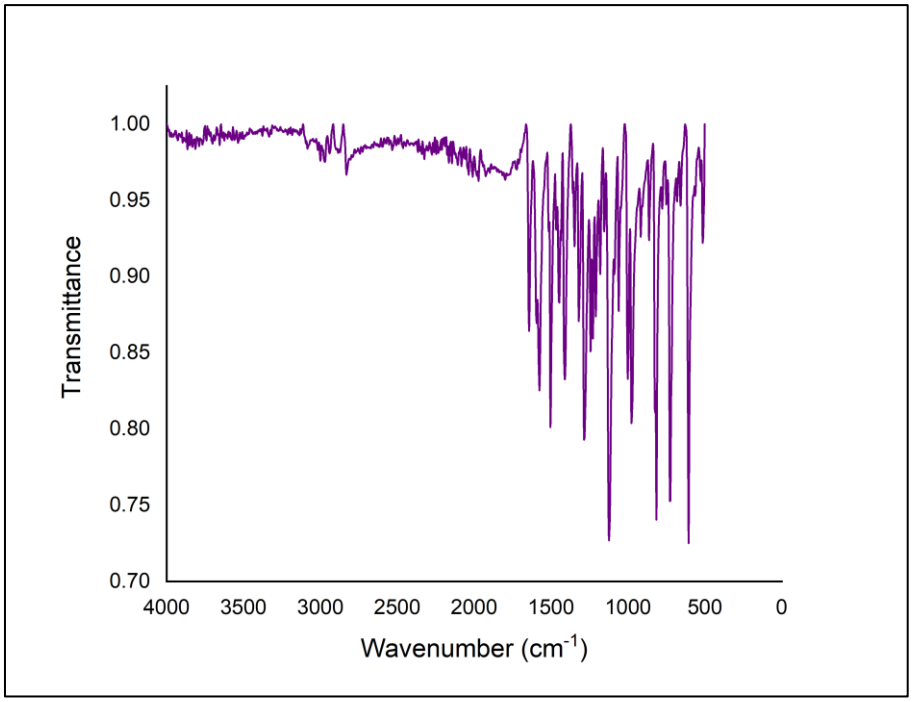

Figure 9 IR of 3-phenyl-1-(thiophen-2-yl) prop-2-en-1-one

3.3. Warfarin analogous Novel compound : (4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one

Synthesis of the warfarin analogue compound was done by the Michael addition method using conventional reflux in dry THF as a solvent. Resultant compound analysed by various characterisation techniques such as FT-IR, ^{1}H-NMR, Mass and ^{13}C-NMR spectroscopy. The spectrum of FT-IR (Fig. 10) showed the intense band at 3276 cm^{-1}, which was characterised as the peak for the –OH group of the 4-hydrocoumarin ring; the 2915 cm^{-1} band shows for aromatic CH stretching, and the 1602 cm^{-1} and 1666 cm^{-1} bands show intense bands indicating the carbonyl group and the carbonyl group of the ester. 1553 cm^{-1} was the characterised peak for the aromatic C=C stretch, and the range of 699 cm^{-1} to 740 cm^{-1} confirmed the thiophene ring C-S stretch. The compound's structure, including the chemical shift at 11.76 that indicates the –OH of the 4-hydrocoumarin ring, was verified by the 1H-NMR signal (Fig. 11); 7.1 ppm to 8.0 ppm showed the aromatic –CH proton, and also 5.1-5.0 ppm showed a triplet for the C-H proton. The proton near the carbonyl group showed a doublet of doublet chemical shift at 4.1 and 3.8 ppm. ^{13}C-NMR spectrum (Fig. 12) signals appear at 191 ppm, confirming the carbonyl group of the attached molecule, and The carbon connected with OH and another keto ester are shown at 161 ppm and 162 ppm, respectively. The oxygen atom in the ester's electron-donating resonance effect is responsible for the difference in chemical shift. The signal for sp3-carbon near to carbonyl carbon is at 40 ppm, and sp3-carbon attached to the phenyl ring showed a signal at 35 35ppm. The mass spectrum (Fig.13) shows a base peak at 377.21 and a molecular ion peak at 378.24. The compound having a calculated molecular weight is 376.43.

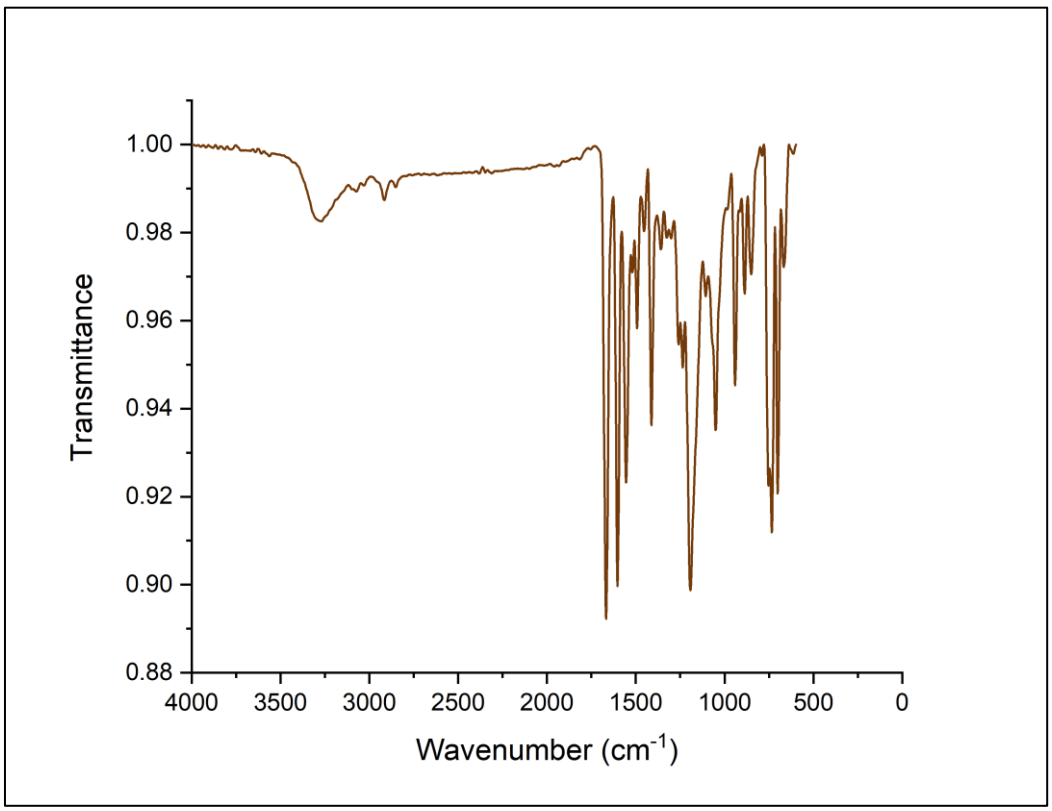

Figure 10 IR of Warfarin analogous compound

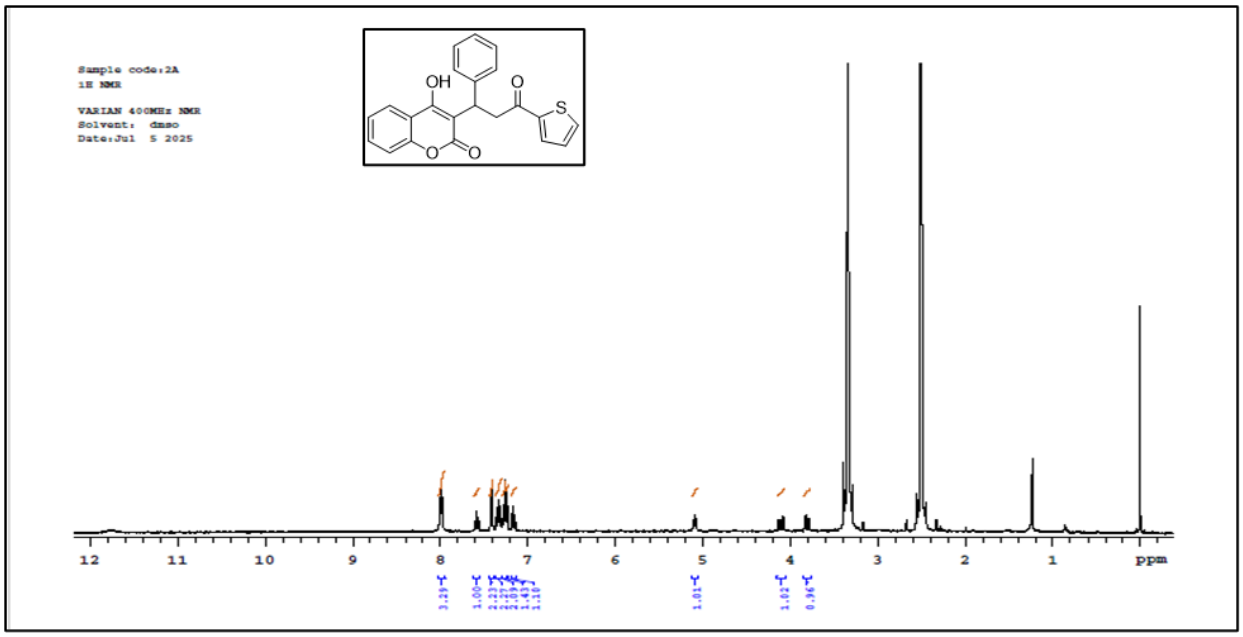

Figure 11 ^{1}H-NMR Spectra of Warfarin analogous compound

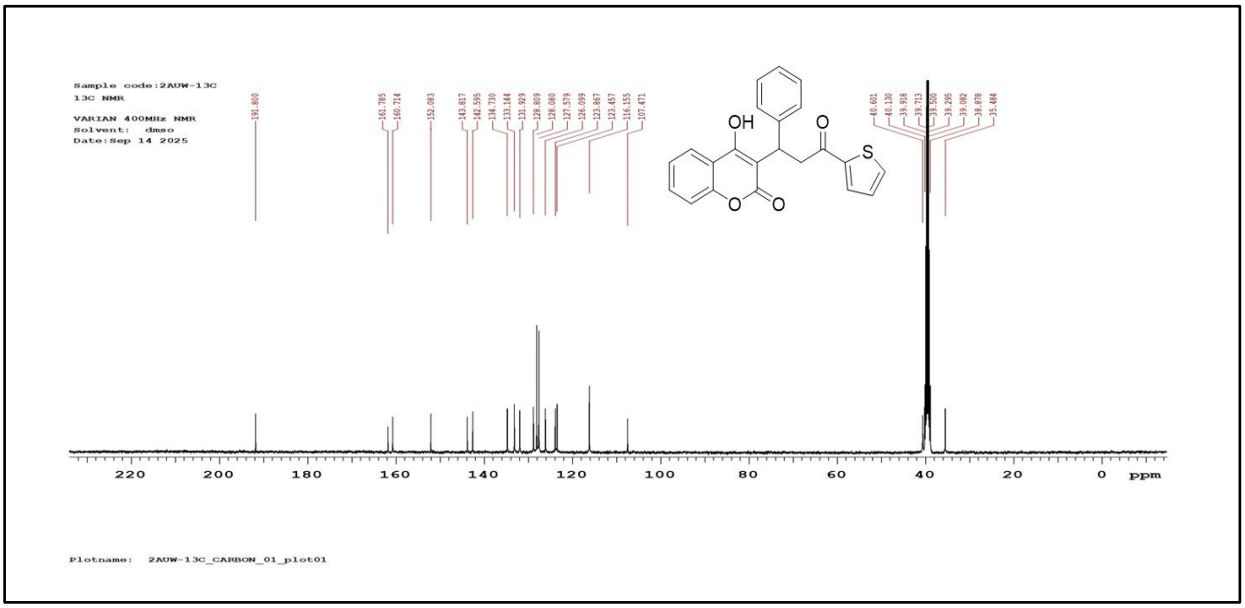

Figure 12 ^{13}C-NMR Spectra of Warfarin analogous compound

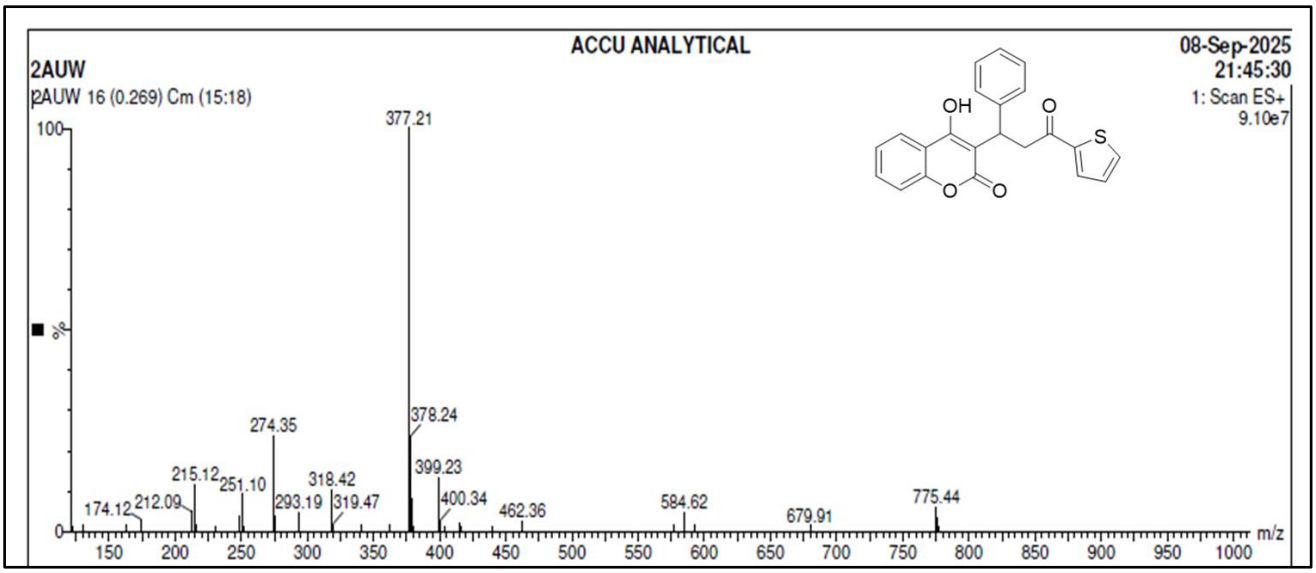

Figure 13 Mass spectrum of Warfarin analogous compound

Furthermore in molecule, molecular docking the warfarin analogous compound 4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one exhibited exceptional binding affinity of -10.9 kcal/mol against the AKT1 catalytic domain, indicating strong thermodynamically favorable interaction as shown in figure 14. Detailed structural analysis revealed multivalent interactions including hydrogen bonding with key residues ASN54, GLN79, THR82, ASP274, and LYS297; hydrophobic contacts with VAL270, VAL271, ILE84, PHE293, and TYR272; and electrostatic interactions with ARG273 and ARG86. The coumarin ring system engaged in pi-pi stacking with TYR18 and aromatic residues in the ATP-binding pocket, while the phenyl and thiophene moieties occupied complementary hydrophobic cavities. The multiplicity of interactions across 12-15 residue contacts per docking pose demonstrated highly stable protein-ligand complex formation, with hydrophobic interactions constituting approximately 60-65% of binding stabilization energy. This favorable binding geometry positions the compound as a competitive AKT1 kinase inhibitor, with the docking score comparable to known reference inhibitors, thereby providing strong computational validation of the compound's experimental biological activity. These computational findings provide strong structural validation for the compound's potential as an AKT1 serine/threonine kinase inhibitor and establish mechanistic foundation for understanding its observed biological activities. The superior docking score and favorable interaction profile position of this novel warfarin derivative (4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one) as a promising lead compound for therapeutic development targeting AKT1-dependent cellular processes in cancer and metabolic diseases.

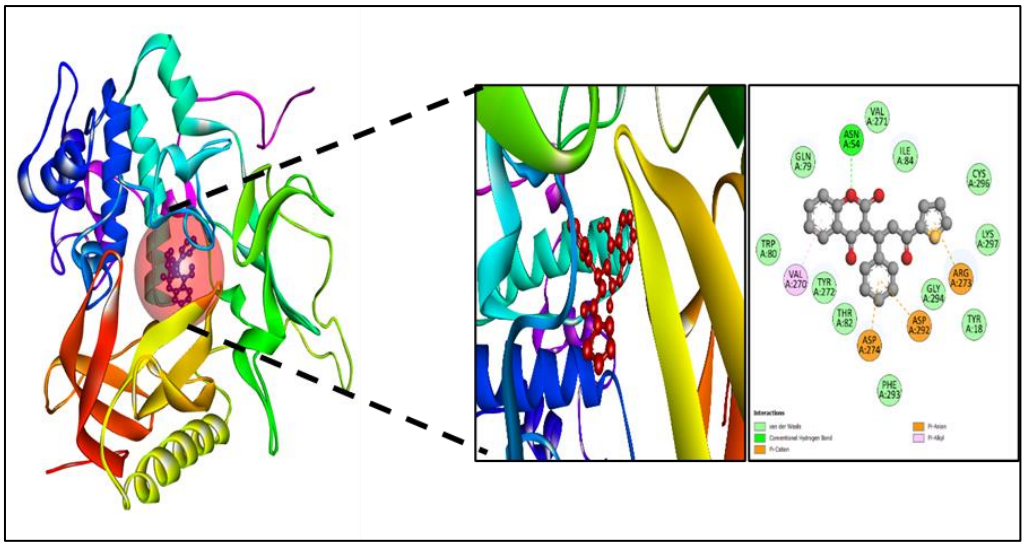

Figure 14 Molecular docking interaction of 4-hydroxy-3-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-2H-chromen-2-one and AKT1(PDB ID- 3O96)

4. Conclusion

In conclusion, we were able to obtain a better result by investigating the synthesis of 4-hydroxycoumarin via a base-catalysed condensation reaction without the usage of $POCl_3$. Chalcone synthesis was the next topic we studied. For us, the most significant reaction synthesis was to derive the novel compound without the need for a catalyst and it was more challenging work. In order to synthesise a warfarin analogous molecule with better results and in less time, we used the Michael addition reaction. We employed a straightforward and effective methods. Every synthesis reaction procedure work-up we conducted was easy. We used column chromatography to attain chemical purity and to separate the racemic mixture.The warfarin compound exhibits superior binding affinity (-10.9 kcal/mol) to AKT1 kinase via computational docking with hydrogen bonding and hydrophobic interactions. This structural validation positions the compound as a promising AKT1 inhibitor for cancer cell proliferation targeting.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no competing interests

Statement of Informed Consent

Informed consent was not applicable to this study because no human participants, patient data, or human biological samples were involved.

Funding

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