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Synthesis, Characterization and Antimicrobial Evaluation of New Schiff Bases Containing 4-Hydroxycoumarin

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Abstract

The goal of this study is to prepare new coumarin derivatives, describe them in detail from a chemical standpoint, and test their antimicrobial properties. New Schiff bases of compound (III) 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide were successfully prepared by the reaction of proper aryl/hetero aromatic aldehydes with compound **(III)** under conventional conditions. Firstly, the compound 4-hydroxycoumarin **(I)** undergoes a reaction with ethylbromoacetate in the presence of potassium carbonate and dry acetone, resulting in the formation of compound (II) ethyl2-((2-oxo-2h-chromen-4-yl)oxy)acetate , which subsequently, in the presence of ethanol, interacted with hydrazine hydrate to create compound **(III)** 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide .In this paper a new coumarin derivatives were prepared and afterwards subjected to characterization using ATR-FTIR Spectroscopy and ^{1}HNMR spectroscopy .The Antimicrobial activity of the recently synthesized Coumarin derivatives were evaluated against a range of microorganisms, including two Gram-negative bacteria (*Escherichia coli* & *Pseudomonas aeruginosa*), two Gram-positive bacteria (*Streptococcus pneumoniae* & *Staphylococcus aureus*), and the *Candida albicans* fungus. The initial investigation into the antimicrobial properties of the last synthetic compounds revealed that compounds **IVa-d** exhibited varying degrees of antibacterial and antifungal activity.

Keywords: Schiff bases, 4-hydroxycoumarin, Aldehydes, Antimicrobisal activity.

Introduction

Schiff bases, which are molecules containing the azomethine group (–C=N–), are often produced by the condensation reaction between primary amines and active carbonyls. Schiff bases are a notable category of molecules within the field of medical and pharmaceutical chemistry, possessing various biological implications such as antibacterial[1,2], antifungal[3-6], and anticancer properties [7-10]. Schiff bases are compounds with imine (–C=N–) functional group, were first described by Hugo Schiff [11-13]. Schiff bases are known to possess a wide range of biological functions, making them of a great importance in the field of medicine and drug development, including anti-inflammatory[14,15], analgesic [16], antimicrobial [17-20], anticonvulsant [21], antitubercular [22], anticancer [23,24], anthelmintic and antioxidant properties [22]. Extensive research has been conducted on this particular group of ligands [25-27].Coumarin derivatives have attracted significant attention due to their involvement in both natural and synthetic organic chemistry. Several compounds that include a coumarin component demonstrate various biological activities, including molluscicidal [28], anthelmintic, hypnotic, insecticidal [29], anticoagulant [30], anticancer [31], and fluorescent brightening properties. It is believed that coumarins including a Schiff base moiety could show improved anticancer and other biological properties, The existence of the functional pharmacophore (-CONH-N=C-) is widely recognized as the underlying cause of the biological activity exhibited by hydrazone drugs. Therefore, Numerous hydrazone compounds containing this active group have shown notable bioactivities against cancer. [32] The compound known as 4-hydroxycoumarin serves as the fundamental skeleton structural for a wide range of naturally occurring substances, medicines, and insecticides. It serves as a critical intermediary for certain anticoagulants and rodenticides. This includes antithrombotic medicines used in humans [33] .Azomethine's nitrogen atom may establish a hydrogen bond with cell components, disrupting normal cell activities [34]. Introducing the Coumarin molecule with a Schiff-base may result in a

molecule with outstanding pharmacological and microbiological efficacy as corrosion inhibitor [35].The objective of this research is to make new 4-hydroxycumarin derivatives, describe them in detail from chemical characteristics, and the evaluate their antimicrobial properties. New Schiff bases of compound (**III**) 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide were successfully prepared by the reaction of proper aryl/hetero aromatic aldehydes with compound (**III**) under conventional conditions.

Materials and Methods

All compounds were obtained from commercial sources and were not purified before application. Merck (Germany) TLC silica gel gf254 sheet was used to conduct ascending thin layer chromatography (TLC). The use of thin-layer chromatography (TLC) was employed to observe the advancement of the chemical reaction and assess the level of purity shown by the resultant products. Examining thin-layer chromatography (TLC) sheets with ultraviolet (UV) light having a wavelength of 254 nm revealed the presence of dots. The melting points were recorded using an Electrothermal capillary apparatus (Stuart SMP30) and have not been corrected. The infrared spectra were acquired using a Shimadzu Specac Spectrometer (Shimadzu, Japan). A Varian model ultra-shield (500 MHz) spectrophotometer was utilized to acquire the proton nuclear magnetic resonance ^{1}HNMR spectra. The internal standard was Tetramethylsilane (TMS), and the sample solvent was Dimethyl sulfoxide (DMSO)-*d6*.The proton nuclear magnetic resonance (^{1}HNMR) spectroscopy experiment was conducted in the Islamic Republic of Iran at Tehran University. The antibacterial properties of the synthesized final products were investigated at a private laboratory called A Saham lab.

Preparation of compound II, ethyl-2-((2-oxo-2H-chromen-4-yl)oxy)acetate: [36,38]

Compound II was synthesized by an ether synthesis process. In 50 mL of dry acetone, 1.76 g (0.01 mol) of 4-hydroxycoumarin (I), 2.5 g (0.015 mol) of ethyl bromoacetate, and 2.07 g (0.015 mol) of potassium carbonate were mixed together. The mixture kept going for about 14 to 16 hours. The solvent underwent extraction at reduced pressure subsequent to the filtration of the mixture. Afterward, the resulting solid precipitate was thoroughly rinsed with a significant amount of water. The purification of the raw product was achieved by the recrystallization by ethanol, resulting in the formation of white crystals.yield:72.2%, white crystal m.p: 97° C, R*f* value: 0.72, solvent system; 1:1 (hexan: ethyl acetate).

FTIR spectra cm^{-1} : 3078.39 aromatic (C-H) Str., 2989.66 asymm. 2943.37 symm. aliph. C-H Str., 1751.36 (C=O) ester, 1701.22 (C=O) coumarin. 1H-NMR (500 MHz, DMSO- *d6*); (1.٤٠-1.47)ppm: (CH_3, t, 3H), (4.17-4.22) ppm: (CH_2, q, 2H),4.٧٩ppm: (CH_2, s, 2H), 5.٣٢ppm: (Arom-H, s,1H), (7.27-7.٩١)ppm: (Arom-H, m, 4H), Calculated for $C_{13}H_{12}O_5$.

Preparation of compound III 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide [39,40]

A solution containing compound **II** (2.6 g, 0.01 moles) in 27 mL of ethanol was subjected to reflux with one hundred percent hydrazine hydrate (1.012 g, 0.021 moles) for a about five hours and monitoring the reaction by TLC. The resulting mixture was left aside until cooling ,then the solvent was evaporated and cold water was added and the final product was obtained by filtration then washed several time by cold distilled water, left to dried then recrystallization from ethanol , resulting in the formation of a white crystalline powder. yield: 60.2% of a white crystalline powder with m.p.:166-167° C, R*f* = 0.51, solvent system; 1:9(methanol :chloroform).

FTIR spectra cm^{-1}: 3402.75 asymm. 3317.55 symm. (N-H) primary amide, 3047.53 aromatic (C-H), 2978.08 & 2916.37 asymm., 2864.93 symm. (C-H) alipha., 1720.5 C=O coumarin, 1674.21 C=O amide. ^{1}H-NMR (500 MHz, DMSO- *d6*); 4.34 ppm: (NH2,s, 2H), 4.81 ppm: (CH2,s, 2H), 5.92 ppm: (Arom-H,s,1H), (6.99-7.98) ppm: (Arom-H,m,4H), 9.43 ppm: (NH,s,1H), Calculated for $C_{11}H_{10}N_2O_4$.

The synthesis of Schiff-base derivatives products of 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide [N-acyl Hydrazones] (IV a-d): [20]

An ethanolic solution (10 ml) of aromatic aldehydes (0.002 mol) with (4-6 drops) of glacial acetic acid were stirred for 10 minutes then, compound III (0.0021 mol) dissolved in 15 ml of absolute ethanol was added to the reaction mixture and refluxed for 16 hours. The required products (**IVa-d**) were obtained by cooling the mixtures to room temperature; the resulting solid masses were filtered and subsequently recrystallized by ethanol.

The following data is provided for Compounds **IVa, IVb, IVc** and **IVd**: their physical appearance, yield, melting point, R*f* value, as well as the ATR-FTIR spectra and ^{1}H-NMR.

Compound (IVa) which is N'-(2-(3,4-dimethylphenyl)ethylidene)-2-((2-oxo-2H-chromen-4-yl)oxy) acetohydrazide

Molecular formula ($C_{21}H_{20}N_2O_4$); White powder, yield: 77.8%, m.p=227–228°C ,R*f* =0.73 (methanol 1:chloroform 9), FTIR spectra cm^{-1}: 3186.4 (N-H) sec. amine, 3086.11 aromatic (C-H), 2981.9 & 2927.94 C-H asymm. (C-H) alipha., 2866.22 & 2854.65 symm. (C-H) alipha., 1725.93 (C=O) coumarin, 1678.07 (C=O) amide, 1624.06 (C=N), 1261.4 (C-N) str., ^{1}H-NMR (500 MHz, DMSO- *d6*); 5.91ppm: (s,1H, Arom-H), 4.81ppm: (CH_2,s, 2H), 11.58ppm: (NH,s,1H), 8.28ppm:

(N=CH,s,1H), 2.38ppm: ($2CH_3$,2s,6H), (6.98-7.73)ppm:(Arom-H,m,6H).

Compound (IVb) N'-[4-hydroxy-3-nitrophenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide

Molecular formula ($C_{20}H_{18}N_2O_7$); Off-white powder, yield: 72.4%, m.p.: 216–217 °C, R*f* = 0.66 (methanol 1:chloroform 9), FTIR spectra cm^{-1}: 3444. (O-H), 3186.4 (N-H) sec. amine, 3089.96 aromatic (C-H),2981.95 & 2935.66 asymm. (C-H) alipha, 2831.5 symm. (C-H) alipha, 1728.22 (C=O) coumarin, 1681.93 (C=O) amide, 1620.21 (C=N).

^{1}H-NMR ; 3.75ppm:($2CH_3$, s,6H,) ,4.80 ppm:(CH_2,s,2H),5.90ppm: (Arom-H, s,1H), (6.98-7.76) ppm: (Arom- H,m,5H), 8.48ppm: (CH,s,1H), 8.87ppm: (OH, s,1H), 11.59ppm: (NH, s,1H).

Compound (IVc) 2-[(2-oxo-2H-chromen-4-yl)oxy]-N'-[(thiophen-3yl)methylidene] acetohydrazide

Molecular formula ($C_{16}H_{12}N_2O_4S$); White powder, m.p.: yield: 56.1%, 260–261 °C, R*f* =0.63 (ethyl acetate 3:hexane 1), FTIR spectra cm^{-1}: 3109.25 (N-H) sec. amine, 3051.55 arom. (C-H), 2970.38 & 2931.8 asymm. (C-H) alipha ,2916.33 symm. (C-H) alipha., 1712.79 (C=O) coumarin, 1685.79 (C=O) amide, 1616.35 (C=N), 1543.05 & 1512.19 (C=C arom).

^{1}H-NMR ; 4.83ppm: (CH_2, s,2H), 5.68ppm: (Arom-H,s,1H), (6.98-7.76)ppm: (Arom-H,m,6H), 8.42ppm: (CH,s,1H), 9.95ppm: (NH,s,1H).

Compound (IVd) 2-[(2-oxo-2H-chromen-4-yl)oxy]-N'-[(1H-pyrrol-2-yl)methylidene] acetohydrazide

Molecular formula ($C_{16}H_{13}N_3O_4$); White powder, yield: 56.1%, m.p.: 243–244 °C, R*f* = 0.29 (ethyl acetate 3: hexane 1), FTIR spectra cm^{-1}: 3255.44 (N-H) pyrrole ring, 3105.39 (N-H) sec. amine, 3051.53,3074 aromatic (C-H), 2924.09] asymm. (C-H) alipha, 2854.66 asymm. (C-H) alipha , 1720.50 (C=O) coumarin, 1637.92 (C=O) amide, 1618.63 (C=N), 1539.2 & 1573.91(C=C) aromatic.

^{1}H-NMR ;4.81ppm: (CH2,s,2H), 5.55ppm: (Arom-H,s,1H), (6.12-7.37)ppm: (Arom-H,m,6H), 7.84ppm: (CH,s,1H), 10.52ppm: (NH,s,1H). 11.37ppm: (NH of pyrrole,s,1H).

Results and Discussion

Chemistry

Figure 1 illustrates the schematic representation of the synthetic route used for the production of the desired compounds. Starting with compound (**I**), 4-Hydroxycoumarin, with ethyl bromoacetate and anhydrous K_2CO_3 refluxing together in dry acetone. The FTIR spectra cm^{-1} of compound **(II)** ethyl-2-((2-oxo-2H-chromen-4-yl)oxy)acetate exhibit absorption band at 1751 because of (C=O) ester carbonyl asymmetric str. and another band at 1184.29 because of ester (C-O) a symmetric str. these two bands indicated the formation of compound II which is ester . The ^{1}H-NMR spectrum showed a triplet peak at (1.44–1.49) ppm because of three hydrogen of CH_3, a quartet peak at (4.17–4.22) because of two hydrogen of CH_2 and a singlet at 4.79 because of two hydrogen of CH_2, the compound **II** react with hydrazine hydrate to give compound **(III**) 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide . The FTIR spectra cm^{-1} for Compound **III** show absorption band at 3402 & 3317 N-H (asymm. & symm.) of primary-amine, 1674.21 because of (C=O) carbonyl group of amide. ^{1}H-NMR spectra showed a singlet at 4.66 ppm because of two hydrogen of CH_2, and another singlet peak at 9.43 ppm because of the hydrogen of (NH) & a singlet at 4.29 ppm because of two hydrogen of (NH_2) which indicate the formation of third compound.

Compounds **IV (a-d)** were prepared by the reaction of compound **III** 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide with various aldehydes in the presence of few drops glacial acetic acid. The FTIR spectra cm^{-1} of these compounds exhibits peaks at the wavenumbers of (1674-1685) cm^{-1}, which can be attributed to the stretching vibration of the carbonyl group (C=O) in the amide. Additionally, absorption bands in the range of (3109-3186) cm^{-1} are observed, corresponding to the stretching vibration of the N-H bond in a secondary amine. Furthermore, absorption bands at wavenumbers of (1261-1269) cm^{-1} are detected, indicating the stretching vibration of the C-N bond.

Antimicrobial Activity

Table 1 presents the results of the assessment of the antimicrobial features of the synthesized compounds over specific microorganisms at a dosage of one milligramme per millilitre.. The antibacterial activity of the synthesised compounds was evaluated against two gram positive bacteria, namely *S. pneumoniae* & *S. aureus*, as well as two gram negative bacteria, namely *E. coli* & *P. aeruginosa*. Additionally, the antifungal activity was tested against the fungi species *C. albicans*. The minimum inhibitory concentration (MIC) of all derivatives in DMSO was set at 1000 µg/mL. Based on the data recorded in table (1), it can be observed that all the derivatives exhibited significant activity against both Gram positive and Gram negative bacteria, when compared to Amoxicillin. However, compounds **IV(a,b,c)** showed moderate activity against *S. pneumoniae*, and compound **IVa** demonstrated moderate activity against *P. aeruginosa*. Furthermore, all the tested compounds demonstrated high activity against *Candida albicans* in comparison to Fluconazole.

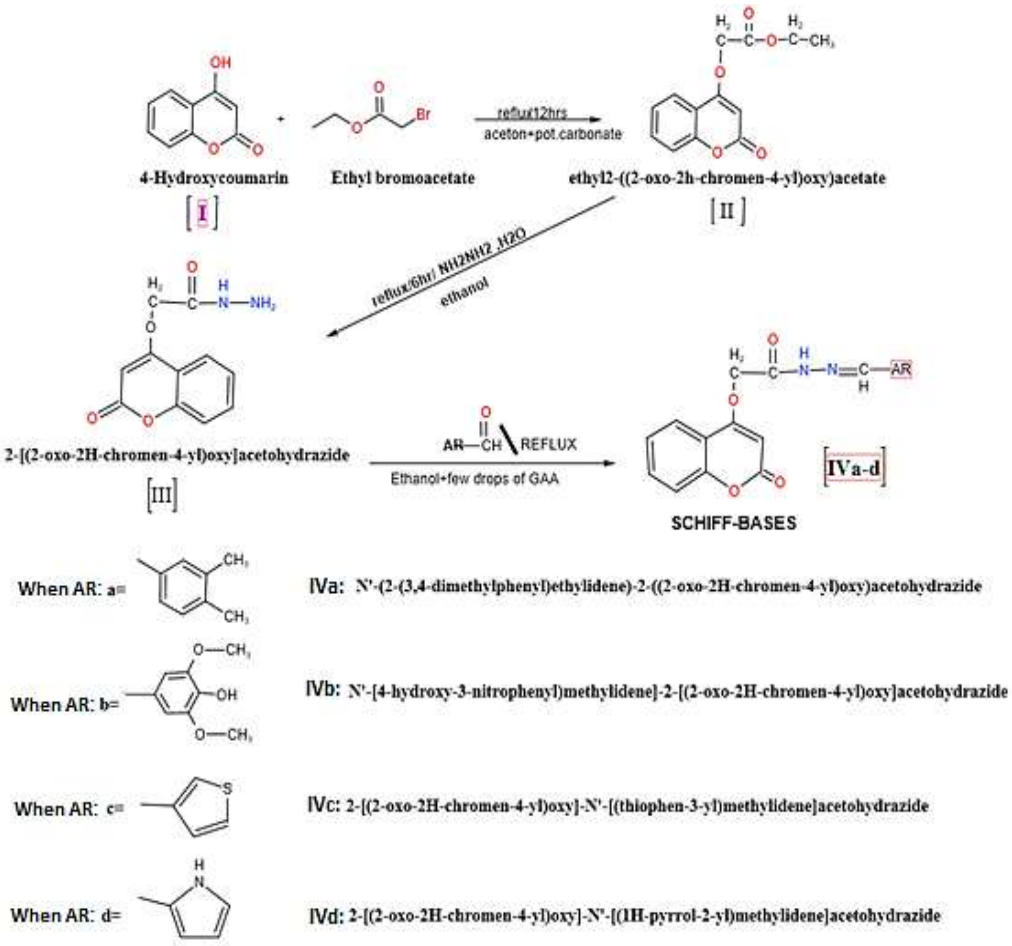

Figure 1. General synthetic pathway of target compounds

Table 1. The in-vitro antibacterial action of the synthesised compounds was evaluated at a concentration of 1000 µg/mL.

Compound	*S. pneuomoniae*	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*
IVa	12	20	25	13	23
IVb	13	23	24	21	25
IVc	16	26	26	22	24
IVd	22	29	23	31	31
Amoxicillin	23	25	29	20	–
Ciprofloxacin	29	25	22	–	–
Fluconazole		–	–	–	22
DMSO	–	–	–	–	–

(-) = No activity, Zones of inhibition between 5 and 10 mm are considered to be slightly active, zones between 10 and 15 mm are considered to be moderately active, and zones more than 15 mm are considered to be very active.[41]

Conclusion

A number of New Schiff bases containing 4-hydroxycoumarin derivatives were synthesized by multistep reaction. This synthesis process consist of the formation of compound **III** 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide which is done by the treatment 4-hydroxycumarin with ethyl bromoacetate to produce compound **II** ,which then react with hydrazine to give compound **III**, then , it reacted with various aldehydes to produce the final compound, which was then clarified by FTIR spectra and ^{1}HNMR, the targeted compounds **(IVa-d)** were successfully synthesized .Comparing the antimicrobial activity of whole targeted chemical

series (**IVa-d**) against Amoxicillin, Ciprofloxacin, and Fluconazole as standard anti-microbial agents , the compounds all exhibited strong to moderate antibacterial and antifungal efficacy which give us promising molecule for further research and overall the most active compounds is **IVd** which exhibited strong activity against all bacgteria and fungi .

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Conflicts of Interest

No competing interests to disclose.

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Ethics Statements

This research was approved by the scientific and ethical committees in the College of Pharmacy/ University of Baghdad.

Author Contribution

Karrar A. Hachim and Mohammad K. Hadi affirm their involvement in the following aspects of the paper: research idea and design, data collecting, analysis and result interpretation, and draught text writing. The final draught of the paper was approved by all authors after they had evaluated the findings.

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تحضير وتشخيص وتقييم مضادات الميكروبات لبعض قواعد شيف الجديدة المحتوية على ٤- هيدروكسي كومارين

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[١]قسم الكيمياء الصيدلانية، كلية الصيدلية، جامعة بغداد، بغداد، العراق .

الخلاصة

الهدف من هذه الدراسة هو تحضير مشتقات جديده لل ٤- هايدروكسي كومارين مع تشخيصها من الناحية الكيميائية وفحص نشاط مضادات الميكروبات لهذه المركبات, تم تصنيع مركبات قواعد شيف الجديدة الخاصة بالمركب(III) المسمى 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide-2 عن طريق تكثيف الالديهايدات المختلفة مع المركب (III) تحت ظروف تقليدية. يتفاعل ٤-هيدروكسي الكومارين (I) مع إيثيل برومو أسيتات في وجود كربونات البوتاسيوم والأسيتون الجاف لينتج المركب (II) (-ethyl2 (2-oxo-2H-chromen-4-yl)oxy)acetate-2)]-2, ، والذي يتفاعل بعد ذلك مع هيدرات الهيدرازين في وجود الإيثانول لإنتاج المركب (III) 2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide والذي بدورهِ يتفاعل مع الالديهايدات المختلفة لكي يتم تحضير مشتقات الكومارين الجديدة حيث تم إخضاعها للتشخيص باستخدام مطياف الاشعة تحت الحمراء وتحليل الرنين المغناطيسي النووي للبروتون ثم تم تقييم نشاط المضادات الحيوية لمشتقات الكومارين الجديدة ضد مجموعة من الكائنات الحية الدقيقة، بما في ذلك نوعين من البكتيريا الموجبة (المكورات العنقودية الذهبية والمكورات العقدية الرئوية)، واثنين من البكتيريا السالبة (الزائفة الزنجارية والإشريكية القولونية)، والفطر المبيضات البيضاء. في هذا البحث أظهرت النتائج الأولية الخواص المضادة للميكروبات للمركبات النهائية وأن المركبات **IVa، IVb، IVc،و IVd** أظهرت درجات متفاوتة من النشاط المضاد للبكتيريا والفطريات.

الكلمات المفتاحية: الالدهايدات ، قواعد شيف، ٤- هايدروكسي كومارين،المضادات الميكروبية.