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Design, Synthesis and Characterization of New Coumarin Derivatives Triazole Hybrid

Hind S. Sdeeq[1], Nasreen R. Jber[1,*], Fatin F. Al-Kazazz[2]

[1]Department of Chemistry, College of science, Al-Nahrain University, Jadriya, Baghdad, Iraq.
[2]Chemistry Department, College of Science, Mustansiriyah University, Baghdad, Iraq.

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Abstract

This study prepares organic compounds with triazole and coumarin rings the synthetic route involves the synthesis of 3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one from 2-oxo 2H-chromene-3-carbohydrazid followed by synthesis of 3-(4-bezylideneamino-5-thioalkyl-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one. The obtaining a series of novel 1,2,3-triazolyl-coumarin hybrid systems were designed as potential antitumor agents and with high biological activity structural units that might be useful against bacteria is the preparation's goal. Triazole and coumarin compounds are well recognized for their capability to interact with microbes and prevent the development of germs. For that, compounds 5a-5e were studied by using methods including FT-IR spectral with 1H-NMR -spectrum of compounds.

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*Corresponding author: nasreen.jber@nahrainuniv.edu.iq

1. Introduction

A multipurpose scaffold that is abundant in nature, coumarin finds extensive use in medicinal chemistry [1]. The coumarin scaffold's synthetic accessibility makes it the ideal material for derivatization and structural modification [2]. A wide range of pharmacological activities of coumarin, including antiviral [3], anticancer [4], antifungal [5], anti-inflammatory [6], and anti-HIV properties [7], have been shown by coumarin-based molecules.

Due to their varied uses, 5-membered heterocycles, notably 1,2,4-triazoles, play an important role in therapeutic chemistry. The synthesis of 1,2,4-triazole compounds is produced by a cycloaddition of hydrazide and carbon disulfide in the presence of KOH [8].

Coumarin ring can readily bind with several biological targets by π-π because of its lipophilic, aromatic, and planar nature. hydrogen or dipole–dipole interactions, and as a result, is integrated into the structure of numerous significant bioactive substances. Furthermore, as demonstrated by simple, bis-, and fused polycyclic coumarins [9,10,11,12], the therapeutic potential of coumarins is highly dependent on their fundamental structure [7].

Additionally, the pharmacological characteristics and biological activities of the resultant molecule can be influenced by the kind and location of substituents on the benzopyrone core. A promising strategy for creating new therapeutic drugs with enhanced and varied activity is the design and synthesis of coumarin-based hybrid compounds by adding one or more heterocyclic moieties to the coumarin core [13]. While the current work primarily concentrated on the preparation and structural characterization of newly synthesized coumarin–triazole hybrid derivatives, these molecular architectures hold substantial pharmaceutical potential. Coumarin derivatives have garnered great interest for their various biological properties and triazole moieties have shown promising clinical utility for therapeutic and drug discovery. The integration of these two pharmacophores within a single molecular structure could provide a potential for further development of multitasking compounds with better physicochemical and pharmacological properties. Moreover, these derivatives and their synthesis can be potential candidates for further biological studies. [14, 15].

In this respect, the present study deals with producing and testing coumarin-triazole hybrid compounds Structural evidence was obtained by spectroscopic analysis.

2. Materials and Methods

2.1 Instruments and chemical reagents

Every substance used in the experiment was sourced from different companies, including Thomas Baker, Merck, and Fluka. Technique of melting point considered for the synthesized compounds was determined by using open capillary method on hot stage (FALC melting point device) at the Department of Chemistry, College of Science, Al-Nahrain University. The infrared spectra were performed using FT-IR spectrophotometer, Shimadzu (University of Baghdad). The 1H-NMR spectra were performed by using BRUKER and Varian spectrometers, 500 MHz (University of Tehran) with (TMS) tetramethyl silane as internal standard solvent and the chemical shift is reported in part per million (δ=ppm) and each sample was dissolved in deuterated DMSO-d6.

2.2. Procedure for Synthesis

2.2.1. General Synthesis Procedure of 2-oxo 2H-chromene-3-carbohydrazid (2) [11]

The combination of solution ethyl 2-oxo-2H-chromene-3-carboxylate (2.18 g, 10mmol) with hydrazine hydrate solution (purity 99%, 1.3 g, 25mmol) in absolute ethanol (50 mL) under reflux for 6 hours at 75°C. The resulting precipitate was filtered, then washed with ethanol and dried. Recrystallization from ethanol yields a yellow-colored powder. precipitate, m.p. 206-207°C, 88 % yield.

2.2.2. General Synthesis Procedure of synthesis 3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one (3) [8].

KOH (0.63 g, 100ml) was added to absolute ethanol (0.200 L). Then, add 2-oxo-2H chromene-3-carbohydrazide, carbon-disulfide (0.15 M) with small or tiny quantities while stirring constantly, in hydrazine hydrate (15 ml, 0.3 M) and reflux for 7 hours with stirring. The resulting material was filtered, precipitated, and thoroughly cleaned with cold water before being recrystallized using ethanol. 81% at 220–221°C.

2.2.3. General Synthesis Procedure of 3-(4-bezylideneamino-5-mercapto-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one (4) [12]

A solution of 1,4-terephthaldehyde (431 mg, 3.220 mmol) dissolved in absolute ethanol (13 mL) with 3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one (3), then three drops of glacial acetic acid were added at room temperature the mixture was agitated for seven hours at 75°C as a catalyst. After refluxing and stirring, a shiny yellow precipitate was formed, m.p. 150-152°C, 90 % yield.

2.2.4. General Synthesis Procedure of 3-(4-bezylideneamino-5-thioalkyl-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one (5a-e) [14].

The Schiff's bases (4) (1mmol,3.09 g) were dissolved in absolute ethanol (20 mL) with potassium hydroxide (2 mol, 1.38g), and after that added (2mmol) of alkyl halide. The reaction mixture was refluxed (24) hrs. at (75) °C. The product results have been filtered. Physical characteristics of produced substances are listed in Table (1).

Table1. Physical information 5 a-e.

Compound	Color	Melting point. (◦C)	RF datum/Solvent System (n-hexane: EtOAc)	Yield (%)
2a	light Yellow	206-207	0.12/6:4	88
3a	Yellow	220-221	0.14/6:4	81
4a	Yellow	150-152	0.15/6:4	90
5a	Green	168-169	0.14/6:4	88
5b	light Yellow	170-171	0.13/6:4	84
5c	Orange	164-165	0.17/6:4	78
5d	Brown	181-182	0.12/6:4	80
5e	Brown	190-192	0.15 / 6:4	75

3. Results and Discussion

The synthetic route had successfully produced a series of coumarin-triazole hybrid derivatives by sequential transformation reactions. 3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one (3) compound was prepared by refluxing 2-oxo-2H-chromene-3-carbohydrazide (2) with KOH, carbon disulfide, and hydrazine hydrate [11], reaction of compound (3) with terephthaldehyde leads to the formation of 3-(4-bezylideneamino-5-mercaptol-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one.

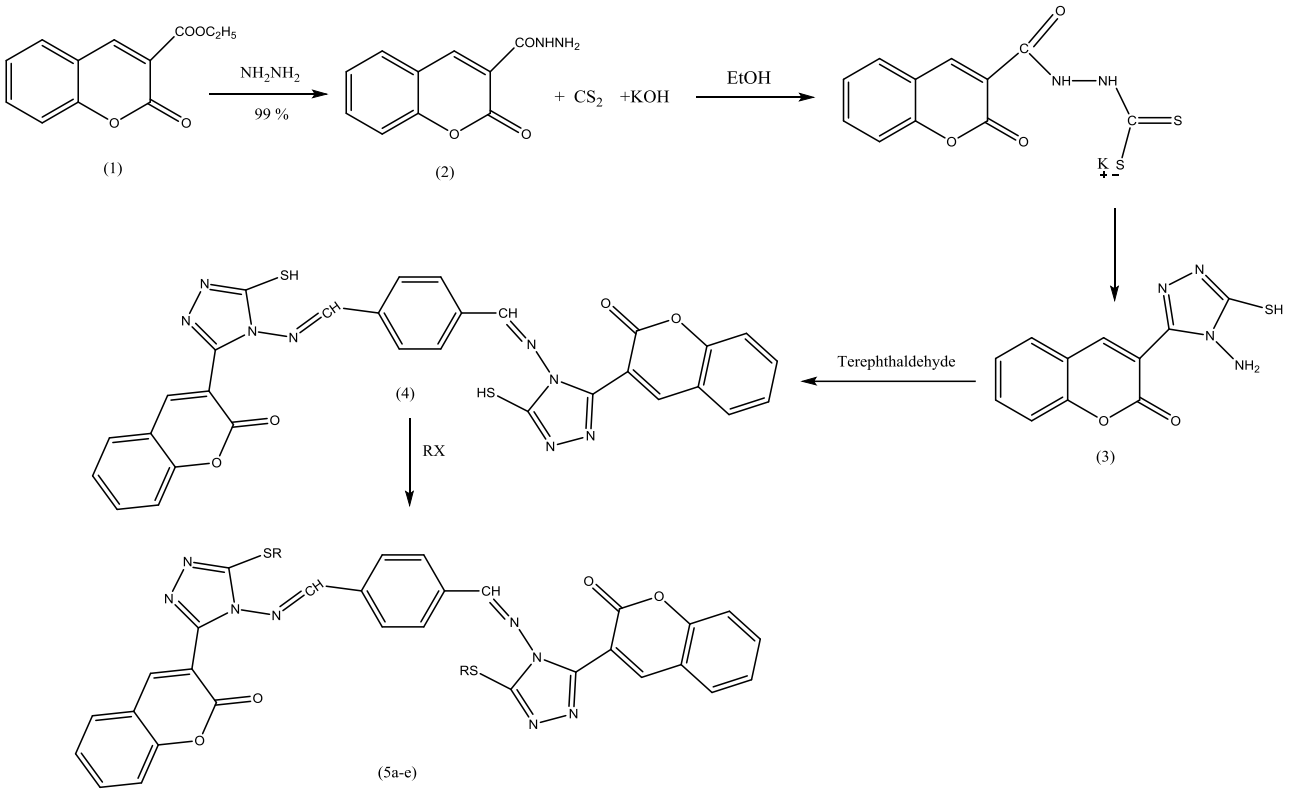
Nucleophilic substitution of the triazole mercapto group with appropriate alkyl halides results in the creation of 3-(4-bezylideneamino-5-thioalkyl-4H-1,2,4-triazol-3-yl)-2H-chromen-2-one. The formation of the triazole nucleus took place due to nucleophilic attack and ring closure under basic conditions. Subsequent condensation of the amino-triazole intermediate with terephthaldehyde produced the corresponding Schiff base derivative, which was produced via azomethine (CH=N) linkages. Finally, S-alkylation of the mercapto group with a number of alkyl halides produced a series of thioalkyl-substituted coumarin-triazole hybrids (5a-5e). It should be emphasized that the synthesized derivatives obtained from different alkyl substituents demonstrate significant differences in melting points, colors, and Rf values, supporting the successful formation of chemically different compounds from their alkyl substitution counterparts at the compound/functional state level.

Spectral Data: FT-IR (cm-1) spectra showed the appearance of aliphatic C-H stretching at 2956 and 2874 for asymmetrical and symmetrical stretching, respectively. Bands at 3054, 1632, 1705, and 834 cm-1 for aromatic C-H, azomethane CH=N [15], lactone carbonyl C = O stretching [16], and out-of-plane bending for p-disubstituted benzene ring, respectively. Many specific bands and their significance are described in Table 2..

Table 2. FT-IR spectral data of compounds 5a-e.

Compound No.	Alkyl Group	FT-IR Spectral data, cm^{-1}			
		v C = O	v C-H (Aromatic)	v C-H (Aliphatic)	v CH=N
5a	CH_3-	1691	3036	2943, 2837	1616
5b	C_2H_5 -	1689	3062	2938, 2817	1600
5c	C_3H_7 -	1702	3043	2920, 2873	1600
5d	C_4H_9 -	1691	3041	2920, 2827	1593
5e	C_5H_{11}-	1705	3045	2966, 2843	1622

The 1H-NMR spectra, Figure 9, (µHz, DMSO-d6) of compound 5b revealed the following events in δ (ppm): The aromatic-protons were detected at (6.985 - 8.541) ppm. Note that at δ: (8.52-8.54, s, 2H) ppm indicates a CH=N group [17]. The signal at δ: (0.958-1.547, t, 6H) ppm is due to methyl fuel, while quenching at δ: (1.623-1.986, q, 4H) ppm is attributed to – CH2. Singlet signal at 2.889 ppm for protons of two methyl-groups [18-20]. The 1H-NMR (ppm), as shown in Figure 10 for derivative 5c showed aromatic-protons and C-H protons in oxazepine rings as 7.36-8.17, and the proton of imine group shows as (s, 8.32-8.34, 2H), while the signal as (0.93- 0.95, t, 6H) attributed to CH2. The proton of -SCH2 group appeared as (t, 2.80-2.83, 2H). The two methyl groups showed as (s, 2.889) [21]. The 1HNMR (ppm), as shown in Figure 11, of derivative 5d show signals for aromatic protons and C-H protons within the oxazepine rings at 6.52 - 8.17 ppm. At δ: (8.32-8.34, s, 2H) ppm CH=N group. At δ δ: (1.04-1.06, t, 6H) ppm methyl specific, while a quarter at δ: (1.74-2.06, q, 8H) ppm is attributed to -CH2CH2. A single at δ: (3.8404.06, t, 4H) ppm is attributed to -SCH2 group [22].



R = CH_3, C_2H_5, C_3H_7, C_4H_9 and C_5H_{11}

Scheme 1. Synthetic route of 5a - 5e.

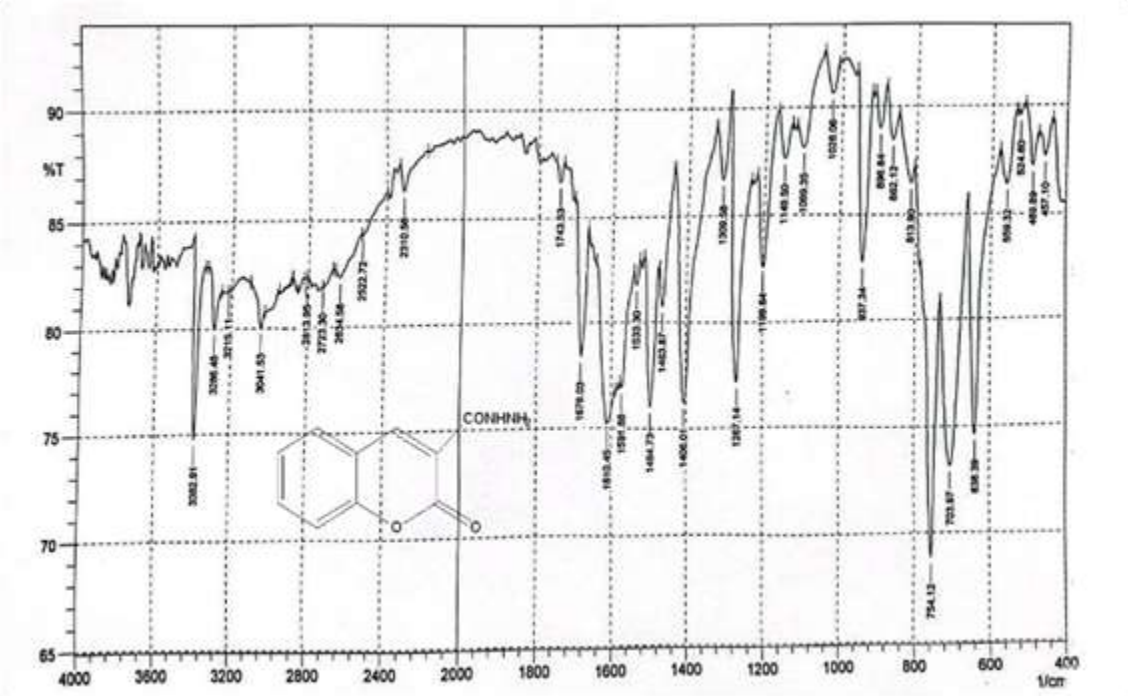


Figure 1. FT-IR -spectrum of (2a).

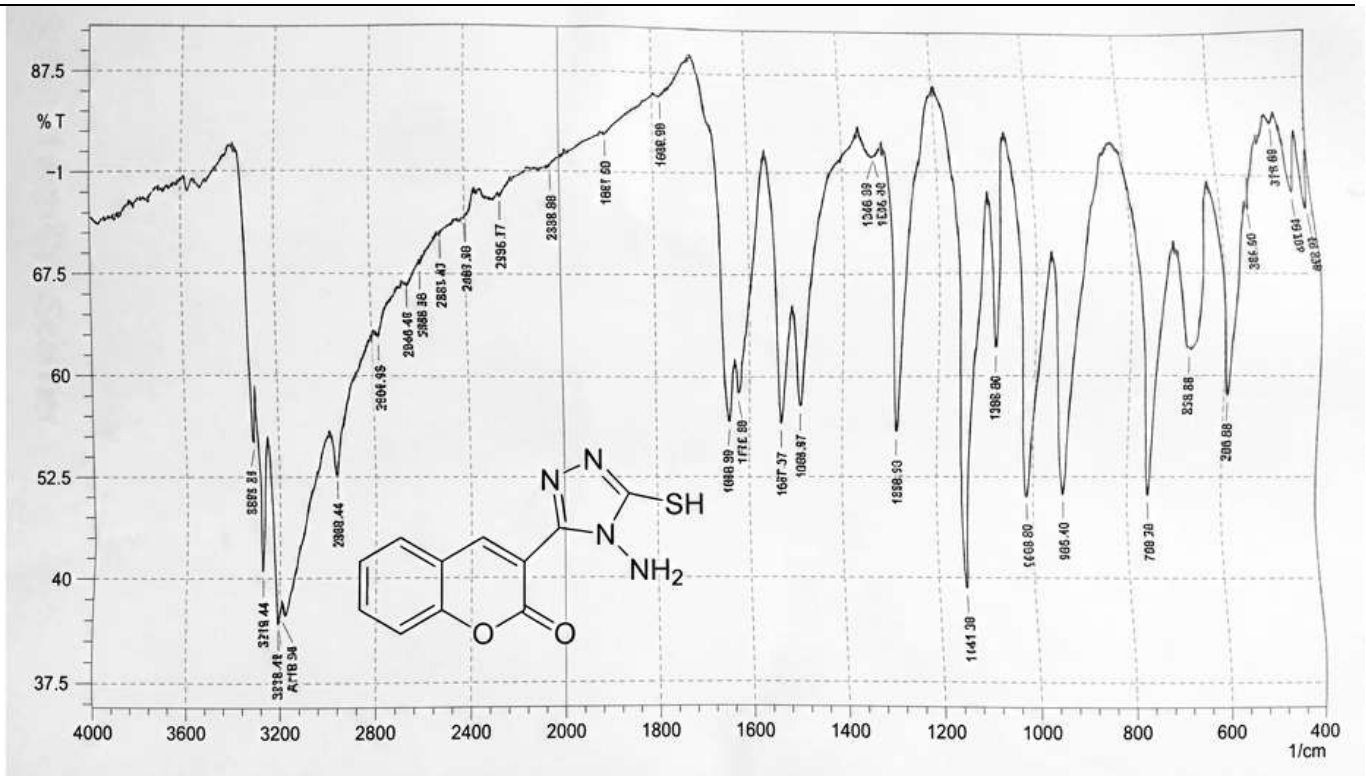


Figure 2. FT-IR -sp
ectrum of (3a).

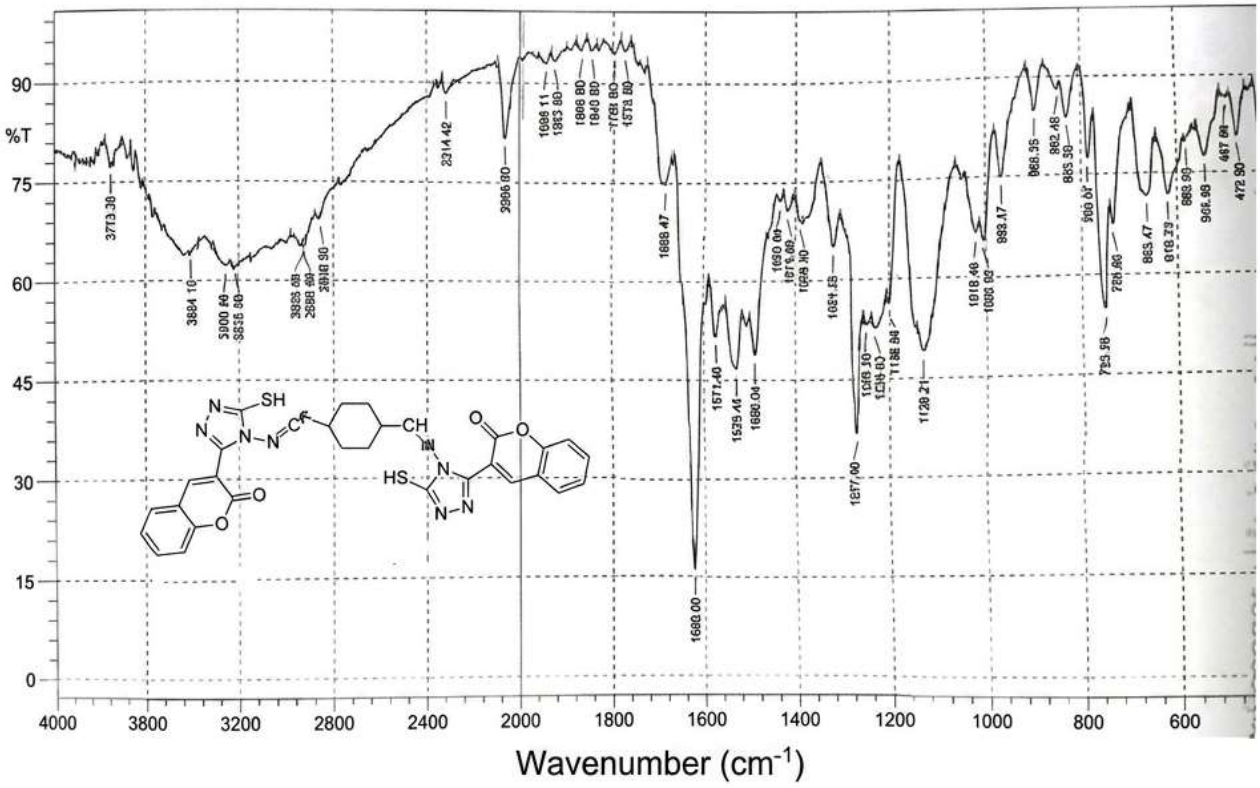


Figure 3. FT-IR -spectrum of (4a).

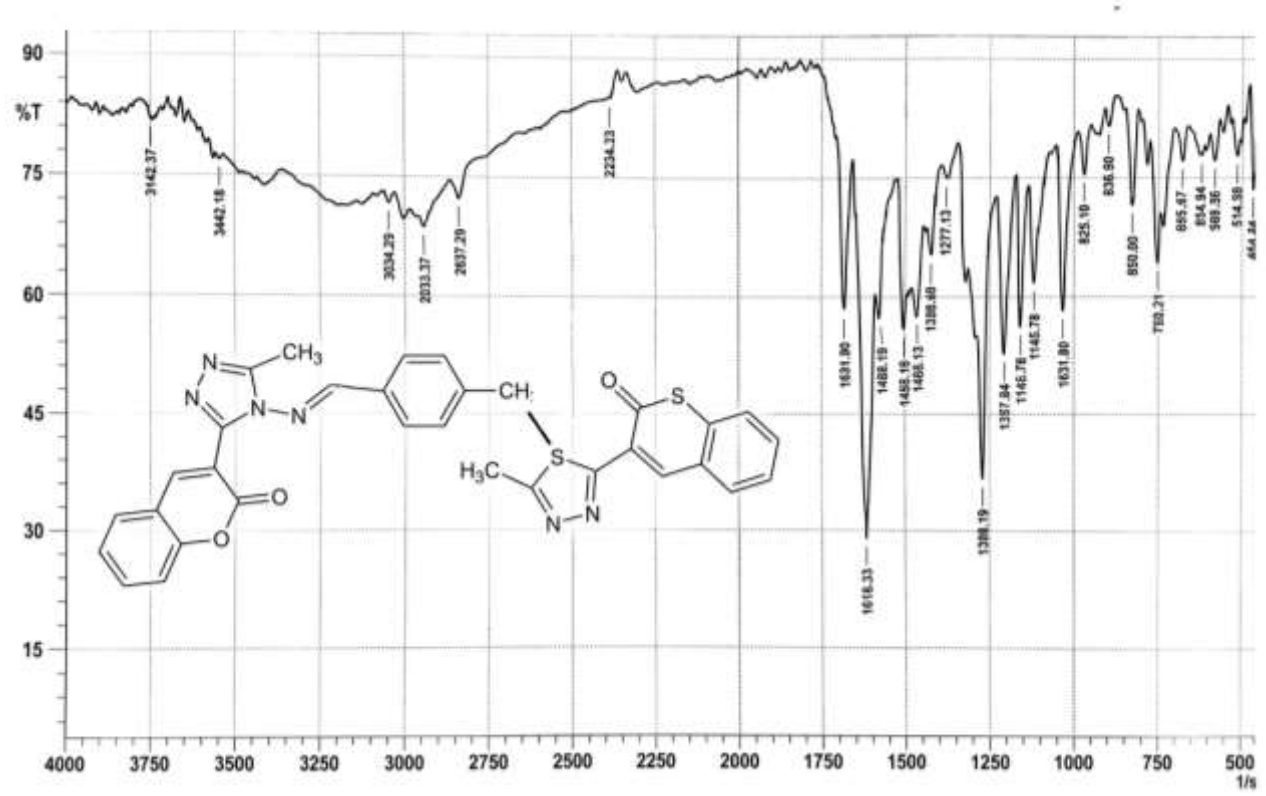


Figure 4. FT-IR -spectrum of (5a).

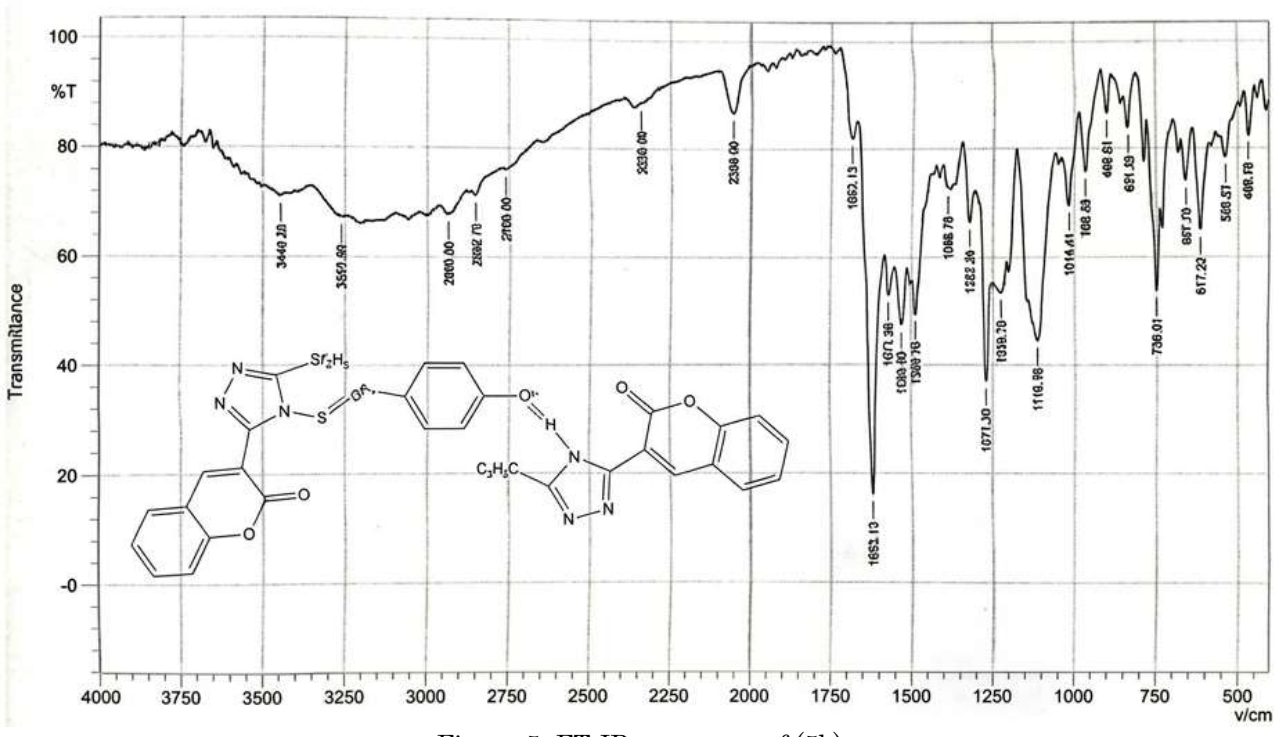


Figure 5. FT-IR -spectrum of (5b).

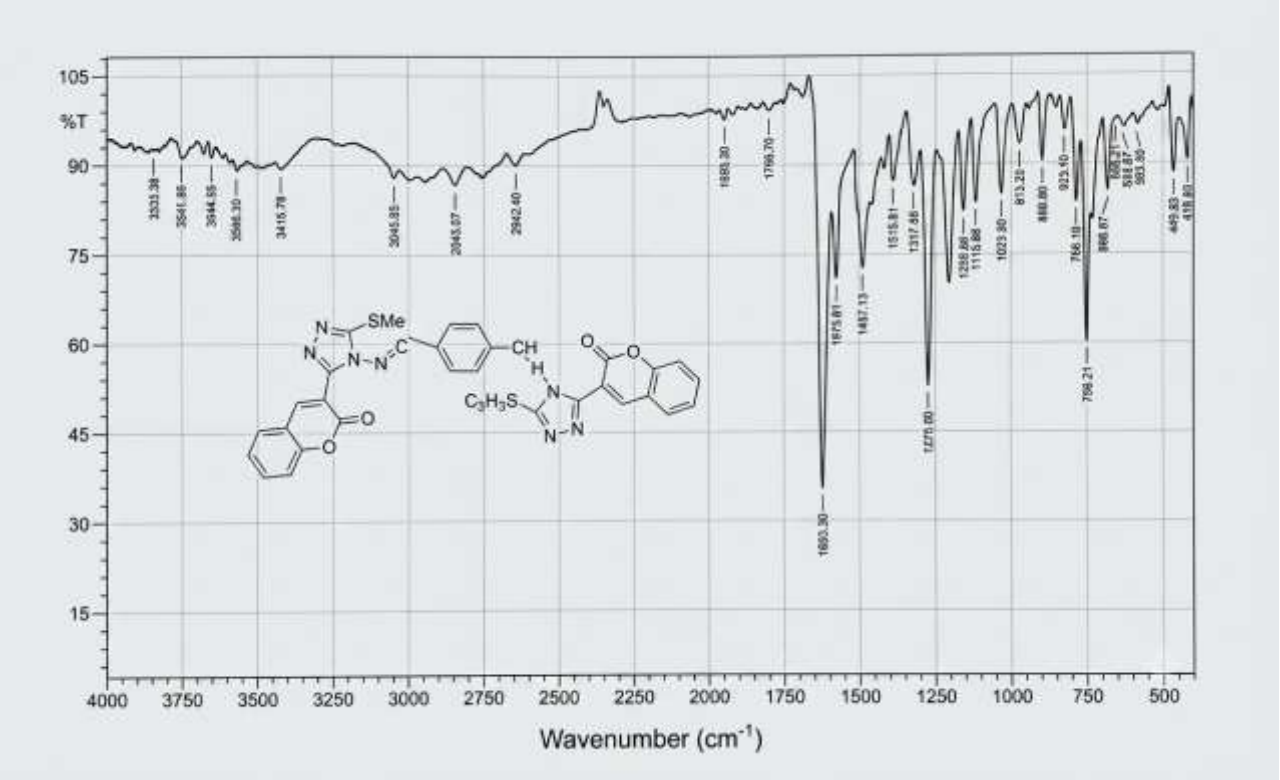


Figure 6. FT-IR -spectrum of (5c).

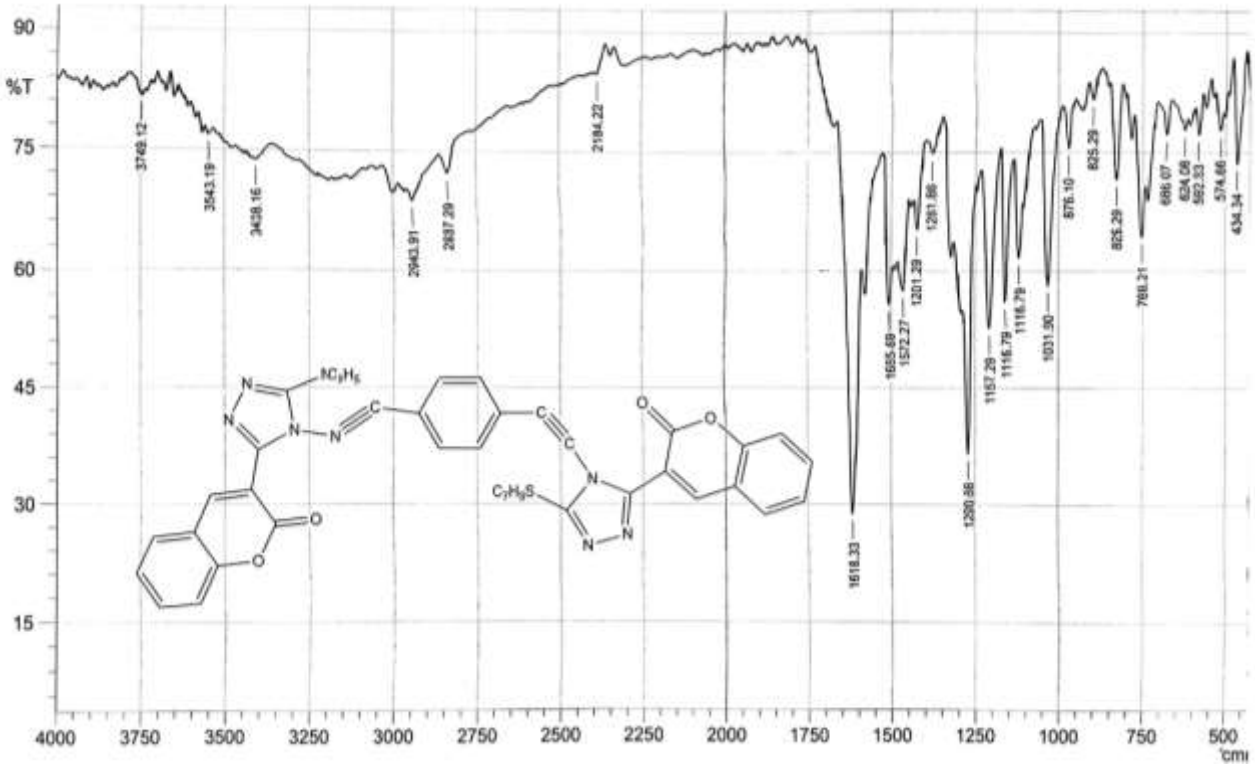


Figure 7. FT-IR -spectrum of (5d).

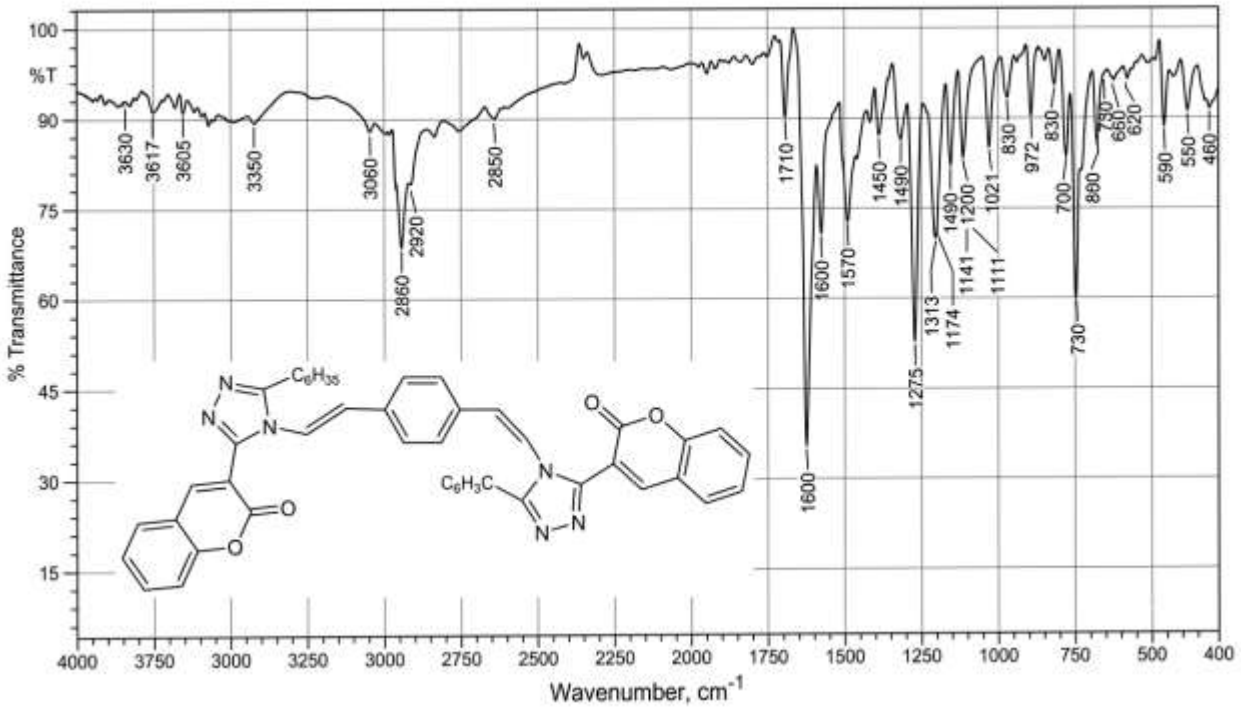


Figure 8. FT-IR -spectrum of (5e).

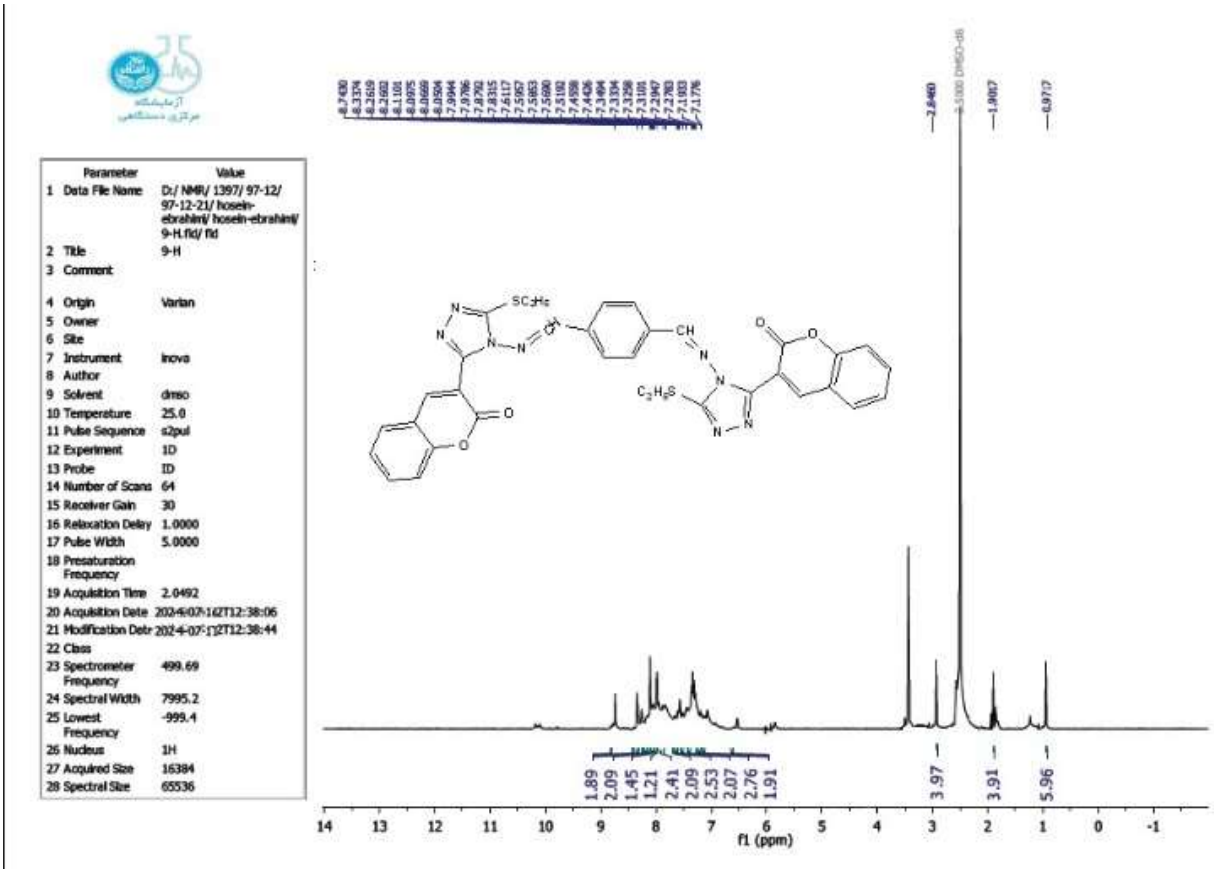


Figure 9. ^{1}H-NMR -spectrum of compound 5b.

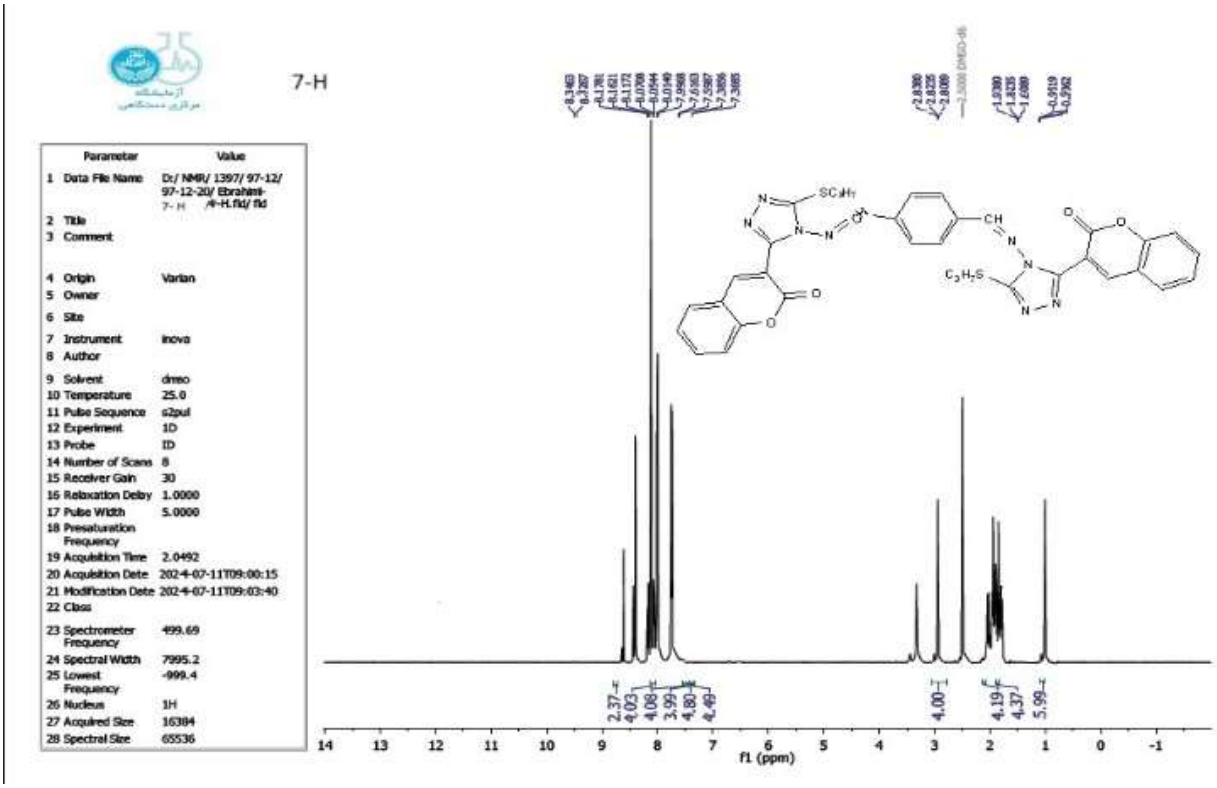


Figure 10. 1H-NMR -spectrum of compound 5c.

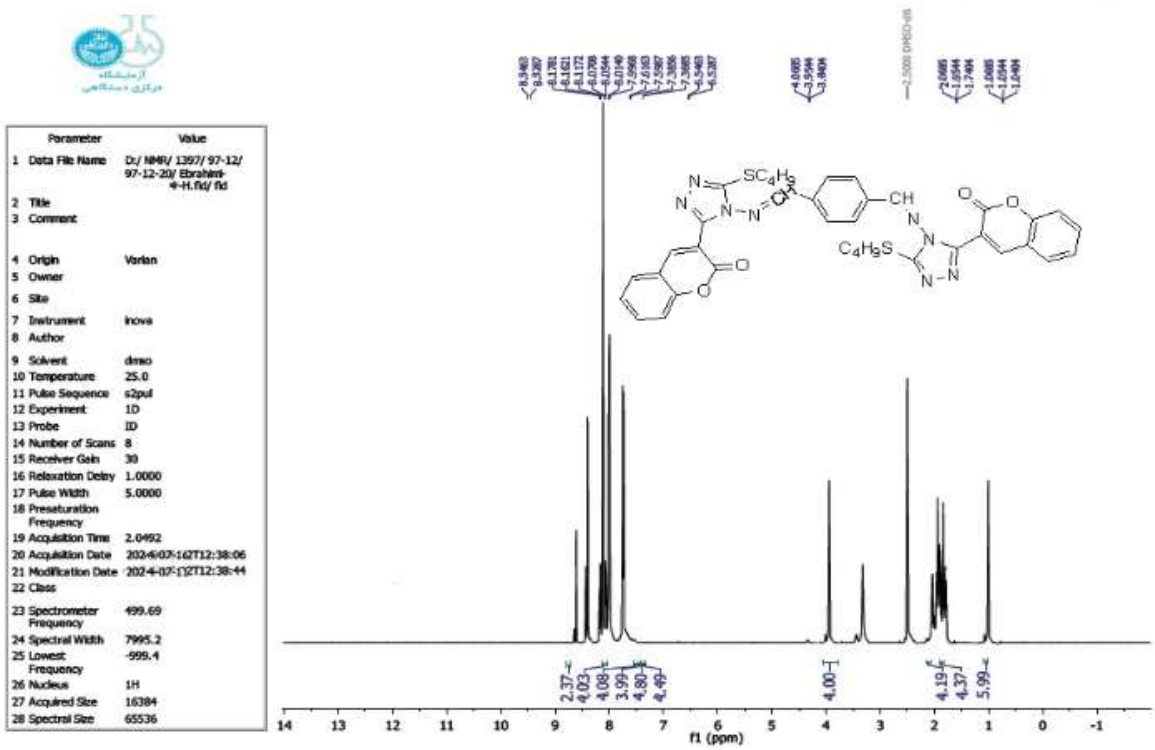


Figure 11. 1H-NMR -spectrum of compound 5d.

A new set of coumarin-triazole hybrid derivatives was successfully synthesized by sequential cyclization, Schiff base formation, and S-alkylation reactions. In summary, the synthetic approach described presented acceptable yields of target compounds under relatively simple and reproducible reaction conditions. FT-IR and ^{1}H-NMR characterization confirmed that the required molecular structures were successfully formed and the planned functional groups were present. The spectroscopic data obtained were in excellent agreement with the suggested structures of all synthesized derivatives. Coumarin and triazole moiety incorporation in a cohesive molecular architecture is an attractive strategy for the synthesis of structurally diverse heterocyclic compounds. The synthetic pathway presented in this work provides a flexible platform for further structural modification by introducing various substituents to extend the range of compounds in the range of coumarin–triazole hybrids. Such structural flexibility might lead to the generation of new derivatives with optimized physicochemical and functional attributes. In addition, the synthesized compounds would serve as helpful intermediates in the pursuit of future medicinal chemical research. [21]. Furthermore, the association of binding affinities will be predicted in molecular docking studies and other computational methodology by means of predicting binding affinities, discovering promising molecular targets for and understanding structure-activity relationships in more detail. Combining experimental biological screening with computational modeling is anticipated to aid in the early detection and classification of promising leads as active compounds. Hence, the current work constitutes a beneficial platform on which to build future pharmaceutical as well as biochemical investigations in the coumarin–triazole-based heterocyclic systems, aiming to help in the discovery of new bioactive molecules of interest with therapeutic potential [22].

4. Conclusions

Such novel coumarin–triazole hybrid derivatives were also successfully synthesized as the product of sequential cyclization, Schiff base formation, and S-alkylation reactions. The synthetic processes provided the intended compounds with satisfactory yields under relatively simple reaction conditions. The structural characterization by FT-IR and ^{1}H-NMR spectra validated the formation of required compounds and confirmed the expected functional groups and structural features. Spectroscopic analysis of the derivatives supported the molecular structures that were hypothesized for all synthesized derivatives. The work shows promising synthetic methodology to build coumarin–triazole hybrid frameworks and contributes to the development of a range of coumarin-based heterocyclic molecules. In addition, the derivatives prepared could be proposed as valuable intermediates for further chemical modification approaches and studies of physicochemical and structural characteristics of related heterocyclic systems.

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