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RESEARCH ARTICLE

Synthesis, Characterization and Biological Activity of New Derivatives of Hetrocyclic Compound

Athraa B. Mohamad, Mahmood S. Magtoof, Ali Abd Alkabir

Department of chemistry, College of Science, Thi-Qar University, Iraq.

Abstract

This study included the preparation and characterization of a series of new derivatives of pyrazoline, isoxazoline by two steps the first step involved the preparation of chalcones by reaction between aldehyde and acetophenone the second step involved the react of chalcones two stepe react chalcones with hydrazine to form pyrazoline also chalcones was reacted with hydroxylamine hydrochloride in present a basic medium for the preparation of the derivative isoxazoline The derivatives has shown moderate to good activity against gram-positive bacteria (*Staphylococcus aureus*), gram-negative bacteria (*Escherichia coli*) when compared with standard antibiotic gentamycin .all prepared compounds were diagnosed by spectra of H^1-NMR, mass.

Keywords: *Isoxazolin, Pyrazoline, Chalcones, Synthesis, Biological activities.*

Introduction

Chalcone (1, 3-diphenyl propenon) is known to have a variety of pharmacological activities, such as anticancer [1] anti-proliferative [2] antimicrobial [3] and [4], insecticides [5] and antioxidants [6]. This compound is the main precursor in the synthesis of a variety of heterocyclic compounds; therefore it is very important to develop the latest strategies in the synthesis of chalcone. Chalcone can be synthesized by Claisen-Schmidt condensation, the condensation reaction between aromatic aldehydes and ketones to form aromatic ketone α, ß-unsaturated.

Among heterocyclic compounds, pyrazole is considered as a unique scaffold possessing nitrogen atom in the five membered rings. Pyrazoline or dihydropyrazole has three possible tautomeric forms. This template attracts attention because of its usefulness in drugs designing. Pyrazole displays various different pharmacological activities such as anti-inflammatory, antipyretic, analgesic [7], antimicrobial [8], anticancer [9], antiviral [10], antihypertensive [11], anti-glaucoma [12], antioxidant [13], antidepressant, anxiolytic, neuroprotective [14] and anti-diabetic [15] activity There are some well-established pyrazoline nucleus containing drugs in market like Aminopyrine (Analgesic and antipyretic), Dipyrone (Analgesic), Antipyrine(antipyretic and anti-rheumatic), Phenylbutazone (NSAIDS), Zeleplon (Hypnotics and sedatives), Celecoxib (Osteoarthritis and rheumatoid arthritis inhibitors), Allopurinol (Treatment of goat), [16, 17] dinitro indazole (Anti-bacterial), 7-amino 5- nitro indazole (Anti- bacterial), Muzolimine (Diuretics). Therefore there is always also an isoxazoline pharmacological activity like antimicrobial [18], anti-inflammatory [19], anti-tubercular [20], and antidepressant [21], antioxidant3.

Experimental

General Procedures for the Synthesis of Chalcones

In general, the ***(chalcones***) are synthesized by mixing of (0.01 or 0.02) mole of 3or4-supstituted-acetophenone (2 equiv,2 or 1gm) 2,3-dimethoxybenzaldehyde(1 equiv,1.2gm) in methanol solution of NaOH(60%).The reaction mixture is refluxed for(4-22) hrs. and the progress of the reaction is monitored by TLC using hexane :ethyl acetate 7:3 as eluent. After the completion of the reaction then was cooled and washed with mixture ice cooled water and ethanol, the separated solid

was filtered and dried in vacuum**,** finally recrystallized from ethanol to afford the desired product in pure form.

Synthesis of (2E)-3-(4-bromophenyl)-1-(2, 3-dimethoxyphenyl) prop-2-en-1-one (1c)

The compound is synthesized by reacting 4-parabromoacetophenone (1equiv, 1gm) and 2, 3-dimethoxybenzaldehyde (1 equiv, 1.2gm), melting point 135 C^0, yield 75 %.

Synthesis of (2E)-1-(2, 3-dimethoxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one (1d)

The compound is synthesized by reaction 4-nitroacetophenone (1equiv, 1gm) and 2, 3-dimethoxybenzaldehyde (1 equiv, 1.1gm), melting point 128 C^0, yield 79%, time 8h.

Table 1: Physical properties of synthesized compounds (1c and 1d)

No.	Comps.	Yield (%)	M.p.(°C)	Colour	Solvent of Recrystallization	Rf
3	1c	75	135-138	Yellow	Ethanol	**0.29**
4	1d	79	128-131	Yellow	Ethanol	**0.29**

Synthesis of Pyrazoline

General Procedures for the Synthesis Compounds of pyrazoline 3(a-c)

In general, compounds of pyrazoline[11] 2(a-c) they are synthesized by mixing of (0.01) mole of chalcone and(0.01) mole hydrazine hydrate in 25 ml of ethanol using 3-5 drops of glacial acetic acid concentration as a catalyst. The reaction mixture is refluxed for (5-30) hrs and the progress of the reaction is monitored by TLC using hexane: ethyl acetate 7:3 as eluent. After the completion of the reaction then was cooled and washed with mixture ice cooled water and ethanol, the separated solid was filtered and dried in vacuum**,** finally recrystallized from ethanol to afford the desired product in pure form. Table (2).

Synthesis of (5-(4-bromophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydro-1H-pyrazole (3a)

The compound is synthesized by reacting of chalcone (0.01 mol,0.5 gm) and hydrazine hydrate 99% (5mL, 0.01 mol) in absolute ethanol (25mL) containing glacial acetic acid (0.5 mL) was refluxed for(5)h. Yield =70.9 %, m.p = 126ºC.

Synthesis of (5-(4-nitrophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydro-1H-pyrazole (3b)

The compound is synthesized by reacting of chalcone (0.01 mol,0.5 gm) and hydrazine hydrate 99% (0.1mole,0.06 ml) in absolute ethanol (25mL) containing glacial acetic acid (0.5 mL) was refluxed for(10)h. Yield =66%, m.p =135 ºC.

Table 2: Physical properties of compounds2 (a-b)

No	Comps	Yield (%)	M.p.(°C)	Colour	Solvent of recrystalization	Rf
1	3a	70.9	123-126	Yellow	Methanol	**0.37**
2	3b	66	132-135	white	Methanol	**0.32**

Preparation of Isoxazoline

General Procedures for the synthesis compounds of isoxazoline 3(d-f)

In general, compounds of isoxazoline2 (d-f) they are synthesized by mixing of (0.01) mole of chalcone and (0.01) mole hydroxyl amine hydrochloride in 25 ml of ethanol using aqueous sodium hydroxide (10%) concentration as a catalyst.

The reaction mixture is refluxed for (5-30) hrs and the progress of the reaction is monitored by TLC using hexane: ethyl acetate 7:3 as eluent. After the completion of the reaction then was cooled and washed with mixture ice cooled water and ethanol, the separated solid was filtered and dried in vacuum**,** finally recrystallized from ethanol to afford the desired product in pure form. Table (3)

Synthesis of (5-(4-bromophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydroisoxazole (3d)

The compound is synthesized by reacting chalcone (0.01 mol,0.5gm) and hydroxyl amine hydrochloride (0.01 mol , 0.2 gm), absolute ethanol (50mL), aqueous sodium hydroxide (10%, 6 mL) were added then the

reaction mixture was heated under reflux for(9)h. Yield =73%, m.p = 208°C.

Synthesis of (5-(4-nitrophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydroisoxazole (3e)

The compound is synthesized by reacting chalcone (0.01 mol,0.5gm) and hydroxyl amine hydrochloride (0.01 mol, 0.2 gm), absolute ethanol (30mL), aqueous sodium hydroxide (10%, 6 mL) were added then the reaction mixture was heated under reflux for 6h. Yield =83%, m.p = 216C.

Table 3: physical properties of compounds (3d and 3e)

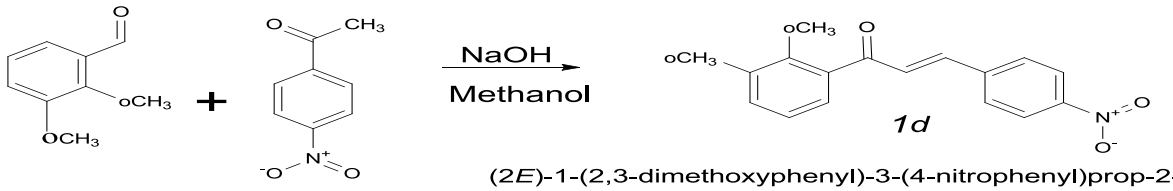
No	Comps.	Yield (%)	M.p.(°C)	Colour	Solvent of Recrystallization	RF
1	3d	73	204-208	White	Methanol	0.34
2	3e	85	125-129	Yellow	Methanol	0.43

Results & Discussion

The staring chalcones required for this study were prepared by reacting subsisted 4-nitro acetophenon and 4-bromo acetophenon with aldehyde, 2, 3-dimethoxybenzaldehyde.

1c

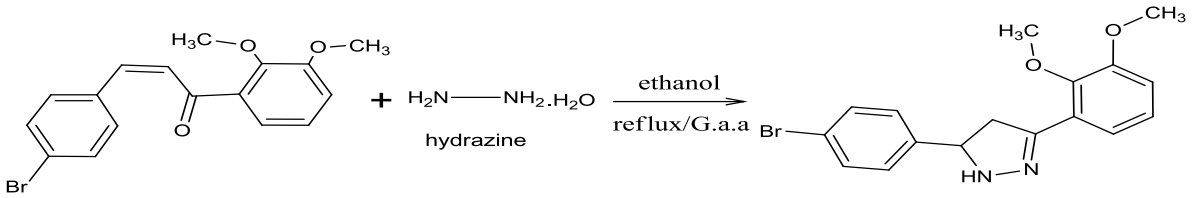
(2*E*)-3-(4-bromophenyl)-1-(2,3-dimethoxyphenyl)prop-2-en-1-one



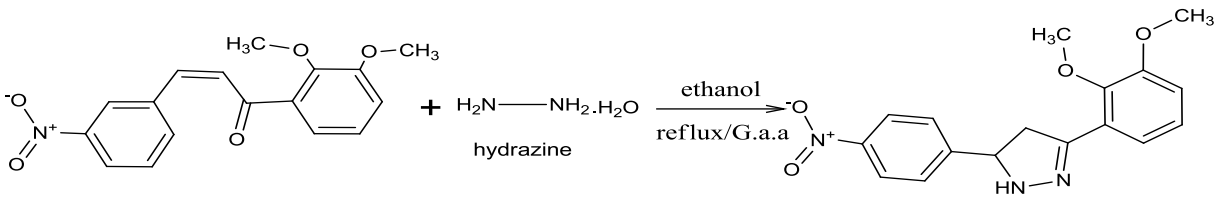
1d

(2*E*)-1-(2,3-dimethoxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one

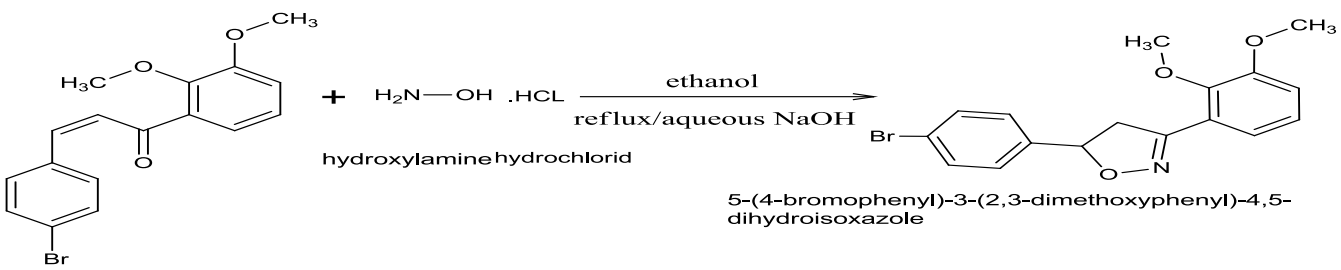
Chalcones derivatives (1c, 1d) its reaction with hydrazine to get pyrazol derivatives likewise (1c, 1d) react with hydroxylamine hydrochloride to get isoxazole.



5-(4-bromophenyl)-3-(2,3-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazole



3-(2,3-dimethoxyphenyl)-5-(4-nitrophenyl)-4,5-dihydro-1 *H*-pyrazole



5-(4-bromophenyl)-3-(2,3-dimethoxyphenyl)-4,5-dihydroisoxazole

Infrared (IR) Spectra of pyrroline

The IR spectra of the pyrroline **3(a-b)** showed the fundamental peaks which include the aromatic C-H, aliphatic C-H, aromatic C=C and NH within the ranges 2977- 3340, 2885-2846, 1681-1651, 1564-1584 respectively.

Table 4: FT-IR spectra of pyrroline

Comp.	Aromatic C-H Stretching cm^{-1}	Aliphatic C-H Stretching	C=N Pyroz	Aromatic C=C stretching cm^{-1}	NH Pyroz
3a	2854 *w*	2800	1604	1597	3340
3b	2885 *w*	2876 *w*	1654	1593	3340

Infrared Spectra (IR) of isoxazol

The IR spectra of the isoxazoline3 (a-b) showed the fundamental peaks which include the aromatic C-H, aliphatic C-H, aromatic C=C and C-O within the ranges 2977-3340, 2885-2846, 1681-1651, 1564-1134 respectively.

Table 5: FT-IR spectra of isoxazoline

Comp.	Aromatic C-H stretching $_{cm^{-1}}$	Aliphatic C-H stretching $_{cm^{-1}}$	Aromatic C=C stretching $_{cm^{-1}}$	C-O ISOXAZOLE
3C	2924 *w*	2800	1550	1134
3D	2924 *w*	2854 *w*	1527	1126

NMR Spectrum

Synthesis of (5-(4-bromophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydro-1H-pyrazole

Synthesis of (5-(4-bromophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydro-1H-pyrazole

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H), 7.89 (dd, J = 78.2, 8.7 Hz, 4H), 7.49-7.25 (m, 2H), 6.59 (d, J = 8.5 Hz, 1H), 3.44 (s, 6HO,CH3), 3.72 (t, J = 10.5 Hz, 1H,CH pyrazole), 2.82 (d, J = 14.6 Hz, 2H,CH,alph).

Synthesis of (5-(4-nitrophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydro-1H-pyrazole

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H, NH), 7.89 (dd, J = 78.2, 8.7 Hz, 6HAr-H), 7.49-7.25 (m, 3HCHarom), 6.59 (d, J = 8.5 Hz, 6H, OCH3), 3.72 (d, J = 10.5 Hz, 2H), 2.83 (d, 2HCH.alph).

Synthesis of (5-(4-bromophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydroisoxazole

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (8J = 78.2, 8.7 Hz, 3H, CH), 7.49 – 7.25 (m, 2HCHArom), 6.59 (d, J = 8.5 Hz, 1H, CH), 3.08 – 2.99 (m, 1H, CH isoxazole), 2.83 (s, 1H, CH Alph).

Synthesis of (5-(4-nitrophenyl)-3-(2, 3-dimethoxyphenyl)-4, 5-dihydroisoxazole

^{1}HNMR (500 MHz, DMSO-d_6) δ 7.89 (S, J = 7.2, NH, 8.7 Hz, 3H, CH), 7.49-7.25 (m, 2HCHArom), 6.59 (d, J = 8.5 Hz, 1H, CH), 3.08-2.99 (m, 1H, CH isoxazol), 2.83 (s, 1H, CHAlph). δ (27.2,50.2 ppm)for CH, and signal at δ(76.1 ppm)for C, and signal at δ (68.3. ppm)for CH-N, and signal at δ(172,205.6)for carbonyl ketone C=O, carbonyl amid C=O-NH. Also multiplet signal at (105.2 -155.3 ppm) for phenyl ring and five ring.

^{13}C-NMR Spectrum

^{13}C-NMR spectrum of 5-(4-bromophenyl)-3-(2,3-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazole (2a) shows signal at Chemical δ(60. 29,64.0 ppm for OCH_3), signal at δ (40.7 ppm for CH_2 carbons) ,and signal at δ (58.8 ppm)for CH, and signal at δ(152 ppm) for C=N, also multiplet signal at(112.8 -155.6 ppm) for phenyl ring. ^{13}C-NMR spectrum of 3-(2,3-dimethoxyphenyl)- 5- (4-nitrophenyl) -4,5-dihydro-1*H*-pyrazole (2b) shows signal at Chemical δ (60.29,58.8 ppm for OCH_3), signal at δ (56.8 ppm for CH_2 carbons) ,and signal at δ (53.5 ppm)for CH, and signal at δ(153 ppm) for C=N, also multiplet signal at(112.8 -155.6 ppm) for phenyl ring. ^{13}C-NMR spectrum of 5-(4-bromophenyl)-3-(2, 3-dimethoxyphenyl)-4,5-dihydroisoxazole (2d) shows signal at Chemical δ (60.29,58.8 ppm for OCH_3), signal at δ (56.8 ppm for CH_2 carbons), and signal at δ (56.8 ppm)for CH, and signal at δ(153 ppm) for C=N, also multiplet signal at(112.4 -155.6 ppm) for phenyl ring.

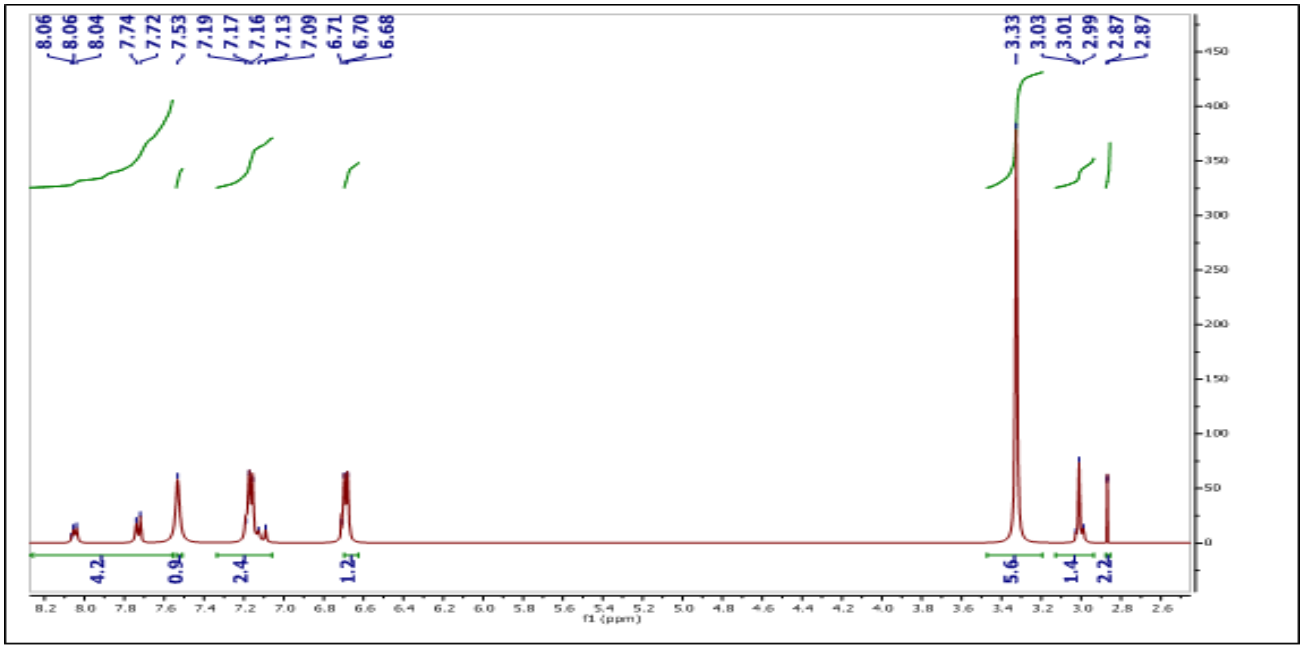


Figure 1: ^{1}H-NMR spectrum of (3a)

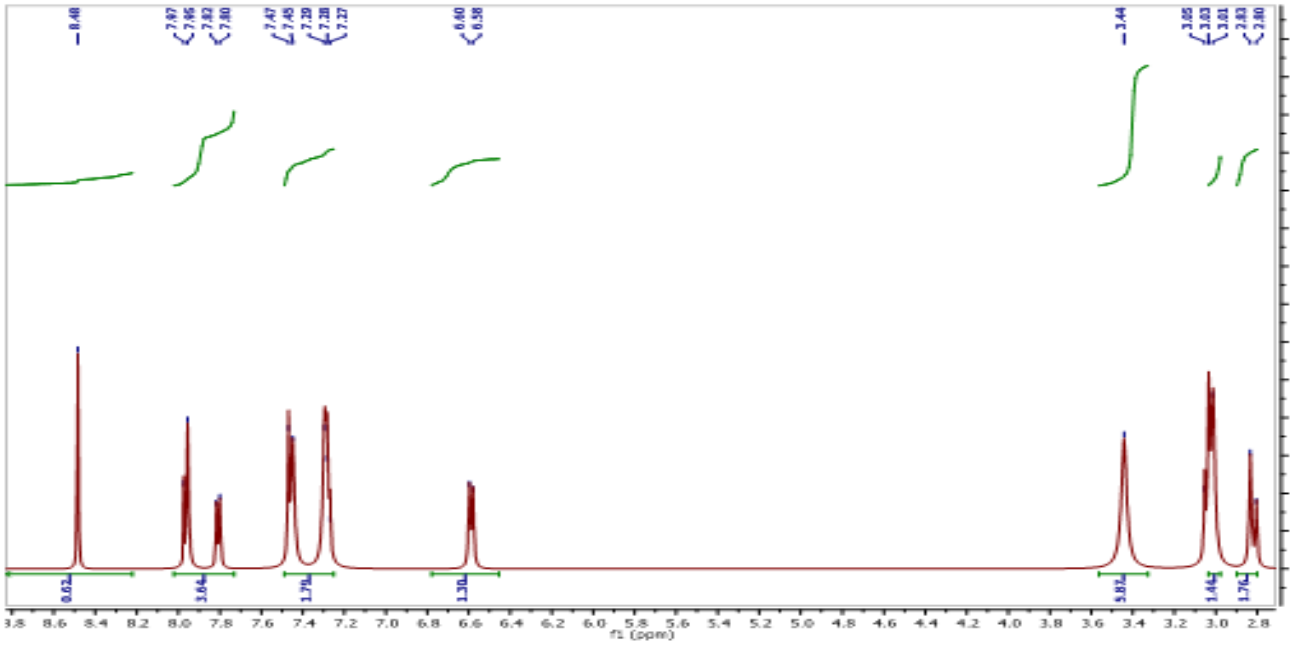


Figure 2: ^{1}H-NMR spectrum of (3b)

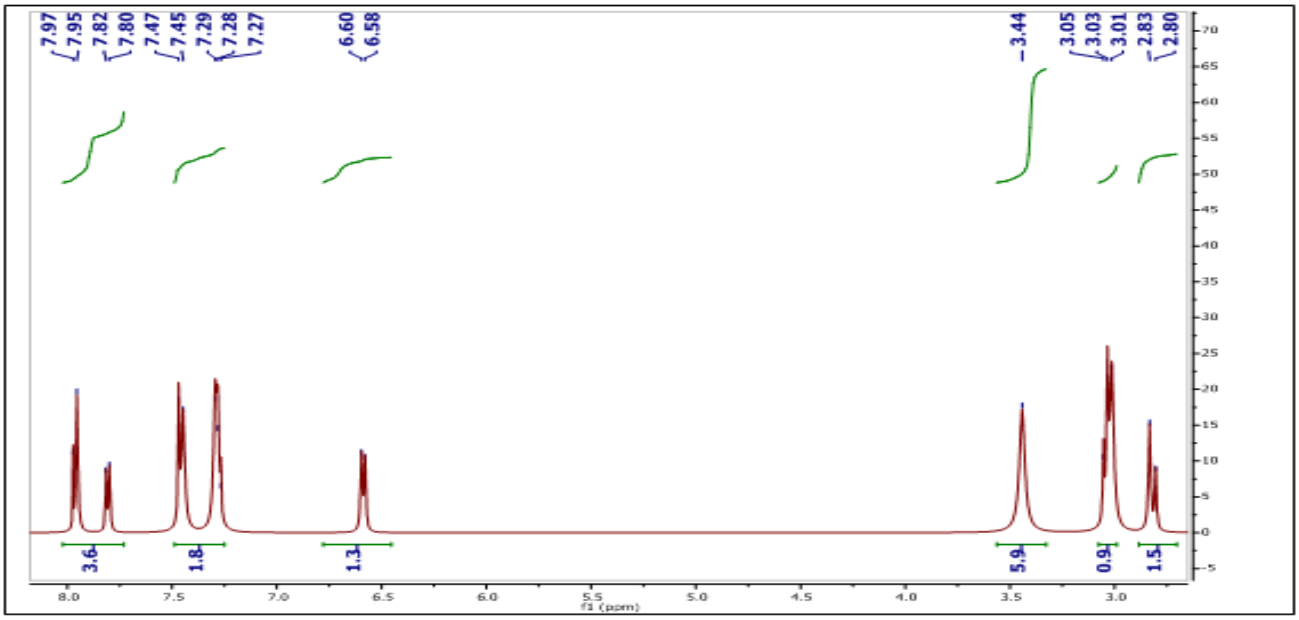


Figure 3: ^{1}H-NMR spectrum of (3c)

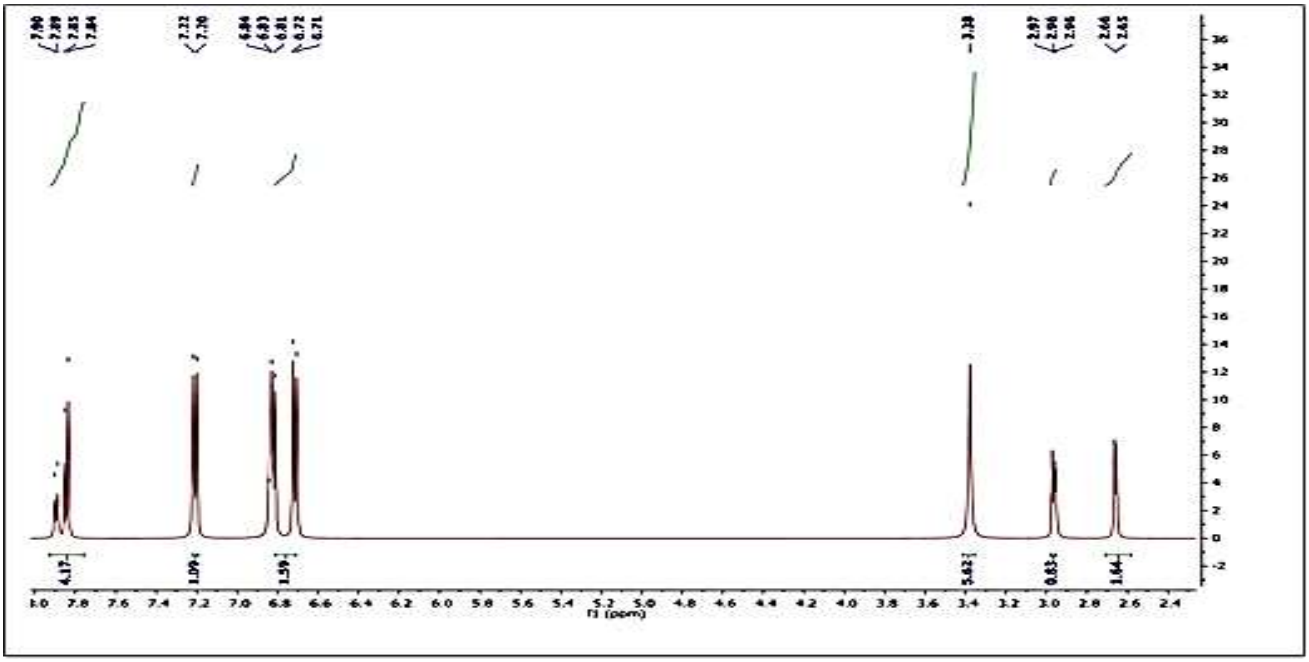


Figure 4: ^{1}H-NMR spectrum of (3d)

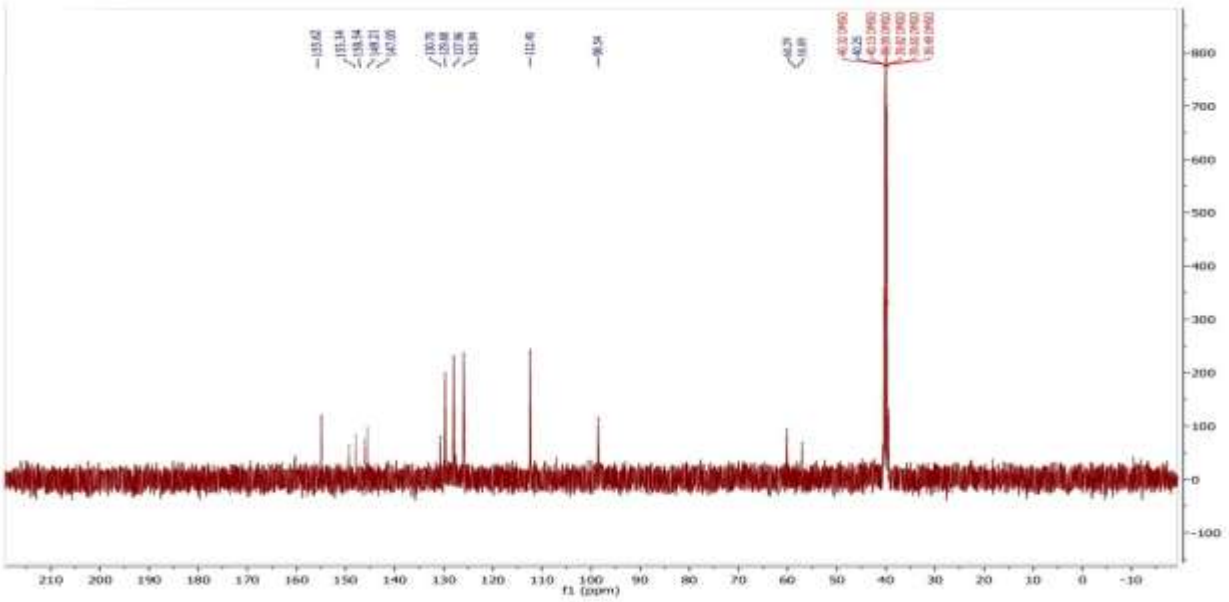


Figure 5:13C-NMR spectrum of (3a)

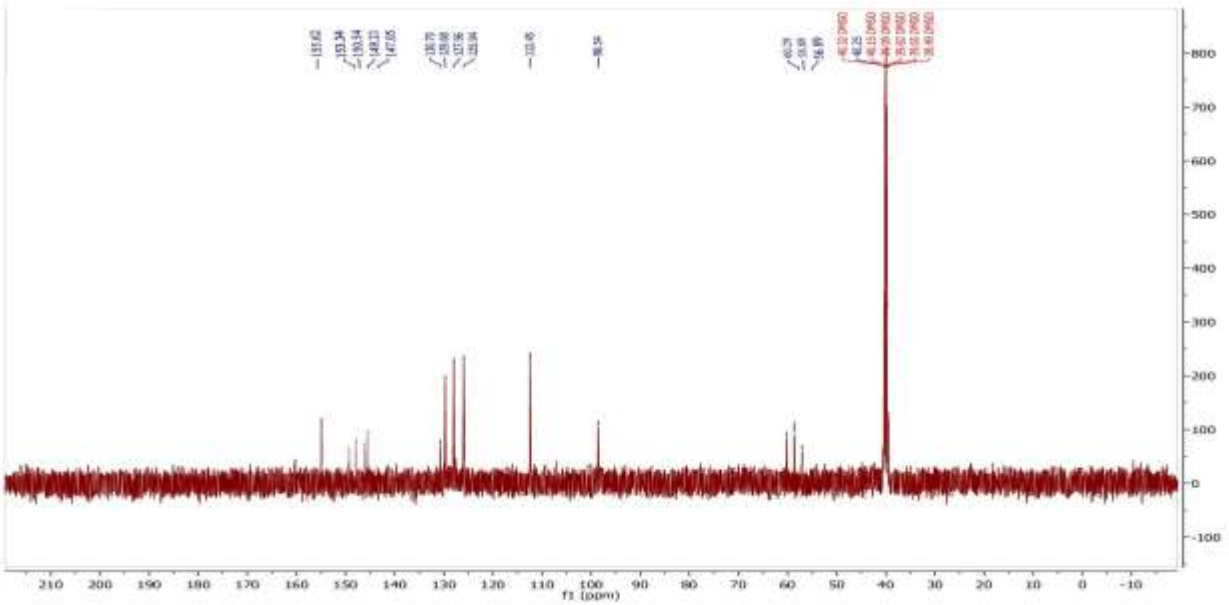


Figure 6:^{13}C-NMR spectrum of (3b)

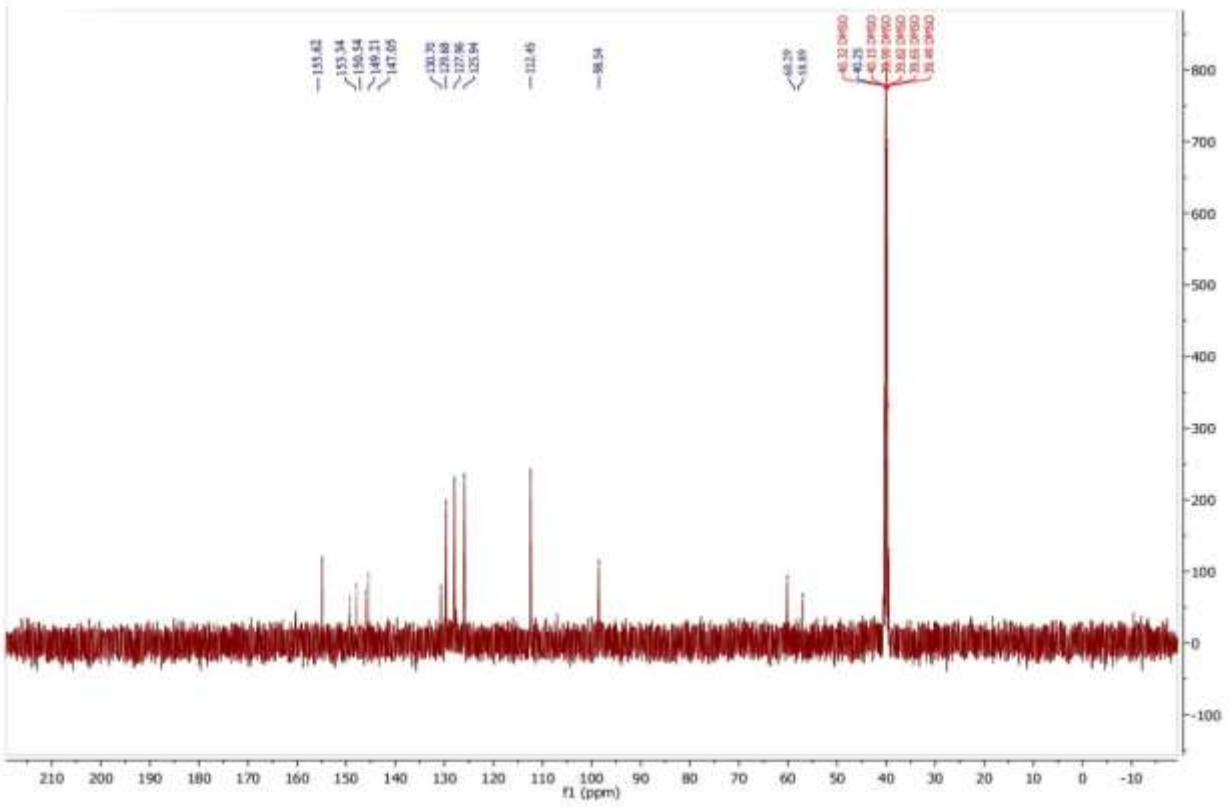


Figure7:^{13}C-NMR spectrum of (3c)

Biological Activity

The pyrazoline, isoxazole were evaluated for antimicrobial activity against gram positive bacteria such as Staphylococcus aureus and gram negative bacteria Escherichia coli, by using agar well diffusion method. All the microbial cultures were adjusted to 0.5 McFarland standards, dimethyl sulphoxide (DMSO) were used to prepare all the test solution .The area of inhibition was measured in millimeter. Nutrient agar used as culture medium.

Table 6: Anti-bacterial data of Compound

Compound	Escherichia coli Inhibition zone(mm)	Staphylococcus Aurens Inhibition zone(mm)
3a	20	12
3b	27	15
3c	15	10
3d	20	10

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