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Synthesis of Some New α, β-Unsaturated Carbonyl Compounds, Thiophene, Imine and Coumarin Derivatives Containing Hydrazide-Hydrazone Moiety

Rahma A. Hassan and Ammar H. Al-Sabawi *

Department of Chemistry, College of Science, University of Mosul, Mosul, IRAQ.

Abstract

A series of new α,β-unsaturated carbonyl compounds , thiophene, imine and coumarin derivatives were synthesized from reaction of hydrazide-hydrazone derivative with different reagents (substituted aromatic ketone, cyclopentanone, cycloheptanone, tetralone, malononitrile, 2-hydroxy-1-benzaldehyde and 2-hydroxy-1-naphthaldehyde) using different conditions. Hydrazide-hydrazone derivative was prepared by the reaction of piperonal with 2-cyanoacetohydrazide under reflux in ethanol. On the basis of their spectral information, the structures of the newly synthesized chemical derivatives were determined.

*Keyword***:** α,β-unsaturated carbonyl compounds , thiophene, imine, coumarin and hydrazide-hydrazone.

Introduction

Hydrazide-Hydrazone is a class of organic compounds that attracts the attention of many medicinal chemists due to its (-CH=N-NH) azomethane group attached to the carbonyl group therefore, hydrozones contain the intermolecular hydrogen bond -NH- of the hydrazone group (Brönsted acid) and carbonyl oxygen (Brönsted base), and in such species they contain both a proton donor and a proton acceptor of great importance in biological systems and responsible for its various pharmaceutical applications [1], they are used as antioxidants [2], anti-inflammatory [3], antimicrobial [4], anti-cancer [5, 6] ,antidepressants [7] ,anti-tubercular [8, 9], anti-HIV [10]. Hydrazones also act as insecticides, rodenticides, plant growth regulators, and sterilizers [11].

On the other hand, α, β-unsaturated carbonyl compounds are very important intermediates not only in organic synthesis, but also for many products in the chemical industry [12]. They are used as starting materials for many compounds such as plastics, resins, pesticides, dyes [13], perfumes [13], pharmaceuticals and many biological activities such as anti-inflammatory [14, 15], antimicrobial [16] ,antivirals [17, 18], antioxidants [19] ,antitumor [20].

In addition, Thiophene is a class of heterocyclic compounds and has applications in various fields of medicine, as it is used as antibacterial [21], analgesic and anti-inflammatory [22], antihypertensive [23] ,antitumor [24] and thiophene derivatives are also used as corrosion inhibitors [25].

Also, Coumarins are aromatic compounds consisting of a large class of compounds of natural and synthetic origin. This type of compound and its derivatives are found in a variety of plants in the form of benzo-pyrone derivatives and have significant effects in the biochemistry of plants, as they were first isolated in 1822 [26, 27]. It is found in high levels in vegetable oils, especially cinnamon bark oil and lavender oil, as well as in green tea [28].These compounds have become important in recent years due to their biological activity. They are used as anticoagulants [29], antimicrobials [30], anti-inflammatory, analgesic [31, 32], antifungals [33], anti-HIV [34], and they are also used as food additives and in cosmetics [35].Some coumarin derivatives have also been shown to be effective anticancer [36].

As a result of these aspects, encouraged by these observations it is worthwhile to synthesize hydrazide-hydrazone, some new α, β-unsaturated compounds thiophene, imine and coumarin derivatives are garnering a lot of interest in regards to synthesis and biological relevance, our current research plan is an extension of our magnificent efforts across design and flexible protocol toward the synthesis to prepare these important compounds shown in the schemes (1-3).

Experimental:

Melting points (m.p.) were measured on Electro-thermal SMP30- Stuart melting point

*Corresponding author e-mail: ammar-alsabawi@uomosul.edu.iq

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apparatus. ^{1}H-NMR & ^{13}C-NMR spectra were recorded using Bruker Spectrophotometer (400 MHz by using TMS as internal standard and using DMSO-d6 as a solvent) [(s) singlet, (d) doublet, (m) multiplet]. Infrared (FT-IR) spectra were recorded using FT-IR Spectrophotometer.

Synthesis of Cyano-acetic acid benzo[1,3]dioxol-5-ylmethylene-hydrazide X2 [37]

cyanoacetohydrazide **X1b** (2gm,0.02mol) is dissolved in (20ml) absolute ethanol and (3gm, 0.02mol) piperonal, then the mixture is refluxed for two hours, cooled, filtered, ethanol washed, and dried to produce a light brown precipitate with a clear luster. m.p. (188-186°C), yield (93%).

Synthesis of α, β-Unsaturated Carbonyl Compounds X3-X14 [38]

Equimolar of hydrazide-hydrazone **X2** (0.346gm,0.0015mol) with (0.0015mol) of aromatic ketone substitutes in (15ml) absolute ethanol and in a base medium of triethylamine (NEt3) (3drops) was refluxed for 4- 5 hours then cooled and poured over crushed ice with stirring to form a precipitate and leave for a period then filter and wash several times with cold water and dried. The physical and spectral data were listed in Table (1, 4, 7, 8).

Table 1: Physical Properties of α, β-Unsaturated Carbonyl Compounds X3-X14

Compd. No.	R	m.p °C	Yield %	Color
X3	H	169-171	65	Pale yellow
X4	4-B_r	135-137	83	Needle yellow
X5	4-F	162-164	47	Light yellow
X6	3-NO_2	165-167	82	Brown
X7	4-Cl	172-174	45	Brown
X8	3-OCH_3	174-176	42	Light brown
X9	4-CH_3	170-171	52	Light brown
X10	2-Acetyl Pyridine	172-174	45	Lead crystals
X11	2,4-CH_3	173-175	40	Lead crystals
X12	2,5-CH_3	175-177	41	Lead crystals
X13	4-OCH_3	188	40	Dark yellow
X14	4-NH_2	128-130	43	Yellow

Synthesis of Thiophene Derivatives X15-18 [39, 40]

A mixture of (0.346gm, 0.0015mol) of hydrazide-hydrazone **X2** with (0.0015mol) of elemental sulfur and (0.0015mg) of cyclic ketones or malononitrile* in (15ml) absolute ethanol and in a basic medium of triethylamine (3drops) for refluxed (4-5 hours) and upon the end of the reflux process, Overnight is left at room temperature, then the formed precipitate is filtered, washed with ethanol and dried. The physical and spectral data were listed in Table (2, 5, 7, 8).

* In the case of reaction of malontrile with hydrazide-hydrazone, follow this method after the completion of the reflux process, cooled at room temperature and then poured over crushed ice with stirring until the precipitate formed, filtered and washed several times and then dried.

Table 2: Physical Properties of Thiophene Derivatives X15-X18

Compd. No.	m.p °C	Yield %	Color
X15	206	50	**Dark brown**
X16	193	45	**Brown**
X17	163	70	**Dark brown**
X18	177-180	65	**Yellow**

Synthesis of Imine Derivatives X19-X20 [41]

Equimolar of hydrazide-hydrazone **X2** (0.692gm, 0.003mol) with 2-hydroxybenzaldehyde or 2-hydroxynaphthaldehyde (0.003mol) and adding to this mixture (3drops) of triethylamine base in (15ml) of absolute ethanol The mixture is reflux for (4hours) and after the end of reflux, the reaction mixture is left to cool at the room temperature, then the formed precipitate is filtered and dried to give a product, while keeping the filtrate for use in the second step. The physical and spectral data were listed in Table (3, 6-8).

Table 3: Physical Properties of Imine Derivatives X19-X20

Compd. No.	m.p °C	Yield %	Color
X19	197-199	60	**Brown**
X20	128-130	85	**Reddish Brown**

Synthesis of Coumarin Derivatives X21-X22 [42]

The coumarin compounds is prepared in two methods:

Method A to preparation compound X21: A filtrate **X19** is added to crushed ice that contains (5drops) of concentrated HCl while stirring, it is left overnight at room temperature, the precipitate formed is filtered and washed with hot ethanol to obtain a precipitate. m.p. (279-281 °C) ; yield (44%).

Method B to preparation compound X22: (4ml) of concentrated HCl is added to the filtrate **X20**, which we kept in the first step, and then left for a period of about an one hour to form a brown precipitate that is filtered and dried. m.p. (178 °C); yield (40%).

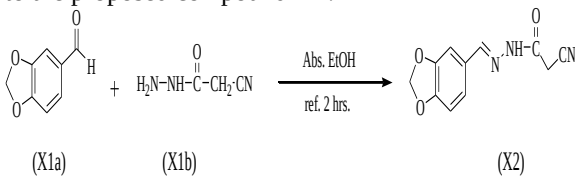
Result and Discussion

In this study, the hydrazide-hydrazone **X2** was reacted in three different paths to obtain many

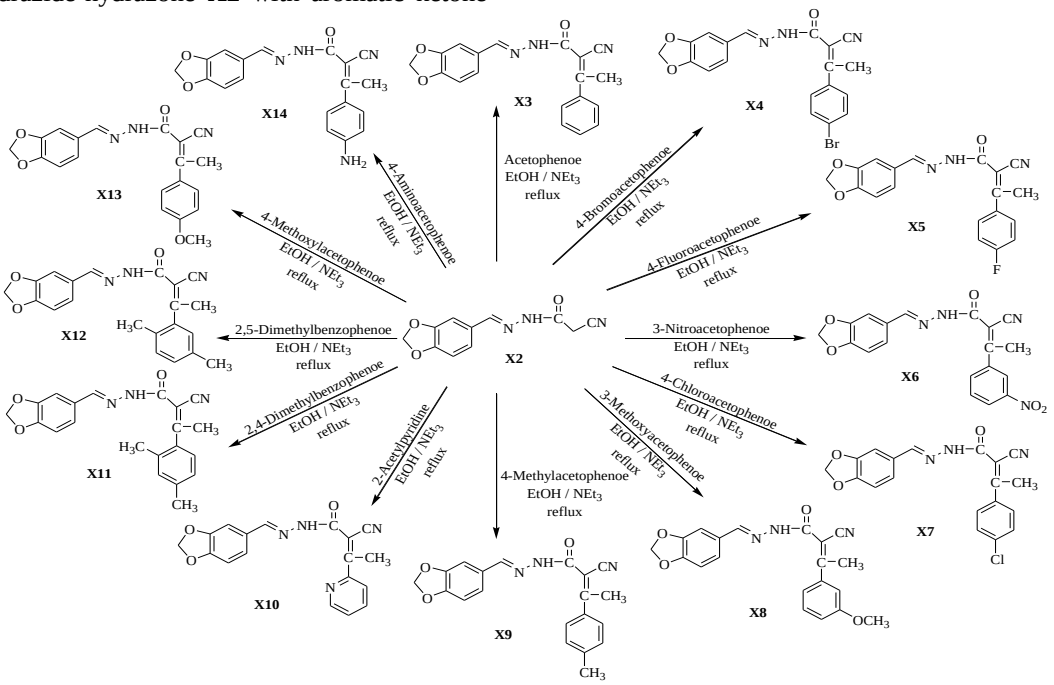
compounds that are expected to be biologically effective as the similar compounds prepared before [4-8]. Where the first path includes the preparation of α,β- unsaturated carbonyl compounds, the second path includes the preparation of heterocyclic compounds (thiophene derivatives), while the third path includes the preparation of heterocyclic compounds represented by imine and coumarin derivatives.

The hydrazide-hydrazone **X2** was prepared from the reaction of piperonal with cyanoacetohydrazide **X1b** by using ethanol as a solvent, as shown in equation (1), and the compound was diagnosed using spectrophotometry (FT-IR & ^{1}H-NMR). The FT-IR spectrum gave two absorption bands for the (C-O-C) group at the frequency 1037 cm^{-1}, 1257 cm^{-1}, as well as an absorption band at 1670 cm^{-1} belonging to the (C=N) group, and also a group the carbonyl that gave an absorption band at 1678 cm^{-1}, in addition, the frequency 2258 cm^{-1} belonging to the (CN) group, and an absorption band for the (NH) group that appeared at 3207 cm^{-1} . The (^{1}H-NMR) spectrum also gave a singlet signal at δ 2.27 ppm for the (-CH2-N) group and a singlet signal at δ (6.87 ppm) for the (O-CH2-O) group, as well as multiple signals belonging to the aromatic ring protons at δ 7.62-8.13 ppm and a singlet signal at δ 8.25 ppm belongs to a proton (CH=N) and a singlet signal at δ 9.32 ppm belongs to a proton (NH).

The new α, β- unsaturated carbonyl compounds **X3-X14** were prepared from the reaction of hydrazide-hydrazone **X2** with aromatic ketone substitutes, using ethanol as a solvent and triethylamine as a base, Scheme (1). The structure of the α, β- unsaturated carbonyl compound X4 was confirmed according to (IR, ^{1}H-NMR,^{13}C-NMR) spectral data . The appearance of a characteristic stretching absorption band, in the IR spectrum, at 1587 cm^{-1} for (C=C) functional group gives an excellent evidence about the compound **X4** formation, in addition to appearance of stretching absorption at 1629 cm^{-1} for (C=N), at 1685 cm^{-1} for (C=O), at 2268 cm^{-1} for (CN), at 3238 cm^{-1} for (NH). The ^{1}H-NMR spectrum of compound **X4** showed the following chemical shifts (δ, ppm): 2.57 (s, 3H, CH3), 6.08 (s, 2H, O-CH2-O), 6.95-7.34(m, 3H, Ar-H), 7.73-7.75(d, 2H, Ar-H, AB system), 7.87-7.90 (d, 2H, Ar-H, AB system), 8.06 (s, 1H, CH=N), 11.70 (s, 1H, -NH). Also, the ^{13}C-NMR spectrum of the compound **X4** gave signals at δ 27.19 ppm and 105.59 ppm belong to ethylene carbon (C = C), and this is a good evidence of the formation of the required product **X4** in addition to the other carbon signals shown in the table (8), where The results were identical to the proposed compound **X4**.

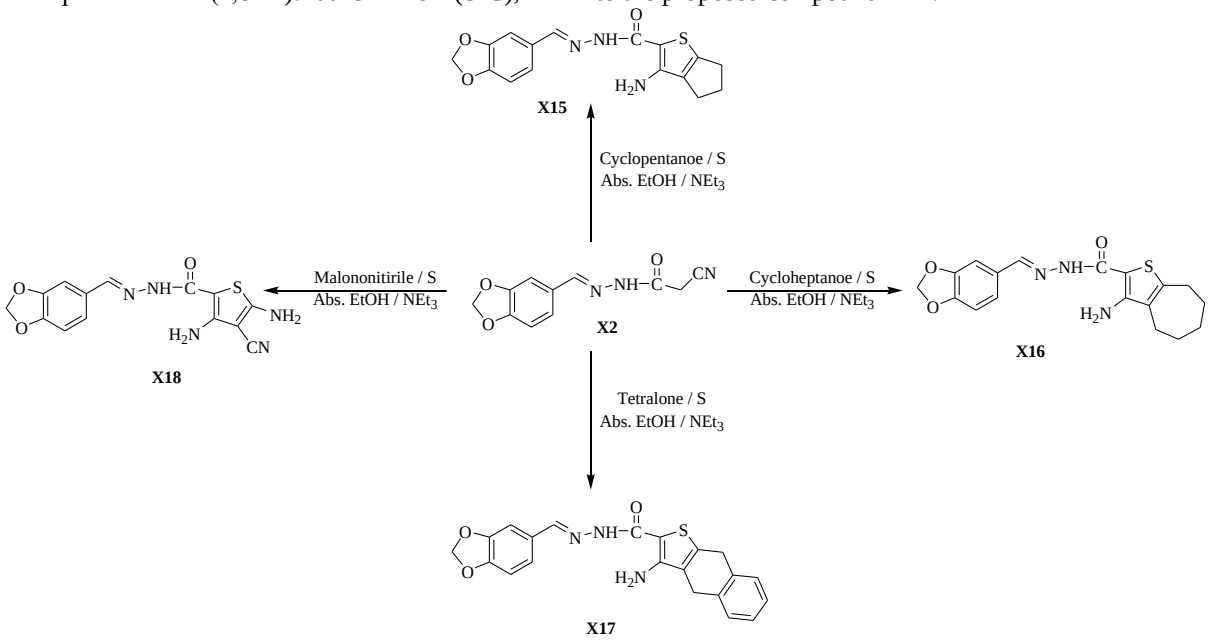


Equation 1: Preparation of Hydrazide-Hydrazone X2



Scheme1: Synthesis of α, β- unsaturated carbonyl compounds X3-X14

The thiophene derivatives **X15-X18** were prepared from the reaction of hydrazide-hydrazone **X2** with cyclopentanone, cycloheptanone and tetralone in the presence of element sulfur in a basic medium of triethylamine and using ethanol as a solvent yielded the thiophene derivatives **X15-X17** respectively , Scheme (2), the reaction runs based on to like reported reactions [43]. Also, reaction malononitrile with hydrazide-hydrazone **X2** under same condition yielded the thiophene derivatives **X18,** Scheme (2), this reaction runs parallel to the reported Gewald's synthesis of thiophene [44].The IR spectrum of compound **X17** showed the following stretching absorption bands (ν,cm^{-1}): at 812 for (S-C), 1595 for (C=C), 1627 for (C=N), 1683 for (C=O), 3217 for (NH), 3446 for (NH_2), and this is a good evidence of the formation of the thiophene compound **X17**, and its ^{1}H-NMR spectrum showed the following chemical shifts (δ, ppm): 3.77 (s, 4H, $2CH_2$ cyclohexane), 4.19 (s, 2H, NH_2), 6.07 (s, 2H, O-CH_2-O),6.95-7.34 (m, 7H, Ar-H), 7.90 (s, 1H, CH=N), 11.68 (s, 1H, NH), While its ^{13}C-NMR spectrum showed the following chemical shifts (δ, ppm): 19.83, 29.34 for 2C of cyclohexane respectively, 127.00, 129.49, 132.61, 133.92 for carbons of thiophene ring respectively, in addition to the other carbon signals shown in the table (8), where The results were identical to the proposed compound **X17**.

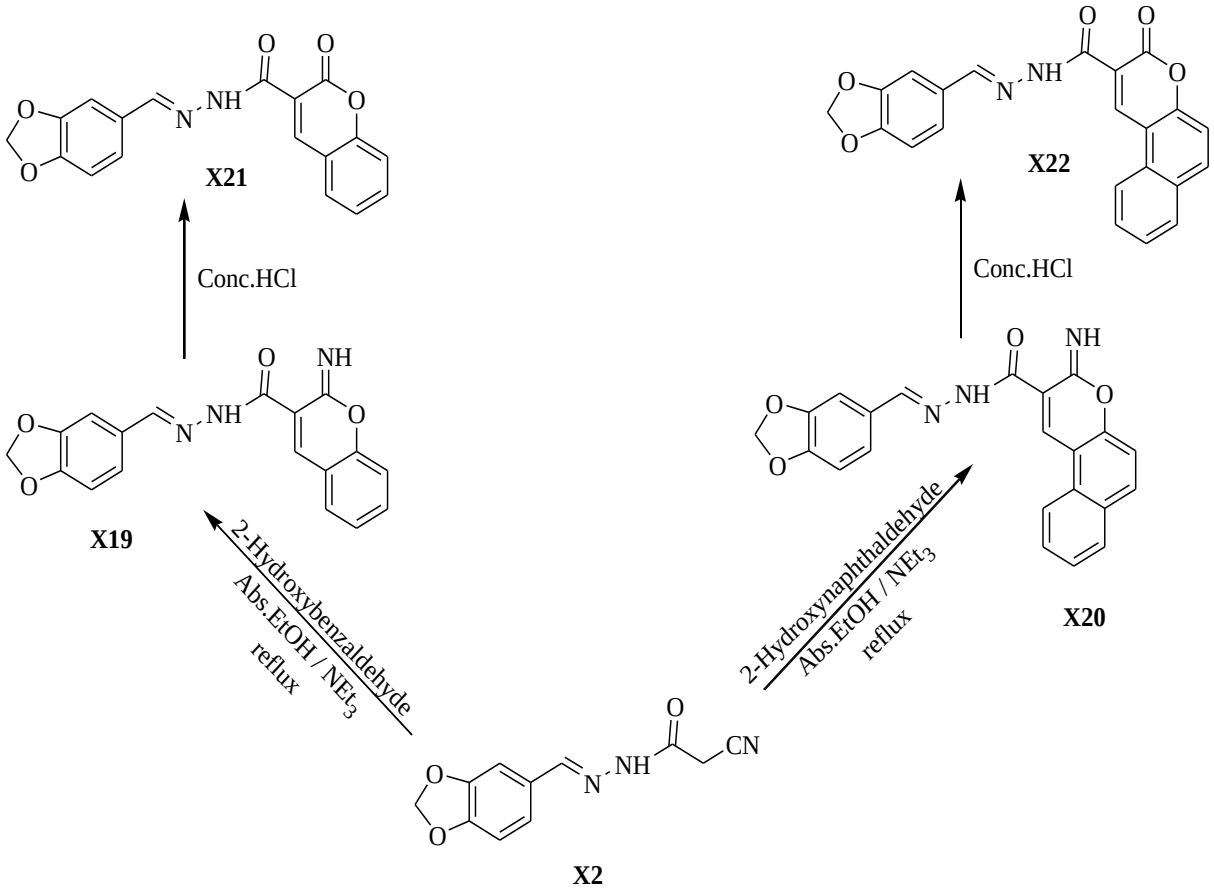


Scheme2: Synthesis of Thiophene Derivatives X15-X18

The last path is the preparation of imine **X19, X20** and coumarin **X21, X2**2 compounds, where they were prepared in two steps: the first is the preparation of imine compounds from the reaction of hydrazide – hydrazine **X2** with 2-hydroxybenzaldehyde or 2-hydroxynaphthaldehyde in a basic medium of triethylamine and using ethanol as a solvent. In the second step, the coumarin compounds are prepared through addition of HCl to imine compounds, Scheme (3). The IR spectrum of compound **X19** showed the following stretching absorption bands (ν, cm^{-1}): at 1643 for (C=N), 1670 for (C=O), 3302 for (NH), what distinguishes the spectrum of this compound is the disappearance of the absorption band (CN) at the frequency 2258 cm^{-1}, that was present in hydrazide-hydrazone (X), and this is a good evidence of the formation of the imine compound **X19**, On the other hand, the ^{1}H-NMR spectrum of the compound **X19** showed clear evidence of the formation of this compound through the appearance of a distinctive signal belonging to the group (C=NH) at 9.22 ppm with the disappearance of the signal (CH=N) at 8.25 ppm that was present in hydrazide-hydrazone **X2**. In addition to other indications that confirm the formation of the imine compound and its ^{1}H-NMR spectrum showed the following chemical shifts (δ, ppm): 6.10 (s, 2H, O-CH_2-O), 6.99-7.84 (m, 7H, Ar-H), 8.28 (s, 1H, CH=N), 8.55 (s, 1H, CH=C), 9.22 (s, 1H, C=NH), 13.52 (s, 1H, NH-CO), while its ^{13}C-NMR spectrum showed the following chemical shifts (δ, ppm): 102.07, 105.91, 108.98, 115.44, 118.90, 124.17, 124.71, 128.93, 130.57, 133.76, 142.25, 148.40, 149.29, 149.80, 153.94, 155.90, 158.53, where The

results were identical to the proposed compound **X19**.

For the IR spectrum of the coumarin compound **X21** showed the following stretching absorption bands (ν, cm^{-1}): at 1624 for (C=N), 1671 for (C=O amide), 1709 for (C=O lactone), 3188 for (NH), and its ^{1}H-NMR spectrum showed the following chemical shifts (δ, ppm): 6.10 (s, 2H, O-CH2-O), 6.92-8.37 (m, 7H, Ar-H), 8.70 (s, 1H, CH=C), 8.91 (s, 1H, CH=N), 11.89 (s, 1H, NH-CO), It is noticed from the ^{1}H-NMR spectrum that a signal disappears at 9.22 ppm that was present in the imine compound **X19**, and this is an excellent evidence for the formation of the coumarin compound, while its ^{13}C-NMR spectrum showed the following chemical shifts (δ, ppm): 102.11, 105.80, 109.01, 116.93, 118.99, 119.93, 124.32, 125.76, 130. 05, 130.80, 132.31, 134.90, 148.46, 150.21, 154.42, 158.00, 160.40, 161.94.



Scheme3: Synthesis of Imine X19, X20 and Coumarin X21, X22

Table 4: FT-IR data of α, β-Unsaturated Carbonyl Compounds X3-X14

Compd. No.	R	FT-IR, ν (cm-1)						
		NH	CN	C=O	C=N	C=C	C-O-C	Other
X3	H	3201	2262	1678	1617	1595	1259 assy. 1037sy.	…….
X4	4-B_r	3238	2268	1685	1629	1587	1259 assy. 1037sy.	C-Br 750
X5	4-F	3211	2268	1683	1627	1597	1249 assy. 1039sy.	C-F
X6	3-NO_2	3190	2264	1681	1616	1598	1255 assy. 1037sy.	NO_2 1502 assy. 1350 sym.
X7	4-Cl	3192	2264	1674	1631	1598	1259 assy. 1037sy.	C-Cl 800
X8	3-OCH_3	3190	2264	1674	1634	1597	1259 assy. 1037sy.	…….
X9	4-CH_3	3196	2262	1676	1621	1600	1259 assy. 1037sy.	…….
X10	2-Acetyl Pyridine	3190	2264	1672	1664	1598	1257 assy. 1035sy.	…….
X11	2,4-CH_3	3190	2262	1674	1631	1597	1229 assy. 1037sy.	…….
X12	2,5-CH_3	3186	2264	1674	1635	1597	1267 assy. 1037sy.	…….
X13	4-OCH_3	3211	2218	1674	1627	1575	1257 assy. 1037sy.	…….
X14	4-NH_2	3223	2202	1681	1627	1597	1255 assy. 1037 sy.	NH_2 3308

Table 5: FT-IR data of Thiophene Derivatives X15-X18

Compd. No.	FT-IR, ν (cm-1)					
	NH_2 , NH	C=O	C=N	C=C	C-O-C	C-S
X15	3350, 3178	1683	1622	1575	1247 assy. 1037sy.	810
X16	3313, 3196	1685	1624	1560	1247 assy. 1035sy.	812
X17	3446, 3217	1683	1627	1595	1255 assy. 1037sy.	812
X18	3323, 3219	1689	1625	1597	1253 assy. 1037sy.	808

Table 6: FT-IR data of Imine X19, X20 and Coumarin X21, X22

Compd. No.	FT-IR, ν (cm-1)				
	NH	C=O (lactone)	C=O (amide)	C=N	C-O-C
X19	3253	…….	1674	1627	1259 assy., 1033 sy.
X20	3302	…….	1670	1643	1259 assy., 1033 sy.
X21	3201	1701	1666	1610	1272 assy., 1035 sy.
X21	3188	1709	1671	1624	1257 assy., 1037 sy.

Table 7: The ^{1}H-NMR spectral data of compounds (X2, X4, X17-X19 and X21).

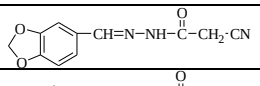
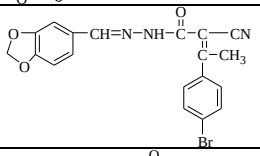
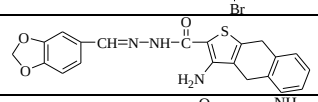
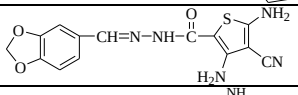
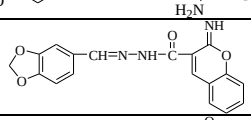
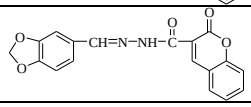
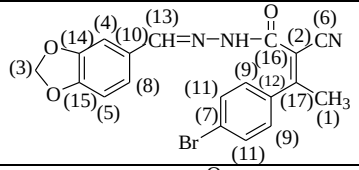
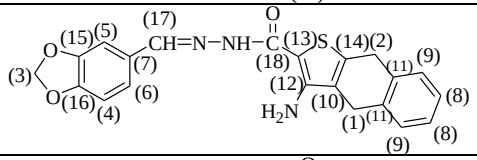
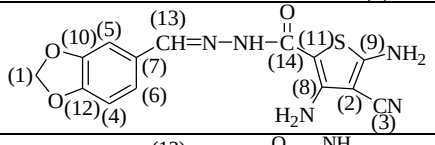
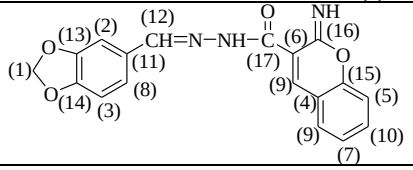
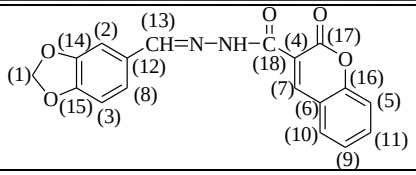
Compd. No.	Structure	^{1}H-NMR, (ppm), DMSO-d6
X2		2.27 [s, 2H, -CH_2-CN], 6.87 [s, 2H, O-CH_2-O], 7.62-8.13[m, 3H, Ar-H], 8.25 [s, 1H, CH=N], 9.32 [s, 1H, -NH]
X4		2.57 [s, 3H, CH_3], 6.08 [s, 2H, O-CH_2-O], 6.95-7.34[m, 3H, Ar-H], 7.73-7.75[d, 2H, Ar-H, AB system], 7.87-7.90[d, 2H, Ar-H, AB system], 8.06 [s, 1H, CH=N], 11.70 [s, 1H, -NH]
X17		3.77 [s, 4H, 2CH_2 cyclohexane], 4.19 [s, 2H, NH_2], 6.07 [s, 2H, O-CH_2-O],6.95-7.34 [m, 7H, Ar-H], 7.90 [s, 1H, CH=N], 11.68 [s, 1H, NH]
X18		3.77 [s, 2H, NH_2], 4.19 [s, 2H, NH_2], 6.07 [s, 2H, O-CH_2-O], 6.95-7.34 [m, 3H, Ar-H], 7.90 [s, 1H, CH=N],11.68 [s, 1H, NH]
X19		6.10 [s, 2H, O-CH_2-O], 6.99-7.84 [m, 7H, Ar-H], 8.28 [s, 1H, CH=N], 8.55[s, 1H, CH=C], 9.22 [s, 1H, =NH], 13.52 [s, 1H, NH-CO]
X21		6.10 [s, 2H, O-CH_2-O], 6.92-8.37 [m, 7H, Ar-H], 8.70 [s, 1H, CH=C], 8.91 [s, 1H, CH=N], 11.89 [s, 1H, NH-CO]

Table 8: The ^{13}C-NMR spectral data of compounds (X4,X17-X19 and X21).

Compd. No.	Structure	13C-NMR, (ppm), DMSO-d6
X4		27.19, 102.01, 105.59, 108.83, 116.65, 123.89, 124.05, 127.76, 128.74, 130.68, 132.22, 136.27, 144.49, 148.44, 149.55, 165.15, 197.66
X17		19.83, 29.34, 102.02, 105.59, 105.74, 108.82, 116.63, 123.89, 126.70, 127.00, 128.74, 129.49, 132.61, 133.92, 144.54, 148.44, 149.55, 165.13
X18		102.01, 105.60, 105.74, 108.83, 108.93, 109.06, 116.63, 123.00, 123.89, 128.74, 144.52, 148.44, 149.56, 165.14
X19		102.07, 105.91, 108.98, 115.44, 118.90, 124.17, 124.71, 128.93, 130.57, 133.76, 142.25, 148.40, 149.29, 149.80, 153.94, 155.90, 158.53

X21		102.11, 105.80, 109.01, 116.93, 118.99, 119.93, 124.32, 125.76, 130.05, 130.80, 132.31, 134.90, 148.46, 150.21, 154.42, 158.00, 160.40, 161.94

Conclusion

In this study, using simple and easy working methods, reaction conditions, available and cheap chemicals, we were able to prepare important compounds such as α,β-unsaturated carbonyl compounds, thiophene, imine and coumarin derivatives and are believed to have medical applications depending on the published literature. Therefore, his research concentrated on these derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

University of Mosul.

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