Synthesis and Preliminary Biological study of New Chalcone Derivatives Containing Isoxazoline Moiety

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Abstract

In this research work, synthesis, antimicrobial and antioxidant bioactivity of a chain of compounds having unsaturated ketones bond and isoxazoline moiety have been described. New chalcone derivatives containing isoxazoline moiety have been synthesized. Generally, Chalcones are unsaturated ketones bearing (-CO-CH=CH-) as reactive ketoethylenic group that give the bright yellow colored compounds due to this chromophore group. Firstly, chalcones (IIa-d) have been prepared by cyclocondensation (Claisen-Schmidt condensation) of triphenyl aminobenzaldehyde with different substituted acetophenone in ethyl alcohol to produce a series of chalcones compounds with bright yellow colored as a starting material,. The next step involving the novel chalcones (IIa-d) reacted with hydroxylamine hydrochloride afforded a new isoxazoline compounds (IIIa-d) in basic medium. The prepared compounds were fully characterized by melting points, FTIR, ^{1}H-NMR spectroscopy, ^{13} C-NMR for some compounds and CHNS techniques. The reactions have been monitored by TLC (Thin Layer Chromatography) technique. The synthesised compound IId showed significant bioactivity against the gram-negative bacteria species. Also, the antioxidant activity of the some new synthesized compounds was evaluated and determined against the DPPH radical (1.1-diphenyl-2-picrylhydrazyl) and compared to that of a standard natural antioxidant, Ascorbic acid, compound IIb showed higher antioxidant activity by using the free radical

DPPH. The outcomes of investigation enhanced the activity of new derivatives as antimicrobial reagent.

Keywords: Chalcone, Isoxazoline, Claisen-Schmidt condensation, Biological activity, Antioxidant activity.

Introduction

The Chemistry of Chalcones has been encourage scientists to developed new synthetic methods due to having a natural group in there structure that introduce an important advantage in drawing the pharmacology of the compounds such as antiviral, antifungal, anticancer and antioxidant . In this work, chalcones derivatives have been prepared by condensation of aromatic aldehyde with substituted acetophenone in alkaline medium [1-5]. To the best of our Knowledge, chalcones are essential precursor for preparing a new chalcone compounds containing Isoxazoline moiety [6-8].

Heterocyclic compounds that have either five or six membered rings with different atoms other than carbon atom like oxygen, nitrogen or sulphur [9]. Isoxazoline ring is one of important heterocyclic moiety with one nitrogen atom next to one oxygen atom in five-membered ring system and have one double bound. In recent years, Isoxazoline moiety were grab the attention of people that work in drug field, for the reason that it can be exist in many naturally occurring compounds that were useful in medicine and agriculture. In somewhat easy to prepare and chemical manipulation include both bonding of isoxazoline with substituted aromatic and non-substituted aromatic, their usually low toxicity [10-11]. Isoxazoline is still a popular core ring in the structure of some biosoteric compounds such as anti-inflammatory, anticancer and antimicrobial.

Our successful route to synthesis natural products including a bioisoteric moiety to promote the pharmacological and biological properties [12-14].

Materials

All chemicals have been supplied from Merck GCC and sigma Aldrich Chemicals Company and have been used as received.

Instrumentation

^{1}H-NMR was recorded on Bruker, DRX 400 spectrometers. Chemical shifts (δ) have been expressed in (ppm). All spectra have been obtained in DMSO with (TMS) tetramethylsilane as internal references unless stated otherwise. TLC has been conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer ofsilica gel (Merck 60-245). Melting points have been determined utilizing a HotStage, GallenKam melting point equipment. IR spectra have been recorded directly in a FT-IR 8400S, Bruker spectrophotometer. The elemental analyser EuroEA 3000/Italy recorded elemental microanalyser (CHN) for carbon , hydrogen, and nitrogen.

General procedure of chalcones synthesise

Note: Thin-layer chromatography technique (TLC) has been conducted to check all reactions, eluting with 0.5: 9.5 ethyl acetate: petroleum ether.

According to the method described by Kalirajan *et al.* [16], 4-(triphenylamino) benzaldehyde (0.01mol) has been mixed with substituted acetophenone (0.01mol), then dissolved in 10 ml absolute ethanol and basified with NaOH (40%, 5 ml). The mixture stirred at ambient temperature for 5 hrs. Cooledwater (10 ml) has been added slowly to the reaction combination then the precipitate which obtained has been filtered, and recrystallized using ethyl alcohol.

3-(triphenylamino) (4-methoxyphenyl)-2-propene-1-one [IIa], ^{1}HNMR DMSO-d_6 (δ, ppm):

3.66 (s, 3H, OCH_3), 6.06 -7.16 (m, H, C-$H_{arm.}$), 6.61-6.91 (m, 2H, COCH=CH), 7.47-7.86 (m, other C-H_{arm}). ^{13}C NMR (δ, ppm): 55.2 (C, OCH_3) $_{alph.}$, 100.6-100.8 (C=C) $_{alph.}$, , 149.5-150.2 (C, C=C)$_{arom}$, 186.5-189.5 (C, C=O).

3-(triphenylamino) (4-hydroxyphenyl)-2-propene-1-one [IIb], ^{1}HNMR DMSO-d_6 (δ, ppm): 6.61-6.91 (m, 2H, COCH=CH), 7.14 -7.29 (m, H, C-$H_{arm.}$), 10.37 (bs, H, OH).

3-(triphenylamino) (4-bromoyphenyl)-2-propene-1-one [IIc], ^{1}HNMR DMSO-d_6 (δ,ppm): 6.23-6.45 (m, 2H, COCH=CH), 6.00-6.25 (m, H, C-H_{arm}). ^{13}C NMR (δ, ppm): 101.3-101.4 (C=C) $_{arm.}$, 180.3-184.5 (C, C=O).

3-(triphenylamino) (2,4-dibromophenyl)-2-propene-1-one [IId], ^{1}HNMR DMSO-d_6 (δ,ppm): 6.33-6.65 (m, 2H, COCH=CH), 7.00-7.99 (m, H, C-H_{arm}).

General synthesis of isoxazoline (IIIa-d).

Chalcones (0.01 mol) that produced in the previous step have been mixed with hydroxylamine hydrochloride (0.02 mol) and sodium hydroxide (0.5g) in 25 ml of distilled water), ethyl alcohol (50ml) has been refluxed for 10 hrs. The reaction combination has been cooled, then the solid obtained has been filtered then washed with water then recrystallized from ethyl alcohol.

3-(4-methoxyphenyl)-5-(triphenylamino) 4,5-dihydroisoxazol [IIIa], ^{1}HNMR DMSO-d_6 (δ,ppm): 3.44-3.66 (brs, 3H, CH_3), 6.78-8.88 (m, 18H, Ar-H), 3.89-4.00 ppm (d, IH, CH isoxazoline ring and 2.66-3.90 (m, 2H, CH_2 isoxazoline.

3-(4-hydroxyphenyl)-5-(triphenylamino)4,5-dihydroisoxazol [IIIb], ^{1}HNMR DMSO-d_6 (δ,ppm): 9.9 (brs, 1H, OH), 6.80-8.77 (m, 18H, Ar-H), 2.99-3.55 (m, 1H, isoxazoline ring, 4.22-4.67 (m, 2H, CH_2 isoxazoline).

3-(4-bromophenyl)-5-(triphenylamino)4,5-dihydroisoxazol [IIIc], ^{1}HNMR DMSO-d_6 (δ,ppm): 7.39-8.90 ppm (m, 18H, Ar-H), 3.89-4.00 ppm (m, IH, CH isoxazoline ring and 2.23-2.99 ppm (m, 2H, CH_2 isoxazoline.

3-(2,4-dibromoyphenyl)-5-(triphenylamino)4,5-dihydroisoxazol [IIId], ^{1}HNMR DMSO-d_6 (δ,ppm): 3.44-3.66 ppm (brs, 3H, CH_3), 7.78-8.58 ppm (m, 17H, Ar-H), 4,23-4.91 ppm (m, IH, CH isoxazoline ring and 2.46-3.95 ppm (m, 2H, CH_2 isoxazoline.

Antibacterial activity

In vitro antimicrobial testing effects of chalcones compounds have been estimated against two bacterial strains, [*Escherichia Coli* (-)] as gram-negative and [*Staphylococcus aureus* (+)] as gram-positive [2]. Also, the straight

inhibitory effect of chalcones derivatives was established using the dilution method. Dimethyl sulfoxide (DMSO) has been run as a control. The antimicrobial activity was determined using by method of spreading the disc into Petri dishes with a diameter of (20) ml which were placed inverted and kept in an incubator at constant temperature at 37 ^{o}C and checking after 24 hrs, and the experiment was performed at 10^{-5} M using DMSO solvent. The diameter of the bacterial growth inhibition zones has been measured and exhibited an activity. Each experiment has been made in triplicate and the average reading was taken.

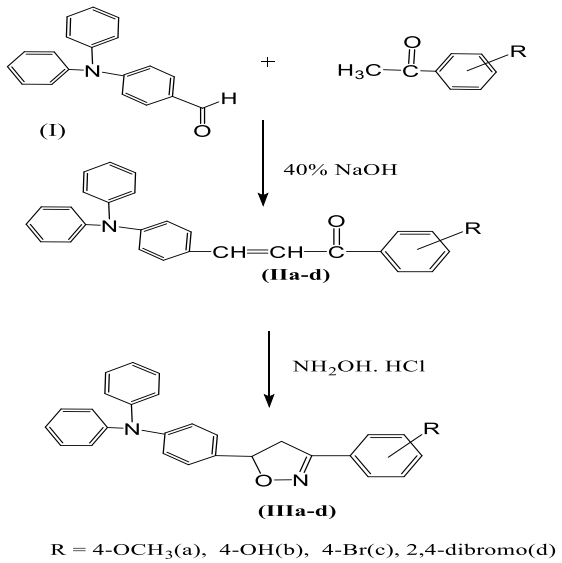
Antioxidant activity

The antioxidant activity of new chalcones derivatives and standard (vitamin C) have been assessed essentially on the radical scavenging effect for the stable DPPH free radical [17]. Generally, a portion of ml of the chalcones derivatives or standard (0.625, and mg/ml) has been added to ml of DPPH solution in a test tube. During incubation at 37^{o}C for half an hour, the absorbance of each solution has been measured at nm utilizing spectrophotometer. Most data have been in triplicate.

Results and discussion

Compounds synthesis

In this scientific paper to gain access to the chalcones (IIa-d), we chose to utilise claisen-Schmidt condensation by treating (triphenylamino) benzaldehyde with different substituted acetophenone with ethanol in alkaline medium (40% NaOH) followed by filtration, to yield the desired chalcones in a moderate yield. The next step is to obtain the isoxazoline compounds (IIIa-d) which have been synthesized by treating compounds (IIa-d) with hydroxylaminehydrochloride in a basic medium. as in Scheme (1) illustrates the synthetic scheme, while Table (1) illustrates the compounds properties.



Scheme 1. Synthesis of Isoxazoline compounds.

Table 1. The physical properties for compounds IIa-d and IIIa-d.

Compd. No.	Nomenclature	Molecular Formula	M.P. °C	Yield %	Nature
IIa	**3-(triphenylamino)(4-methoxyphenyl)-2-propene-1-one**	$C_{28}H_{23}N_1O_2$	120	79	Yellow solid
IIb	**3-(triphenylamino)(4-hydroxyphenyl)-2-propene-1-one**	$C_{28}H_{21}N_1O_2$	136	60	Orange solid
IIc	**3-(triphenylamino)(4-bromoyphenyl)-2-propene-1-one**	$C_{27}H_{20}N_1OBr$	140	51	Yellow solid
IId	**3-(triphenylamino)(2,4-dibromophenyl)-2-propene-1-one**	$C_{27}H_{19}NOBr_2$	120	68	Brown solid
IIIa	**3-(4-methoxyphenyl)-5-(triphenylamino)4,5-dihydroisoxazol**	$C_{28}H_{24}N_2O_2$	181	71	Orange solid
IIIb	**3-(4-hydroxyphenyl)-5-(triphenylamino)4,5-dihydroisoxazol**	$C_{27}H_{22}N_2O_2$	171	69	Yellow solid
IIIc	**3-(4-bromophenyl)-5-(triphenylamino)4,5-dihydroisoxazol**	$C_{27}H_{21}N_2OBr$	131	54	Light-orange solid
IIId	**3-(2,4-dibromoyphenyl)-5-(triphenylamino)4,5-dihydroisoxazol**	$C_{27}H_{20}N_2OBr_2$	157	66	Orange solid

FTIR spectroscopy

The compounds (IIa-d) were characterized by FTIR spectroscopy. The FTIR spectrum for compounds (IIa-d) showed appearance stretching band at (1218) cm^{-1} due to C-OCH_3, broad band O-H at (3408) cm^{-1}, stretching band at (693-694) cm^{-1} due to C-Br, respectively. Also, the FTIR spectrum showed stretching bands at (11656-1685) cm^{-1} due to C=O starching, sharp band at (1580-11581) cm^{-1} due to C=C (CH-CH) of chalcone bond (Table 2). Additionally. The spectra reveals disappearance identification bands from the starting materials. Figures 1 and 2 FTIR spectrum of IIa and IIb. Furthermore, the FTIR spectra of (IIIc) showed disappearance the bands of C=O and C=C that belonged to the chalcone unit with the appearance of new bands for C-H_{aliph}. at (2995)cm^{-1}. Also, appearance of a stretching band at (1636) cm^{-1} due to C=N of isoxazoline moiety (endo cyclic), C-O of isoxazoline moiety at (1028) cm^{-1} (Table 3).

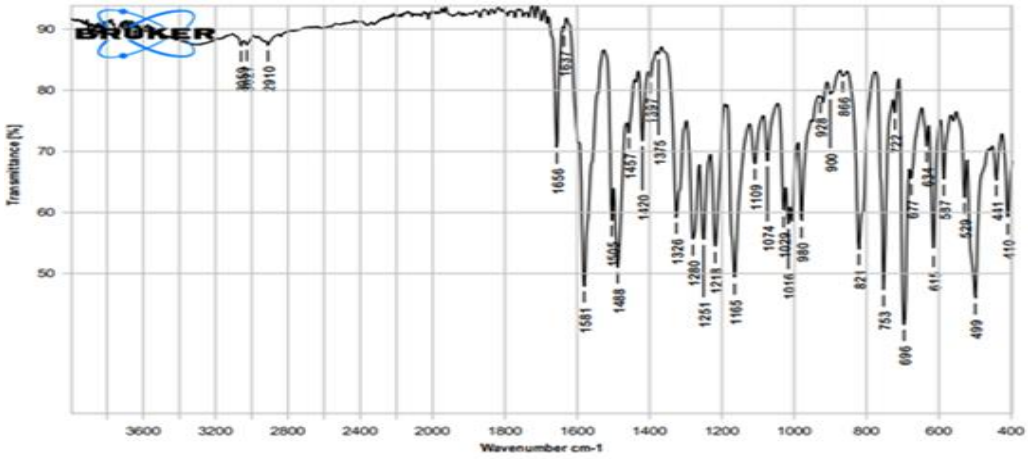


Figure 1. FTIR spectrum of dervative (IIa)

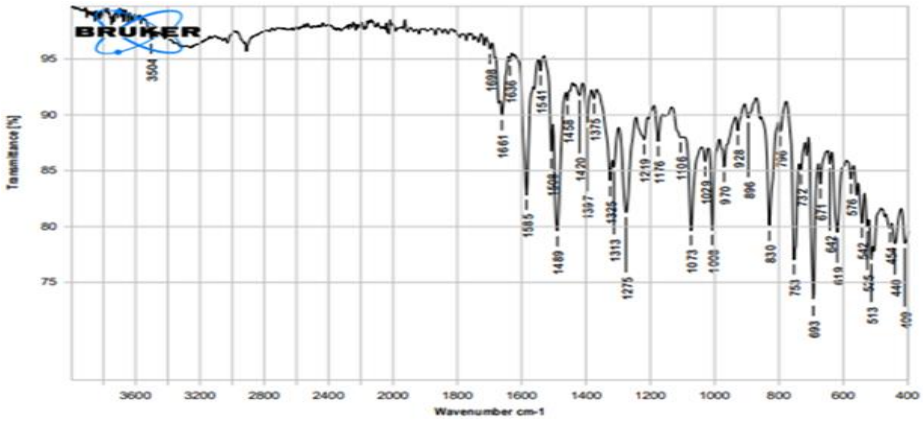


Figure 2. FTIR spectrum of dervative (IIb)

Table 2. FTIR data for derivatives (IIa-d)

Comp. No.	V(C-H) arom./cm^{-1}	V(C-H) aliph./cm^{-1}	V(C=O) endocyc./cm^{-1}	V(CH=CH) cm^{-1}	V others cm^{-1}
IIa	3057	2980	1656	1580	p-OCH_3 (1218)
IIb	3032	2932	1656	1580	p-OH (3408)
IIc	3033	2902	1652	1575	P-Br (693)
IId	3038	2741	1685	1581	2,4-di-Br (694)

Table 3. FTIR data for derivatives (IIIa-d)

Comp. No.	V(C-H) arom./cm^{-1}	V(C-H) aliph./cm^{-1}	V(C=N) endocyc./cm^{-1}	V(C=C) arom./cm^{-1}	V(C-O) endocyc./cm^{-1}	V others cm^{-1}
IIIa	3060	2981	1636	1586	1073	p-OCH_3 (827)
IIIb	3033	2949	1646	1584	1085	p-OH (3194)
IIIc	3058	2995	1636	1585	1028	P-Br (867)
IIId	3049	2996	1671	1584	1084	2,4-di-Br (827)

^{1}H-NMR spectra

The (IIa) structure was characterized by ^{1}H-NMR; the two protons of ketoethylenic group (COCH=CH) have been appeared as a multiplet at 6.61-6.99 ppm as well as other aromatic hydrogens, three protons due to OCH_3 as a singlet at 3.66 ppm, while the multiplet appear at 7.15- 7.86 ppm related to aromatic hydrogen's (Figure 3). In addition, the multiplet signal at. ^{1}H-NMR for the compound (IIb) showed a broad signal at 10.37 ppm due to (OH) proton, a multiplet at 6.23-6.45 ppm for CH=CH, a multiplet at 7.14-7.29 ppm related to aromatic hydrogens. ^{1}H-NMR for IIc and IId showed a multiplet at 6.00-6.25ppm and 7.80-7.99 ppm for CH=CH, respectively.

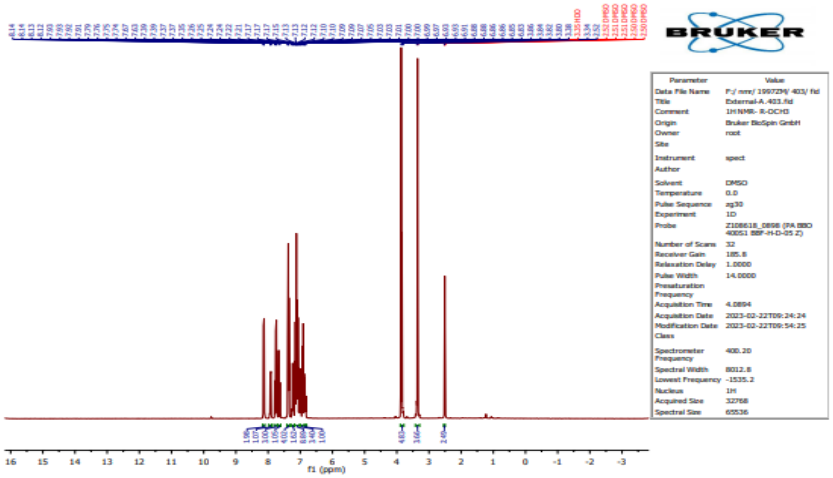


Figure 3: ^{1}H-NMR spectrum of compound (IIa)

Compound IIIa was also characterised by ^{1}H-NMR and has been showed signal at 3.44-3.66 ppm for three protons (OCH_3) and multiplet at 6.78-8.88 ppm for aromatic ring. Also, a doublet at 3.89-4.00 ppm for ne proton (CH isoxazoline ring) and the spectrum also showed a signal at 2.66-3.90 ppm for 2H, CH_2 isoxazoline. Compound IIIb, ^{1}HNMR spectrum show occurrence broad signals at 9.9 ppm for one proton related to OH, and occurrence signals 6.80-8.77 ppm attributed to 18H to aromatic rings, 2.99-3.55 ppm (m, 1H, isoxazoline ring, 4.22-4.67 ppm (m, 2H, CH_2 isoxazoline).

IIIc, ^{1}HNMR spectrum show multiplet signals at 7.39-8.90 ppm for 18 protons to (Ar-H), 3.89-4.00 ppm (m, IH, CH isoxazoline ring and 2.23-2.99 ppm (m, 2H, CH_2 isoxazoline.

IIId, ^{1}HNMR spectrum show occurrence signals at 7.78-8.58 ppm for 17H to aromatic rings, also the spectrum showed a multiplet signals at 4,23-4.91 ppm for IH, CH isoxazoline ring and 2.46-3.95 ppm for 2H, CH_2 isoxazoline.

^{13}C-NMR spectra for IIa and IIc

^{13} C spectrum also have been assigned of the compound IIa, the solvent DMSO signal appears at 39ppm, while the signal at 5.22 ppm refers to carbon atom of the methoxy group. The carbon atoms of CH=CH group appears at 100.6-

100,8 ppm, while the aromatic ring carbons appear at 149.5- 150.2. The carbonyl group appears in the range 186.5-189.5 ppm Figure 4 and 5 of compounds IIa , IIc . .While ^{13}C-spectrum of Compound IIc has been showed disappear the signal at 50-60 ppm due to the aromatic ring substituted with bromide. Table 4 illustrated the elemental analysis for the synthesised compounds.

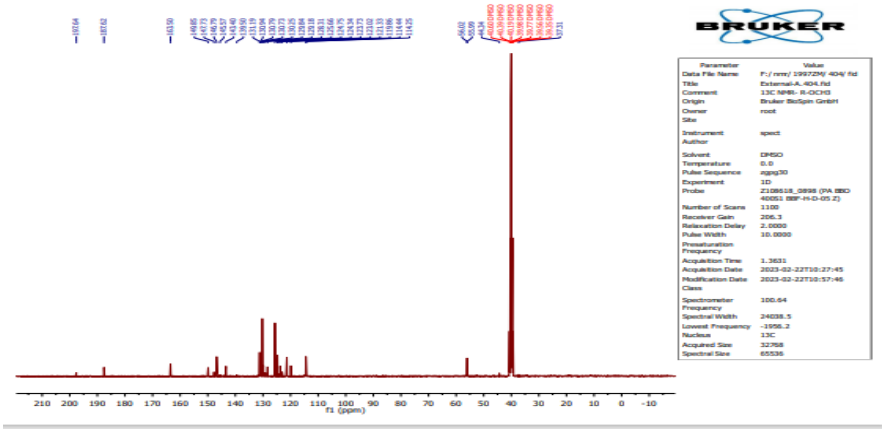


Figure 4. ^{1}3C-NMR spectrum of compound (IIa)

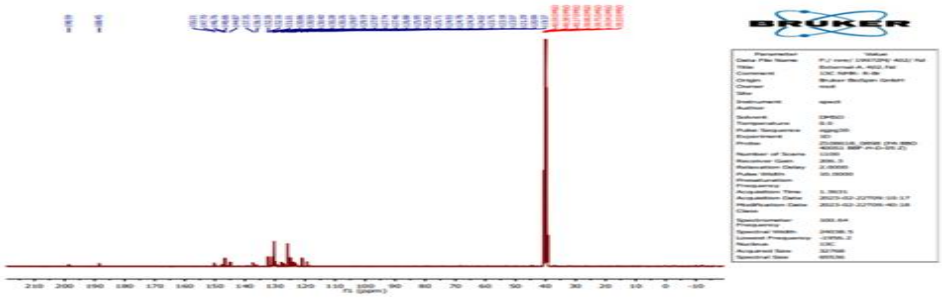


Figure 5: ^{13}C-NMR of compound IIc

Table 4: Elemental analysis for synthesised compounds [11a-IId and IIIa-IIId].

Com. No.	C %		H %		N %	
	calculated	Found	calculated	Found	calculated	Found
IIa	82.96	83.78	5.20	5.46	3.72	3.90
IIb	83.37	82.43	5.21	5.27	3.47	3.93
IIc	71.36	72.52	4.40	4.89	3.08	3.55
IId	60.67	59.71	3.55	3.92	2.62	2.67
IIIa	80.01	80.81	5.71	5.48	6.66	6.33
IIIb	79.80	78.59	5.41	5.90	6.69	6.89
IIIc	69.08	69.53	4.47	4.21	5.97	5.62
IIId	59.12	59.87	3.64	3.43	5.10	5.76

Antibacterial activity

Antibacterial outcomes have been indicated that the prepared compounds have a broad spectrum against the secerned bacteria species (gram-negative and gram positive) for certain bacteria strains. Derivative (IId) having chalcone bond is the most significant activity against gram- negative ones. In contrast the compound IIIa has weak activity for the same ones. Regarding to the gram-positive species, the results showed that the compound IId having the highest activity towards gram-positive ones compared to other compounds. The outcomes of this study was summarized in Table (4).

Table 4. Antibacterial evaluation of compounds $II_{a,b,d}$ and $III_{a,b,d}$.

		Gram-positive	**Gram-negative**
Comd. No.	Conc.	*Staphylococcus S-aureus*	*Escherichia Coli E-Coli*
IIa	10^{-5}	14	17
IIb	10^{-5}	15	16
IId	10^{-5}	17	24
IIIa	10^{-5}	13	11
IIIb	10^{-5}	14	12
IIId	10^{-5}	7	18

Antioxidant activity

The radical DPPH is considered the best scavenging in *vitro* model. This method was widely used to assess antioxidant efficacy. Antioxidant compounds can react with DPPH and produce the radical 1,1-diphenyl-2-picryl-hydrazine. The reducing capabilities of the screened compounds have been evaluated by their interaction with the stable free radical 1,1-diphenyl-2-picryl-hydrazine at three different concentrations for 30 minutes. The highest scavenger potential has been noticed in (IIb), which could be attributed to the presence hydroxyl substituent. In conclusion, all the compounds showed a good scavenging activity towards PDDH, but achalcone compound and compounds with isoxazoline ring in conc, (0.5 mg/ml) that substituted with hydroxyl and methoxy groups exhibited highest antioxidant activity than other compounds.

The capability to scavenging DPPH radical has been studied as the equation below:

DPPH radical scavenging activity (%) = $\left(1- \frac{\text{Absorbance of Sample}}{\text{Absorbance of Standard}}\right) \times 100$

A process that generates hydrogen peroxide in vivo by some oxidase enzymes, and which product hydroxyl radical that in turn can harm the biological systems. The antioxidant potential of some new synthetic compounds have been assigned by its scavenging for the stable (DPPH) free radical [18-20]. From the outcomes in Figures (4 and 5), the concentration (0.5 mg/ml) is most likely to be more scavenging potential when compared with other concentrations. Although, the antioxidant activity of IIb showed higher than IIIb (involving Isoxazoline moiety with methoxy group) in the same concertation (0.5gm/ml) which attributed havingg unsaturated ketones bearing (-CO-CH=CH-) as reactive ketoethylenic group surrounded with phenolic hydroxyl. Generally, the scavenging activity outcomes of some synthetic compounds illustrated in Table (5).

Table 5. Scavenging activity of some synthetic compounds (IIa, IIb, IIIa, IIIb).

Conc. gm/ml	**Scavenging % (Mean ± SD)**				
	IIa	**IIb**	**IIIa**	**IIIb**	**Ascorbic acid**
0.5	60.00±2.6	67.14±2.79	62.33±1.91	53.23±2.38	76.±5001.04
0.25	55.582±1.20	51.45±1.2	54.42±2.77	46.94±2.58	68.23±4.90
0.125	44.42±3.0	42.82±2.26	42.85±.1.6	41.56±1.29	57.03±6.85

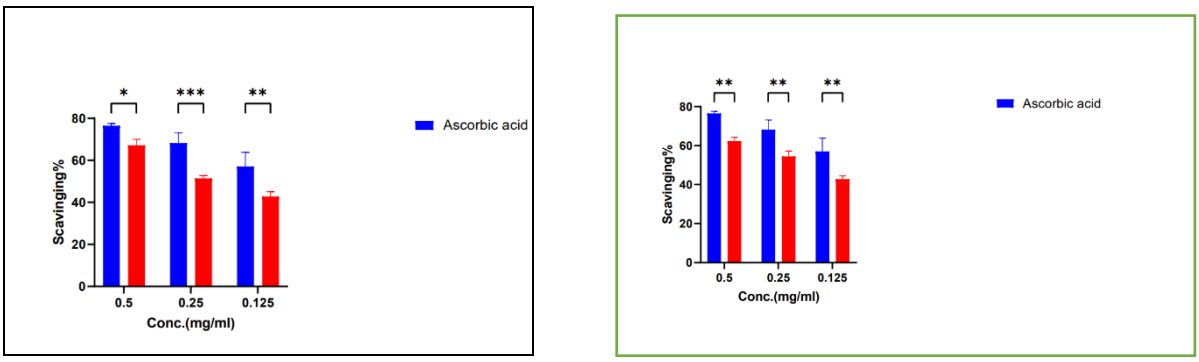


Figure 4. Scavenging activity of IIb and IIIa using DPPH.

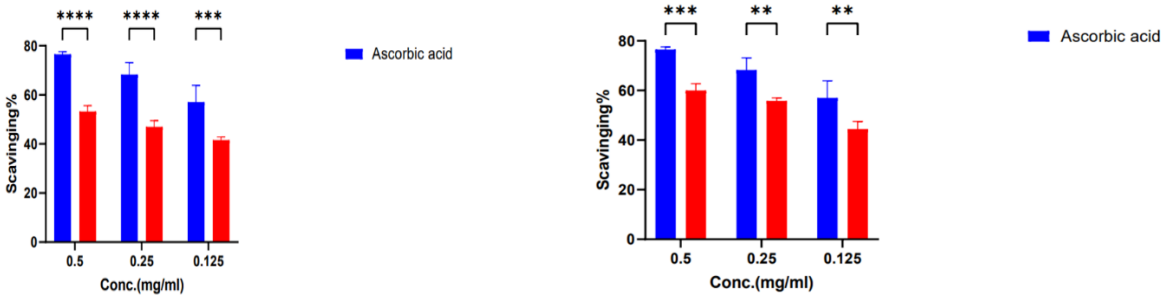


Figure 5. Scavenging activity of IIa and IIIb using DPPH.

Conclusion

To summarize, new isoxazoline derivatives have been successfully prepared and characterized utilizing spectroscopic techniques like FTIR and NMR. Some of the prepared derivatives have been investigated for antimicrobial study against Gram-negative bacteria and Gram-positive bacteria and the results have been showed that the compounds IId has a greater inhibition for the certain bacteria species in comparison to the other compounds. In addition, the derivatives IIb and IIIa they were evaluated the highest scavenging potential.

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CONFLICT OF INTEREST

The authors declare no conflict of interest about current manuscript.

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