Article

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Microwave-Assisted Synthesis of Five and Seven-Membered Heterocycles from Ibuprofen and Study Their Biological Activity

Ashwaq Abbas Ali and Nadia Sadiq Majeed
Chemistry department/Faculty of Education for Girls/ Kufa University
ashwaqa.alkhaffaf@student.uokufa.edu.iq, nadia.albobaid@uokufa.edu.iq

Abstract :

The carboxylic acid group of ibuprofen, which is responsible for some of its side effects, is converted into a hydrazide group by reacting it with hydrazine. the hydrazide then reacts with specific aldehyde to create highly active Schiff base. These Schiff bases react with certain amino acids to form imidazolidinone molecules(K7-K10). Schiff bases also react with anhydrous acids and hydroxy succinimide to produce seven-membered heterocyclic rings (K3-K6) The synthesized compounds were tested against two types of bacteria at various concentrations. .

These new compounds showed significant antibacterial efficacy, while ibuprofen itself exhibited no activity against the bacteria The melting points of the new compounds were found to be higher than ibuprofen,indicating greater stability. Additionally, the new compounds exhibited improved solubility due to the formation of intramolecular and intermolecular hydrogen bonds.unlike ibuprofenwhichhaspoorwatersolubility.

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Keywords:Ibuprofen,azomethine,imidazolidin-4-one,oxazepine,*Staphylococcaland Klebsiella*

Introduction:

Molecular hybridization is a new concept in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to

produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs .Ibuprofen non-steroidal anti-inflammatory medication, ibuprofen is aryl-propionic acid[1]. It primarily functions as a nonselective inhibitor of COX-1 and COX-2, two cyclooxygenase (COX) enzymes. A portion of the adverse effects that may manifest at the gastric, renal, or hepatic levels are caused by its free carboxyl group, which also permits a range of structural modifications [2, 3]. It was mentioned that chemicals that are more selective for the COX-2 isoform may result from changing the carboxyl group. The main purpose of ibuprofen is as an analgesic for fever,discomfort and inflammatory conditions including rheumatoid arthritis and osteoarthritis [4] However, because it contains a number of beneficial (COOH) ingredients, we can add groups like Hydrazine and turn ibuprofen into a derivative that has biological and medicinal significance, including attending annular rings five and seven [5]. However, long-term use of butte can cause side effects like peptic ulcer, nausea, stomach problems, dyspepsia, and Al zehymer [6] .

When primary (aromatic) amines condense with aldehydes or ketones to produce azomethine (imine) (-CR=N-), schiff bases are produced.[7, 8] The azomethine group has been demonstrated to be required for bioactivity in a variety of pharmacological activities, indicating that they are adaptable pharmacophores[9]. Schiff bases, for instance, whether natural or artificial, have demonstrated encouraging antiviral, antibacterial, antifungal, antitubercular, and anticancer qualities.[10,11]. .

The usual structure of imidazolidine is a heterogeneous ring with five member, formula C3H8N2O[12,13].These structures are highly recognized as a family of heterocyclic compounds with a variety of biological applications because of their important functions as building blocks in the production of bioactive chemicals [14].

Because it serves as the foundation for the synthesis of bioactive compounds, the imidaolidin-4-one ring is essential [15]. Additionally, it has anti-viral, anti-fungal, and anti-cancer properties. [16] Apart from its debut in the antibiotic industry,Heterocyclic compounds called oxazepine compounds have one oxygen atom, one nitrogen atom, and five carbon atoms[17, 18]. The compounds oxazepine have three isomers: 1,2, 1,3, and 1,4 oxazepine[19]. This numbering is based on where the nitrogen and oxygen atoms are located within the ring, beginning with the oxygen atom and going like this:

In addition to its medical use, oxazepine has anti-inflammatory, anti-cancer, anti-bacterial, and anti-fungal properties [20].

Experimental

Chemicals, Biologicals and Instrumentation

From Merck, Sigma, BDH, Difco, Santacruze, Flow labs, and GCC, all supplies were purchased. We used Silica gel precoated aluminum sheets from Merck for thin layer chromatography (TLC) to calculate Rf and To follow the progress of the reaction. Using melting point equipment from Cole-Parmer Ltd. in the UK, the melting points were ascertained in open capillary. On Shimadzu, Japan, a Fourier Transform Infrared Spectrophotometer was captured. For 1 H and 13 C NMR, deuterated DMSO was utilized as the solvent with a Bruker Avance 400 MHz NMR spectrometer.

The Methods.

Preparation of acid hydrazide compound (K1): **2 - (4-isobutylphenyl) propanehydrazide [21,22]**

Green synthetic method for carboxylic acid hydrazides . General Procedure ethyl 2-(4-isobutylphenyl) propanoic acid (1g,4.8mmol) and NH2NH2-H2O80%(0.2g,4mmol) were taken i The reaction mixture was irradiated under microwaves for 60-200 seconds at 900 Watt . The reaction mixture was cooled to -20o C.follow-up interaction mediated (TLC)(ethanol 3:2benzen) .and let the mixture for 24 hrs after that washing with methyl alcohol and let dry material then we recrystallisation .then we drain the material in the form of pure white crystals melting point (118-121C) (K1)

Schiff base compound preparation (K2)[23]

2-[4-phenyl(2-methylpropyl)][(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene] -N'-propane hydrozide

The overall procedure for Schiff base compound preparation (K2)

Dissolve (0.5g, 2.27mmol) of the compound (K1) in 3ml of dry benzene, adding (o.33g, 2mmol) of 4-Nitrobezldehyed . Then, place the mixture in a microwave oven set at 120 watts for 20 minutes. After that, use chromatography TLC to monitor the reaction using a solvent of (2 ml benzene: 3 ml EtOH abs). The excess solvent is then evaporated, and the precipitate is re-crystallized from diethyl ether and 99% absolute ethanol.

Preparationthe Compounds (K3-K10) from Schiff base.

Equivalent moles are taken (1:1 mole) of K2 with Fthalic anhydride, Malic anhydride, succinic anhydride, N-Hydroxy succinimide, phenyl alanine, alanine, tyrosine, and glycine, in 3 ml of dry benzene. The mixture was then microwaved at (120 W) for 20–10 minutes. The reaction was checked using TLC (2 ml benzene: 3 ml EtOH abs). The resultant solid substance crystallized from pure ethanol.

Results and Discussion[24]

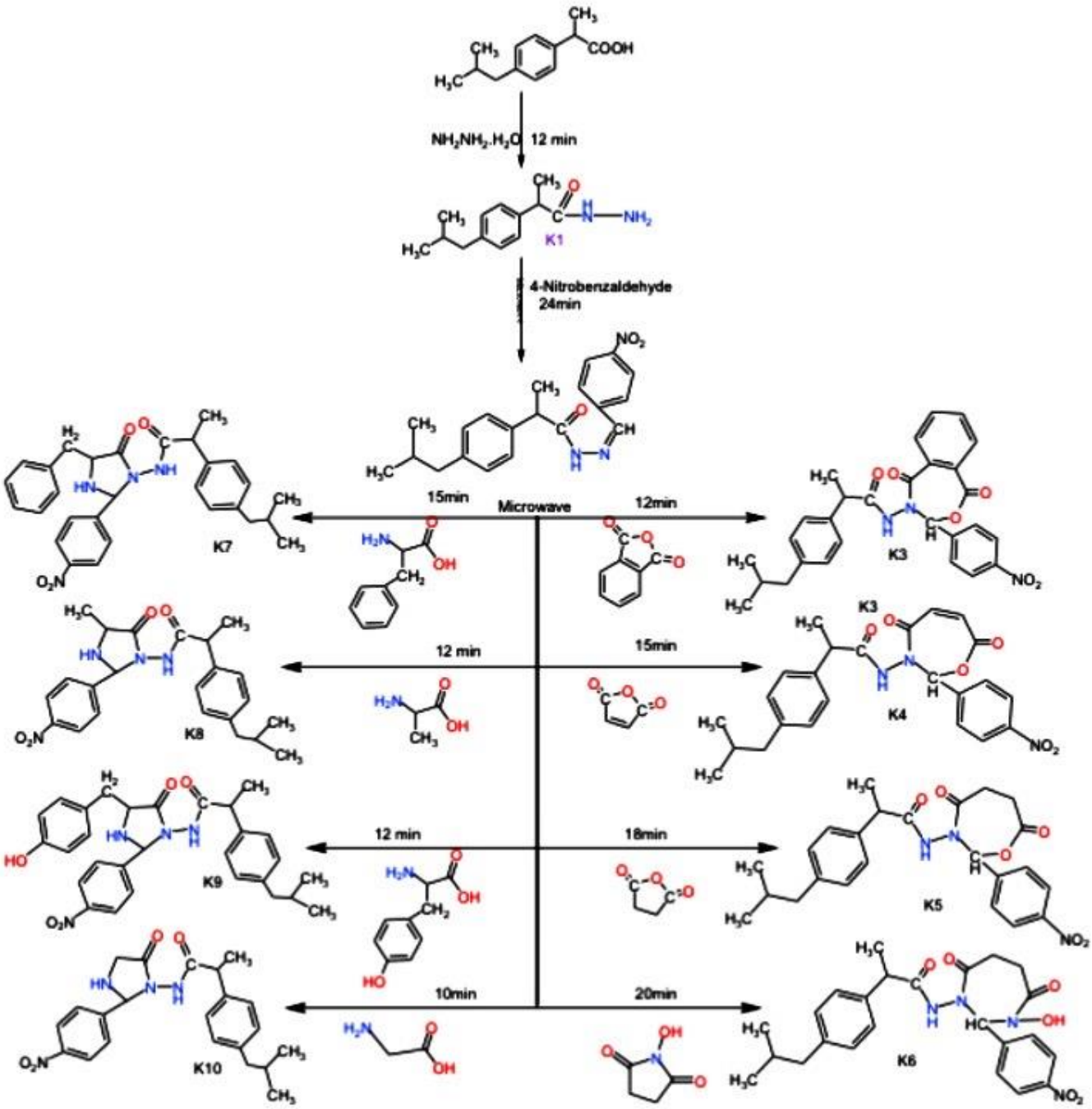
. Compound (K1)that were diagnosed using FT-IR. The characteristic absorption bands in the regions (3363,3315) cm-1,(3207) cm-1and(1676)cm-1due to the (NH2),(NH)and amide carbonyl group, Figure (1).The 1H-NMR spectrum for (K1) showed singlet signals at δ (1.92, 1.90) ppm for (d,6H,2CH3)groups, other signals also appeared at 2.52 ppm for DMSO, as solvent and signals δ (7.05 - 7.10) ppm (d,4H,Ar-H) due to aromatic protons, singlet signals δ (5.23) ppm,(10.32)ppm, for NH2 ,NH group Figure (2) .the(13 C-NMR) Spectrum appearance of a signal between (17-50)ppm for the aliphatic (C-C) Which comes back to part ibuprofen and The appearance of a signals at (167) ppm belonging to the carbon of amide (C=O) In addition to significant signals between (97 -130) ppm belonging to the aromatic .

The spectrum FT-IR for K2 showed in (1587)cm-1for the imine group.The 1H-NMR spectrum for (K2) showed singlet signals at δ (1.65, 1.68) ppm for (d,6H,2CH3)the signal of imine proton CH=N in (8.91)ppm, other signals also appeared at 2.52 ppm for DMSO, as solvent and signals δ (7.76 - 7.40) ppm (d,4H,Ar-H) due to aromatic protons, signal at δ (8.91) ppm due to NH group The (13C-NMR) Spectrum For (K2)The appearance of a signals at (150) ppm belonging to the carbon of (C-NO2) group. While a signals appeared at (158) ppm, referring to carbon of (C=N) group. In addition to significant signals (172) ppm belonging to the carbon of amide (C=O) .figure(6)

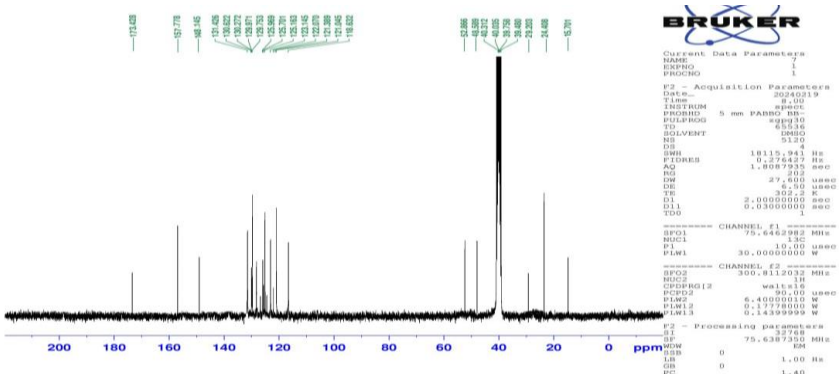
The FT-IR spectrum for the compounds (K3-K6)shows that an absorption band with the Schiff bases' azomethine group has disappeared, and a stretch band of the lactone carbonyl group's bond has appeared at the frequencies between (1693-1782)cm-1 and (1602-1686)cm-1, returns to lactam carbonyl group's absorption band. The 1H-NMR spectrum for (K4) showed singlet between δ (2.09-0.18)ppm for the alkyl group Which comes back to part of ibuprofen also appeared at 2.51 ppm for DMSO, as solvent and signals δ (7.19-7.02) ppm (d,4H,Ar-H) finally signals at δ (9.88) ppm due to NH group.

The (13 C-NMR) Spectrum For (K4)The appearance of a signals at (148) ppm belonging to the carbon of (C-NO2) group. While a signals appeared at (162) ppm referring to carbon of amide (C=O) . In addition to significant signals (175) ppm for lactame and (179)ppm for Lactone group.wMultiple signals appeared at (130-118)ppm related to the carbon of the aromatic rings,

The FT-IR Spectrum for The compounds imidaolidin-4-one (K7-K10) , exhibits an absorption band at frequency between (3211-3207) cm -1 which can be attributed to the (NH) band stretchingand (1693)cm-1returns to lactam carbonyl group's absorption band.The1H-NMR spectrum for (K8)The spectrum showed appearance of poly-aromatic signals at (7.10, 7.05)ppm and single signal at (9.82)ppm belonging to the (NH) amide group , as well as the appearance of a single signal at δ(10.32)ppm belonging to the (NH).



Scheme (1) preparation all Compounds (K1-K10)



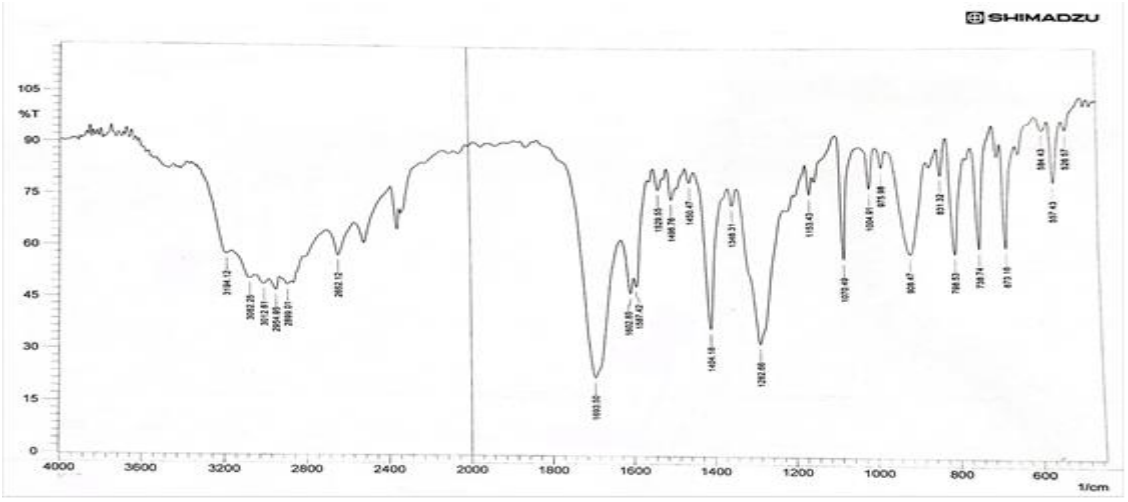


Figure 6;FTIR Spectrum for Compound k3

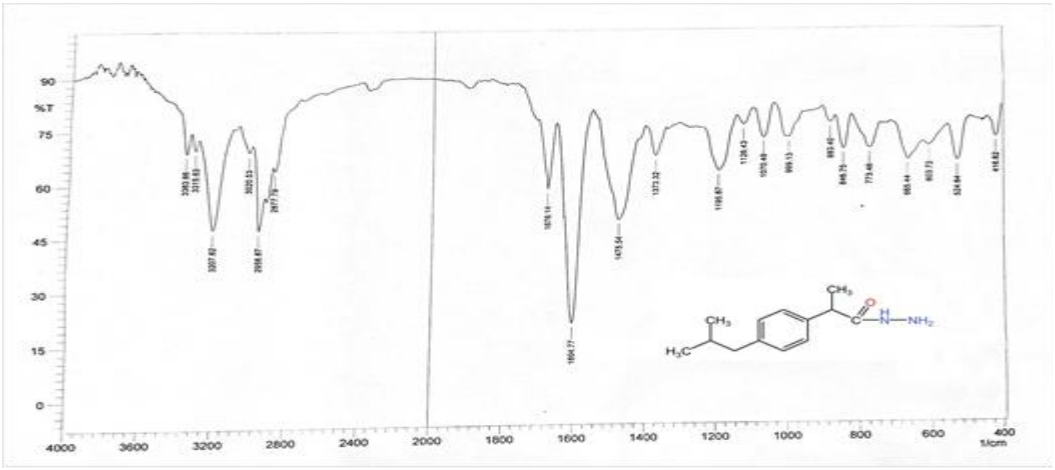


Figure 1:FT-IR spectrum for Compound (K1)

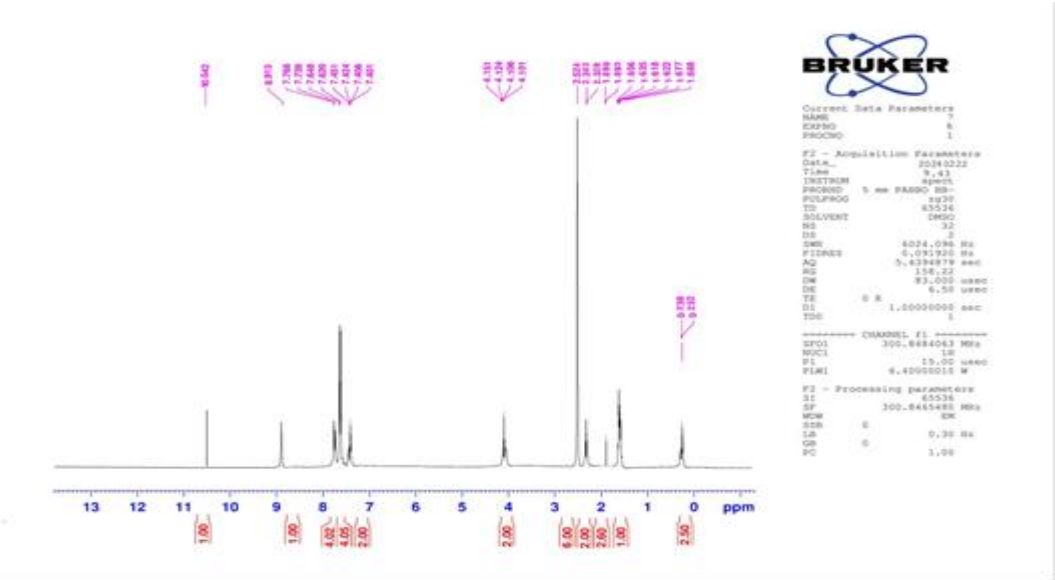


Figure 2 :1HNMR Spectrum for Compound K1

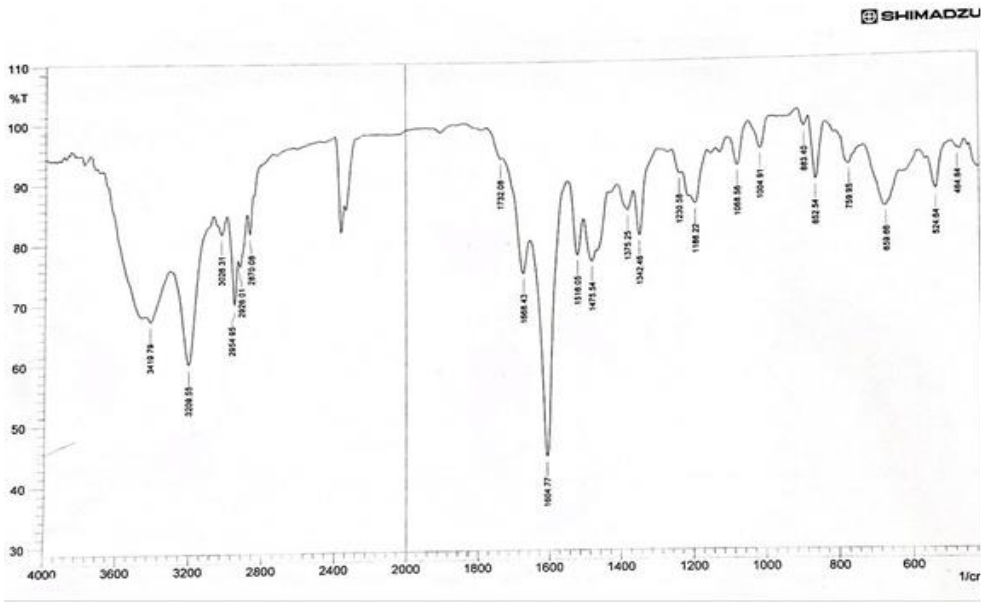


Figure 7;FTIR Spectrum for Compound k4

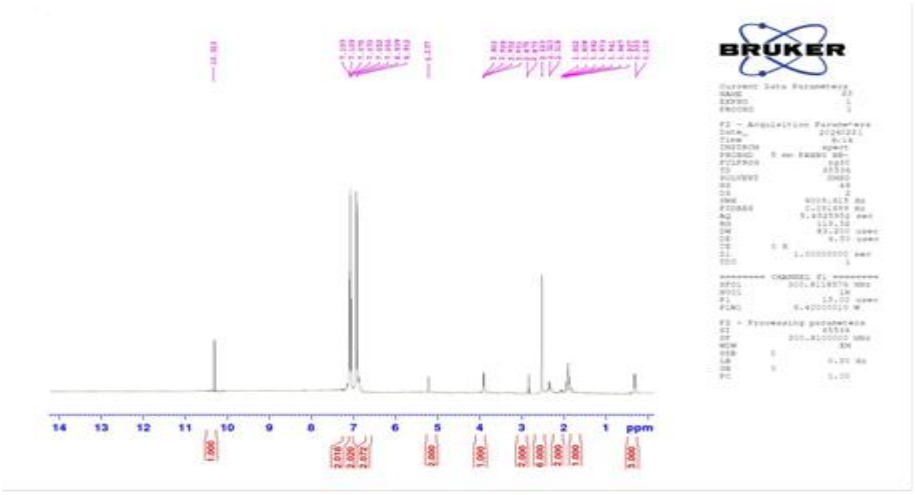


Figure 4 ;1HNMR Spectrum for Compound K2

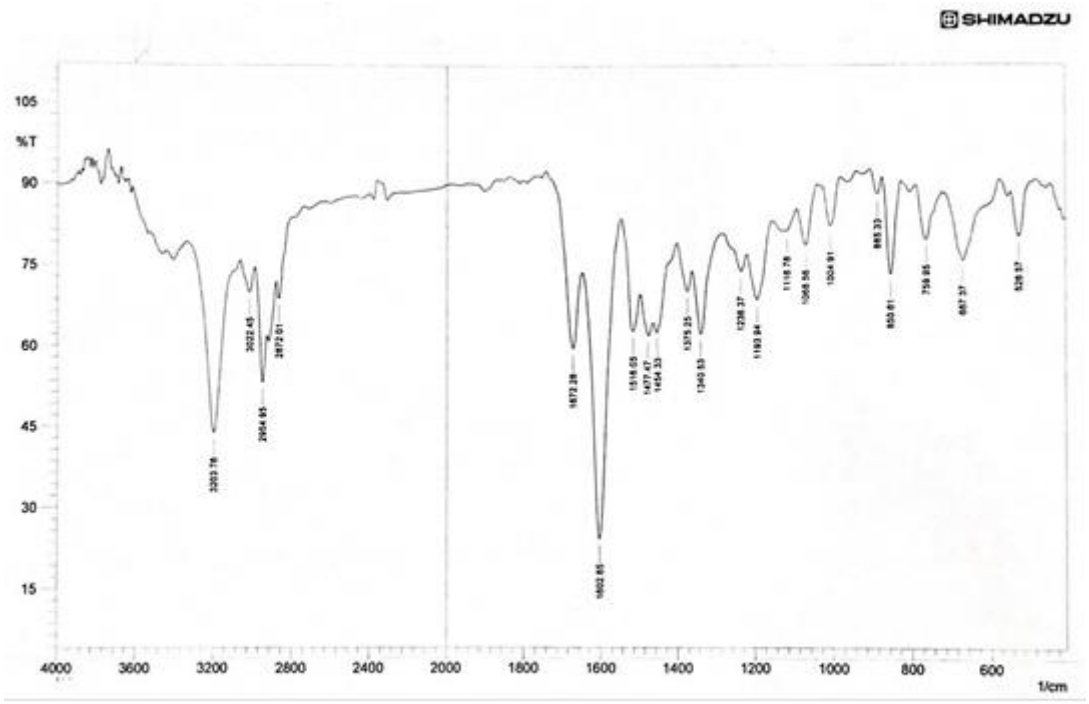


Figure 3;FTIR Spectrum for Compound k2

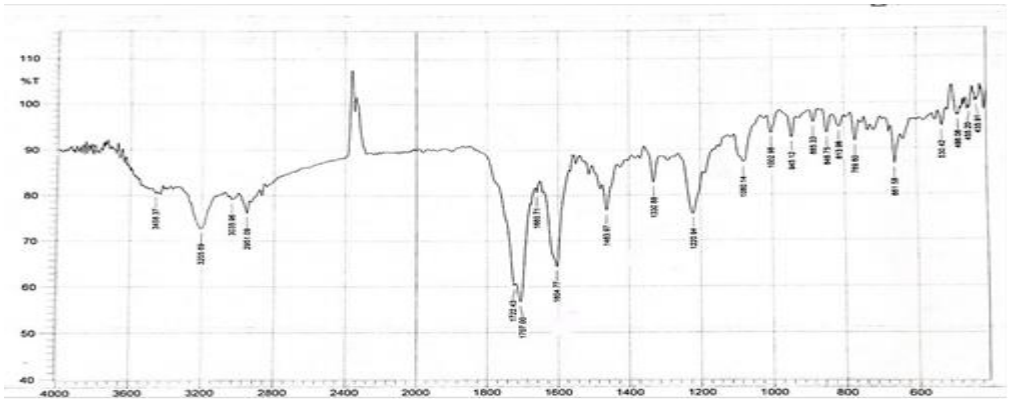


Figure 11;FTIR Spectrum for Compound k6

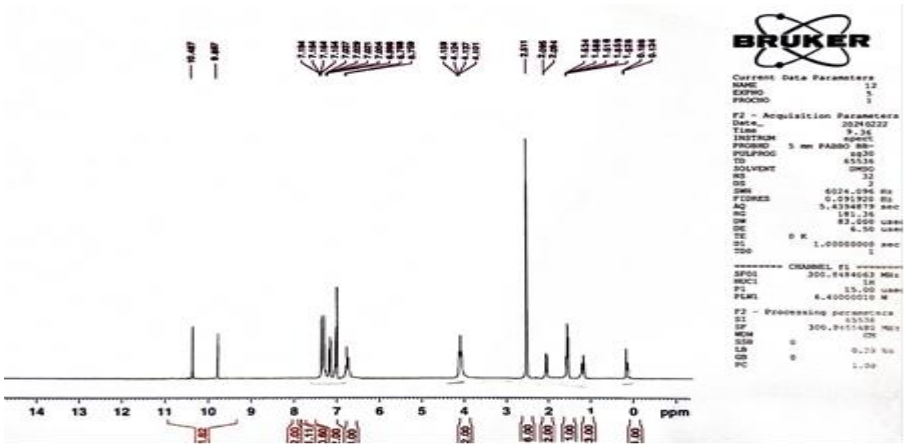


Figure 8 ;1HNMR Spectrum for Compound k4

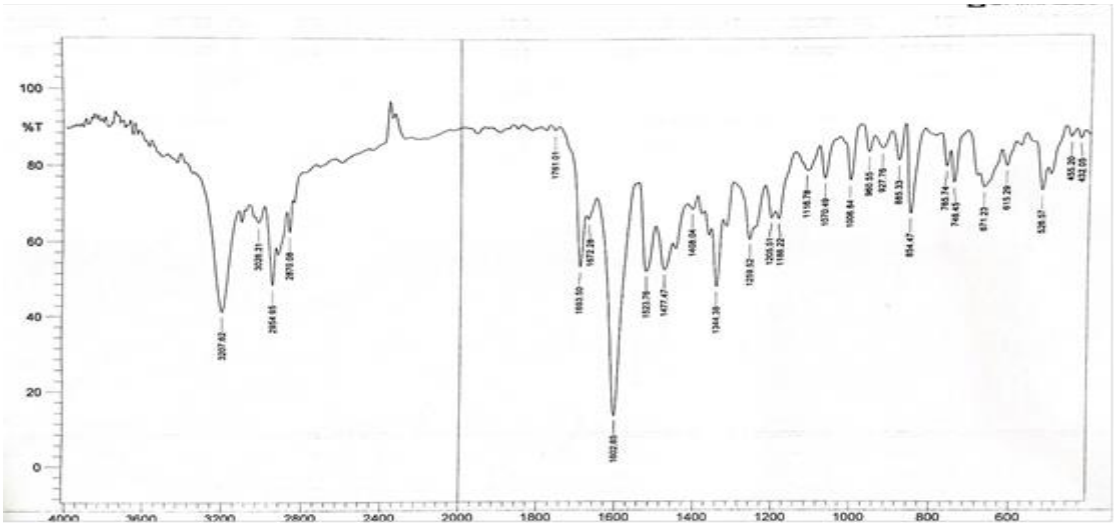


Figure 12 ;FTIR Spectrum for Compound k7

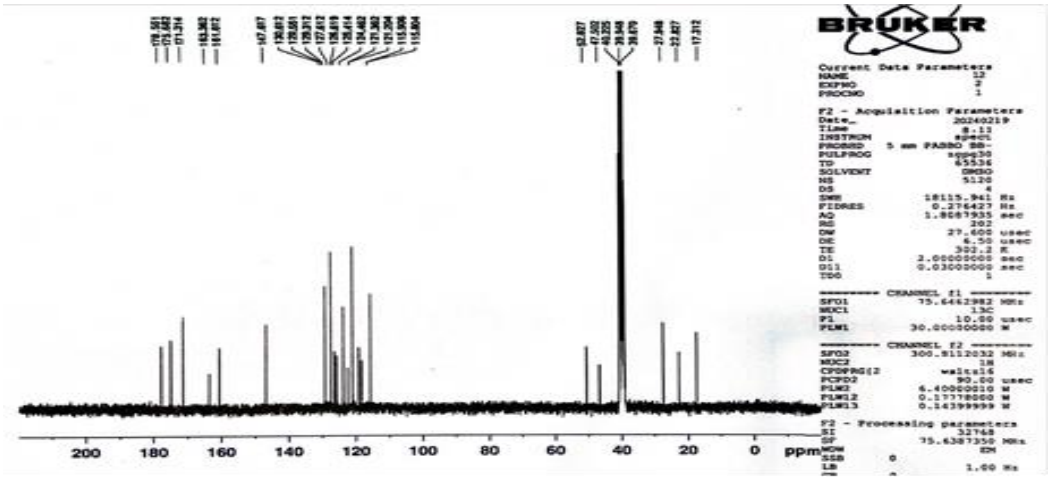


Figure 9 ;13CNMR Spectrum for Compound k4

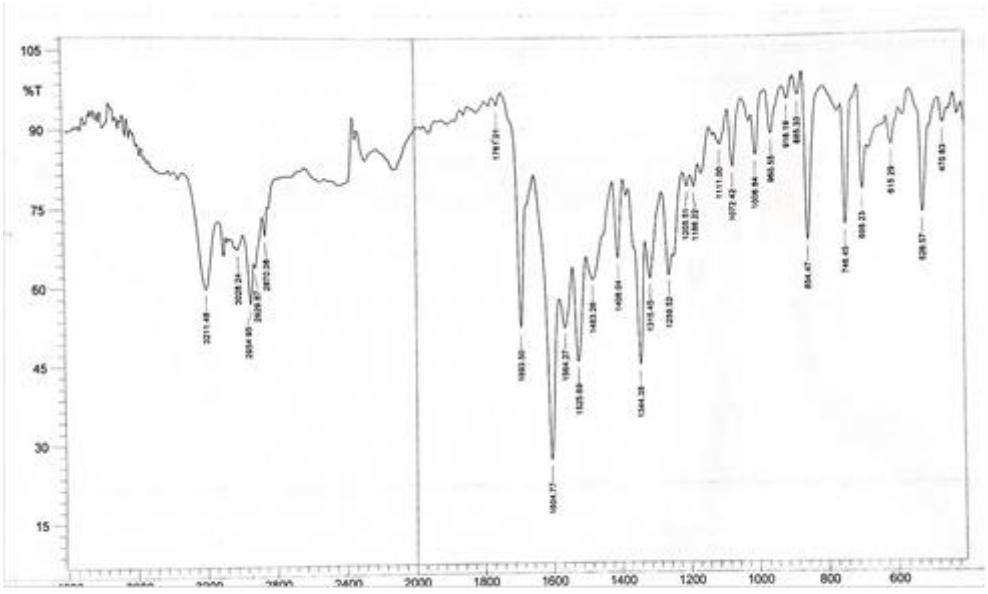


Figure 10;FTIR Spectrum for Compound k5

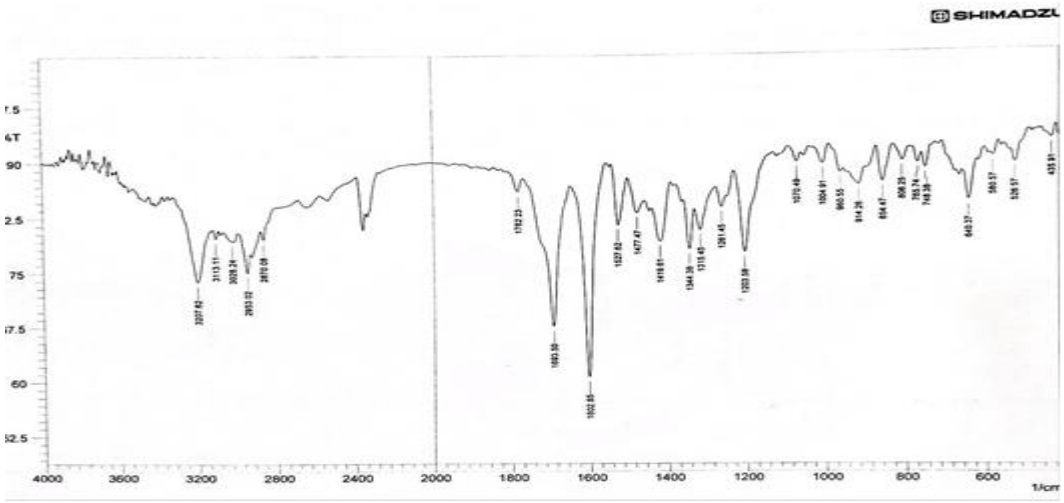


Figure 13;FTIR Spectrum for Compound k8

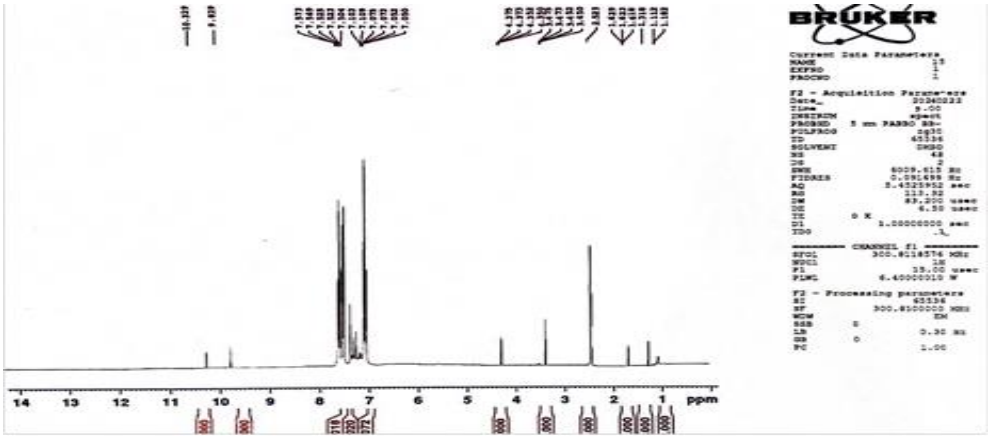


Figure 14 ;1HNMR Spectrum for Compound k8

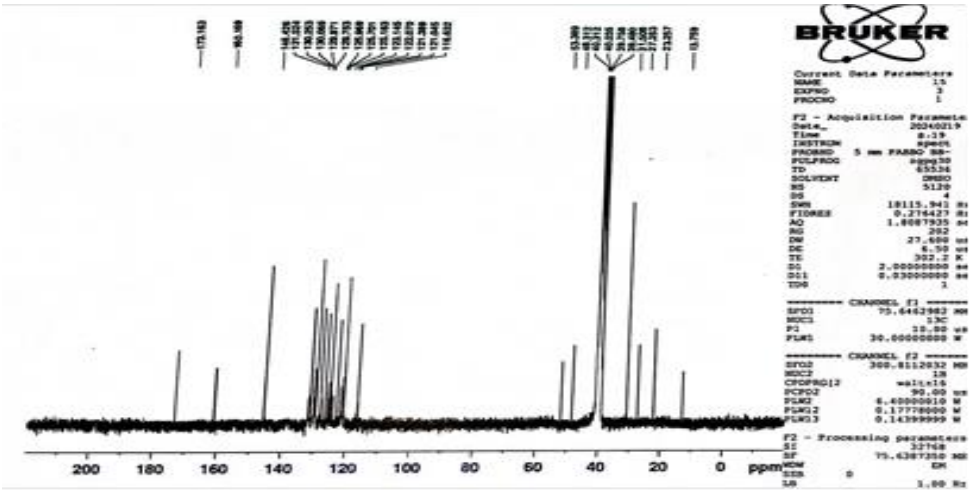


Figure 15:13CNMR Spectrum for Compound k8

Assay of biological activity:

Here we examined the antibacterial activity of some of the compounds prepared. These activities were determined in vitro with a good propagation method against three pathogenic strains of(Staphylococcus aureus) gram positive and (Escherichia coli) gram negative. The obtained results showed that some of these compounds showed measurable activity as shown in Table(1) .

Table (1) biological activity for the compounds

Compound and intermediates	Empirical formula	Molecular weight (g/mol)	Description	Yield%	Melting point c	R*f* value
Ibuprofen	C13H18O2	206*	White powder	……	78-79	0.85*
Acid hydrazide (K1)	C13H20ON2	220*	White powder	96*	118-121	0.75*
K2	C20H23O3N3	353.42*	Yellow powder	70.8*	166-168	0.71*
K3	C28H27O6N3	501.54*	Yellow powder	75.9*	173-175	0.56*
K4	C24H25O6N3	451.48*	Light yellow	76.2*	183-185	0.89*
K5	C24H27O6N3	453.50*	Dark yellow	81.7*	176-178	0.77*
K6	C24H28O6N4	468.51*	Light yellow	77.4*	212-214	0.58*
K7	C24H32O4N4	500.60*	Light yellow	70.6*	172-174	0.45*
K8	C23H28O4N4	424.50*	Brown	66.8*	190-192	0.67*
K9	C29H32O5N44	516.60*	Yellow	65.7*	193-195	0.83*
K10	C22H26O4N4	410.47*	Light yellow	87.5*	208-210	0.48*

(K1-K10) physical properties for the compound Table (2)

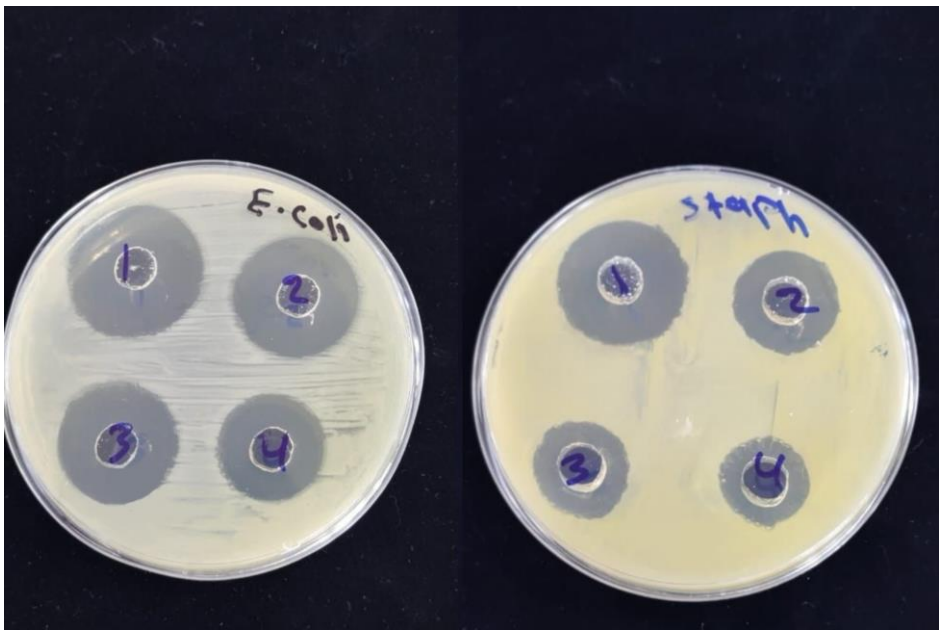


Figure (5): Effect of compounds (k1) against *E.coli and Staphylococcus.*

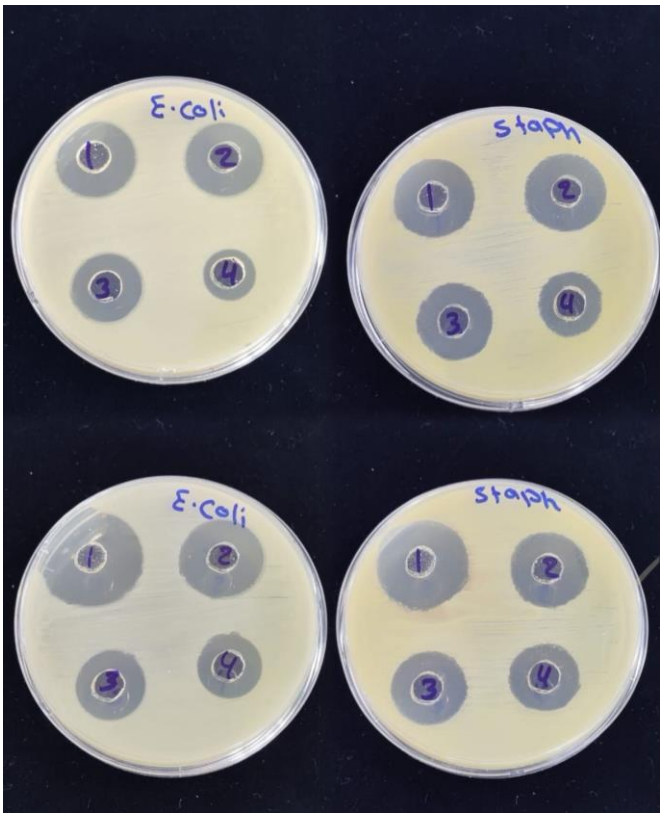


Figure (6): Effect of compounds (k2,k3) against *E.coli and Staphylococcus.*

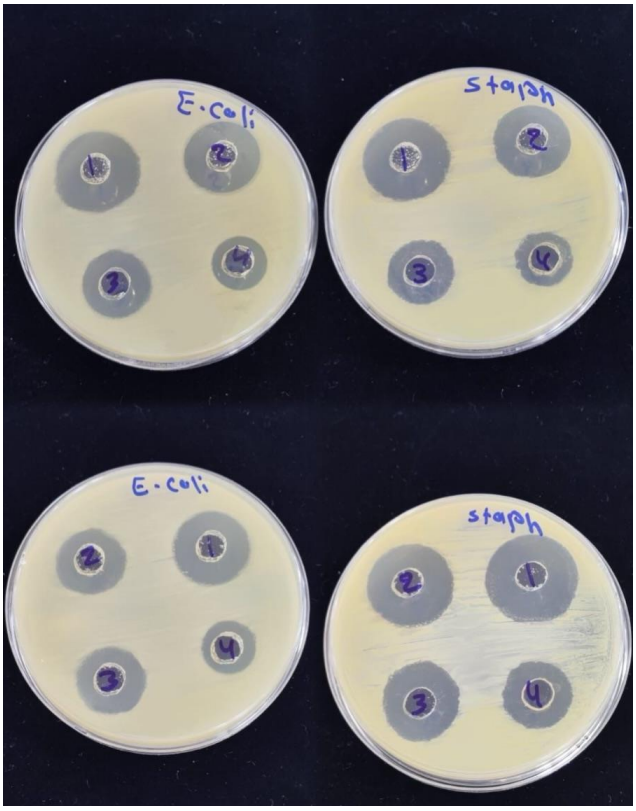


Figure (7): Effect of compounds (k7,k9) against *E.coli and Staphylococcus.*

References

1- Al-Shidhani A, Al-Rawahi N, Al-Rawahi A,Murthi P S. Non-steroidal anti-inflammatory drugs (NSAIDs) use in primary health care centres in A'Seeb,Muscat:A clinical audit. Oman Med J. 2015;30(5):366-371.

2-Croft LJ. Use of NSAIDs in treating patients with arthritis. arthritis Res Ther. 2013;15(3): 1-10

3-Tagreed O. Synthesis and Preliminary Pharmacological Evaluation of Esters and Amides Derivatives of Naproxen as Potential Anti-Inflammatory Agents. Iraqi J Pharm Sci.2013;22(1):120–127

4-Abdellatif KRA, Elsaady MT, Amin NH, Hefny AA. Design, Synthesis and biological evaluation of some novel indole derivatives as selective COX-2 inhibitors. J Appl Pharm Sci.2017;7(8):069–77.

5-Lolli ML, Cena C, Medana C, Lazzarato L,Morini G, Coruzzi G, et al. A new class of ibuprofen derivatives with reducedgastrotoxicity. J Med Chem. 2001;44(21):3463–3468.

6-Sharma N. Synthesis , Characterization & Biological Evaluation of Mutual Prodrugs of Some Selected NSAIDs conjugated with different antioxidant via different amino acids.Org Med Chem Int J. 2017;4(4):1–5.

7-Raczuk, E., Dmochowska, B., Samaszko-Fiertek, J. & Madaj, J. Different Schiff bases—Structure, importance and classification. *Molecules* 27, 787 (2022).

8- Pei T., Huijing W., Wen Z. et al, "Asymmetric catalytic hydrogenation of imines and enamines in natural product synthesis" Green Synthesis and Catalysis 1, 26–41, 2020.

9-John A. Joule "Heterocyclic Chemistry", 5th edition, UK A John Wiley and Sons, Ltd., Publication, Blackwell Publishing Ltd, 2010.

10-R. V. Savalia, A. P. Patel, P. T. Trivedi, H. R. Gohel and D. B. Khetani, Res. J. Chem. Sci., 3, 97-99 (2013).

11-. A. Ashraf, K. Mahmood and A. Wajid, Int. Conference on Chemistry and Chemical Process, 10, 1-7 (2011).

12-Minghui W., Ruixuan G., Mengmeng Z., Peng S. et al, "Development of Bis-Cyclic Imidazolidine-4-one Derivatives as Potent Antibacterial Agents", Journal of Medicinal Chemistry 63, 24, 15591–15602, 2020. Doi: 10.1021/acs.jmedchem.0c00171

13- Jaroslaw S., Alan L. H. and Apolonia R., "2-[(Arylmethoxy)Imino]Imidazolidines WithPotential Biologica.2009 Nov-Dec;66(6):671-80

14- halosuccinimides for cyclization with the formation of five-membered heterocyclic compounds Chem. Heterocycl. Compd. 56, 1–29 (2020).

15-Matos-Rocha, T. J., Lima, M. D. C. A. D., Silva, A. L. D., Oliveira, J. F. D., Gouveia , A. L. A., Silva,V. B. R. D., ... & Pitta, M. G. D. R. Synthesis and biological evaluation of novel imidazolidine derivatives as candidates to schistosomicidal agents. Revista do Instituto de Medicina Tropical de São Paulo, 59(2017)

16-.Mahmood, Rabab Mahdi Ubaid, and Rajaa Abdul Ameer Ghafil. "Synthesis and Characterization some Imidazolidine Derivatives and Study the Biological Activity." Annals of the Romanian Society for Cell Biology (2021): 569-584

17-P. González-Andrés, L. Fernández-Peña, C. Díez-Poza, C. Villalobos, L. Nuñez, A. Barbero, Mar. Drugs, 2021, 19, 78.

18-.Al-lami, Naeemah, and Khawla Jabbar Salom. "Pharmacological studies on some new 3 -cycli oxazepine-2-aryl imidazo (1, 2-a) pyridine derivatives." Journal of Pharmaceutical Sciences and Research 11.1 (2019): 125-130

19-. S. Jasim, Synthesis Characterization and EvaluationAntibacterial Activity of Some Schiff Bases and (1,3-Oxazepine or Diazepine-4,7Dione, Kirkuk University Journal/Scientific Studies (KUJ SS) Volume 14, Issue 2, June 2019 , pp. (249-272). saadsalem@uokirkuk.edu.iq.

20-B. Gadhiya, M. Rajput, A. Bapodra and K. Ladva, Rasayan J. Chem., 9(3), 355-372 (2016).

21-Ajoy S.R. Kumar and Rajendra k. Development and Assessment of Green Synthesis of Hydrazides.April 2010Indian Journal of Chemistry -Section B 49:526-531

22- Razzaq T & Kappe C O, Chem Sus Chem, 1, 2008, 123.

23- Samah H.H. andFaez A. Alrammahi Microwave-Assisted Synthesis of Five and Seven-Membered Heterocycles and Study Their Biological Activity Journal of Kufa for Chemical Sciences Vol. (2)No.(10) Jun 2023.

24-Ramdhan G, Asep B (2021): How to Read and Interpret 1H-NMR and 13C-NMR Spectrums. Indonesian J SciTech., 6(2): 267-298.