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The synthesis, characterization, and assessment of new Oxazepine compounds produced by Bromoibuprofen concerning biological activities.

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ABSTRACT

At this research, new compounds have been synthesized from Ibuprofen (propanoic acid 2- [4-(2 methyl propyl) Phenyl]), through two main reactions: (1) Halogenation with bromine (2). Oxidation. The esterification product reacted with hydrazine hydrate to produce hydrazide compounds (3). Three new derivatives have been synthesized from hydrazone compounds (4-6), through condensation reaction between substituted aroma carbonyls and hydrazine derivatives (Schiff base reactions), in addition cyclization reaction to hydrazone derivatives with malic anhydride has been done in order to produce 1,3-oxazepine compounds (7-9). For the characterization; FT-IR, ¹H-NMR, ¹³C-NMR and TLC used to identify the chemical structures of the product compounds. The biological activity against antibacterial has been studied for the new synthesized compounds.

تحضير وتشخيص وتقييم الفعالية البيولوجية لمركبات الاوكسازيبين الجديدة المشتقة من البروموايبوبروفين

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كلية التربية الأساسية / الشرقاط ، جامعة تكريت ، تكريت ، العراق

الملخص

في هذا البحث، تم إنتاج مواد جديدة محضرة من الإيبوبروفين (حامض البروبانويك 2-[4-(2-ميثيل بروبيل)فينيل]). تم التحضير من تفاعلين رئيسيين هما: (1) الهلجنة (2) الأكسدة. تمت بعد ذلك معالجة الناتج المؤسّر باستخدام هيدرات الهيدرازين لإنتاج مركبات الهيدرازيد. (3). بعد ذلك، تم تحضير ثلاثة مشتقات من مركبات الهيدرازون الجديدة (4-6)، عبر تفاعل التكثيف بين الكربونيلات العطرية المستبدلة ومشتقات الهيدرازين (تفاعلات قواعد شف). بالإضافة إلى ذلك، تم إجراء تفاعل الغلق الحلقي لمشتقات الهيدرازون مع المالك انهدريد، مما أدى إلى إنتاج مركبات 1،3-أوكسازيبين (7-9). تم استخدام الطرق التحليلية مثل التحليل الطيفي للأشعة تحت الحمراء (FTIR) و التحليل الطيفي بالرنين النووي المغناطيسي (¹H-NMR، ¹³C-NMR، NMR) بالإضافة إلى كروماتوغرافيا الطبقة الرقيقة (TLC) لتحديد الصيغة التركيبية للمركبات الناتجة. تم استخدام هذه القياسات للتأكد من صحة التراكيب الكيميائية لجميع المركبات المحضرة. تم استخدام تقنية انتشار اللوحة لتقييم النشاط

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البيولوجي لجميع مشتقات الأوكسازيبين. تم اختبار النشاط المضاد للميكروبات للمواد الكيميائية المصنعة حديثاً بدقة. حيث قدمت هذه الدراسة معلومات مفيدة حول الأنشطة المضادة للبكتيريا المحتملة للمركبات الكيميائية التي تم تحضيرها.

1. Introduction

Ibuprofen. It is a non-steroidal anti-inflammatory medicine (NSAID) that may be bought over the counter. the substance, ranking it among the most commonly used substances worldwide. Ibuprofen, naproxen, and diclofenac are the three NSAIDs that are most often used in both Europe and the US [1]. Ibuprofen is among the top ten drugs that are marketed worldwide. Because it resembles arachidonic acid, phenylacetic acid is primarily responsible for its potent analgesic effects. Ibuprofen's carboxyl group inhibits both COX-1 and COX-2 enzymes, which stops arachidonic acid from being converted into prostaglandins, by forming salt contact with the arginine in the cyclooxygenase conduit [2]. inhibition of the COX-1 and COX-2 enzymes, which stops arachidonic acid from being converted into prostaglandins. The enzyme COX transforms certain fatty acids into prostaglandins, which are chemicals that promote inflammation and aid the brain in sensing pain. Ibuprofen also lowers fever by preventing prostaglandin production in the hypothalamus, the area of the brain in charge of regulating body temperature. Ibuprofen's medicinal analgesic, antirheumatic, and antipyretic actions are derived from these characteristics. [3, 4]

The standard formula for Schiff's rule is $RN=CR'R''$, where R, R', and R'' can be any of the following chemical compounds: alkyl, aryl, heteroaryl, or cycloalkyl. The $-C=N$ -imine bond in Schiff bases has a unique role in endowing these compounds with a broad spectrum of biological activity. The electrophilic carbon and nucleophilic nitrogen in the $-C=N$ -imine link, which provides excellent binding opportunities with a variety of nucleophiles and electrophiles, inhibit targeted diseases, enzymes, or DNA replication. antibacterial and antifungal properties were discovered in the metal complexes of Schiff bases that were produced by the reaction of 5-chlorosalicylaldehyde [5] or indole-3-carboxaldehyde [6] with different sulfonamides, including sulfanilamide, sulfaguanidine, sulfathiazole, sulfamethoxazole, 4-(2-aminoethyl) benzenesulfonamide, etc.

According to studies, derivatizing the carboxylate function of some NSAIDs led to an increase in anti-inflammatory efficacy and a decrease in ulcerogenic effect. Additionally, it has been shown that several molecules with 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole nuclei have strong anti-inflammatory activity [7,8]. The significance of reactive oxygen species in inflammation has drawn a lot of attention over the past 20 years. One of the effects of oxidative stress is inflammation, and interleukins and adhesion molecules are just a couple of the mediators of inflammation that are produced by pathways that are

stimulated by oxidative stress [9]. To find novel and effective medications to treat inflammatory illnesses, we have substituted the hydrazone group for the carboxylic acid group. The synthesized compounds were physicochemically and spectrally characterized and their antioxidant and antimicrobial potential were assessed.

2. Experimental.

2.1. Materials.

(2-(4-isobutyl-phenyl) propionic acid), hydrazine hydrate, aromatic aldehydes (4-OH-benzaldehyde, 4-Nitrobenzaldehyde and 4-(N,N-dimethylbenzaldehyde) organic solvents (p.a. quality), standard reagents for antioxidant and antimicrobial tests, were purchased from Sigma Aldrich Company. All solvents and reagents were used without further purification.

2.2. Instruments.

2.2.1 Fourier Transformed Infra-Red Spectroscopy FTIR.

The FT-IR spectra were recorded by Shimadzu 8400 spectrophotometer ($400-4000\text{ cm}^{-1}$) using KBr disks technique at Chemistry Department Labs, College of Science, Tikrit University, Iraq.

2.2.2 ^1H , and ^{13}C Nuclear Magnetic Resonance.

Proton nuclear magnetic resonance (^1H -NMR; 500 MHz) spectra were recorded on a Bruker DRX500 NMR spectrometer (Zürich, Switzerland) in DMSO- d_6 related to tetramethylsilane (for ^1H NMR, 500MHz) at Tarbiat Modares University, Tehran, Iran.

2.3. Synthesis (R)-2-(3-bromo-4-isobutylphenyl)propionic acid (1).

placed 6.85 g. (50 ml) of (2-(4-isobutyl-phenyl) propionic acid) and 1.0 g. of iron powder. The mixture is heated to $(76-82)^\circ\text{C}$ using a water bath, vigorous stirring is begun, and 30.8 ml. of bromine is added over 30 minutes. Following the bromine addition, the reaction mixture is stirred for a further two hours while being kept at a temperature between $(75-80)$ degrees. After vigorously swirling the reaction mixture into 250 ml of ice-cold 10% sodium hydroxide solution, the solid is allowed to settle and the liquid supernatant is decanted. 50 ml of glacial acetic acid are added to the residual, and the mixture is heated until the solid is melted. Stirring to fully combine the two liquid phases, the mixture is cooled to 5°C in an ice bath, and the liquid supernatant is then decanted. After that, the product is heated to room temperature with 50 ml of 10% acetic acid, stirring constantly. After decanting the aqueous liquid, 50 ml of 1% sodium hydroxide solution are used to repeat the cycle. Using a Buchner funnel, collect solid propionic acid (R)-2-(3-bromo-4-isobutylphenyl) and wash carefully with 50 ml of Non-ionic distilled water. The next step of the

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synthesis can use the wet product straight away. At (178–180) C°, it may be dried to provide 90% of the light-brown substance that melts.[10,11]

2.4. ethyl (R)-2-(3-bromo-4-isobutylphenyl)propanoate (2)

(0.015 mol, 4.7 g) of (R)-2-(3-bromo-4-isobutylphenyl)propionic acid is dissolved in 50 mL of absolute ethanol and 3 mL concentrated sulfuric acid. This mixture was refluxed for 4 hours, the reaction residue was evaporated, washed with sodium bicarbonate, and extracted with diethyl ether (3*30mL). The solvent portion was evaporated at reduced pressure, poured over ice to form a precipitate filter, and recrystallized with ethanol to get compound (2).[12]

2.5. Synthesis of 2-(3-bromo-4-isobutylphenyl)propanehydrazide (3).

This compound was synthesized by mixing (20 mmole, 5.98 g) ester (2) with (20 mmole, 1 g) hydrazine hydrate at 89% yield and m.p. (177-180 C°).[13]

2.6. Synthesis of (R)-2-(3-bromo-4-isobutylphenyl)propionic acid derivatives (4-6).

The corresponding (20 mmol, 1 g) hydrazide (3) was condensed with various aromatic aldehydes (20 mmol, 2.98 g 4-(dimethylamino)benzaldehyde, 20 mmol, 3.02 g 4-nitrobenzaldehyde and 20 mmol, 2.44 g 4-hydroxybenzaldehyde), resulting in hydrazone derivatives (4-6) of ibuprofen. All formulas of the compounds (4-6) have been confirmed by infrared spectrophotometer.[14,15] (Scheme 1).

Table 1: physical properties of compound (4-6).

Compounds	X	Chemical Formula	Color	m.p. °C	Yield (%)
4	-N(CH ₃) ₂	C ₂₂ H ₂₈ N ₃ OBr	Orange	223-225	63
5	-NO ₂	C ₂₀ H ₂₂ N ₃ O ₃ Br	Orange	210-213	82
6	-OH	C ₂₀ H ₂₃ N ₂ O ₂ Br	Orange	204-205	90

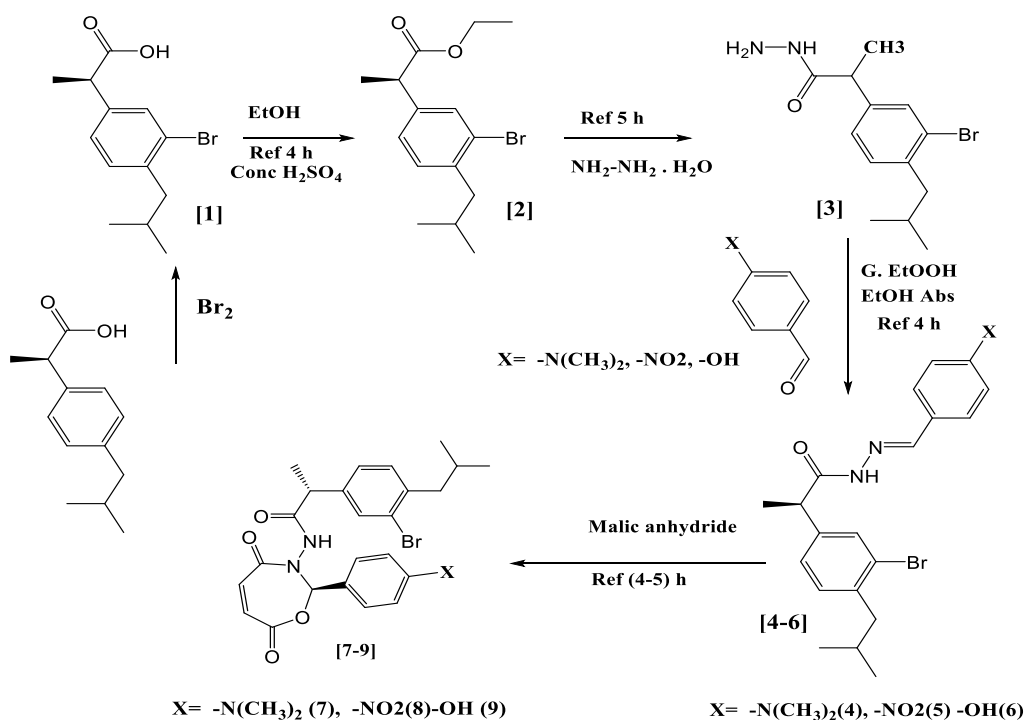
2.7. Synthesis of Oxazepine derivatives. (7-9)

Maleic anhydride (10 mmol, 1 g) and its hydrazine derivatives (7) (10 mmol, 4.21 g), (8) (10 mmol, 4.23 g), and (9) (10 mmol, 3.94 g) were mixed with 20mL of dry THF. Refluxing this mixture for 4-5 hours,

cooling it, and then pouring it over crushed ice resulted in a precipitate that was filtered, dried, and recrystallized with ethanol to yield compounds (7-9).[16] Table (2).

Table 2: physical properties of compound. (7-9).

Compounds	X	Chemical Formula	Color	m.p. °C	Yield (%)
9	-N(CH ₃) ₂	C ₂₆ H ₃₀ N ₃ O ₄ Br	Deep red	212-211	68
7	-NO ₂	C ₂₄ H ₂₄ N ₃ O ₆ Br	Magenta	212-213	84
8	-OH	C ₂₄ H ₂₅ N ₂ O ₅ Br	Brown	209-210	89



Scheme 1

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2.8. Activity against bacteria.

The microbiological activities [17, 18] were carried out at the microbiology Lab, Department of Biology, College of Pure Education Science, Tikrit University, using the diffusion plate method [19]. A sterilized filter paper disk containing 25 μ L of the measured sample (1 mg/mL) was put on a plate (9 cm diameter) with solid bacterial medium. After 24 hours of incubation at 37°C for bacteria, the clear zone of inhibition around the sample is measured to determine its inhibitory strength against the test organism (% inhibition = sample inhibition zone (cm)/plate diameter $\times$ 100). All experiments were performed in methanol, a solvent with little inhibitory action. The antimicrobial activity of the new compounds was examined against Gram-positive bacteria *Staphylococcus aureus*, as well as Gram-negative bacteria *Pseudomonas aeruginosa*.

3. Results and discussions

3.1. The infrared spectrum :

The preliminary inference of its preparation was done through some physical properties and infrared spectra in the extent (4000-400) cm^{-1} . The infrared spectrum of the prepared compounds showed an absorption band at the range (3172 - 3236) cm^{-1} due to the stretching of the (N-H) bond and where it was observed that the absorption band belonging to the imine group (C=N) at the range (1595 - 1604) cm^{-1} and the occurrence of an absorption band at the region (1670-1679) cm^{-1} due to the stretching of the group (C = O) and the occurrence of an absorption band at The region (3004-3069) cm^{-1} is due to the stretching of the aromatic (C-H) group, and the occurrence of absorption bands at the region (1554-1557) cm^{-1} is due to the stretching of the aromatic (C=C) group. As shown in Table (3).

Table 3: : FT-IR spectrum data of compounds (4-6)

Comp. No.	R.	=C-H Ar.	C=O	C=N	C=C Ar.	N-H	Others
4	4-NO ₂	3069	1677	1595	1554	3169	NO ₂ 1370
5	4-OH	3060	1779	1604	1557	3172	OH 3465
6	4-N(CH ₃) ₂	3004	1670	1596	1556	3236	CH ₃ 2986

The appearance of stretching bands of (C=O) lactone group (-O-CO-) were observed. at (1709-1754) cm^{-1} , as well as stretching bands of the lactam carbonyl group (-N-CO-) at (1652-1657) cm^{-1} , and the stretching bands of the (NH) group appeared at the frequency (3197-3260) cm^{-1} , also the stretching

bundles of the group (C = C) of the aromatic ring appeared at (1521-1592) cm^{-1} and the stretching bundles of the group (=C-H) appeared at (3025-3082) cm^{-1} . Table No. (4) shows The most important absorbance's of the prepared compounds (7-9).

Table 4 FT-IR spectrum data of compounds (7-9)

Comp. No.	R.	=C-H Ar.	C=C Ar	C=O	C=O L.N	C=O L.M	C=O E.R	N-H	Others
7	4-NO ₂	3082	1592	1669	1754	1654	1205	3199	NO ₂ 1372
8	4-OH	3025	1530	1673	1709	1657	1191	3197	OH 3364
9	4-N(CH ₃) ₂	3030	1521	1720	1676	1652	3260 1225		CH ₃ 2996

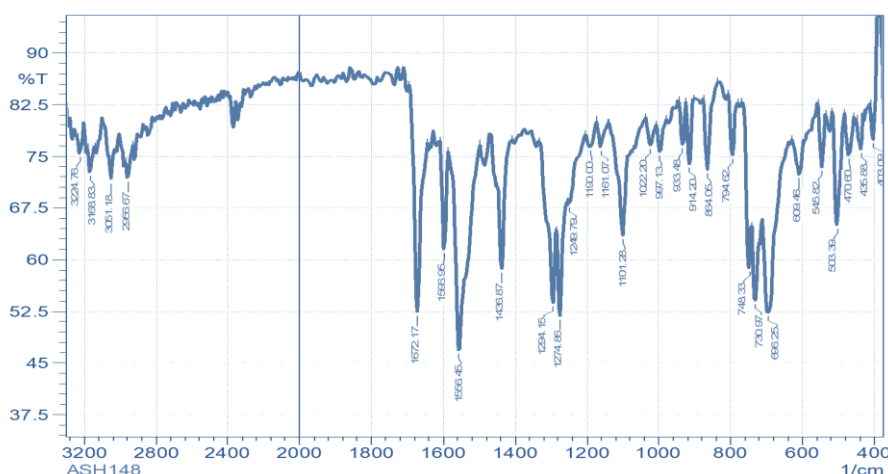


Fig. 1: IR spectrum of compound 4

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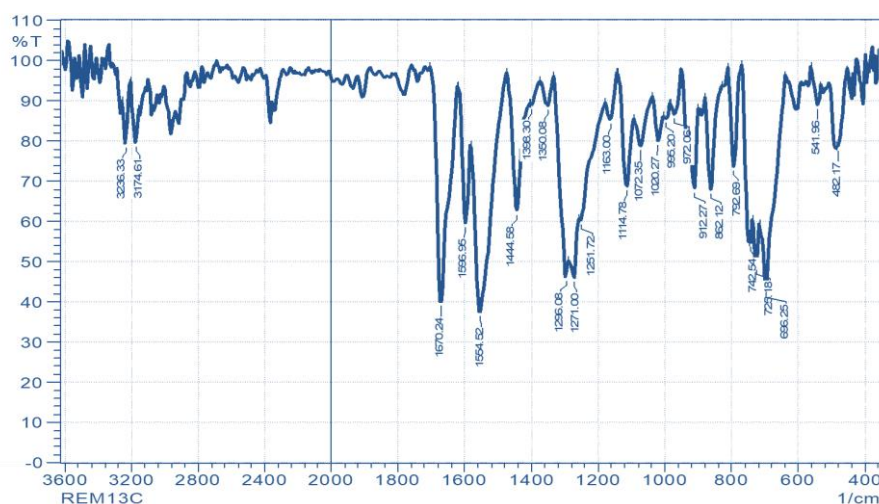


Fig. 2: IR spectrum of compound 6

^{13}C NMR (125 MHz, DMSO -d₆) spectrum of Compound (1) (δ = 179, 1C (C=O) (δ = 141, 1C 1-Ar) (δ = 138, 1C 4-Ar) (δ = 130.6, 1C 2-Ar) (δ = 128-127, 2C 5,6-Ar) (δ = 124, 1C 3-Ar (C-Br)) (δ =

44, C CH₂ alph) (δ = 42, 1C CH-CO alph) (δ = 29, 1C CH-(CH₃)₂) (δ = 22.5, 2C (CH₃)₂) (δ = 18.79, 1C CH₃-CH).

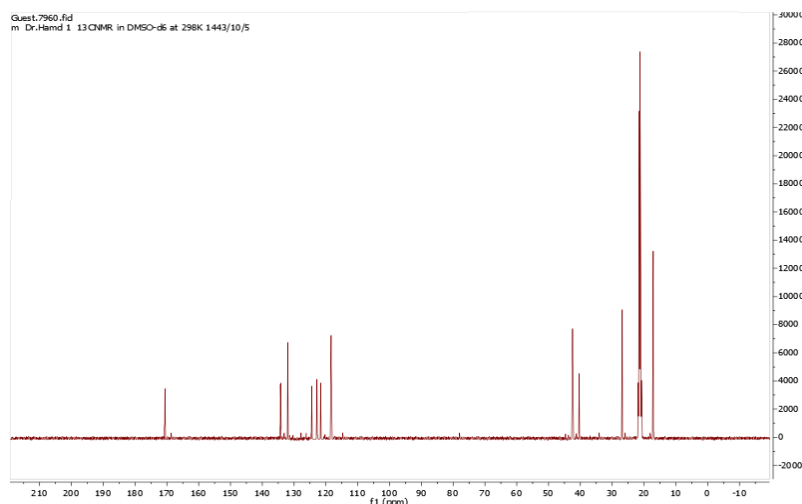


Fig. 3: ^{13}C NMR spectrum of Compound 1

3.2. ^1H - Nuclear Magnetic Resonance.

Through ^1H -NMR analysis in the diagnosis of synthesized organic compounds, compound 1 showed multiple signals for 3H of the aromatic ring as a result of the replacement of the bromine atom in the meta site when (7.4-8.2) ppm was displaced, while the hydroxyl proton signal for compound 2 disappeared when (12.6) ppm was displaced, and aliphatic proton signals appeared when (1.5 CH₃ and 3.4 CH₂) ppm was displaced. Compound (3) showed individual signals when the proton of the two amine atoms was displaced (9.6 NH and 4.5 NH₂) ppm, while in compounds (4-6) the signal for the amine proton NH₂ disappeared upon displacement (4.5) ppm and a proton signal N=C-H appeared at a displacement ranging between (9.1-9.5) ppm and the OH proton signal appeared when (10) ppm is displaced for the

compound 6, and the sign of 6 protons, N-(CH₃)₂, when (2.9) ppm for the compound (4), and in compounds (7-9), the sign of the right proton, N=C-H, disappears when (8.2-8.6) ppm is displaced, and the proton signal of the two allylic carbon atoms appears when (6.5) ppm is displaced, as in the following figures (1-9).

The ^1H -NMR (DMSO-d, 500 MHz) illustrates compound 1 in Figure1, which shows chemical shift, δ (ppm), singlet in 12.4 ppm (OH), single in 8.1 ppm (1 H, CH ortho aromatic), multiple in 7.2-7.4 ppm (2H, CH Ar), qd signals in 4.5 ppm (1H, CH alph), doublet signals in 2.9 ppm (2H, alph-CH₂), hept in 2.3 ppm (1H, alph-CH), doublet signal in 1.85 (3H, CH₃ alph) and doublet signal in 1.2-1.3 (6H, CH₃ alph).

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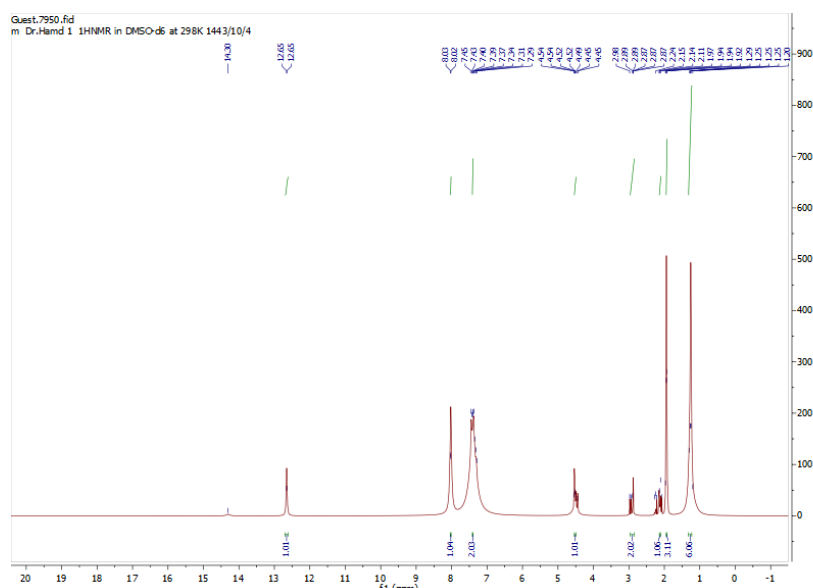


Fig. 4: ^1H NMR spectrum of Compound 1

The ^1H -NMR (DMSO- d_6 , 500 MHz) illustrates **compound 2** in **Figure 5**, which shows chemical shift, $\delta(\text{ppm})$, single in 7.1 ppm (1 H, CH ortho aromatic), multiple in 6.87 ppm (2H, CH Ar), qd signals in 4.4 ppm (2H, $\text{CH}_2\text{-O}$ ester), qd signals

in 4.1 ppm (1H, $\alpha\text{-CH-CO}$ ester), doublet signal in 3.3 ppm CH_2 α , hept in 2.3-2.4 ppm (1H, $\alpha\text{-CH}$), doublet signal in 1.9 (3H, CH_3 α), doublet signal in 1.4 (3H, $\text{CH}_3\text{-CH}_2$ α) and doublet signal in 0.8-0.95 (6H, CH_3 α).

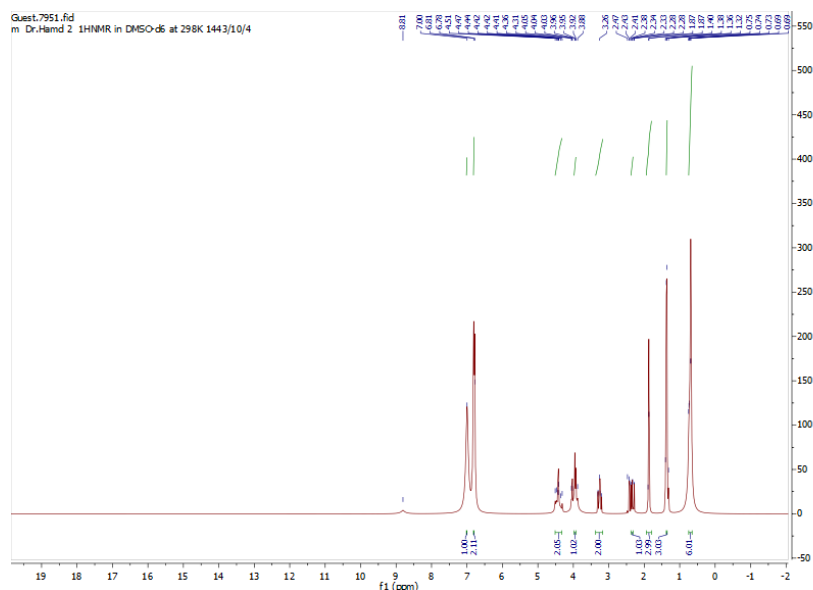


Fig. 5: ^1H NMR spectrum of Compound 2

The ^1H -NMR (DMSO- d_6 , 500 MHz) illustrates **compound 3** in **Figure 6**, which shows chemical shift, $\delta(\text{ppm})$, tp single in 9.6 ppm (1H, NH), single in 7.4 ppm (1 H, CH ortho aromatic), multiple in 7 ppm (2H, CH Ar), doublet signal in 4.7 ppm (2H,

NH_2), qd signals in 4.2 ppm (1H, CH α), doublet signals in 2.87 ppm (2H, $\alpha\text{-CH}_2$), hept in 1.9 ppm (1H, $\alpha\text{-CH}$), doublet signal in 1.5 (3H CH_3 α) and doublet signal in 0.9-1.1 (6H, CH_3 α).

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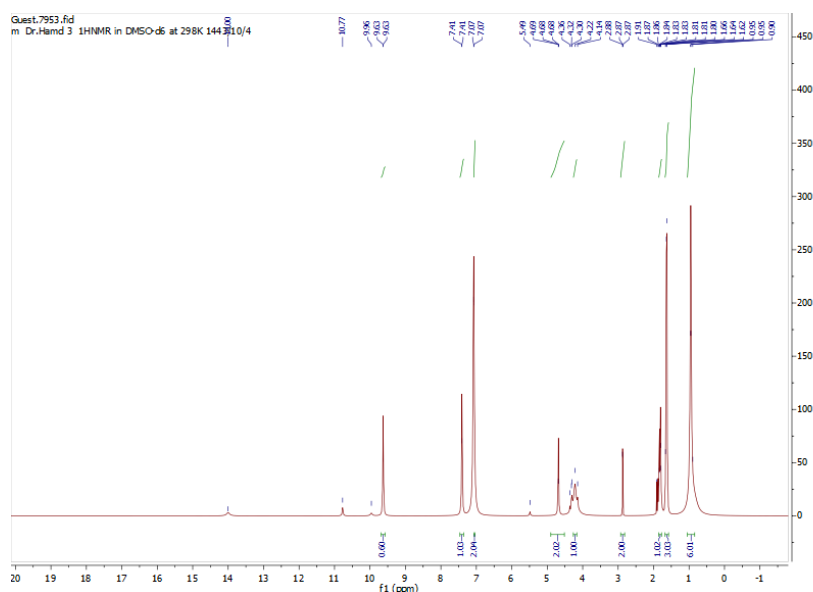


Fig. 6: ^1H NMR spectrum of Compound 3

The ^1H -NMR (DMSO- d_6 , 500 MHz) illustrates **compound 4** in **Figure 7**, which shows chemical shift, $\delta(\text{ppm})$, singlet in 9.4 ppm (1H, N=C-H), singlet in 8.2 ppm (1H, NH), multiple in 6.5-7.8 ppm (7H, all CH Ar), qd signals in 4.02 ppm (1H, CH

alpha), mono signal in 3 ppm (6H, N-(CH $_3$) $_2$), doublet signal in 2.4 ppm (2H, alpha-CH $_2$), hept in 1.6 ppm (1H, alpha-CH), doublet signal in 1.4 (3H, CH $_3$ alpha) and doublet signal in 0.7-1 (6H CH $_3$ alpha).

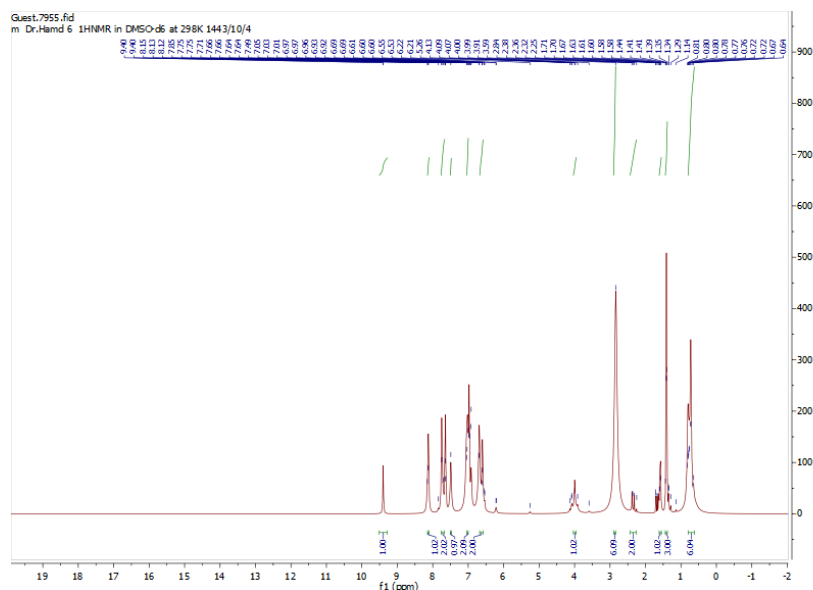


Fig. 7: ^1H NMR spectrum of Compound 4

The ^1H -NMR (DMSO- d_6 , 500 MHz) illustrates **compound 5** in **Figure 8**, which shows chemical shift, $\delta(\text{ppm})$, singlet in 9.3 ppm (1H N=C-H), singlet in 8.1 ppm (1H, NH), multiple in 6.4-7.9 ppm (7H, all CH Ar), qd signals in 3.9 ppm (1H, CH alpha),

doublet single in 2.5 ppm (2H, alpha-CH $_2$), hept in 1.5 ppm (1H, alpha-CH), doublet signal in 1.2 (3H CH $_3$ alpha) and doublet signal in 0.6-0.7 (6H, CH $_3$ alpha).

The ^1H -NMR (DMSO- d_6 , 500 MHz) illustrates **compound 6** in **Figure 9**, which shows chemical Schiff, $\delta(\text{ppm})$, mono single in 9.9 ppm (1H, O-H), single in 9.1 ppm (1H, N=C-H), single in 8.3 ppm (1H, NH), multiple in 6.9-7.8 ppm (7H, all CH Ar),

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Dr.Hamid 8 1HWMR in DMSO-d6 at 298K 1443/10/4

1H NMR spectrum (400 MHz, DMSO-d₆) of compound 8. The x-axis represents the chemical shift in ppm (δ), ranging from 19 to -2. The y-axis represents the intensity in arbitrary units (a.u.), ranging from 0 to 80. The spectrum shows several peaks, with integration values provided for each peak.

Chemical shift (ppm): 9.86, 9.85, 9.84, 9.83, 9.82, 9.81, 9.80, 9.79, 9.78, 9.77, 9.76, 9.75, 9.74, 9.73, 9.72, 9.71, 9.70, 9.69, 9.68, 9.67, 9.66, 9.65, 9.64, 9.63, 9.62, 9.61, 9.60, 9.59, 9.58, 9.57, 9.56, 9.55, 9.54, 9.53, 9.52, 9.51, 9.50, 9.49, 9.48, 9.47, 9.46, 9.45, 9.44, 9.43, 9.42, 9.41, 9.40, 9.39, 9.38, 9.37, 9.36, 9.35, 9.34, 9.33, 9.32, 9.31, 9.30, 9.29, 9.28, 9.27, 9.26, 9.25, 9.24, 9.23, 9.22, 9.21, 9.20, 9.19, 9.18, 9.17, 9.16, 9.15, 9.14, 9.13, 9.12, 9.11, 9.10, 9.09, 9.08, 9.07, 9.06, 9.05, 9.04, 9.03, 9.02, 9.01, 9.00, 8.99, 8.98, 8.97, 8.96, 8.95, 8.94, 8.93, 8.92, 8.91, 8.90, 8.89, 8.88, 8.87, 8.86, 8.85, 8.84, 8.83, 8.82, 8.81, 8.80, 8.79, 8.78, 8.77, 8.76, 8.75, 8.74, 8.73, 8.72, 8.71, 8.70, 8.69, 8.68, 8.67, 8.66, 8.65, 8.64, 8.63, 8.62, 8.61, 8.60, 8.59, 8.58, 8.57, 8.56, 8.55, 8.54, 8.53, 8.52, 8.51, 8.50, 8.49, 8.48, 8.47, 8.46, 8.45, 8.44, 8.43, 8.42, 8.41, 8.40, 8.39, 8.38, 8.37, 8.36, 8.35, 8.34, 8.33, 8.32, 8.31, 8.30, 8.29, 8.28, 8.27, 8.26, 8.25, 8.24, 8.23, 8.22, 8.21, 8.20, 8.19, 8.18, 8.17, 8.16, 8.15, 8.14, 8.13, 8.12, 8.11, 8.10, 8.09, 8.08, 8.07, 8.06, 8.05, 8.04, 8.03, 8.02, 8.01, 8.00, 7.99, 7.98, 7.97, 7.96, 7.95, 7.94, 7.93, 7.92, 7.91, 7.90, 7.89, 7.88, 7.87, 7.86, 7.85, 7.84, 7.83, 7.82, 7.81, 7.80, 7.79, 7.78, 7.77, 7.76, 7.75, 7.74, 7.73, 7.72, 7.71, 7.70, 7.69, 7.68, 7.67, 7.66, 7.65, 7.64, 7.63, 7.62, 7.61, 7.60, 7.59, 7.58, 7.57, 7.56, 7.55, 7.54, 7.53, 7.52, 7.51, 7.50, 7.49, 7.48, 7.47, 7.46, 7.45, 7.44, 7.43, 7.42, 7.41, 7.40, 7.39, 7.38, 7.37, 7.36, 7.35, 7.34, 7.33, 7.32, 7.31, 7.30, 7.29, 7.28, 7.27, 7.26, 7.25, 7.24, 7.23, 7.22, 7.21, 7.20, 7.19, 7.18, 7.17, 7.16, 7.15, 7.14, 7.13, 7.12, 7.11, 7.10, 7.09, 7.08, 7.07, 7.06, 7.05, 7.04, 7.03, 7.02, 7.01, 7.00, 6.99, 6.98, 6.97, 6.96, 6.95, 6.94, 6.93, 6.92, 6.91, 6.90, 6.89, 6.88, 6.87, 6.86, 6.85, 6.84, 6.83, 6.82, 6.81, 6.80, 6.79, 6.78, 6.77, 6.76, 6.75, 6.74, 6.73, 6.72, 6.71, 6.70, 6.69, 6.68, 6.67, 6.66, 6.65, 6.64, 6.63, 6.62, 6.61, 6.60, 6.59, 6.58, 6.57, 6.56, 6.55, 6.54, 6.53, 6.52, 6.51, 6.50, 6.49, 6.48, 6.47, 6.46, 6.45, 6.44, 6.43, 6.42, 6.41, 6.40, 6.39, 6.38, 6.37, 6.36, 6.35, 6.34, 6.33, 6.32, 6.31, 6.30, 6.29, 6.28, 6.27, 6.26, 6.25, 6.24, 6.23, 6.22, 6.21, 6.20, 6.19, 6.18, 6.17, 6.16, 6.15, 6.14, 6.13, 6.12, 6.11, 6.10, 6.09, 6.08, 6.07, 6.06, 6.05, 6.04, 6.03, 6.02, 6.01, 6.00, 5.99, 5.98, 5.97, 5.96, 5.95, 5.94, 5.93, 5.92, 5.91, 5.90, 5.89, 5.88, 5.87, 5.86, 5.85, 5.84, 5.83, 5.82, 5.81, 5.80, 5.79, 5.78, 5.77, 5.76, 5.75, 5.74, 5.73, 5.72, 5.71, 5.70, 5.69, 5.68, 5.67, 5.66, 5.65, 5.64, 5.63, 5.62, 5.61, 5.60, 5.59, 5.58, 5.57, 5.56, 5.55, 5.54, 5.53, 5.52, 5.51, 5.50, 5.49, 5.48, 5.47, 5.46, 5.45, 5.44, 5.43, 5.42, 5.41, 5.40, 5.39, 5.38, 5.37, 5.36, 5.35, 5.34, 5.33, 5.32, 5.31, 5.30, 5.29, 5.28, 5.27, 5.26, 5.25, 5.24, 5.23, 5.22, 5.21, 5.20, 5.19, 5.18, 5.17, 5.16, 5.15, 5.14, 5.13, 5.12, 5.11, 5.10, 5.09, 5.08, 5.07, 5.06, 5.05, 5.04, 5.03, 5.02, 5.01, 5.00, 4.99, 4.98, 4.97, 4.96, 4.95, 4.94, 4.93, 4.92, 4.91, 4.90, 4.89, 4.88, 4.87, 4.86, 4.85, 4.84, 4.83, 4.82, 4.81, 4.80, 4.79, 4.78, 4.77, 4.76, 4.75, 4.74, 4.73, 4.72, 4.71, 4.70, 4.69, 4.68, 4.67, 4.66, 4.65, 4.64, 4.63, 4.62, 4.61, 4.60, 4.59, 4.58, 4.57, 4.56, 4.55, 4.54, 4.53, 4.52, 4.51, 4.50, 4.49, 4.48, 4.47, 4.46, 4.45, 4.44, 4.43, 4.42, 4.41, 4.40, 4.39, 4.38, 4.37, 4.36, 4.35, 4.34, 4.33, 4.32, 4.31, 4.30, 4.29, 4.28, 4.27, 4.26, 4.25, 4.24, 4.23, 4.22, 4.21, 4.20, 4.19, 4.18, 4.17, 4.16, 4.15, 4.14, 4.13, 4.12, 4.11, 4.10, 4.09, 4.08, 4.07, 4.06, 4.05, 4.04, 4.03, 4.02, 4.01, 4.00, 3.99, 3.98, 3.97, 3.96, 3.95, 3.94, 3.93, 3.92, 3.91, 3.90, 3.89, 3.88, 3.87, 3.86, 3.85, 3.84, 3.83, 3.82, 3.81, 3.80, 3.79, 3.78, 3.77, 3.76, 3.75, 3.74, 3.73, 3.72, 3.71, 3.70, 3.69, 3.68, 3.67, 3.66, 3.65, 3.64, 3.63, 3.62, 3.61, 3.60, 3.59, 3.58, 3.57, 3.56, 3.55, 3.54, 3.53, 3.52, 3.51, 3.50, 3.49, 3.48, 3.47, 3.46, 3.45, 3.44, 3.43, 3.42, 3.41, 3.40, 3.39, 3.38

The ¹H-NMR (DMSO-d, 500 MHz) illustrates **compound 7** in **Figure10**, which shows chemical Schiff, δ(ppm), mono single in 9.5 ppm (1H, N-H), single in 8.25 ppm (1H, N-CH-O oxazepin), multiple in 6.85-7.9 ppm (7H, all CH Ar), doublet single in 6.6-6.8 ppm (2H, allylic -CH the heptad ring of

oxazepine) qd signals in 4.1 ppm (1H, CH alph) , mono single in 3.1 ppm (6H, N-(CH₃)₂, doublet single in 2.5 ppm (2H alph-CH₂), hept in 1.6 ppm (1H alph -CH), doublet signal in 1.35 (3H, CH₃ alph) and doublet signal in 0.8-0.9 5 (6H, CH₃ alph).

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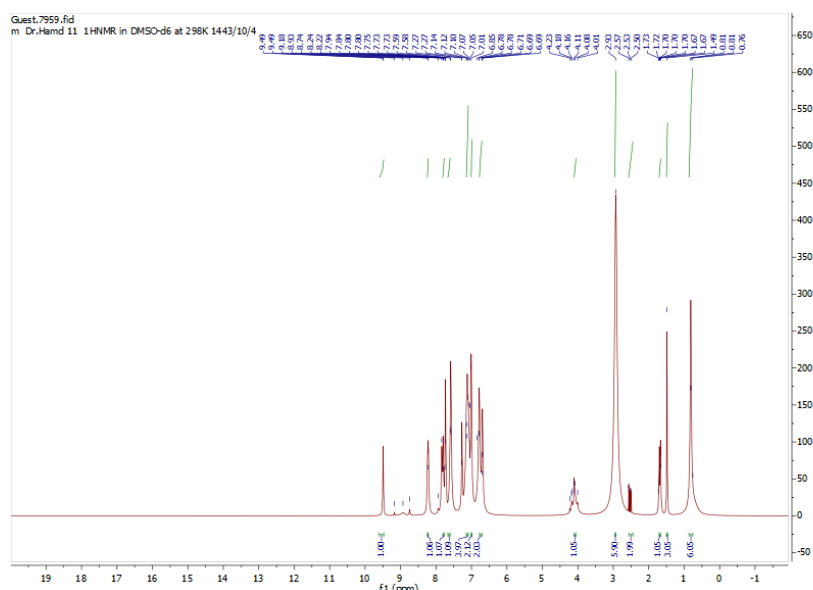


Fig. 10: ^1H NMR spectrum of Compound 7

The ^1H -NMR (DMSO- d_6 , 500 MHz) illustrates **compound 8** in **Figure11**, which shows chemical Schiff, $\delta(\text{ppm})$, mono single in 9.3 ppm (1H, N-H), single in 8.3 ppm (1H, N-CH-O oxazepin), multiple in 6.7-7.8 ppm (7H, all CH Ar), doublet single in 6.5

ppm (2H, allylic -CH the heptad ring of oxazepine) qd signals in 4.5 ppm (1H, CH alph), doublet single in 2.6 ppm (2H, alph- CH_2), hept in 1.5 ppm (1H alph -CH), doublet signal in 1.3 (3H, CH_3 alph) and doublet signal in 0.6-0.8 (6H, CH_3 alph).

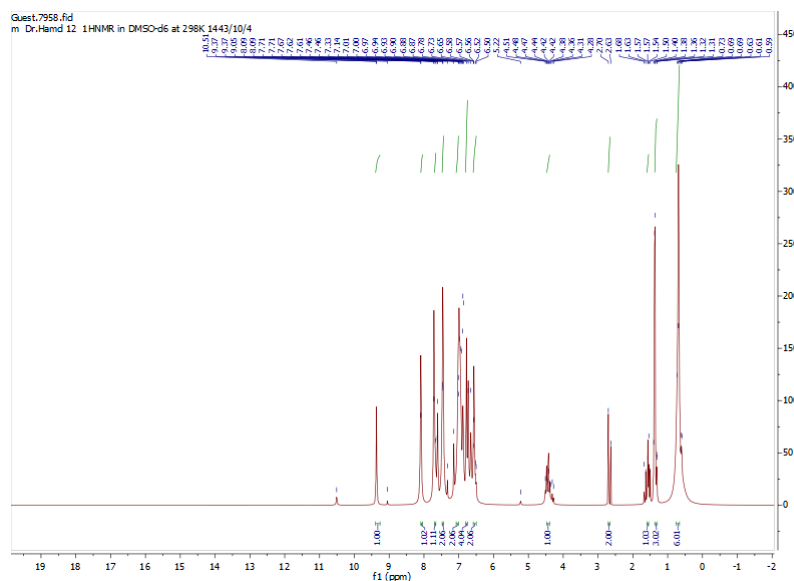
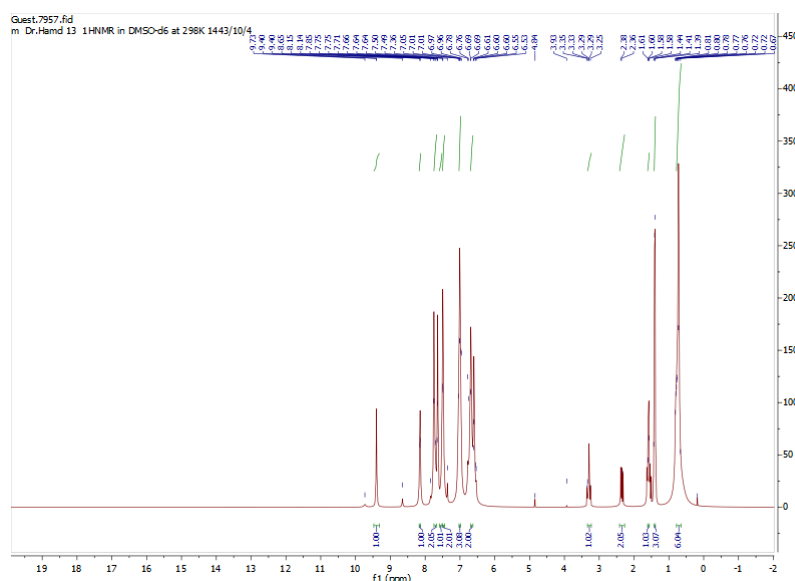


Fig. 11: ^1H NMR spectrum of Compound 8

The ^1H -NMR (DMSO- d_6 , 500 MHz) illustrates **compound 9** in **Figure12**, which shows chemical Schiff, $\delta(\text{ppm})$, mono single in 9.4 ppm (1H, N-H), mono single in 8.4 ppm (1H, O-H), single in 7.8 ppm (1H, N-CH-O oxazepin), multiple in 6.6-7.7 ppm (7H, all CH Ar), doublet single in 6.5 ppm (2H,

allylic -CH the heptad ring of oxazepine) qd signals in 3.15 ppm (1H, CH alph), doublet single in 2.2 ppm (2H, alph- CH_2), hept in 1.6 ppm (1H alph -CH), doublet signal in 1.4 (3H, CH_3 alph) and doublet signal in 0.7-0.9 (6H, CH_3 alph).

Fig. 12: ^1H NMR spectrum of Compound 9

4. Antibacterial activity

Biologically active aromatic compounds (BACs) are a significant class of pharmacological medicines used in numerous medical purposes. Examples of aromatic compounds include anthracycline antibiotics (e.g., daunomycin, doxorubicin, topotecan, mitoxantrone) that treat solid tumors and leukemia, quinolone antibiotics (e.g., norfloxacin, oxacin) with broad antibacterial activity, aromatic vitamins (e.g., riboflavin, nicotinamide) used as antioxidants in chemotherapy, methylxanthines found in high concentrations in food, and many others.[20] Ibuprofen belongs to a group of medications called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs),

which work to inhibit the production of prostaglandins, which are substances that the body releases in response to illness or injury. Ibuprofen derivatives work to inhibit prostaglandins by inhibiting the enzymes responsible for their production, which are cyclooxygenases, which cause inflammation and pain in the body.

The new compounds were tested for their in vitro antibacterial activity against the Gram-positive *Staphylococcus aureus* and the Gram-negative *Pseudomonas aeruginosa* bacteria using the diffusion plate technique. Figures 13–15 and Table 5 display the results.

Table 5: data of the antibacterial testing

Compound No	Concentration (ml/ mg)	<i>Staphylococcus</i>	<i>Pseudomonas</i>
4	0.0001	++	+
	0.001	+	++
	0.01	++	+
5	0.0001	+	++
	0.001	+	+
	0.01	++	+
6	0.0001	++	+
	0.001	+	++
	0.01	+	++

+: inhibition with diameter 5-10, ++: inhibition with diameter 15-20.

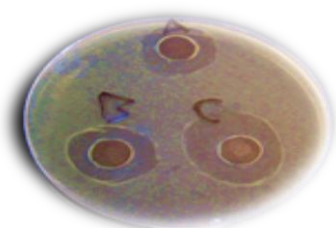


Fig. 13: Inhibition of compound 4

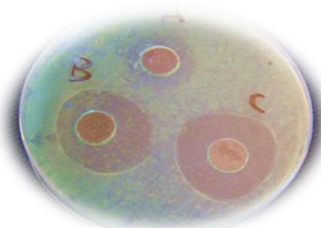


Fig. 14: Inhibition of compound 5

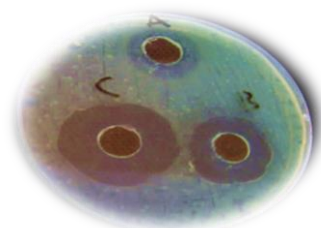


Fig. 15: Inhibition of compound 6

<https://doi.org/10.25130/tjps.v29i3.1602>

5. Conclusion

Because of its excellent health characteristics, ibuprofen, a propanoic acid NSAID with anti-inflammatory, analgesic, and antipyretic properties, is widely available over-the-counter for the treatment of self-limiting illnesses. Due to its physical features, it can be successfully synthesized into a variety of dosage forms, although consideration must be given to its undesirable taste, low solubility in acidic environments, and poor compaction capabilities. All the synthesized compounds had their chemical

structures confirmed by infrared spectroscopy as well as nuclear magnetic resonance spectroscopy. The biological activity of all of them was now conducted. Among those compounds, (4-6) compounds showed positive and effective results against the bacteria studied. In this research, we found that the compounds that showed Positive activity against bacteria were related to the different active groups of the compounds above, which are less restricted by stereo effect compared to compounds (7-9).

References

- [1] McNeely, W., & Goa, K. L. (1999). Diclofenac-potassium in migraine: a review. *Drugs*, 57, 991-1003.
- [2] Andini, S., Bolognese, A., Formisano, D., Manfra, M., Montagnaro, F., & Santoro, L. (2012). Mechanochemistry of ibuprofen pharmaceutical. *Chemosphere*, 88(5), 548-553.
- [3] Gonzalez-Rey, M., & Bebianno, M. J. (2011). Non-steroidal anti-inflammatory drug (NSAID) ibuprofen distresses antioxidant defense system in mussel *Mytilus galloprovincialis* gills. *Aquatic toxicology*, 105(3-4), 264-269.
- [4] Rao, P., & Knaus, E. E. (2008). Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. *Journal of pharmacy & pharmaceutical sciences*, 11(2), 81s-110s.
- [5] Janz, J. M., & Farrens, D. L. (2003). Assessing structural elements that influence Schiff base stability: mutants E113Q and D190N destabilize rhodopsin through different mechanisms. *Vision research*, 43(28), 2991-3002.
- [6] Chohan, Z. H., Hernandez, M. Z., Sensato, F. R., Moreira, D. R. M., Alves Pereira, V. R., Neves, J. K. D. A. L., ... & Lima Leite, A. C. (2014). Sulfonamide-metal complexes endowed with potent anti-Trypanosoma cruzi activity. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 29(2), 230-236.
- [7] Melnikova, I. (2005). Future of COX2 inhibitors. *Nat Rev Drug Discov*, 4(6), 453-4.
- [8] Jayashankar, B., Rai, K. L., Baskaran, N., & Sathish, H. S. (2009). Synthesis and pharmacological evaluation of 1, 3, 4-oxadiazole bearing bis (heterocycle) derivatives as anti-inflammatory and analgesic agents. *European Journal of Medicinal Chemistry*, 44(10), 3898-3902.
- [9] Manjunatha, K., Poojary, B., Lobo, P. L., Fernandes, J., & Kumari, N. S. (2010). Synthesis and biological evaluation of some 1, 3, 4-oxadiazole derivatives. *European journal of medicinal chemistry*, 45(11), 5225-5233.
- [10] Bunnett, J. F. & Rauhut, M. M. (1958). Org. Synth., 38, 11. DOI: 10.15227/orgsyn.038.0011
- [11] Wang, W., Yang, X., Dai, R., Yan, Z., Wei, J., Dou, X., ... & Jiao, N. (2022). Catalytic Electrophilic Halogenation of Arenes with Electron-Withdrawing Substituents. *Journal of the American Chemical Society*, 144(29), 13415-13425.
- [12] Al-Jubori, H. M. S., & Fandi Al-Mathkuri, T. S. (2022). Synthesis, Characterization, and biological activity of some Heterocyclic compounds that derived from Ibuprofen. *Egyptian Journal of Chemistry*, 65(11), 795-802.
- [13] Kh Ahmad, A., & R Butti, L. (2013). Synthesis of some azetidonone and 1, 3-oxazepine derivatives from thymol. *Journal of Education and Science*, 26(4), 40-46.
- [14] A Kherallah, B. (2014). Synthesis and Identification of some 1, 3-oxazepine derivatives containing p-methoxy phenyl and studying their antibacterial activity. *karbala journal of pharmaceutical sciences*, 5(7), 31-41.
- [15] Jirjees, I. Design and characterization of oxazepine new derivatives. *International Journal of Health Sciences*, (II), 7380-7387.
- [16] Allamy, A. K. N., & Mejbil, S. A. (2022). Preparation, characterization and biological activity of some new seven-membered heterocyclic compounds. *World Journal of Advanced Research and Reviews*, 15(1), 662-678.
- [17] Grayer, R. J., & Harborne, J. B. (1994). A survey of antifungal compounds from higher plants, 1982-1993. *Phytochemistry*, 37(1), 19-42.
- [18] Brooks, G. F., Carroll, K. C., Butel, J. S., Morse, S. A., & Mietzner, T. A. (2014). Microbiologia Médica de Jawetz, Melnick & Adelberg-26 (2 edición). *AMGH Editora*.
- [19] Banoon, S., Ali, Z., & Salih, T. (2020). Antibiotic resistance profile of local thermophilic *Bacillus licheniformis* isolated from Maysan province soil. *Comunicata Scientiae*, 11, e3291-e3291.
- [20] Evstigneev, M. P. (2013). Physicochemical mechanisms of synergistic biological action of combinations of aromatic heterocyclic compounds. *Organic Chemistry International*, 2013.