Synthesis, Characterization and Antibacterial Activity of New Derivatives of Imidazolidine having Sulfamethoxazole Moiety

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Abstract:

This work includes Synthesis of new series of sulfa drugs derived from sulfamethoxazole containing substituted Imidazolidine moiety. These compounds expected to have antibacterial activity, due to their Imidazolidine moiety This work includes synthesis of some new Schiff bases (II1-5) by condensation of sulfamethoxazole drug(I) with some aldehydes (1-5) (benzaldehyde, p-chloro benzaldehyde, p-nitro benzaldehyde, p-hyroxy benzaldehyde and p-N, N-dimethyl amino benzaldehyde). These Schiff bases were found to react with glycine, to prepared new imidazolidine derivatives (III1-5). The prepared compounds were characterized by physical properties, FT-IR and of the 1H-NMR spectroscopy. The preliminary study of antibacterial activity of final compounds has considered by well diffusion method. The tested compounds displayed effect against gram negative bacteria:(Acinetobacter species and Pseudomonas aeruginosa) and gram-positive bacteria (Streptococcus pyougenes and Staphylococcus aureus bacteria), which compared to DMSO as control, and good activity compared to sulfamethoxazole as standard.

Key words: Sulfamethoxazole, Schiff bases, Imidazolidine, Antibacterial Activity.

تحضير وتشخيص ودراسة الفعالية المضادة للبكتريا لمشتقات جديدة من الايميدازوليدين تحتوي على سلفاميثوكسازول.

ايناس قاسم عبد العزيز *, اياد محمد رشيد **, كريمة فاضل علي**
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****فرع الكيمياء الصيدلانية ,كلية الصيدلة ,الجامعة المستنصرية, بغداد ,العراق.**

الخلاصة:

يشمل هذا العمل تحضير سلسلة جديدة من دواء السلفا (سلفاميثوكسازول) تحتوي على إيميدازولدين ا لغير متجانسة. هذه المركبات من المتوقع أن يكون لها نشاط مضاد للبكتريا . يتضمن هذا العمل تحضير بعض قواعد الشيف بيس (II1-5) من تفاعل السلفاميثوكسازول I مع خمسة انواع مختلفة من البارا -بنزالديهايد الحلقية . هذه القواعد تتفاعل مع الكلايسين لتحضير مشتقات ايميدازولين جديدة (III1-5) . تم توصيف المركبات المصنعة باستخدام الخواص الفيزيائية , قياس اطياف الاشعة تحت الحمراء واطياف الرنين المغناطيسي. . تم تقييم الدراسة الأولية لفعالية المركبات النهائية كمضادات للبكتريا بطريقة الانتشار. وقد أظهرت المركبات التي تم اختبارها تأثيرًا ضد البكتيريا سالبة الغرام: أنواع اسينيتوباكتام وسيدومونس ايروجينوزا والبكتيريا الموجبة الغرام ستافلوكوكس اوريس، ستربتوكوكس بايوجينز(البكتريا المراكدة والزائفة الزنجارية) والبكتيريا الموجبة الغرام (المكورات العنقودية الذهبية، المكورات العقدية المقيحة) والتي تم مقارنتها مع DMSO كمجموعة ضابطة ، وفعاليةجيدة مقارنة مع السلفاميثوكسازول كمعيار .

الكلمات المفتاحية: سلفاميثوكسازول, شيف بيس, إيميدازولدين, نشاط مضاد للبكتريا.

Introduction:

Sulfonamide was the first antibiotic to be used systematically. Sulfonamide derivatives are well-known pharmacological agents because this group has been the main functional part of most pharmaceutical structures due to stability and tolerance in humans.[1] Sulfamethoxazole (SMX) belongs to the sulfonamide group of antibiotics. It is effective against both gram-positive and gram-negative bacteria and inhibits growth by a competitive binding into dihydropteroate synthetase that inhibits conversion of para-aminobenzoic acid (PABA) to dihydropteroate, a precursor to tetrahydro folic acid, which is essential for the synthesis of nucleic acids. An additional mechanism of action is that sulfonamides inhibit cross-membrane transport of glutamic acids which also is an essential component of folic acid synthesis.[2]

Schiff's bases are an important compound; they were first reported by Hugo Schiff in 1864. [3] Schiff bases are synthetically accessible and structurally diverse compounds, typically obtained by facile condensation between an aldehyde, or a ketone with primary amines. The Schiff bases contain an azomethine bond (-C= N-) that combines two or more biologically active heterogeneous / annular scaffolds to form different molecular hybrids with interesting biological properties. [4] Schiff's bases have also been shown a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, anti-viral, and antipyretic properties. [5,6]

Heterocyclic compounds mainly five and six membered heterocyclic have attracted the attention of pharmaceutical researches over the years due to their therapeutic values.[7] Imidazolines (dihydro imidazole) are important five membered heterocycles.[8] Imidazolidine derivatives are important key components in the development of bioactive compounds that used for the treatment of many diseases, such as hypertension, neoplasia, inflammation, and nasal decongestion.[9] Also, as well as many studies showed imidazolidine derivatives have strong antibacterial effects against pathogenic agents such as *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus aureus* [10]

Recently, imidazolidine compounds have attention of researchers to employ their derivatives to inhibit cancer cells, aspergillus, leishmania parasite and Fusarium fungi. [11]

Materials and Methods:

Chemicals and Instrumentation

All chemicals used were supplied from AG and Virchow Laboratories Limited (VLL), Himedia, Fluka Chemicals Company. The melting points were recorded using capillary method on Bamstead/Electro-thermal 9100 an electrical melting point apparatus (England). Determinations of infrared bands were done and documented as a KBr picture using FTIR Shimadzu (Japan), in Mustansiriyah University, College of Pharmacy. ^{1}HNMR bands (solvent DMSO-d_6) were were recorded using 300 MHZ spectrometer on 300 MHZ spectrometer. Bruker DMX-500 spectrophotometer with TMS as internal standard which were made in Tahran University, College of Science.

Methods:

1.General Procedure for the synthesis of 4-(Arylideneamino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (II_{1-5}). [12] Figure (1).

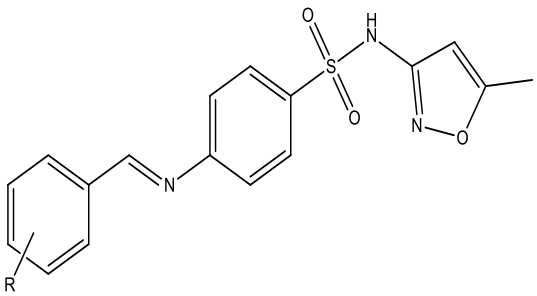


Figure (1): Compounds (II^{1-5})

The solution of sulfamethoxazole (I) (0.253gm, 0.001 mol) in absolute ethanol (30 ml) was slowly added to a solution of aldehyde derivatives (1-5) (0.001 mol) in absolute ethanol (20 ml), then a few drops of glacial acetic acid were added to the mixture. The stirred reaction mixture was refluxed for (8hrs.) at tempreture 80 c^0. After cooling, a precipitate was formed which was collected by filtration, then washed with cold ethanol, and recrystallized from ethanol.

(benzylideneamino)-N-(5-methyli-soxazol-3-yl)benzenes-ulfonamide(II_1) :
(Off white) (90% yield); mp 175-177°C; IR (KBr) v (cm^{-1}): 3282 ,3144 (NH st. of sulfonamide), 1624 (C=N st. of Schiff base);^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.61(S,1H, H-C=N of Schiff base) and δ 11.62 (s, 1H, N-HSO_2), δ 2.29(S ,3H, CH3 of isoxazole ring), δ 6.17(S,1H, C-H of isoxazole), δ 7.34-8.03(complex,8H, C-H of oromatic ring)

4-((4-chlorobenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (II_2) :
(Light yellow) (85% yield); mp 153-155°C; IR (KBr) v (cm−): 3387(NH st. of sulfonamide), 1622 (C=N st. of Schiff base);1H-NMR (DMSO-d_6, 300 MHz): δ 8.64 (S,1H, H-C=N of Schiff base) and δ 11.5 (s, 1H, N-HSO_2) δ 2.32 (S ,3H, CH3 of isoxazole ring), δ 6.13 (S,1H, C-H of isoxazole), δ 6.73-7.98 (complex,8H, C-H of oromatic ring) .

N-(5-methylisoxazol-3-yl)-4-((4-nitrobenzylidene)amino)benzenesulfona mide(II_3):
(Yellow) (70% yield); mp 63-65°C; IR (KBr) v (cm^{-1}): 3387 (NH st. of sulfonamide), 1612 (C=N st. of Schiff base);^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.80 (S,1H, H-C=N of Schiff base) and δ 11.46 (s, 1H, N-HSO_2) δ 2.32 (S ,3H, CH3 of isoxazole ring), δ 6.13 (S,1H, C-H of isoxazole), δ 6.77-8.42 (complex,8H, C-H of oromatic ring).

4-((4-hydroxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenes-ulfonamide(I_4):
(Light brown) (70% yield); mp 160-163°C; IR (KBr) v (cm^{-1}): 3389 (NH st. of sulfonamide), 1641 (C=N st. of Schiff base);1H-NMR (DMSO-d_6, 300 MHz): δ 8.16 (S,1H, H-C=N of Schiff base) and δ 10.87 (s, 1H, N-HSO_2) δ 2.2(S ,3H, CH3 of isoxazole ring), δ 6.14(S,1H, C-H of isoxazole), δ 6.62-7.89 (complex,8H, C-H of oromatic ring), δ 9.81(S,1H,of O-H) .

4-((4-(dimethylamino)benzylidene) amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (II_5) :
(Dark yellow) (90% yield); mp 226-228°C; IR (KBr) v (cm^{-1}): 3284,3144 (NH st. of sulfonamide), 1606 (C=N st. of Schiff base);^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.39 (S,1H, H-C=N of Schiff base) and δ 11.53 (s, 1H, N-HSO_2), δ 2.29 (S ,3H, CH3 of isoxazole ring), δ 3.01(S,6H OF (CH3)2-N), δ 6.15(S,1H, C-H of isoxazole), δ 7.34-8.03 (complex,8H, C-H of oromatic ring).

2. General procedure for the synthesis N-(5-methylisoxazol-3-yl)-4-(5-oxo-2-arylimidazolidin-1-yl)benzenes-ulfonamide(III_{1-5}):[13] Figure(2).

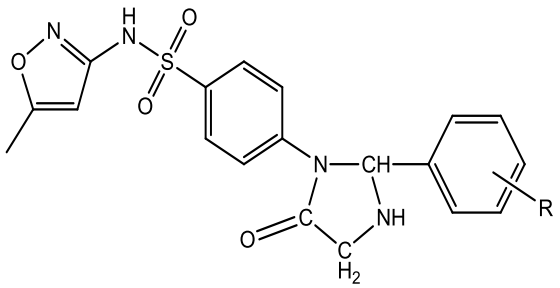


Figure (2): Compounds (III^{1-5})

A mixture of Schiff bases (II_{1-5}) (0.001 mol) dissolved in THF (15 ml) and glycine (0.154gm, 0.002 mol) was dissolved in THF(tetrahydrofuran) (15 ml) and refluxed for (24 hrs.) at tempreture 80 c^0 . The reaction was then cooled and the resulting

solid compounds were recrystallized from absolute ethanol.

N-(5-methylisoxazol-3-yl)-4-(5-oxo-2-phenylimidazolidin-1-yl)benzenesulfonamide (III_1):
(Yellow) (80% yield); IR (KBr) v (cm^{-1}): 3333 (NH st. of sulfonamide), 1712 (C=O st. of oxoimidazolidin);^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.81 (d,1H, of CH of imadozolidinone) , δ 2.93 (d,1H, of CH of imadozolidinone) ,δ 3.7 (d, 1H, HC-N of imadozolidinone) , δ 8.24 (s,1H, of N-H of imadozolidinone), δ 6.08(S,1H, OFCH of isoxazole ring, δ 6.64-7.71(complex,9H,of CH of oromatic ring) .

4-(2-(4-chlorophenyl)-5-oxoimidazolidin-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (III_2):
(yellow) (70% yield); mp 175°C; IR (KBr) v (cm^{-1}): 3387 (NH st. of sulfonamide), 1687(C=O st. of oxoimidazolidin);^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.83 (d,1H, of CH of imadozolidinone) , δ 2.98 (d,1H, of CH of imadozolidinone) ,δ 3.67 (d, 1H, HC-N of imadozolidinone) , δ 10.94 (s,1H, of N-H of imadozolidinone), δ 11.27 (S,1H, of HN-SO_2 of sulfamethoxazole) δ 6.08(S,1H, OFCH of isoxazole ring, δ 6.55-7.94 (complex,8H,of CH of oromatic ring) .

N-(5-methylisoxazol-3-yl)-4-(2-(4-nitrophenyl)-5-oxoimidazolidin-1-yl)benzenesulfonamide (III_3):
(orange) (70% yield); mp 90°C; IR (KBr) v (cm^{-1}): 3385 (NH st. of sulfonamide), 1703(C=O st. of oxoimidazolidin);^{1}H-NMR (DMSO-d_6 ,300 MHz): δ 2.49(d,1H, of CH of imadozolidinone) , δ 2.87 (d,1H, of CH of imadozolidinone) ,δ 3.33 (d, 1H, HC-N of imadozolidinone) , δ 8.80 (s,1H, of N-H of imadozolidinone)and δ 10.93 (S,1H, of HN-SO_2 of sulfamethoxazole) δ 6.07(S,1H, OFCH of isoxazole ring, δ 6.54-8.18 (complex,8H,of CH of oromatic ring) .

4-(2-(4-hydroxyphenyl)-5-oxoimidazolidin-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (III_4):
(Brown) (70% yield); IR (KBr) v (cm^{-1}): 3389 (NH st. of sulfonamide), 1668 (C=O st. of oxoimidazolidin);1H-NMR (DMSO-d_6, 300 MHz): δ 2.49 (d,1H, of CH of imadozolidinone) , δ 2.86 (d,1H, of C of imadozolidinone) ,δ 3.34 (d, 1H, HC-N of imadozolidinone) , δ 8.44 (s,1H, of N-H of imadozolidinone) ,δ 10.75 (S,1H, of HN-SO2 of sulfamethoxazole) and δ 11.36 (s,1H, of O-H) δ 6.08(S,1H, OFCH of isoxazole ring, δ 6.58-7.94 (complex,8H,of CH of oromatic ring) .

4-(2-(4-(dimethylamino)phenyl)-5-oxoimidazolidin-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (III_5) :
(Brown) (80% yield); IR (KBr) v (cm^{-1}): 3356 (NH st. of sulfonamide), 1680 (C=O st. of oxoimidazolidin); ^{1}H-NMR (DMSO-d6, 300 MHz): δ 2.49 (d,1H, of CH of imadozolidinone) , δ 2.86 (d,1H, of CH of imadozolidinone) ,δ 3.44 (d, 1H, HC-N of imadozolidinone) , δ 8.39 (s,1H, of N-H of imadozolidinone) ,δ 10.63 (S,1H, of HN-SO_2 of sulfamethoxazole)and δ 3.02 (s,6H, of $(CH_3)_2N$) δ 6.09(S,1H, OFCH of isoxazole ring, δ 6.57-7.82 (complex,8H,of CH of oromatic ring).

Preliminary Antibacterial Of The Synthesized Compound`S (III1-5):
The biological activities were determined in the Department of Clinical Laboratory Science, College of Pharmacy, Mustansiriyah University. A preliminary antibacterial have been carried out according to well diffusion method.
The synthesized compounds (III1-5) have been studied for their antimicrobial activity in vitro against four tested bacteria (Acinetobacter species, Pseudomonas aeruginosa, as gram negative bacteria and (Staphylococcus aureus, Streptococcus pyougenes as gram positive bacteria) which clinical activated and maintained on

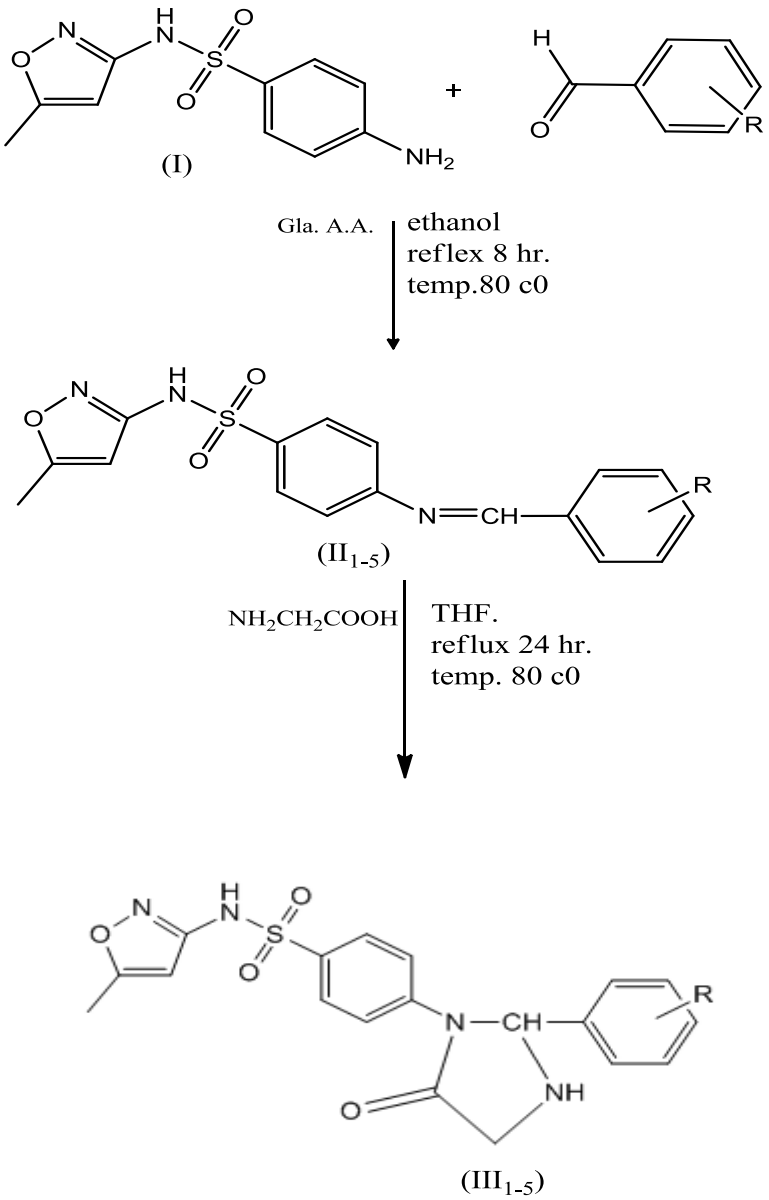
nutrient agar medium for testing antibacterial activity.
Sulfamethoxazole was used as a standard drug for antibacterial activity.

Sensitivity Assay:
The antibacterial activities of each derivatives compound were determined by agar well diffusion assay was carried out by using pure isolates of four type of bacteria was first subculture in Brain heart infusion broth at temperature 37°C for 18-24 hour. select 3-5 colonies of bacteria isolates by loop and transfer them to tube containing 3 mL normal saline and vortex well.
Approximately one hundred microliters of the standardized inoculum bacterial suspension of around (1.5×108 CFU/mL) gained from McFarland turbidity standard (number 0.5). of each bacterium were used to inoculated by use glass spreader on the surface of Mueller Hinton Agar (MHA) plates. The additional liquid was air dried under a sterile hood or repeat the spreading process. the plate was allowed to dry and punched wells (five)in diameter 6 mm. into agar. Subsequently, in each agar plate of tested bacteria five wells were made and (100µl) of dilutions of derivatives compound (500,250,125 and 62.5 µg/mL) introduced into wells on MHA plate. DMSO used as the negative controller.
The plates were incubated at 37 °C for (24hrs) and the antimicrobial action was estimated by determining the diameter of the inhibition zone (IZ) all over the place the disc in mm..
The valuation of antibacterial action was based on extent of the diameter of inhibition zone formed all over the place the well as shown in Table(1).

Table (1): Antibacterial activity of synthesized compounds (III_{1-5}):

Sample code and standard	Concentration (µg/ml)	Zone of inhibition (mm)			
		Gram negative		Gram positive	
		Acinetobacter species	*Pseudomonas aeruginosa*	*Streptococcus pyougenes*	*Staphylococcus aureus*
III_1	500.0	8	8	-	-
	250.0	-	-	-	-
	125.0	-	-	-	-
	62.5	-	-	-	-
III_2	500.0	16	16	6	-
	250.0	10	10	6	-
	125.0	4	10	8	-
	62.5	10	10	-	-
III_3	500.0	16	8	-	-
	250.0	10	8	-	-
	125.0	8	8	-	-
	62.5	8	6	-	-
III_4	500.0	20	10	-	-
	250.0	16	6	-	-
	125.0	12	12	-	-
	62.5	12	12	-	-
III_5	500.0	8	20	-	7
	250.0	8	14	-	-
	125.0	8	6	-	-
	62.5	8	6	-	-
Sulfamethoxazole	500.0	20*	4	30	30
	250.0	16	6	24	20
	125.0	16	6	16	14
	62.5	8	12	16	10
DMSO	-	-	-	-	-

Chemical Synthesis: The chemical synthesis of Intermediates(I_{1-5}) and target compounds (II_{1-5}) was achieved in the following procedure



R = H, Cl, NO_2, OH, $N(CH_3)_2$

Scheme (1): Synthesis of new intermediates and final compounds.

Results and Discussion:

The preparation of five Schiff's bases with different specific aldehydes in ethanol as a solvent and catalyst (glacial acetic acid) resulted in five series of Schiff's bases with the general formula RHC =N-R.The compounds of Schiff base were identified by physical properties (color and melting point). The structure of compounds Schiff base was confirmed by their FT-IR spectroscopy. The IR spectrum clearly shows the characteristic absorption band at (3387-3282 cm^{-1}) is for υ NH stretching of $NHSO_2$, band of υ C=N stretching at region (1606 -1641 cm^{-1}) and disappear of primary amine υNH2 stretching at region (3469 cm^{-1}) as showed in Figures (3) to (7).

^{1}H-NMR spectra for the compounds (II_{1-5}) showed the broad singlet at (11.46-11.53 ppm) integrated for $HNSO_2$ proton, the spectrum also shows signal at (8.16-8.80 ppm) integrated for one proton assigned for the proton of imine (CH=N) group. As showed in Figures (13) to (17).

The final compounds (III_{1-5}) were obtained by a mixture of Schiff base (II_{1-5}) with glycine in tetrahydrofuran (THF) under refluxing for 24h, as showed in Scheme (1). The structure of compounds (III_{1-5}) was characterized by physical properties (color and melting point). The structure of oxoimadazolidine compounds (III_{1-5}) was confirmed by their FT-IR spectroscopy. The IR spectrum clearly show disappearance of the band of stretching vibration of (C=N) group of Schiff base at (1606 -1641 cm^{-1}) and appearance of absorption band of (C=O) at (1668-1712cm^{-1}) and (N-H) secondary sulfonamide at (3356-3389 cm^{-1}) as showed in Figures (8)to(12) . ^{1}H-NMR spectra of compounds (III_{1-5}) showed the integrated for broad singlet at (10.63-11.27ppm), integrated for NH amide proton, and appearance of N-H, N-CH and CH_2 of imadozolidinone signal at (8.24-10.94ppm), (δ 3.33- δ 3.67) and (δ 2.49- δ 2.98) respectively as showed in Figures (18) to (22).

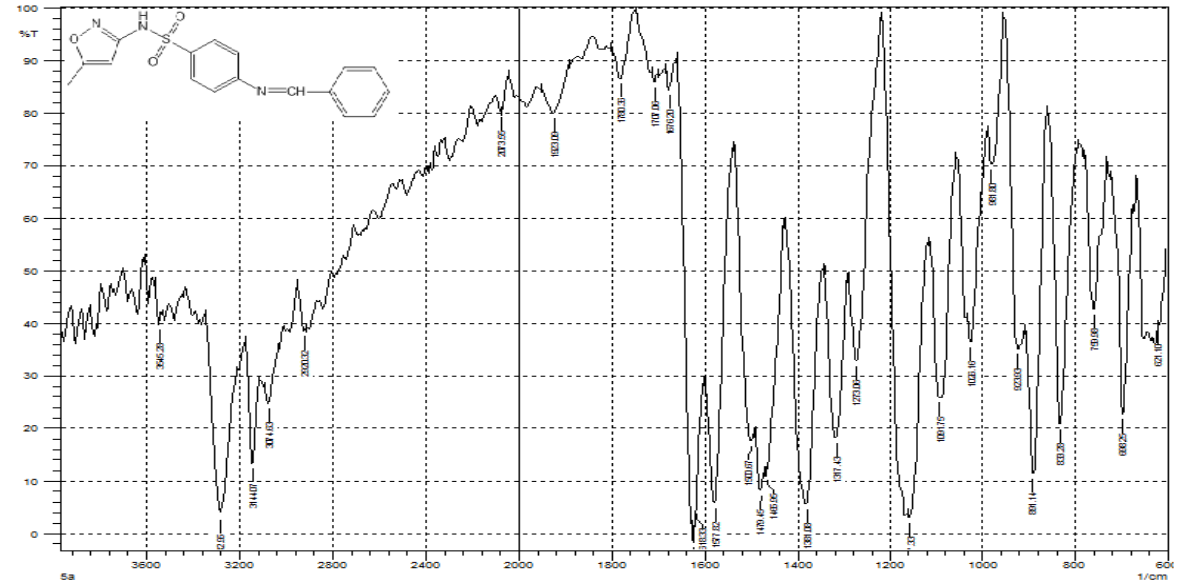


Figure (3): FT-IR spectra for compound (II_1)

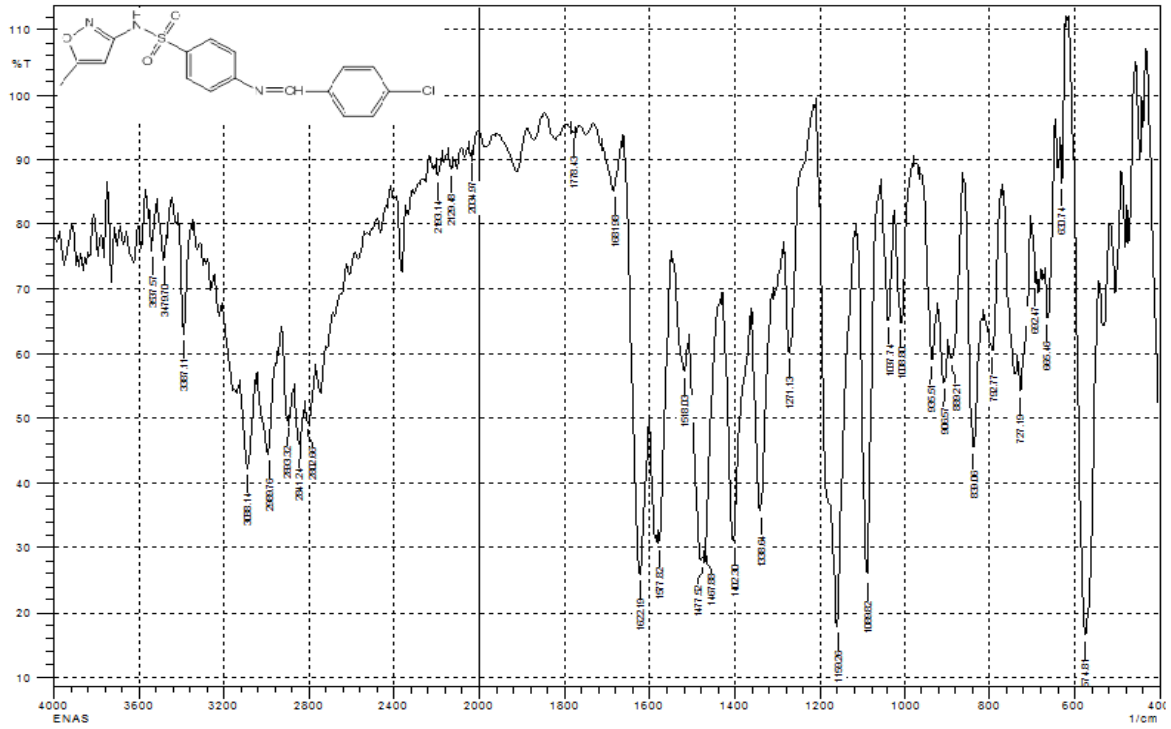


Figure (4): FT-IR spectra for compound (II_2)

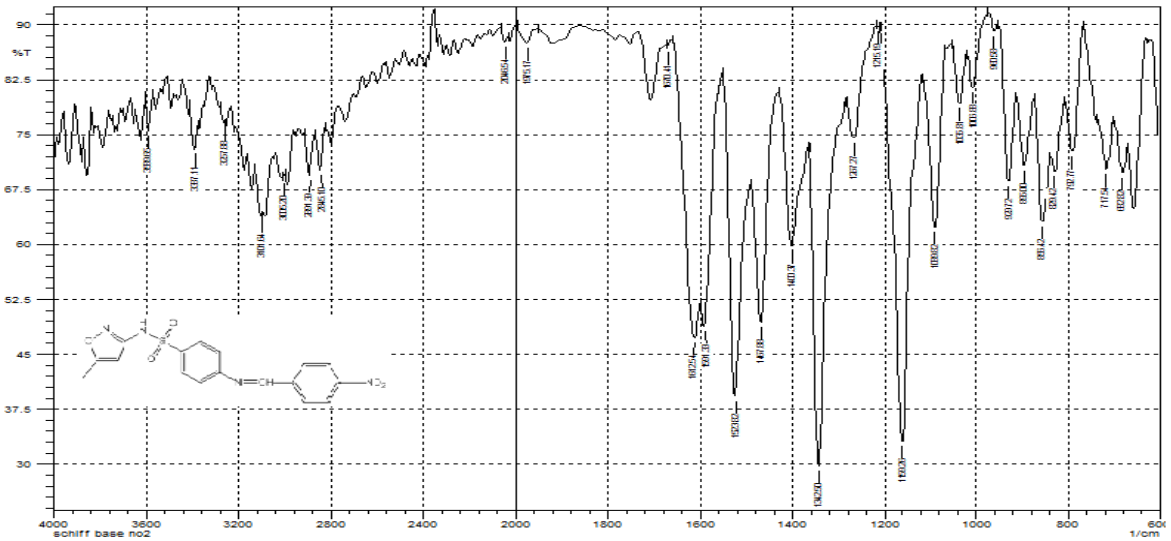


Figure (5): FT-IR spectra for compound (II_3)

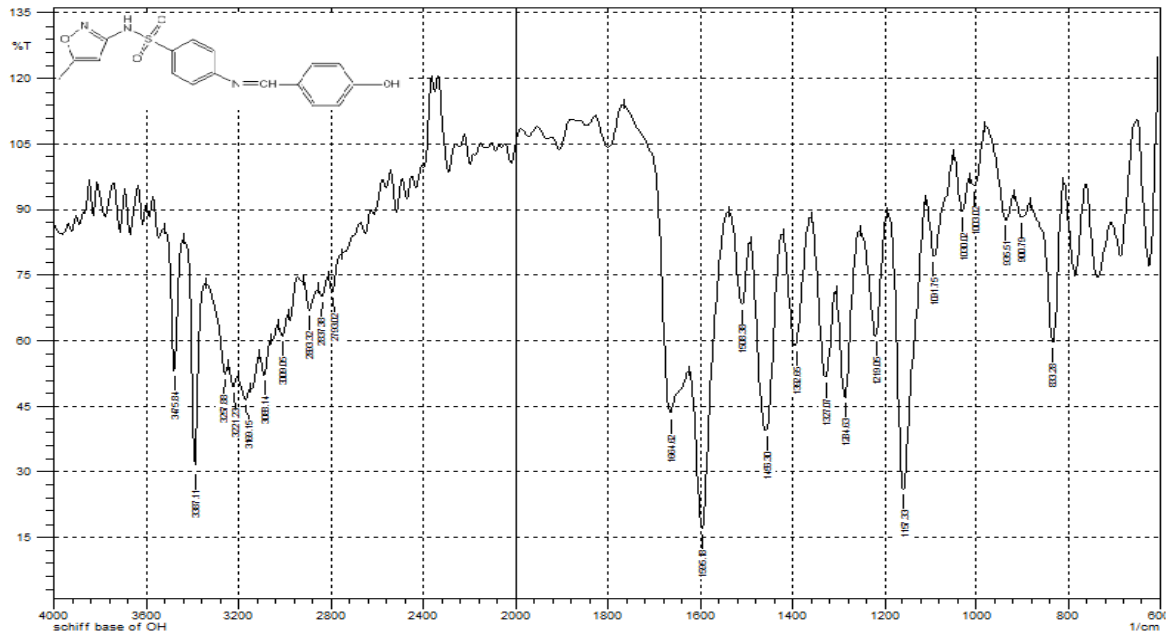


Figure (6): FT-IR spectra for compound (II_4)

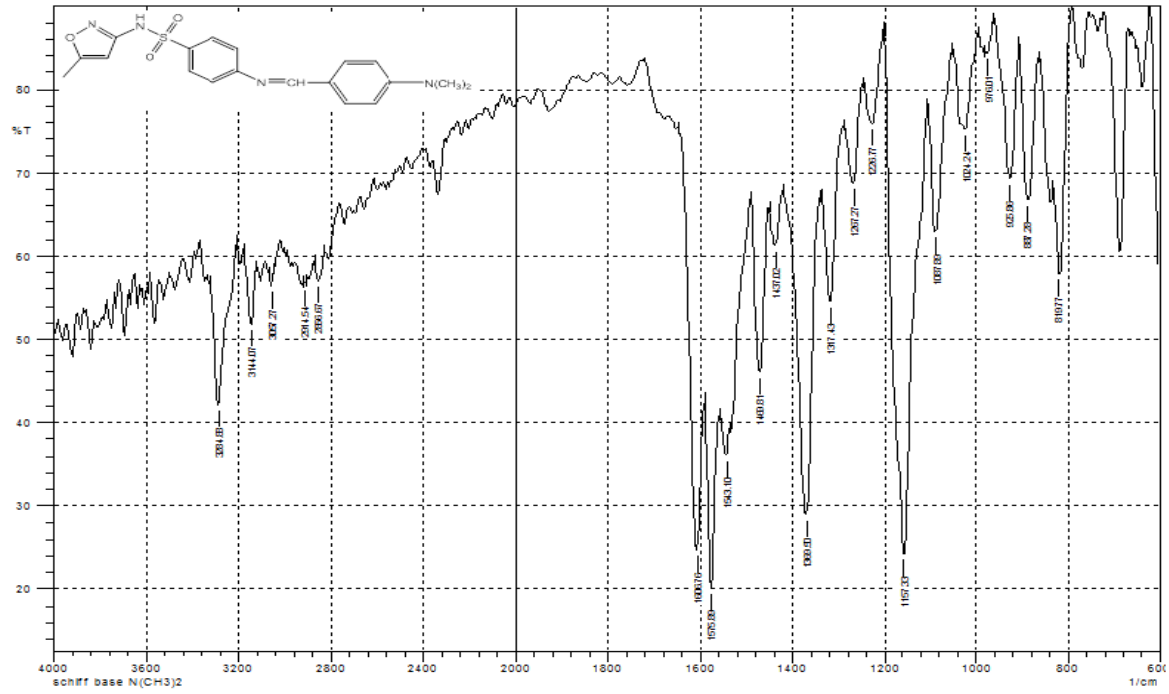


Figure (7): FT-IR spectra for compound (II_5)

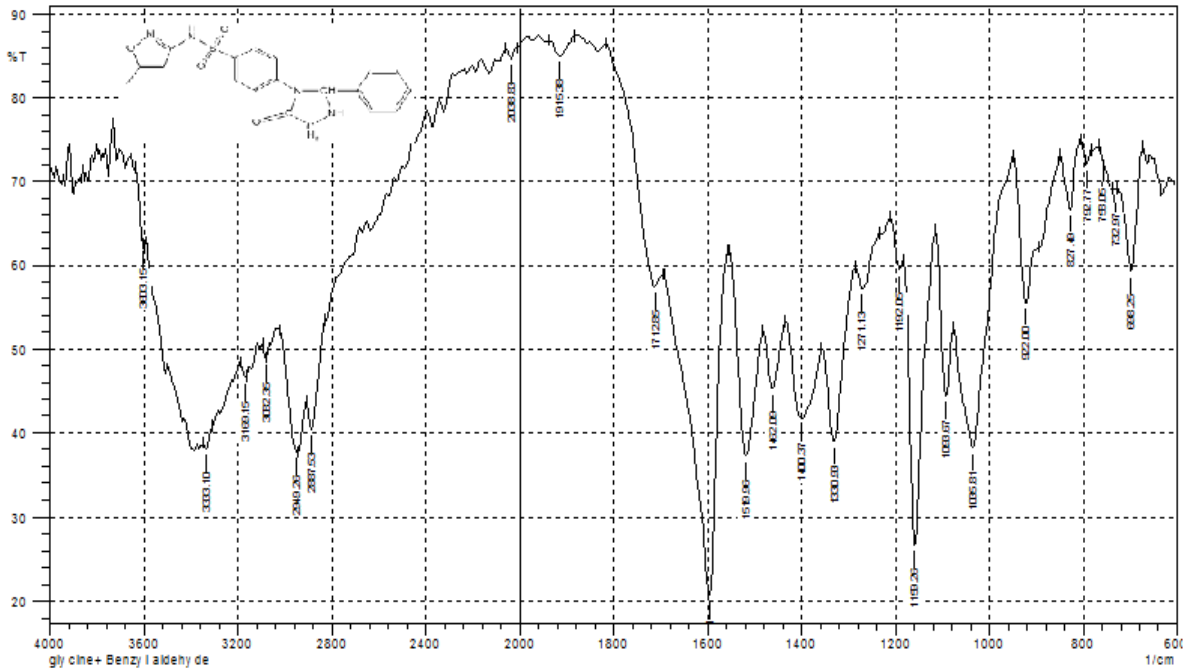


Figure (8): FT-IR spectra for compound (III1)

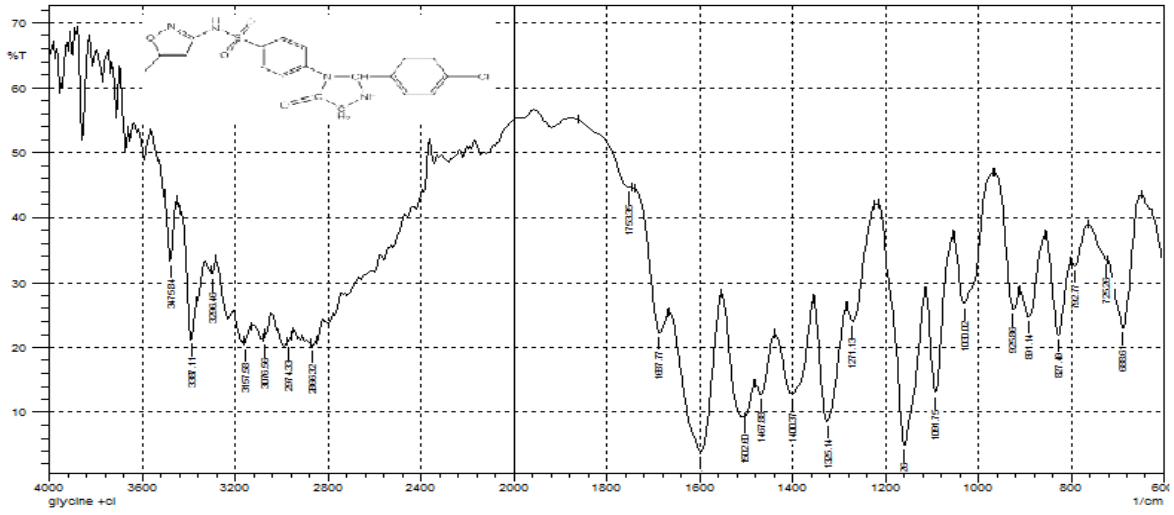


Figure (9): FT-IR spectra for compound (III_2)

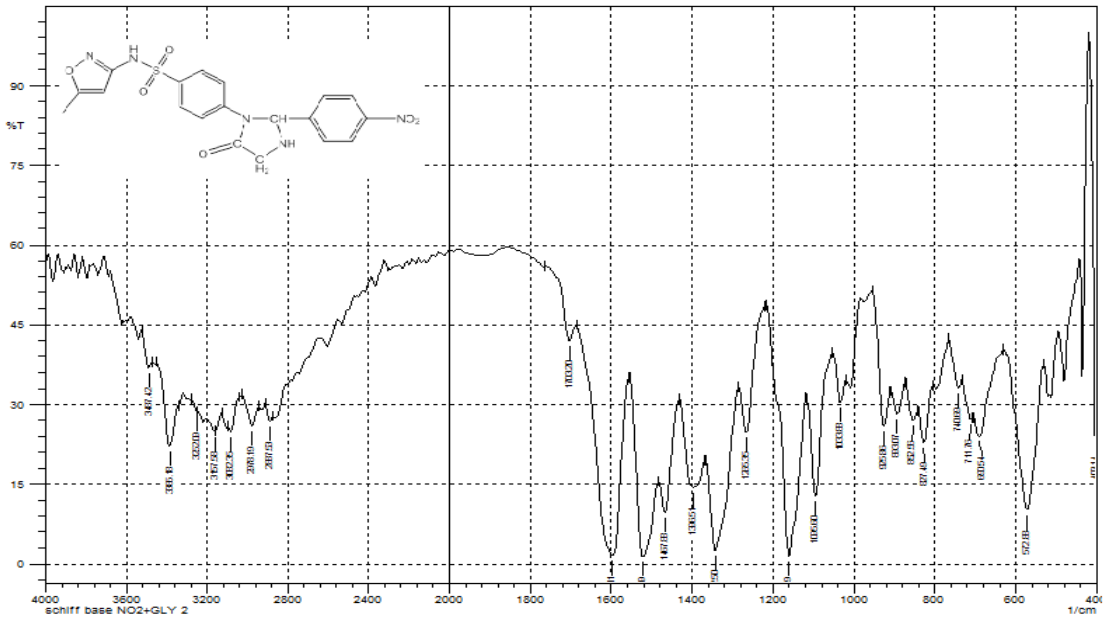


Figure (10): FT-IR spectra for compound (III_3)

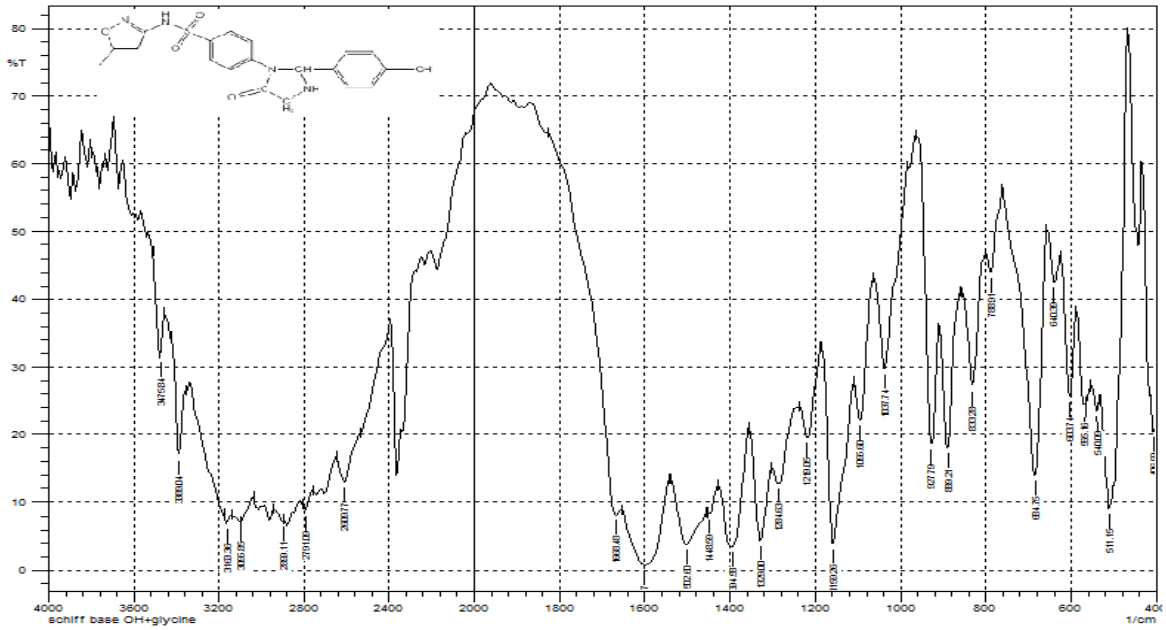


Figure (11): FT-IR spectra for compound (III_4)

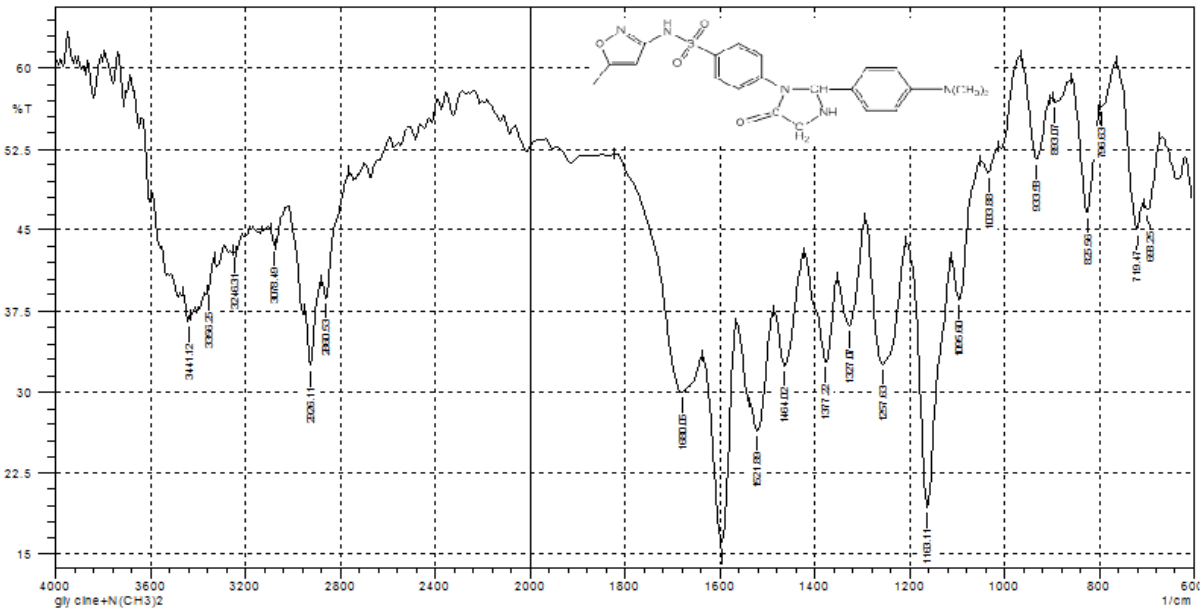


Figure (12): FT-IR spectra for compound (III_5)

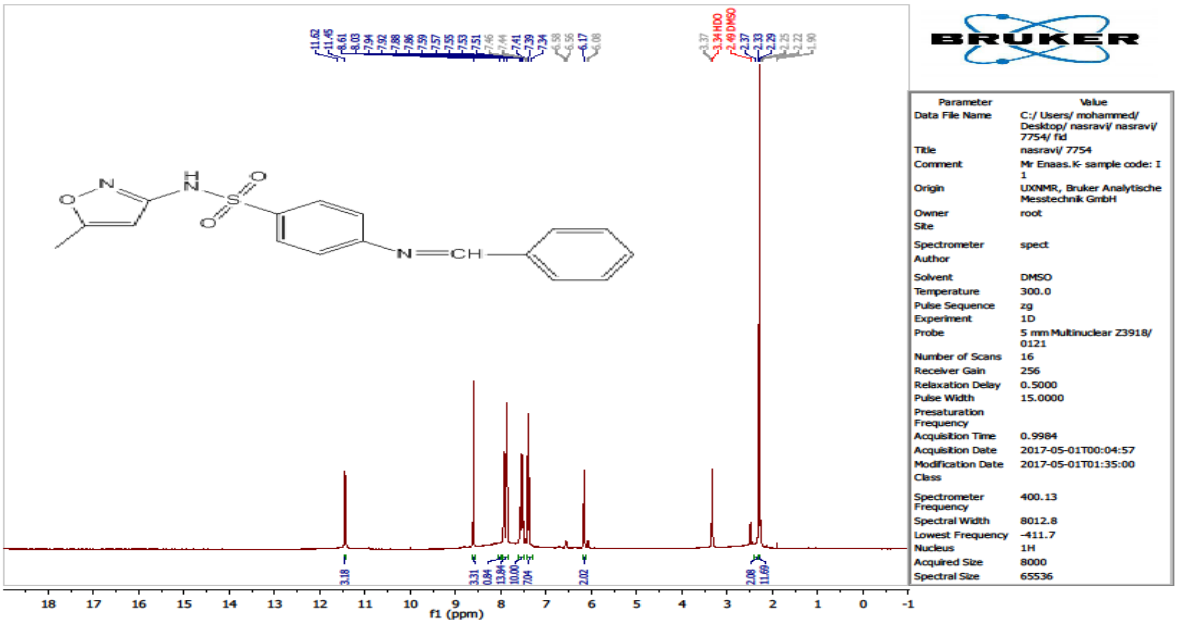


Figure (13): ^{1}H-NMR spectra for (I_1)

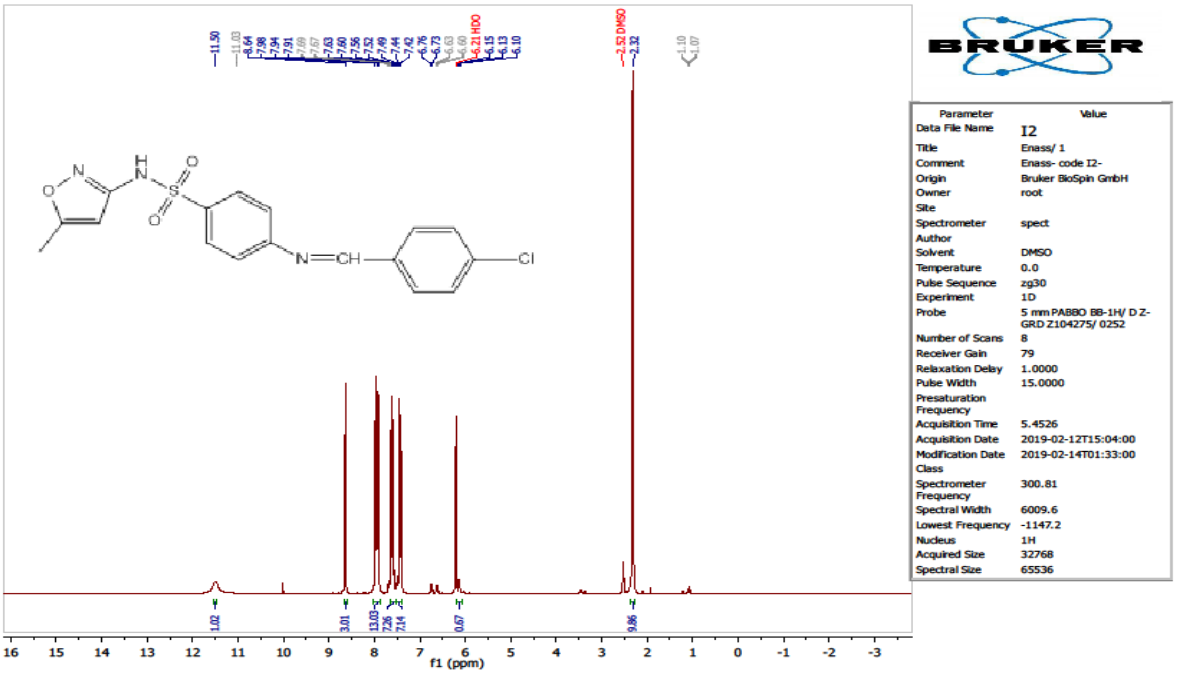


Figure (14): ^{1}H-NMR spectra for (I_2)

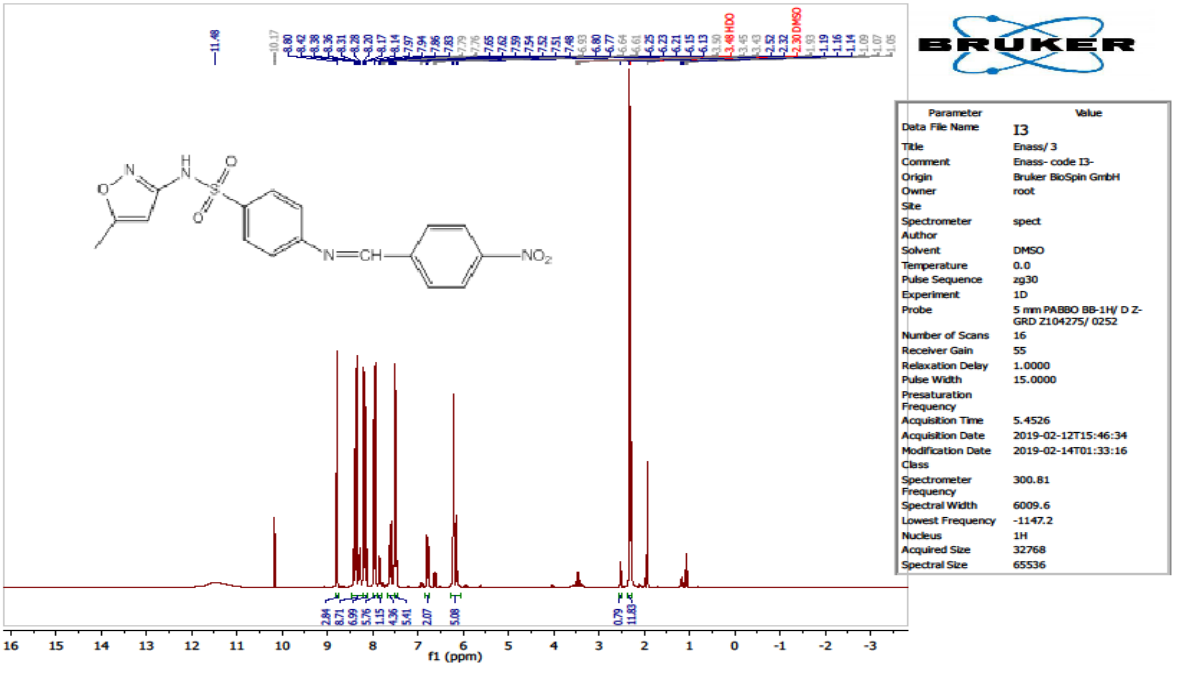


Figure (15): ^{1}H-NMR spectra for (I_3)

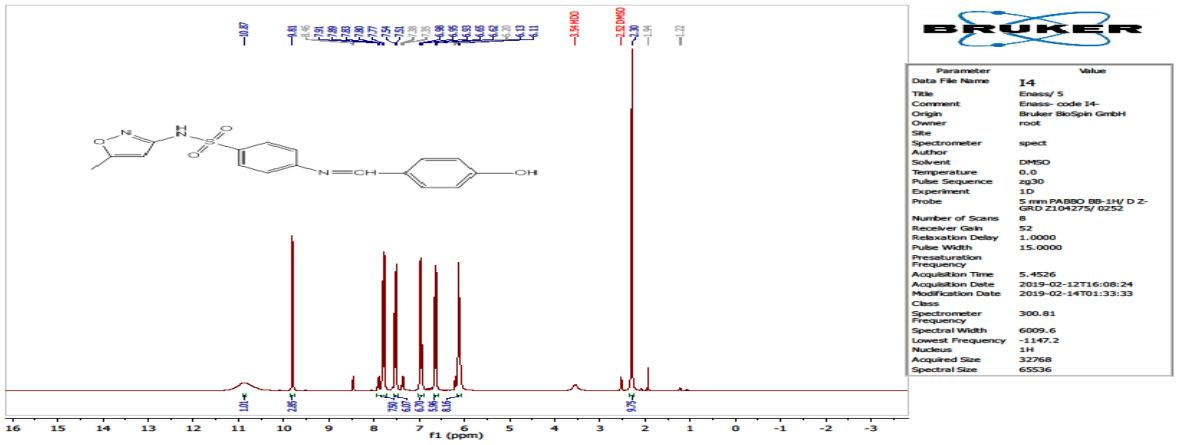


Figure (16): ^{1}H-NMR spectra for (I_4)

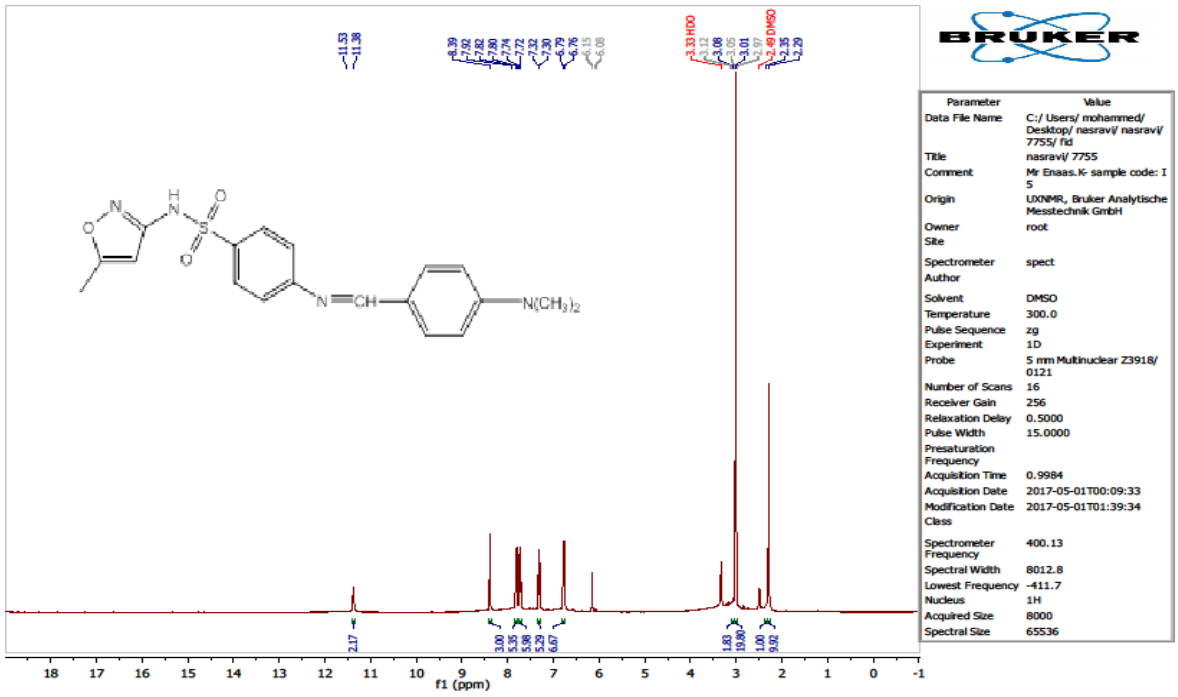


Figure (17): ^{1}H-NMR spectra for (I_5)

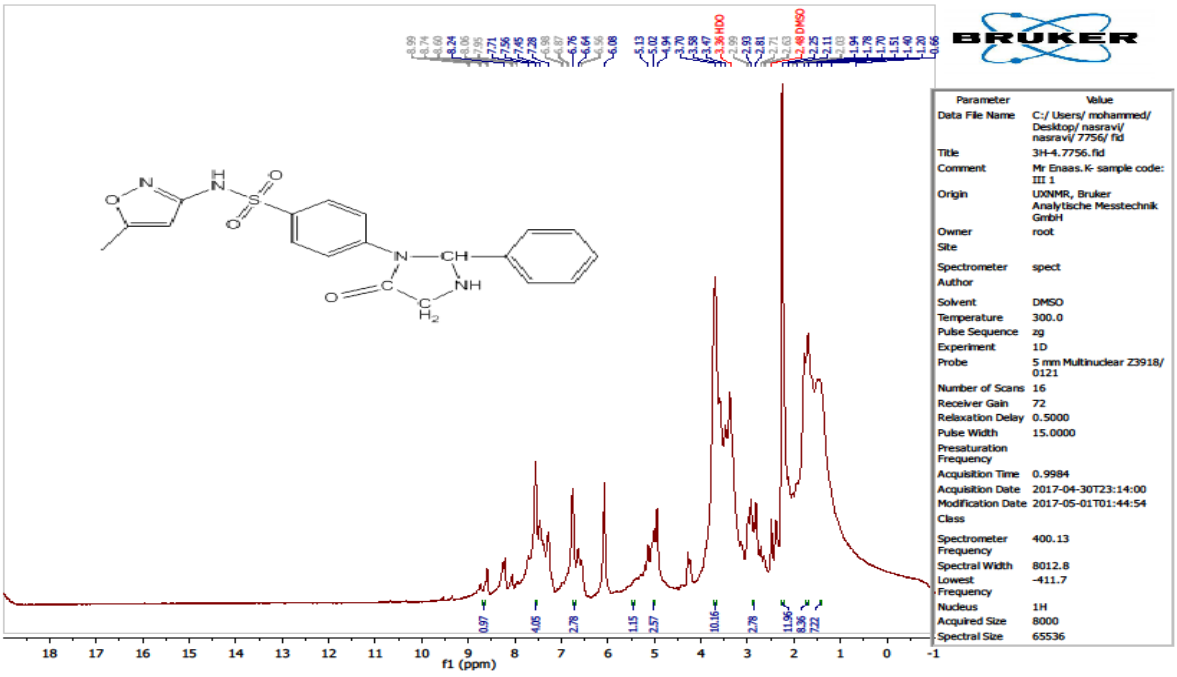


Figure (18): 1H-NMR spectra for (III1)

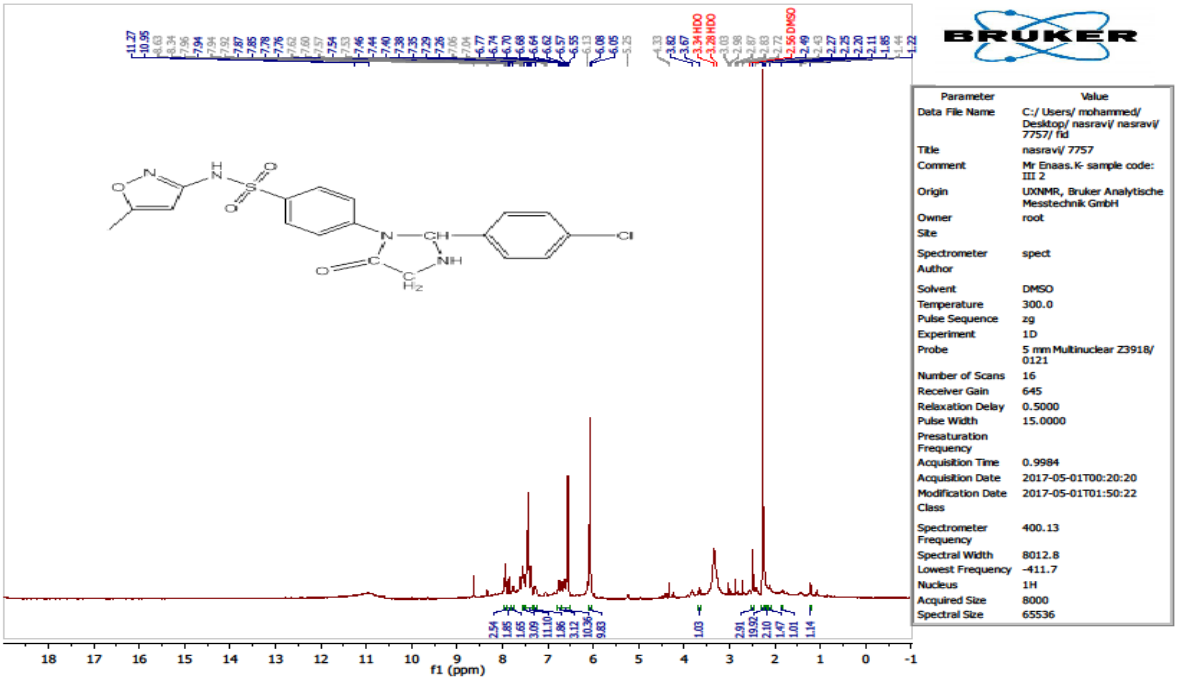


Figure (19): 1H-NMR spectra for (III2)

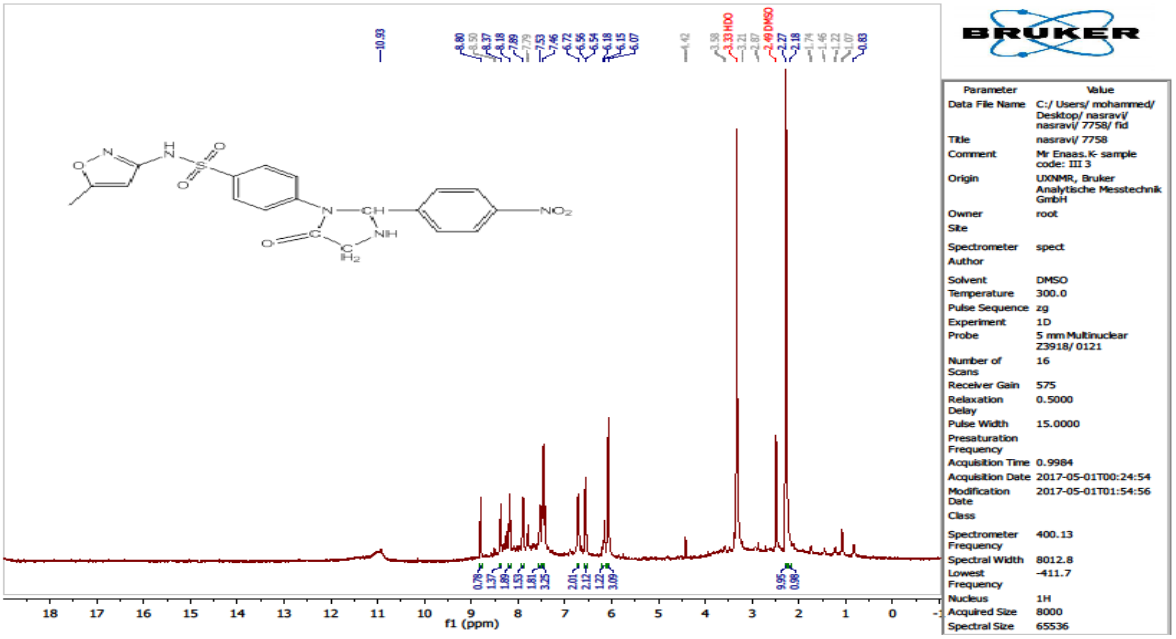


Figure (20): 1H-NMR spectra for (III3)

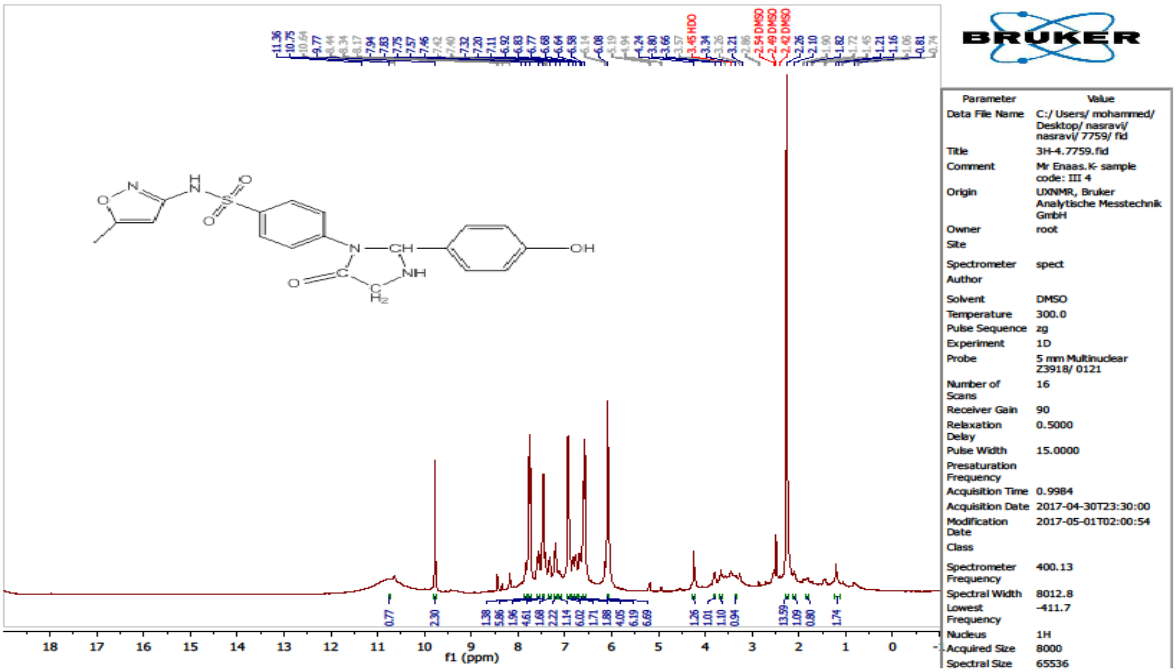


Figure (21): 1H-NMR spectra for (III4)

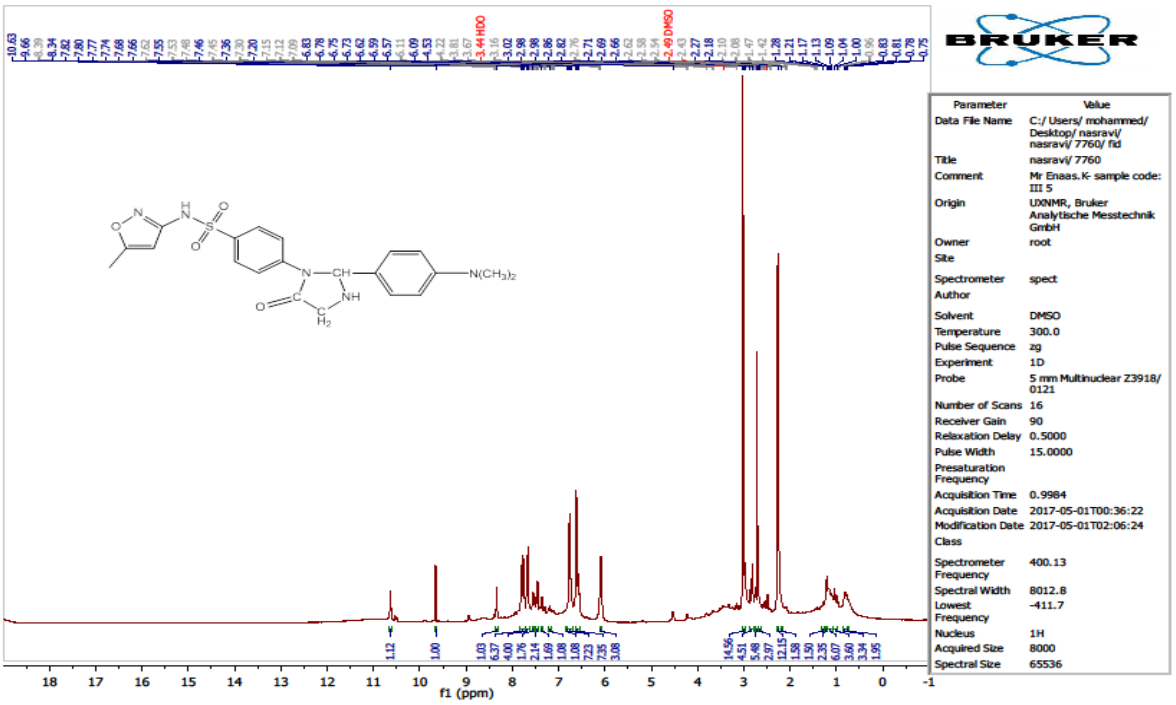


Figure (22): 1H-NMR spectra for (III5)

Antibacterial study:

Sulfamethoxazole used as a reference, DMSO used as a control and the synthesized compounds (III1-5) were screened for their antibacterial activity against gram negative bacteria (*Acinetobactum species* and *Pseudomonas aeruginosa*) and gram-positive bacteria (*Streptococcus pyougenes* and *Staphylococcus aureus bacteria*) at concentrations of (62.5,125, 250 & 500 µg/ ml) except the control which used in pure state. Table (1) listed the inhibition zone in (mm) for each concentration of the tested compounds. In general, the tested compounds showed lower activity against *Streptococcus pyogenes* and *Staphylococcus aureus* bacteria in comparison with sulfamethoxazole, while compound III4 showed the highest activity against *Acinetobacter species*. for *Pseudomonas aeruginosa* the compounds (III2) and (III5) in concentration (500 µg /ml) showed a higher inhibition zone than sulfamethoxazole, these two compounds were primarily the better choice and showed higher activity than sulfamethoxazole. As showed in Figures (23) to (26). These obtained results are compatible with many studies showed that sulfonamides have good antibacterial an especially sulfathiazole, sulfadiazine and sulfamethoxazole. [14-16] Also Imidazolidine derivative showed good antibacterial activity.[17]

The antibacterial effect of tested compounds (III_{1-5}) in comparison to standard compound (sulfamethoxazole) on the growth of *Acenitobactum* species in different concentrations showed results as shown in Table 1, the statistical analysis at concentration 500(µg/ml) showed highly significant differences comparable effect from III_2 and III_3 in comparison with the standard drug & significantly lower effect from III_1 and II_5 compound,while III_4 show no significant differences with same effect in comparison with sulfamethoxazole($p \leq 0.05$) . at concentration 250(µg/ml) when compared with standard compound showed all compounds were significantly lower effect, except III_4 show no significant differences with same effect in comparison with sulfamethoxazole ($p \leq 0.05$).

At concentration 125(µg/ml) showed that all compounds significantly lower effect, except III_4 show highly significant differences comparable effect ($p \leq 0.05$).

The effect of concentration 62.5(µg/ml) of compounds showed significantly higher effect from III_4 compound, while III_3 and III_5 show no significant differences with same effect in comparison with sulfamethoxazole ($p \leq 0.05$). On the other hand, the comparison among compounds themselves shows that there was a significant difference in all concentrations under test against *Acenitobactum* species, so III_4 in concentration 500 (µg/ml) and 250 (µg/ml) may regard the strongest one as shows in Figure (23).

The evaluation of antibacterial effect against *Pseudomonas aeruginosa* illustrated in Table 1 which showed that there was a high significant higher effect for all compounds (III_{1-5}) when compared with standard drug at concentration 500(µg/ml) at ($p \leq 0.05$).

At concentration 250(µg/ml) when compared with standard compound showed that there was a high significant difference with higher effect from III_2, III_5 and III_1, except III_4 show no significant differences with same effect in comparison with sulfamethoxazole at ($p \leq 0.05$).

The effect at concentration 125 showed that there was a high significant difference with higher effect from III_4 and no effect from III_1 in comparison with the standard drug, while II_3 and II_5 compounds were showed no significant differences at ($p \leq 0.05$).

At concentration 62.5(µg/ml) showed that there was a high significant difference with lower effect from III_1, III_3 and III_5 compounds and significantly comparable effect from III_4 in comparison with the standard drug, while II_2 and II_4 compounds were showed no significant differences at ($p \leq 0.05$) , since II_4 compound give higher effect in comparison with sulfamethoxazole.

The comparison between compounds themselves shows that there was a significant difference in all concentrations under test against *Pseudomonas aeruginosa*, so III_2 and III_5 in concentration 500(µg /ml) were the strongest compounds as show in Figure(24) The antibacterial effect of tested compounds (III_{1-5}) in comparison to standard compound (sulfamethoxazole) on the growth of *Streptococcus pyougenes* in different concentrations showed as shown in Table 1. In concentration 500,250,125,62.5(µg/ml) the statistical analysis shows that all compounds were significantly lower effect in comparison with the standard drug at ($p \leq 0.05$).

The averages of differences in the inhibition zones among were rarely significant in regarding to the results of inhibition zone Table, the compounds (III_{1-5}) show no antibacterial activity on the growth of *Streptococcus pyougenes* with weak affect from III_2 compound as show in Figure (25).

Staphylococcus aureus was the fourth gram positive bacteria used to evaluate the antibacterial effect of the compounds in different concentrations as shown in Table 1, the findings of concentrations 500,250,125,62.5(µg/ml) the statistical analysis shows that all compounds were significantly lower effect in comparison with the standard drug at ($p \leq 0.05$).

The effector compound on *Staphylococcus aureus* when compared among all experimental compounds according to statistical analysis, the compounds (III_{1-5}) show no antibacterial activity with very weak affect from III_5 compound as shown in Figure (26).

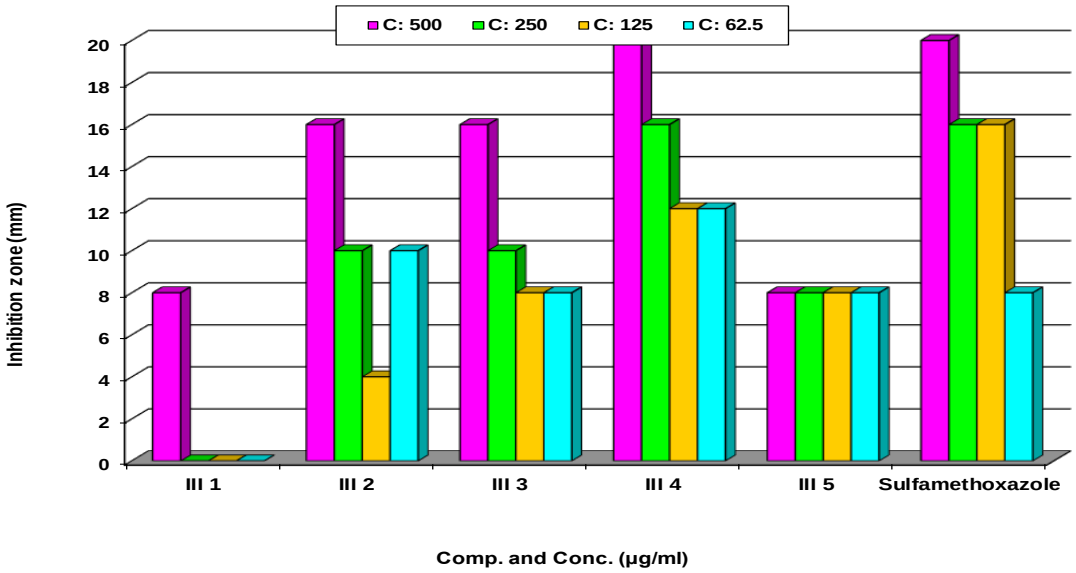


Figure 23. Antibacterial activity of synthesized compounds (III 1-5) against tested Acenitobactum species

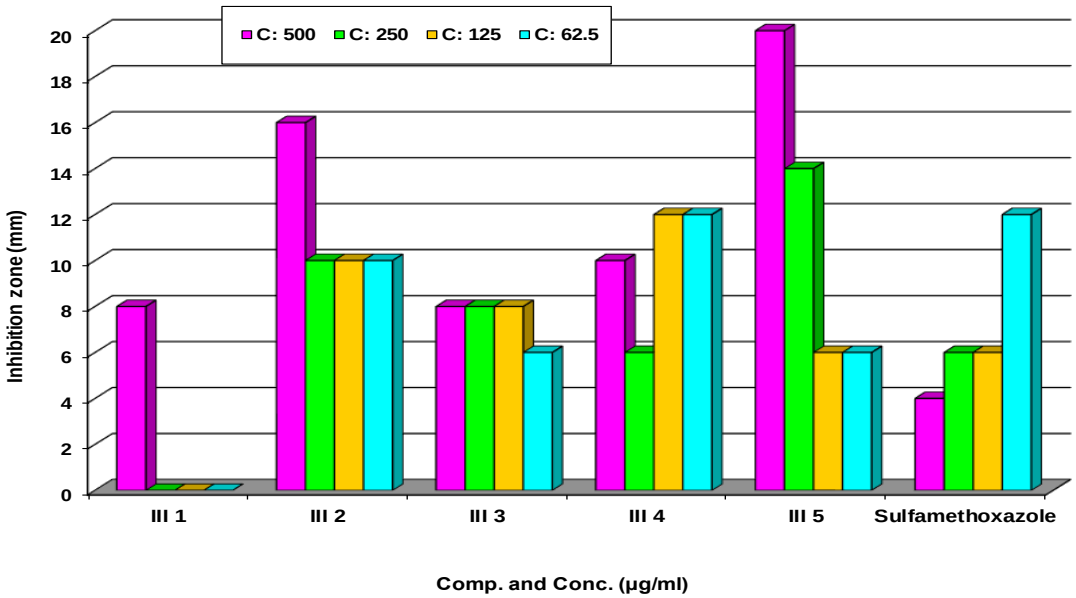


Figure 24. Antibacterial activity of synthesized compounds (III 1-5) against tested Pseudomonas aeroginosa

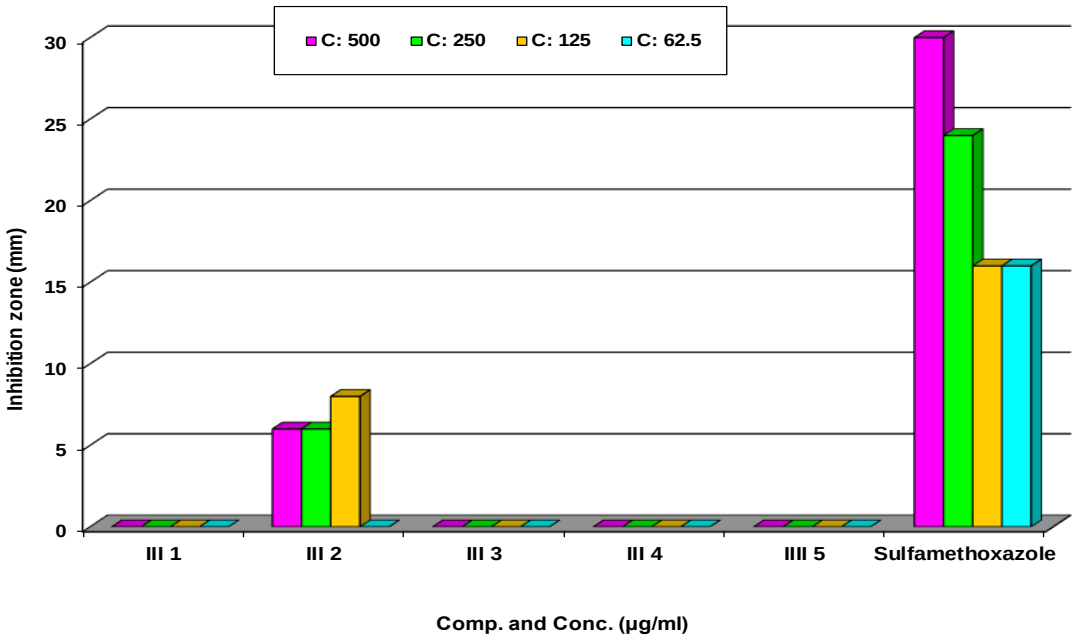


Figure 25. Antibacterial activity of synthesized compounds (III 1-5) against tested *Streptococcus pyougenes* bacteria

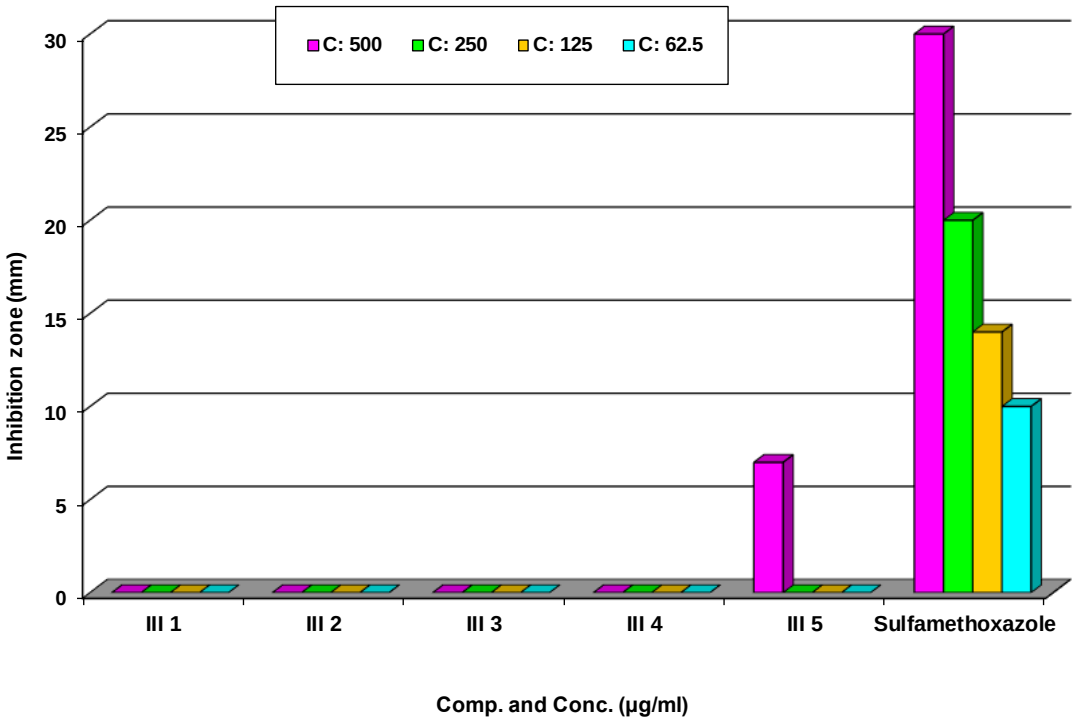


Figure 26. Antibacterial activity of synthesized compounds (III 1-5) against tested *Staphylococcus aureus* bacteria

Conclusion:

The synthesis of the designed compounds has been successfully achieved. Characterization and identification of the synthesized compounds has been determined by physical properties, FT-IR spectroscopy, ^{1}HNMR spectra and elemental microanalysis. The Preliminary antibacterial activity study of the synthesized compounds displayed significant action against gram negative and gram-positive bacteria. All tested

compounds maintained or increased their effect versus the selected gram negative and gram-positive bacteria with highest activity specially against Pseudomonas aeruginosa, *III*2 and *III*5 in concentration (500µg /ml). Under test against Acinetobacter species the compound *III*4 showed the highest activity. Regarding gram-positive bacteria, all derivative showed lowest activity than sulfamethoxazole.

Acknowledgments

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