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Synthesis of New Pyrimidine Derivatives From 3-Acetylcoumarin–Chalcone Hybrid and Evaluation Their Antimicrobial Activity

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Abstract

3-coumarin/chalcone B1-B3 hybrids served as malleable antecedents for the development of novel bioactive pharmacophores. In this study, the matching coumarin-chalcones hybrid was obtained from 3-acetylcoumarin (comp A) via condensation with several aromatic aldehydes in ethanolic piperidine solution. To further modify these hybrids, we reacted them with thoiurea in the presence of base in ethanol, yielding pyrimidine derivatives C1- C3. Their chemical characteristics and spectroscopic data were used to characterize the newly synthesized heterocycles. The antibacterial efficacy of all synthesized compounds was tested. Compound (C3) was shown to have the highest antibacterial activity as compared to ciprofloxacin against both gram positive and gram negative bacteria, whereas compound (C2) displayed a moderate antibacterial activity and compound C1 had low activity. C1-C3 were shown antifungal activity as compared to fluconazole that showed antifungal efficacy against C. ablicans.

Keywords: 3-coumarin-chalcone hybrid , Thiourea , Pyrimidine derivatives , Antimicrobial activity .

تخليق مشتقات البيريميدين الجديدة من هجين ٣ - استيل كومارين –جالكون وتقييم نشاطها المضاد للميكروبات

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الخلاصة

تعد مركبات ٣- استيل الكومارين - الجالكون B1- B3 الهجينة مركبات وسطية قابلة لتطوير أدوية جديدة نشطة بيولوجيًا. في هذه الدراسة ، تم الحصول على هجين الكومارين - الجالكون المتجانس من ٣- استيل كومارين(مركب A) عن طريق التكثيف مع العديد من الألديهايدات الاروماتية في محلول البيبريدين الإيثانولي ثم تم تفاعلها مع الثيويوريا في وجود قاعدة في الإيثانول ، للحصول على مشتقات بيريميدين C1 - C3. تم استخدام خصائصها الكيميائية وبياناتها الطيفية لتوصيف الحلقات غير المتجانسة المصنعة. تم اختبار الفعالية المضادة للبكتيريا لجميع المركبات المصنعة. أظهر المركب (C3) أعلى نشاط مضاد للجراثيم ضد كل من البكتيريا موجبة وسالبة الجرام بالمقارنة مع سيبروفلوكساسين ، بينما أظهر المركب (C2) نشاطًا معتدلًا مضادًا للبكتيريا وكان للمركب C1 نشاطًا منخفضًا. أظهرتC1 ، C2 ، C3 فعالية مضادة للفطريات بالمقارنة مع فلوكونازول الذي اظهر فعالية مضادة للفطريات ضد.C. ablicans

الكلمات المفتاحية: هجين ٣-كومارين-جالكون ، ثيويوريا ، مشتقات بيريميدين ، نشاط مضاد للميكروبات.

Introduction

The field of heterocyclic chemistry is rapidly expanding as one of the most important subfields of organic chemistry [(1)]. Around 60% of all chemical synthesis in 1998 was of heterocyclic compounds [(1)]. New heterocyclic compounds are now being published from a wide variety of fields, including medicines, biology materials, and others [(2)]. Six-membered nitrogen-containing compounds, or pyrimidines, are useful in a number of different contexts. The pyrimidine nucleus plays an important role in many naturally occurring substances, including nucleic acids and vitamin B1 [(3)]. Invaluable pharmacological activity is often linked to the pyrimidine ring system. [(4)]particularly being antifungal[(5)] , antitubercular[(6)] , antibacterial, antiviral[(7)], anticancer [(8)]and antioxidant[(9)]. Numerous alterations have been made to pyrimidines in order to generate derivatives with \novel biological characteristics [(7)]. Coumarins are a unique class of molecules that play an important function in the natural world. They are a type of plant secondary metabolite known as flavonoids, which have been linked to many different functions in the body [(10)]. Coumarin chemicals, whether they come from nature or the lab, play a vital role. Multiple coumarin-containing compounds have diverse biological and pharmacological effects[(11)], like anti-HIV[(12,13)], anticoagulant[(14)], antibacterial[(15)], antioxidant[(16)] and antifungal activities[(17)]. Natural compounds called chalcones (1,3-diaryl-2-propen-1-ones) are a significant group within the flavonoid family. They exhibit intriguing biological actions. Both rings contain a bi-electrophilic keto-vinyl chain that is extremely reactive and has an active interesting antimicrobial, anti-inflammatory[(18,19)] , anticancer[(20)], anti-HIV[(12)].

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It is common knowledge that chalcone can be used as a starting material in the production of a wide range of heterocyclic compounds. Heterocyclic compounds with nitrogen-containing rings, such as pyrazoline and pyrimidine, are produced through the cyclization of chalcone [21]. Scientific community uses an approach of synthetic molecular hybridization between coumarins and chalcones to design a variety of coumarin-chalcone hybrids for therapeutic potentials due to their biological importance [22]. As a result of combining heterocycles, it is now possible to design innovative multicyclic molecules with enhanced biological activity [23].

To identify bioactive pharmacophores and assess their antibacterial activity, the current study employed a hybridization technique to create pyrimidine derivatives by combining coumarin chalcone hybrids with thiourea.

Materials and Methods

Chemicals and solvents and other reagents that used in the synthesis were bought from commercial sources. Using thin-layer chromatography (GF254, Merk, Germany), we tested termination of the reaction on the UV-induced reactions (254nm). A pair of different solvent systems were used, A and B which are n-hexane: ethyl acetate in a 3:1 ratio , and chloroform :methanol in a 3:1 ratio, respectively .The Stuart SMP3 melting point equipment was used to determine the melting points in open capillary tubes, and these values have not been modified in any way. The infrared spectra were created with a Shimadzu FT-IR spectrophotometer from Japan. The IR experiments were carried out at Baghdad university, college of pharmacy . ^{1}H-NMR spectra were made using a bruker model ultra-shield 400 MHz spectrophotometer, tetramethylsilane (TMS) as an internal standard, DMSO-d6 as a sample solvent, chemical shift values reported as (=ppm). The ^{1}HNMR experiments were carried out at Al-Basra University , College of Science and Research central laboratory in Buali Institute, Mashhad university of Medical Sciences .

Synthesis of 3-acetylcoumarin(compound A)

A mixture of ethylacetoacetate (0.1 mol, 13g) and salicylaldehyde (0.1 mol, 12.2g) was swirled and cooled in an ice bath to near 0 C. Then, dropwise, 0.5 mL piperidine was added and left to react for 5 minutes. A yellow paste resulted. The residue was separated by filtration and washed with ethanol. Absolute ethanol was used to recrystallize the precipitated product. 3-Acetyl coumarin was obtained with a 85% yield[24].

3-acetylcoumarin(Compound A)

Powder yellow, Yield: 85%, m.p: (121 °C), IR(cm^{-1}): (3032 cm^{-1}) aromatic C-H stretching , (2931 cm^{-1}) CH3 stretching ,(1735 cm^{-1})C=O stretching of ester , (1674 cm^{-1}) C=O of stretching conjugated ketone , (1608 cm^{-1},1554 cm^{-1})C=C stretching, (1207 cm^{-1}) C-O-C stretching. ^{1}H-NMR: δ 2.57 (s, 3H) of (O=C-CH3), δ 7.37-7.9 (m, 4H) of benzene , δ 8.61 (s, 1H) of lactone ring. Figures (1-1) and (1-2) show the compound's FT-IR spectra and ^{1}HNMR spectrum, respectively.

Synthesis of chalcone (compounds B1- B3) the 3-acetyl-2H-chromen-2-one (1.88 g, 0.01 mole) and three different aldehydes (thoiphene-2-carboxaldehyde(1.12g), pyrrole- 2-carboxaldehyde(0.95g),para-methoxybenzaldehyde (1.36 g)) (0.01 mole) were each individually combined, agitated, and heated (below 60 ºC) in 25 ml of ethanol in order to form a clear solution. Following that, (0.01 mole , 0.85 g)of piperidine was added very slowly, and the mixture was allowed to reflux for a total of 8 hours. After the reaction was finished (according to TLC monitoring using solvent system (A)), the mixture was cooled down and the product was isolated by filtration . Ethanol was used to recrystallize a precipitate [25].

3-(3-(thiophen-2-yl)acryloyl)-2-H-chromen-2-one(CompoundB1):(yellow powder): 50% yield, m.p : (164 °C), R_f: 0.56 (A), and IR(cm^{-1}): (1724 cm-1)C=O stretching of ester , (1674 cm^{-1}) C=O stretching of conjugated ketone, (3023cm^{-1}) C-H stretching of aromatic ring, (1548 cm^{-1}, 1556 cm^{-1}), C=C stretching of α, β- unsaturated ketone and aromatic ring and (1195 cm^{-1}) C-O-C stretching.^{1}H-NMR: δ 7.34-7.86 (m, 4H) of coumarin's benzene ring, δ 8.69 (s, 1H) of coumarin's –C(=O)-C=C, δ 7.22, 7.74(m, 2H) of α, β- unsaturated ketone (chalcone) and δ 6.24 (m, 3H) of (thiophene ring). Figures (1-3) and (1-4) show the compound's FT-IR spectra and ^{1}HNMR spectrum, respectively.

3-(3-(1H-pyrrol-2-yl)acryloyl)-2-H-chromen-2-one (Compound B2): powder orange, 60% yield, m.p: (155 °C), R_f: 0.48 (A), IR(cm^{-1}): (1720 cm^{-1}) C=O stretching of ester , (1608cm^{-1}) C=O stretching of conjugated ketone , (3020cm^{-1})C-H stretching of aromatic ring, (3240cm^{-1})N-H stretching, (1573 cm^{-1}, 1539cm^{-1})C=C stretching . ^{1}H-NMR: δ 6.24-6.93(m, 3H)of (pyrrole ring), δ 7.51-7.8 (m, 4H)of coumarin's benzene ring, δ 7.14, 7.75 (m, 2H) of α, β- unsaturated ketone (chalcone), δ 8.56(s,1H) of coumarin's-C(=O)-C=C and δ 11.78(s,1H)of pyrrole's NH. Figures (1-5) and (1-6) show the compound's FT-IR spectra and ^{1}HNMR spectrum, respectively.

3-(3-(4-methoxyphenyl)acryloyl)-2-H-chromen-2-one (Compound B3): yellow, 50% yield, m.p:(170°C), R_f: 0.5 (A), IR(cm^{-1}): (1720 cm-^{1})C=O stretching of ester , (1674cm^{-1})C=O stretching of conjugated ketone, (3043cm^{-1}) C-H stretching of aromatic ring , (1608 cm^{-1}, 1573cm^{-1}) C=C stretching. ^{1}H-NMR: δ 3.82(s, 3H)of OCH3, δ 7.6-7. 86 (m,4H)of coumarin's benzene ring , δ 7.03, 8.82(m, 2H)of chalcone, δ 8.64(s,1H) of

coumarin's-C(=O)-C=C and δ7.06-7.68 (m,4H) of benzene ring of chalcone. Figures (1-7) and (1-8) show the compound's FT-IR spectra and ^{1}HNMR spectrum, respectively.

Synthesis of compounds(C1-C3):

A mixture of appropriate chalcones (0.001 mole) (0.28 g of B1, 0.26 g of B2, 0.3g of B3) and thiourea (0.002 mole, 0.15 g) in ethanol (50 ml) and sodium hydroxide (0.002 mole, 0.08 g) mixed in a little amount of water was refluxed on a water bath for 12 hrs (according to TLC monitoring using solvent system (A)) before being pured into 250 ml of cold water and neutralized with dilute HCL. The solid that separated in each example was filtered, washed with water, and recrystallized from ethanol : chloroform. (8:2)[26].

3-(2-mercapto-6-(thiophen-2-yl)pyrimidin-4-yl)-2H-chromen-2-one(Compound C1):(dark green powder): 30% yield, m.p: (200 °C), R_f: 0.50 (A), and IR(cm^{-1}): (3105 cm^{-1})N-H stretching, (1720 cm^{-1})C=O stretching, (1573 cm^{-1}, 1558 cm^{-1}) C=C stretching of aromatic ring, and (1608 cm^{-1})C=N stretching. ^{1}H NMR: δ 6.86-8.44 (m, 8H) protons of aromatic and thiophene ring and pyrimidine ring, δ 8.63 (s, 1H) proton of coumarin's –C(=O)-C=C and δ 11.23 (s, 1H) S-H of pyrimidine ring. Figures (1-9) and (1-10) show the compound's FT-IR spectra and ^{1}HNMR spectrum, respectively.

3-(2-mercapto-6-(1H-pyrrol-2-yl)pyrimidin-4-yl)-2H-chromen-2-one(Compound C2):(green powder): 50% yield, m.p : (190 °C), R_f: 0.56 (A), and IR(cm^{-1}): (3302 cm^{-1}, 3113cm^{-1})N-H stretching, (1720 cm^{-1}),C=O stretching, (1604 cm^{-1}) C=N stretching, (1558 cm^{-1}, 1589 cm^{-1})C=C stretching of aromatic ring, and (1180cm^{-1}) C-O-C stretching.^{1}H NMR: δ 6.62,6.94 (m, 3H) of (pyrrole ring), δ 7.34-7.86 (m, 5H) of coumarin's benzene ring and H of pyrimidine ring, δ 8.95 (s, 1H) of coumarin's –C(=O)-C=C, δ 11.04 (s,1H) of pyrrole (N-H) ring and δ 11.35(s,1H) S-H of pyrimidine ring. Figures (1-11) and (1-12) show the compound's FT-IR spectra and ^{1}HNMR spectrum, respectively.

3-(2-mercapto–6– (4– methoxy) pyrimidin – 4 – yl) –2H– chromen – 2 – one (Compound C3):(yellow powder): 50% yield, m.p : (178 °C), R_f: 0.56 (A), and IR(cm^{-1}): (3101cm^{-1}) N-H stretching, (3051 cm^{-1}) aromatic C-H, (2877cm^{-1}) CH3 stretching , (1720cm^{-1})C=O stretching, (1600 cm^{-1}) C=N stretching , (1577 cm^{-1}, 1554 cm^{-1})C=C stretching, and(1176 cm-1) C-O-C stretching.^{1}H-NMR: δ 3.81 (s,3H) of OCH3, δ 6.79- δ 8.64 (m, 9H) of coumarin's benzene ring, aromatic ring and H of pyrimidine ring, δ 8.23 (s, 1H) of coumarin's –C(=O)-C=C and δ 11.67(s,1H) S-H of pyrimidine ring. Figures (1-13) and (1-14) show the compound's FT-IR spectra and ^{1}HNMR spectrum, respectively.

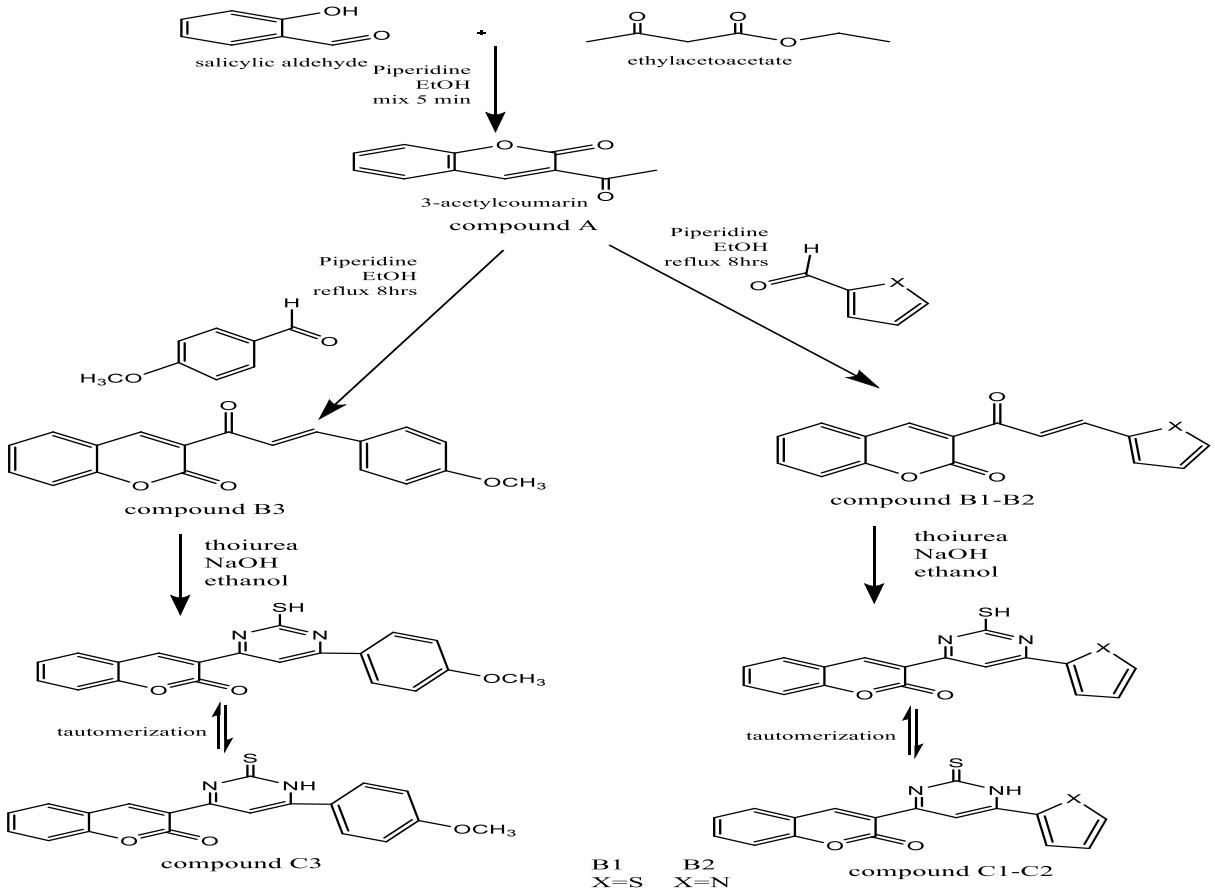
Results and Discussion

Chemistry

Salicylic aldehyde is first combined with ethyl acetoacetate and piperidine as a catalyst to form 3-acetylcoumarin. This is followed by reactions with additional aldehydes, such thoiphene-2-carboxaldehyde, pyrrole- 2-carboxaldehyde and 4-methoxy benzaldehyde to get the hybrid of coumarin -chalcone. According to scheme1, a number of pyrimidine derivatives can be synthesized from the coumarin-chalcone hybrid by reacting with thoiurea as explain in scheme 1 .

The produced chemicals' FTIR spectra showed distinctive bands in cm-1. The emergence of the absorption band of the carbonyl groups C=O stretching at(1735 cm-1, 1674cm-1),C=C stretching at 1554 cm-1, 1608 cm-1, and C-O-C stretching at 1207 cm-1 allowed researchers to identify compound (A). The synthesis of chalcone is indicated by the carbonyl group C=O stretching in compounds (B1-,B3), which was relocated lower than the band of 3-acetylcoumarin due to conjugations (1720 cm-1 in B1, B2 and B3). Compounds (C1-C3) showed characteristic absorption band at 1600-1608 cm-1 (C=N) stretching which confirm the formation of pyrimidine ring. According to the interpretation of the ^{1}H-NMR spectra, compound (A) exhibits sharp singlet signal at (2.57) ppm owing to (O=C -CH3) proton of acetyl group, multiplate signals at (7.37-7.9) ppm due to protons of aromatic ring, and singlet signal at (8.61) ppm due to proton of coumarin. A strong coupling constant (J) of 14–16 Hz and two doublets at 7.2–7.9 ppm were seen in the ^{1}H-NMR spectra of the chalcone compounds (B1-B3), which supports the synthesis of chalcones. Compounds (C1-C3) (1H-NMR)'s spectra displayed singlet at (11.23-11.35,11.67) ppm respectively, due to protons of N-H that formed due to tautomerization with S-H indicating the development of a new ring (pyrimidine ring).

The resultant compounds (C1-C3) were tested for their ability to suppress the growth of gram-negative bacteria, gram-positive bacteria, and Candida albicans. Standard antibacterial drug (ciprofloxacin) and an antifungal drug (fluconazole) were tested utilizing the well diffusion method. To serve as both a solvent and a baseline, DMSO was selected. Compound (C3) was shown to have the highest antibacterial activity against both gram positive and gram negative bacteria, whereas compound (C2) displayed a moderate antibacterial activity and compound C1 had low activity. C1-C3 were shown antifungal activity as compared to fluconazole that showed antifungal efficacy against C. ablicans.



Scheme1.the synthesis of the target compounds (C1-C3).

Table 1. Antimicrobial activity of target compounds (C1-C3) at 1000 µg/ml concentration.

Compound No.	Inhibition zone (IZ) in mm				
	Escherichia coli	***Pseudomonas aeroginosa***	***Staphylococcus aureus***	***Streptococcus pyogenes***	***Candida ablicans***
Ciprofloxacin *	22	……	18	15	…..
Fluconazole **	…….	……	……	……	30
DMSO	…….	……	……	……	…..
C1	8	10	11	10	25
C2	7	15	13	14	22
C3	10	17	16	16	20

*standard for bacterial strains,**standard for fungi .
No activity, mildly active (inhibition zone 5-10 mm), moderately active (inhibition zone 10-20 mm), and very active (inhibition zone more than 20 mm)[27].

Conclusion

The target compounds were successfully produced. Their chemical structures were validated using FT-IR spectroscopy and 1HNMR. The antibacterial activity of target compounds C1,C2,C3) was investigated using the well-diffusion method using bacteria suspension broth (1.5×108 CFU/ml) produced from the McFarland turbidity standard (number 0.5). Which was used to inoculate MHA plates by swabbing the surface, with the excess liquid dried by air under sterile conditions. Each agar plate of bacteria was divided into four wells , and (80 µl) of each produced chemical was. used. The antimicrobial activity was determined bydetermining the zone of inhibition diameter in (mm) surrounding the well after 72 hours of incubation at 30 °C (fungi species) and 24 hours at 37 °C (bacteria species). When compared to Standard drug (ciprofloxacin and fluconazole), the synthesized compounds had antibacterial activity, with (C3) compound having more antibacterial activity and (C1-C2) having slightly antibacterial activity. (C1) has more antifungal activity than other compounds.

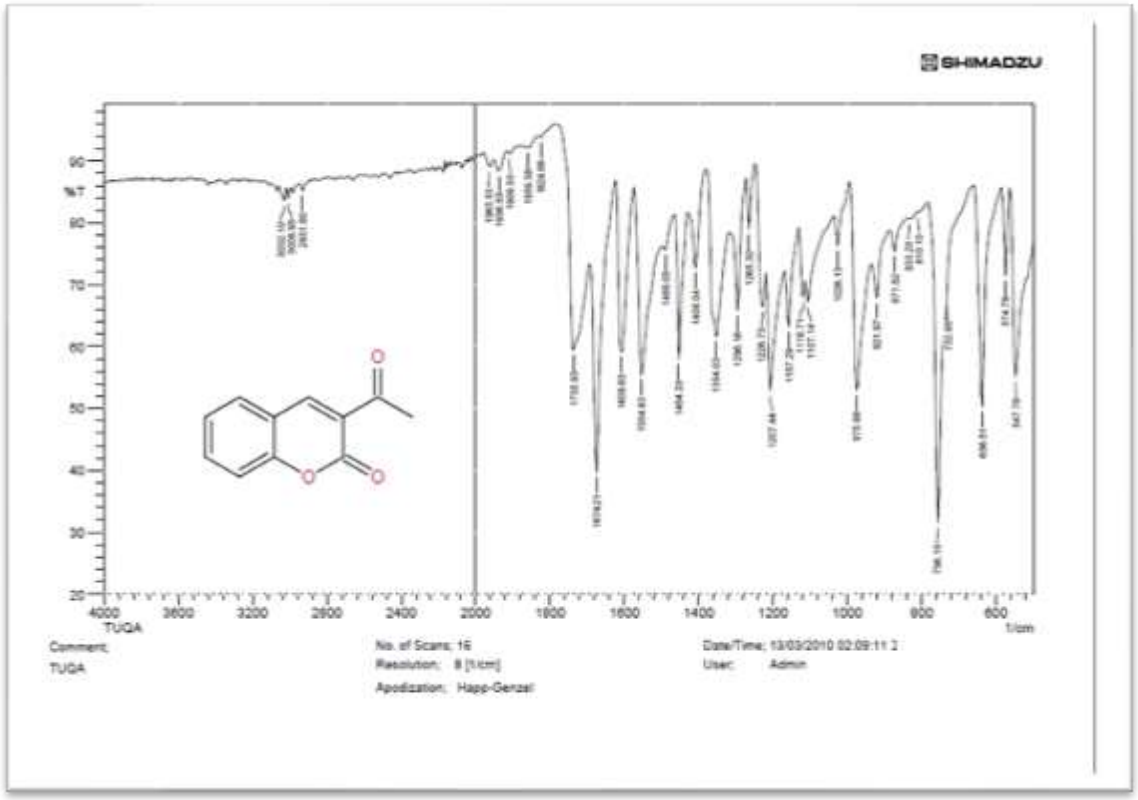


Figure 1. IR spectrum of compound A

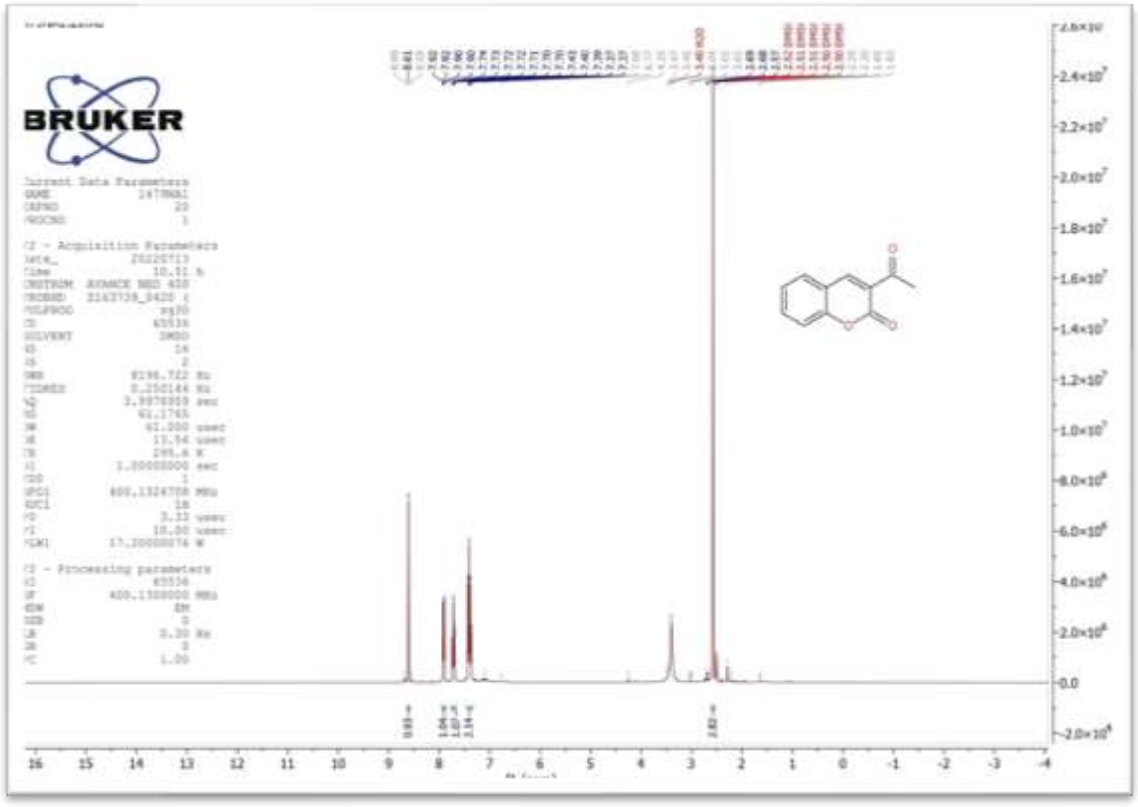


Figure 2. ^{1}H-NMR spectrum of compound A

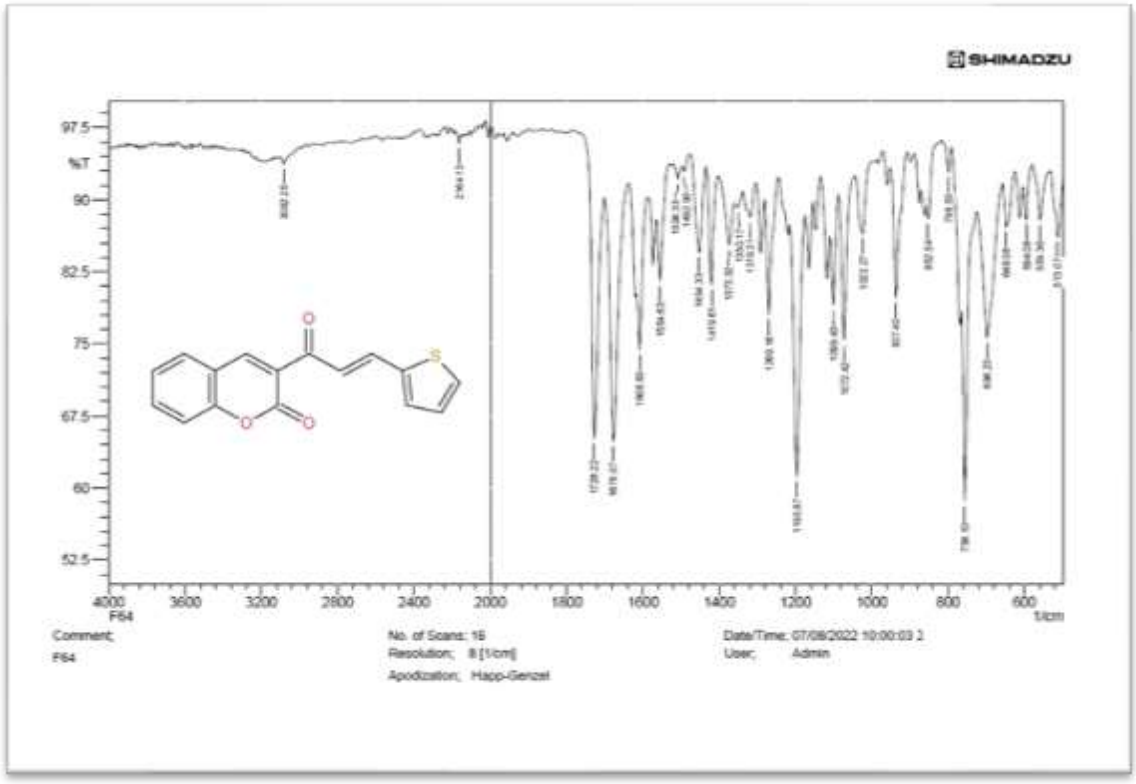


Figure 3. IR spectrum of compound B1

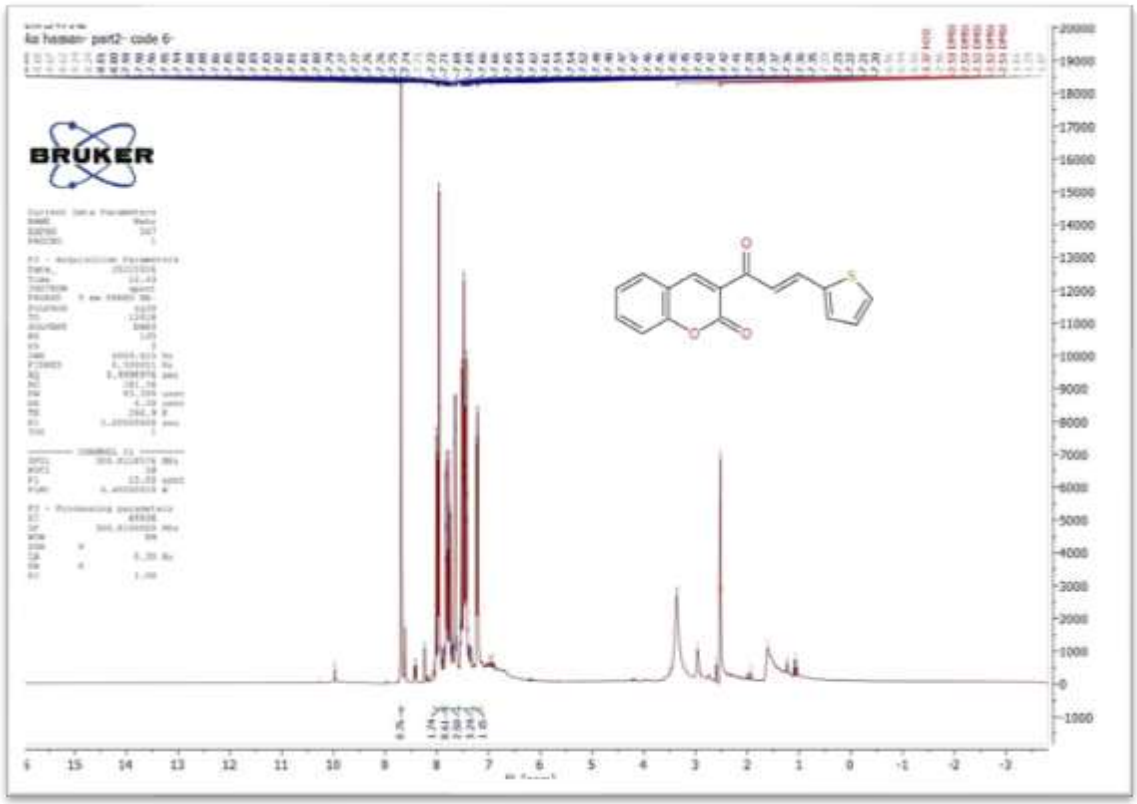


Figure 4.^{1}H-NMR spectrum of compound B1

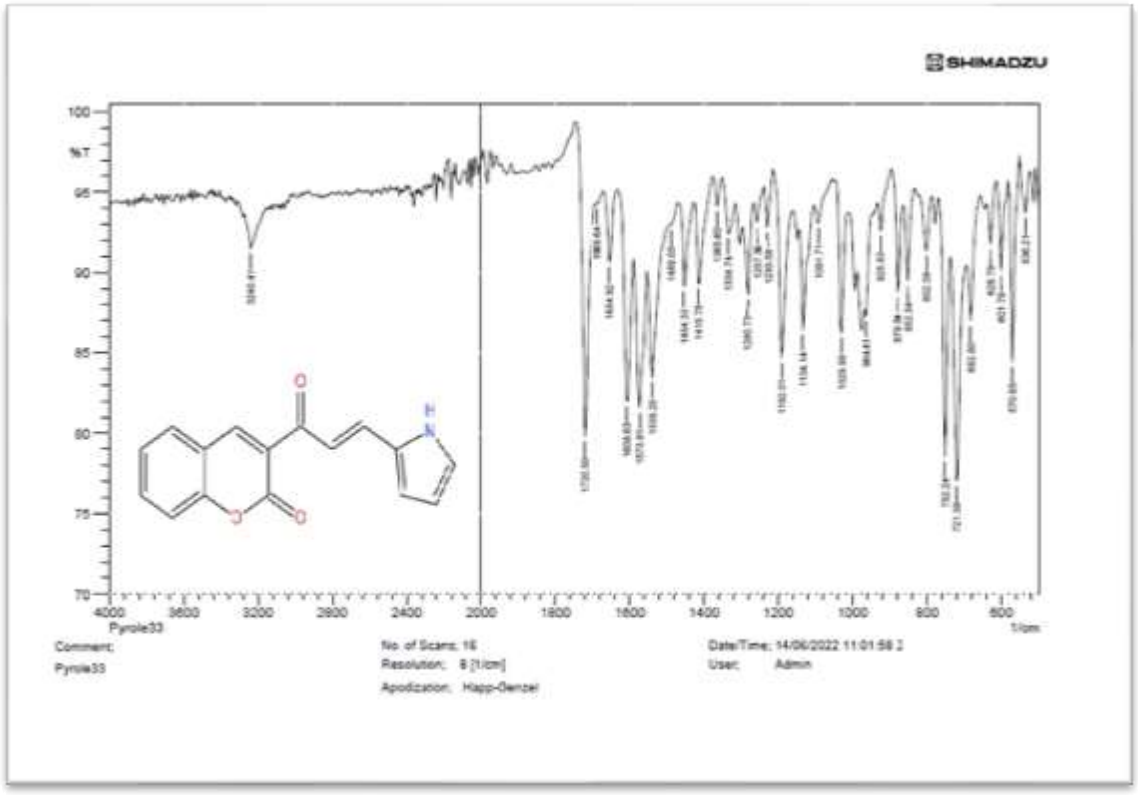


Figure 5. IR spectrum of compound B2

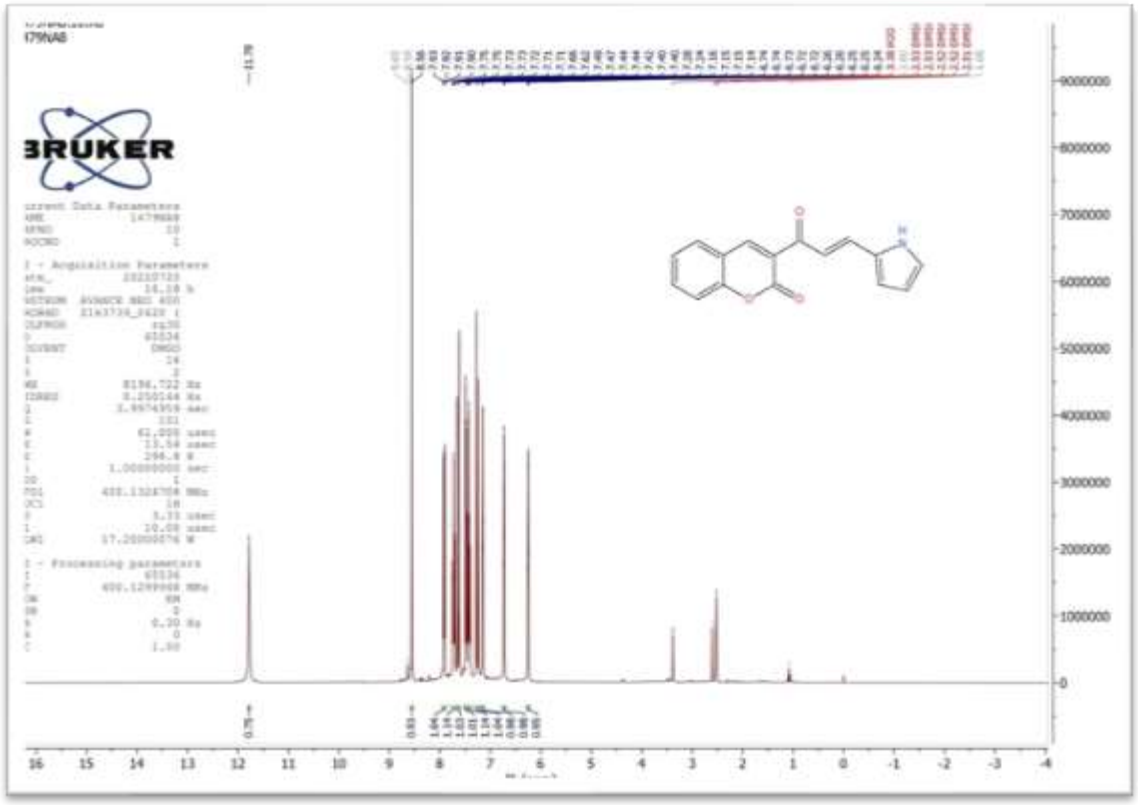


Figure 6. ^{1}H-NMR spectrum of compound B2

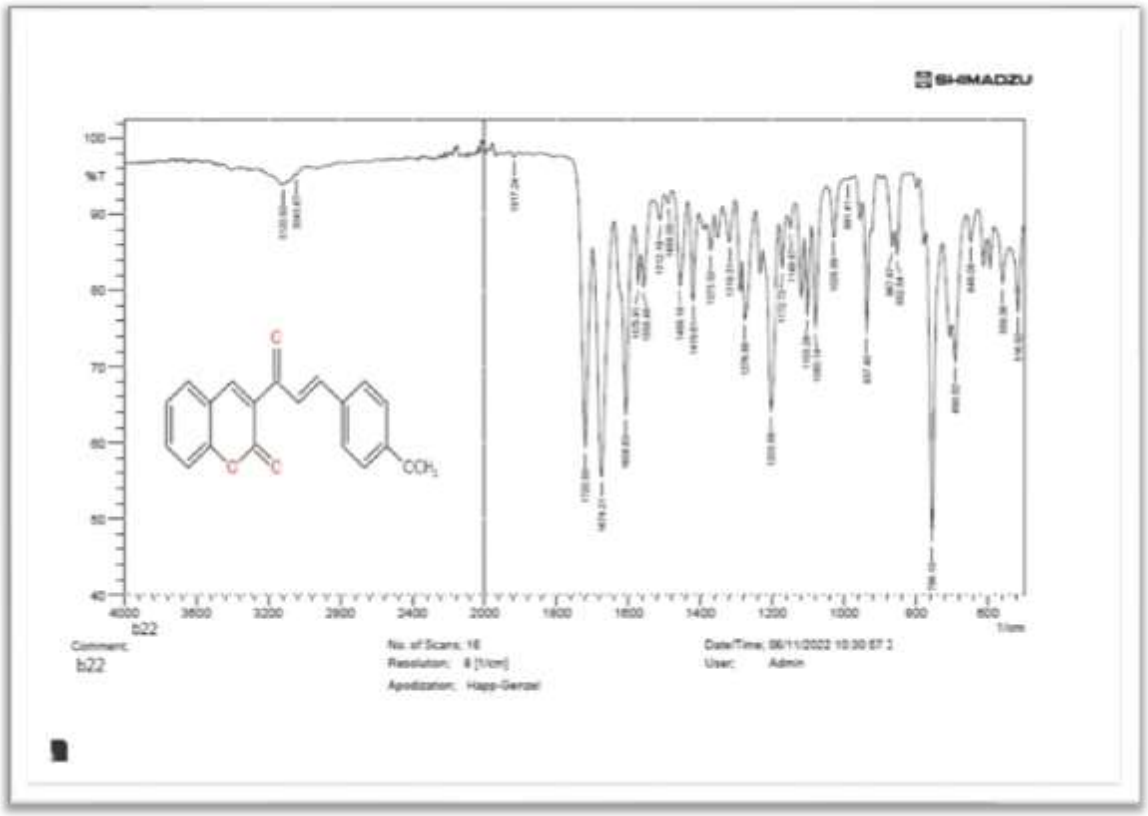


Figure 7. IR spectrum of compound B3

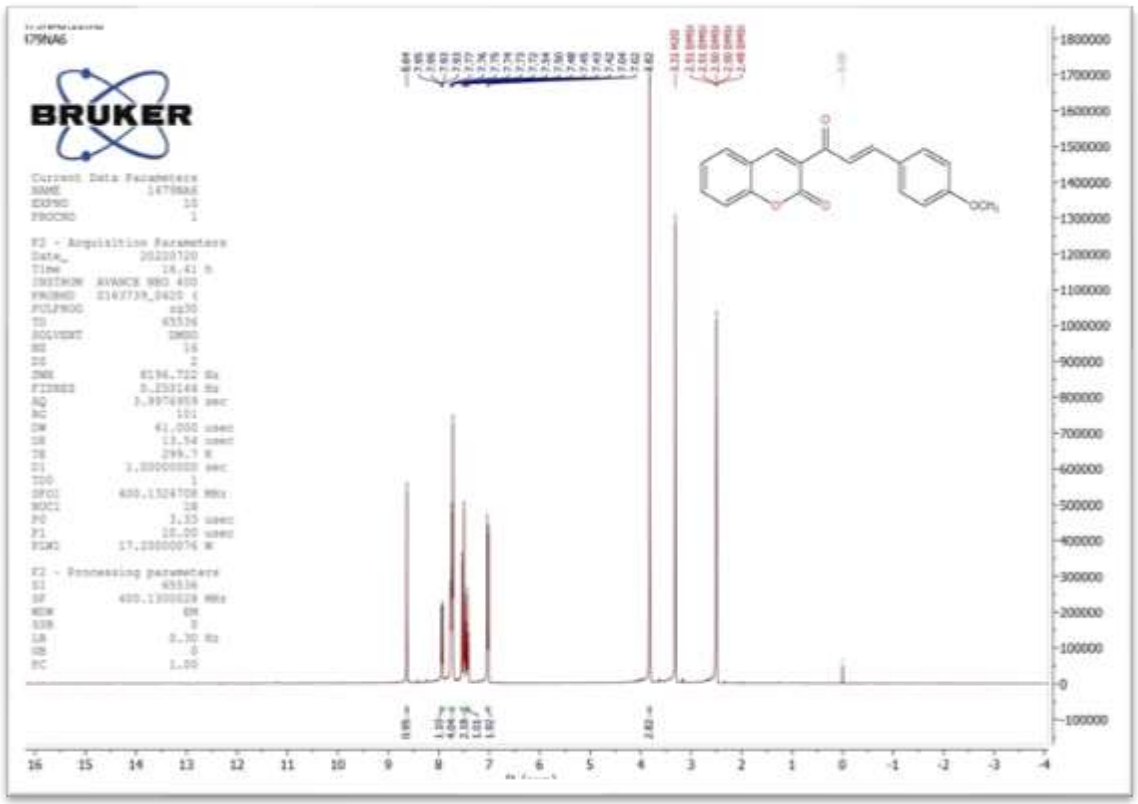


Figure 8.[1]H-NMR spectrum of compound B3

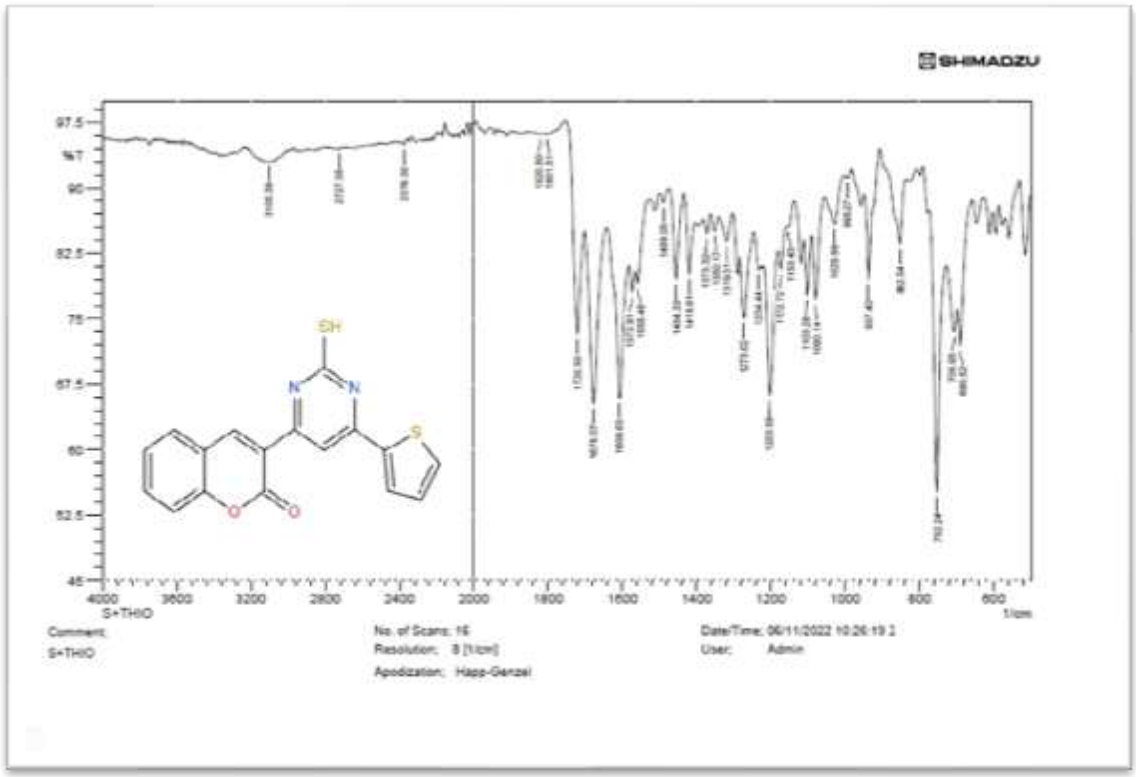


Figure 9. IR spectrum of compound C1

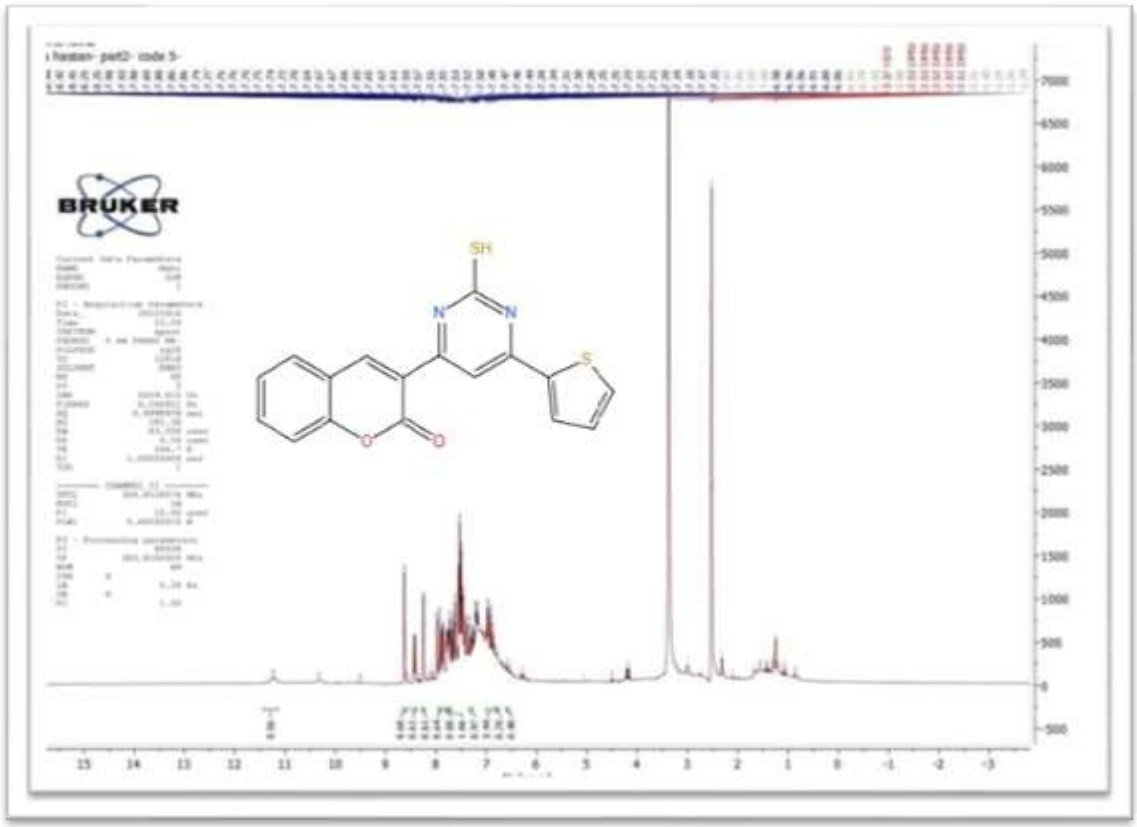


Figure 10. ^{1}H-NMR spectrum of compound C1

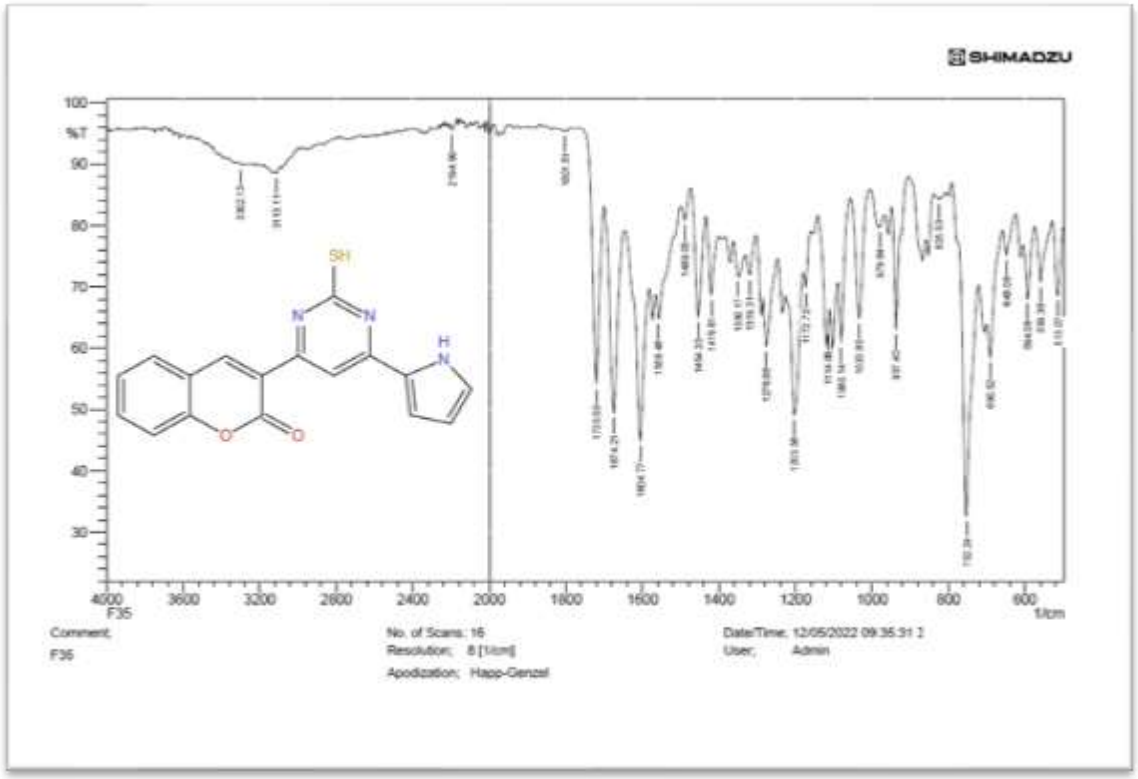


Figure 11. IR spectrum of compound C2

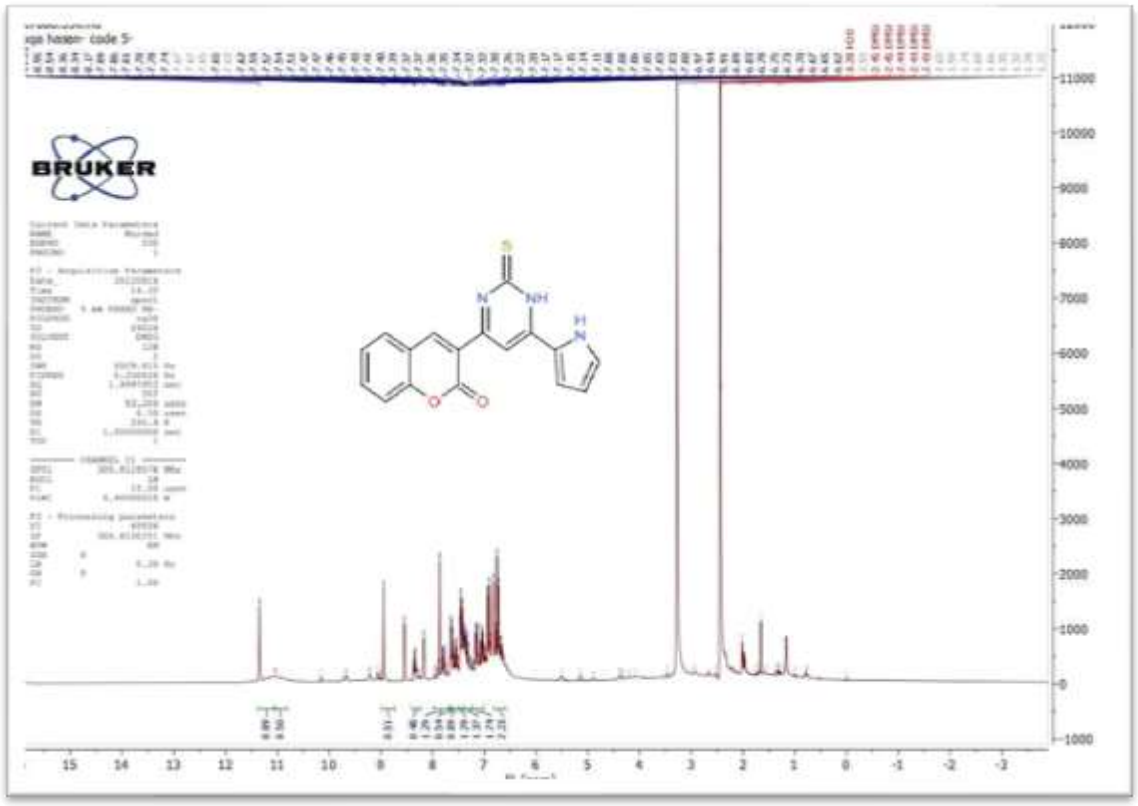


Figure 12.[1]H-NMR spectrum of compound C2

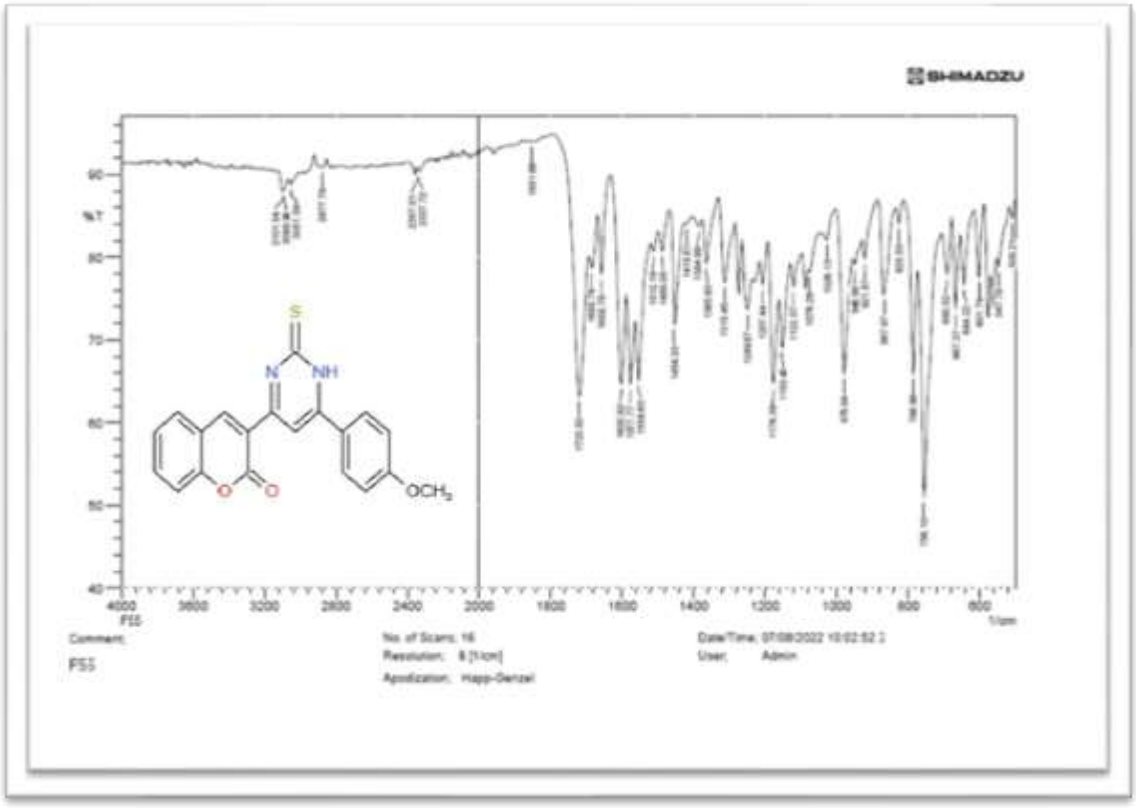


Figure 13. IR spectrum of compound C3

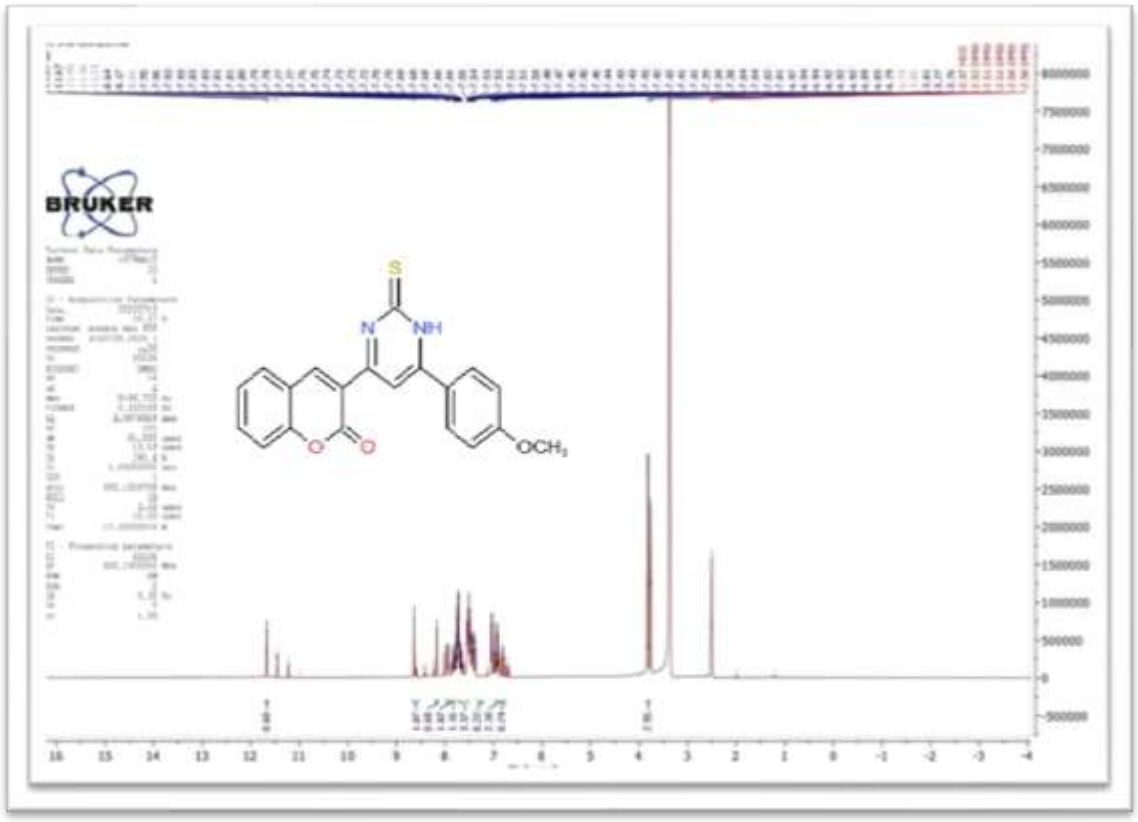


Figure 14. ^{1}H-NMR spectrum of compound C3

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Conflicts of interest

There is no conflict of interest in the manuscript .

Funding

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Ethics statements

The authors did not use animals in the study .

Authors contribution

The authors confirm contribution to the paper . all authors reviewed the results and approved the final version of the manuscript .

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