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# Preparation and biological study of new (Tetrazole, β-Lactam, Thiazolidinedione, Oxazepine, and Imidazole) derive from 2-aminobenzimidazol

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***Abstract*---**Through this study, a group of heterocyclic compounds represented by a five-membered ring, seven rings, and a tetracyclic ring, represented by Oxazepine, β-lactam, Thiazolidines, and Imidazolidines, were prepared by depending on the intermediate compound, Schiff bases, that prepared from the reaction of a 2-Aminobenzimidazol with a 4-Bromobenzaldehyde to form (azomethine-CH=N) compound, the above compounds were formed by the pathway of this bond. All new derivatives were created by Fourier Transform Infrared Spectroscopy (FT-IR) Analysis, 1HNMR spectroscopic data, and the13C NMR spectrum. The biological activity of the prepared compounds and their effect on negative and positive bacteria (Escherichia coli) (Staphylococcus aureus) and Efficacy have been studied with Penicillium mushrooms.

***Keywords*---**Tetrazole, β-lactam, thiazolidinedione, oxazepine, imidazoline.

## Introduction

Schiff bases represent compounds consisting of the azomethine group (C = N)(Räisänen 2007). The initial reports of this type of reaction were Hugo Schiff published in 1864. By condensing (Faridbod, et al. 2008). The reaction of an aliphatic or aromatic ketone with an aldehyde or ketone with a primary amine (aromatic or aliphatic) and amino acids (Ogata and Sawaki 1973). These heterocyclic compounds contain one (or more) carbon atoms in the ring, such as


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nitrogen, oxygen, sulfur, mercury, phosphorous, or lead (Joule, et al. 2020). Tetrazole is a five-membered ring in which four carbon atoms have been replaced by a nitrogen atom(Joule and Mills 2012). While (β-lactam) is heterocyclic, consisting of one nitrogen atom and a three-carbon atom(Hwu, et al. 2003). As for the thiazolidine compound, it is a pentagonal compound that contains a sulfur and nitrogen group with its bond to a carbonyl group (C=O), that has been used for many biological activities represented in the treatment of diabetes TZDS as well as anti-inflammatory and antiviral(Kung and Henry 2012; Manjal, et al. 2017). Oxazepine is a seven-membered ring that has been replaced by a carbon atom with oxygen and another atom with nitrogen(Hassan and Hame 2019). It has wide applications, such as pharmaceuticals (Aftan, et al. 2021), and industrial chemicals(Hahn, et al. 2021). Imidazolidines are a heterogeneous compound with the formula $C_3H_8N_2$ effective in treating asthma and hypertension(Wang, et al. 2020).

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## Materials and Methods

### Materials and Measurements

The chemicals all used were (BDH, Alpha Chemika) chemicals. FT-IR spectra were listed on an FTIR-400 (SHIMADZU) spectrophotometer (FTIR) (400-4000 cm-1) in a KBr-made disc, Infrared spectrometer (BRUKER), and TLC was used on glass plates coated with a silica gel compound layer that Iodine vapour was used to detect them. The $^{1}$HNMR and $^{13}$C NMR. Ultra Shield 500 MHz, Bruker, Tehran University, Iran implemented spectrum.

### Preparation of the intermediate compound Schiff bases

(E)-N-(1H-benzo[d]imidazol-2-yl)-1-(4-bromophenyl)methanimine [M .]Schiff base was prepared by dissolving (1.86 g, 0.014 mL) 2-aminobenzimidazole with (2.7 g, 0.014 mL) 4-bromobenzaldehyde aldehyde and used in 30 mL absolute ethanol to which four drops of glacial acetic acid were added. The mixture is reflowed at 78 °C for seven h. The reaction is monitored using mobile phase TLC (benzene-ethanol) in a ratio (4:1) (Bakır and Lawag 2020).

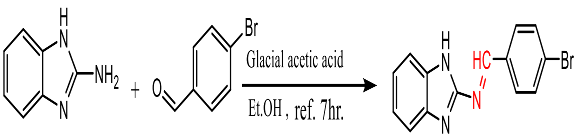


Figure 1. Reaction prepares a compound [M] to form a Schiff base

**Preparation of Oxazepine compounds**

3-(1H-benzo[d]imidazol-2-yl)-2-(4-bromophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione [MI ]
4-(1H-benzo[d]imidazol-2-yl)-3-(4-bromophenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione [MII]
Oxazepine was prepared using (maleic anhydride, phthalic anhydride) (1.6 mmol) with a Schiff derivative (1.6 mmol), and the mixture was heated after dissolving Schiff base and anhydride with dry benzene. The reflux was carried out at a temperature (of 65° C) for (35,38 hr), and TLC monitored the reaction in a ratio of( 4:1) (benzene-methanol)(Sallal and Ghanem 2011).

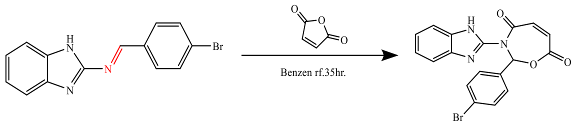


Figure 2. Reaction prepare a compound [MI]

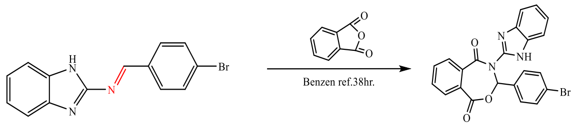


Figure 3. Reaction prepare a compound [MII]

**Preparation of Tetrazole compounds**

2-(5-(4-bromophenyl)-4, 5-dihydro-1H-tetrazole-1-yl)-1H-benzo[d]imidazole [MIII]
The compound was made by dissolving (9 mmol) of the derivative in (30 ml) of 1, 4-dioxane in a circular flask with a magnetic stirrer and a condenser, then mixing (9 mmol) of sodium azide. The mixture was heated for 62 hours at a temperature (of 50-55℃). The reaction was followed up using TLC technology using the mobile phase (benzene: ethanol) at a ratio of (4:1) (Jeminejs, et al. 2021; Shekouhy, et al. 2020).

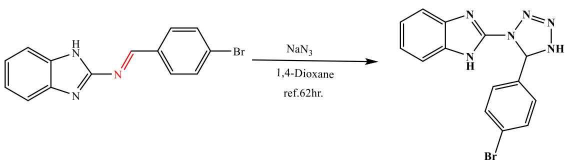


Figure 4. Reaction prepare a compound [MII]

**Preparation of β-lactam compounds**

1-(1H-benzo[d]imidazol-2-yl)-4-(4-bromophenyl)-3-chloroazetidin-2-one [MIV]
The Schiff base derivative (1 mmol) was mixed with (2 mmol) of triethylamine in (25 mL) of 1, 4-dioxane, then added to this mixture and cooled at (10 °C) (0.002 mol) in the form of drops of chloroacetyl Chloride with Stirring continuously for (12 hours), TLC thin layer chromatography was used to monitor the reaction. Using mobile phase (benzene: ethanol) in a ratio (4:1), then filtered, the filtrate was taken, dried, and recrystallized with absolute ethanol (Aftan, et al. 2021).

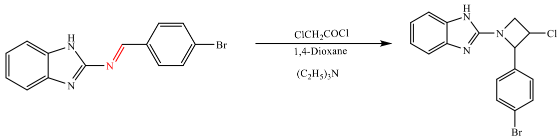


Figure 5. Reaction prepare a compound [MIV]

**Preparation of Thiozolidine compounds**

3-(1H-benzo[d]imidazol-2-yl)-2-(4-bromophenyl)thiazolidin-4-one [MV]
Thiozolidine was prepared by mixing (0.001 mol) of Schiff base derivative with (0.001 mol) thioglycolic acid in (25 mL) 1,4-dioxane and refluxed at (78 ℃) for (28 h). The solution was cooled down and recrystallized with ethanol to obtain On the filtrate, and the reaction was followed by thin-layer chromatography using phase (benzene: methanol) in a ratio (4:1) ( Gupta V, et al . 2013 ).

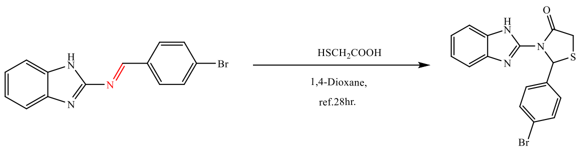


Figure 6. Reaction prepare a compound [MV]

**Preparation of imidazoline compounds**

3-(1H-benzo[d]imidazol-2-yl)-2-(4-bromophenyl)imidazolidin-4-one[MVI]
An amount (0.0012 mmol) of Schiff's compound dissolved in (30 mL) of THF with an amount of glycine (0.0012 mmol) was taken. The mixture was refluxed for 23 hours. The reaction was followed up using TLC technology, and then the precipitate was allowed to dry and then recrystallized with absolute ethanol (Gupta and Pandurangan 2013).

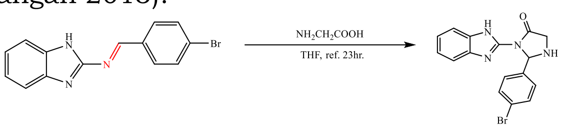


Figure 7. Reaction prepare a compound [MVI]

**Results and Discussions**

The physical properties of the derivatives are listed in Table (1)

Table 1
Physical properties For Chemical Compounds

| Deriv. | Formula | M.wt (g/mol) | Melting point ℃ | Colour | R*f* | Yield % |
|---|---|---|---|---|---|---|
| M | $C_{14}H_{10}BrN_3$ | 300.16 | 122 | Yellow | 0.81 | 75.6 |
| MI | $C_{18}H_{12}BrN_3O_3$ | 398.2 | 186 | Dark Yellow | 0.70 | 79.1 |
| MII | $C_{22}H_{14}BrN_3O_3$ | 448.3 | 197 | White | 0.76 | 83.5 |
| MIII | $C_{14}H_{11}BrN6$ | 343.2 | 232 | Light Yellow | 0.68 | 75.2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| MIV | $C_{16}H_{11}BrClN_3O$ | 376.6 | 125 | Silver | 0.85 | 66.3 |
| MV | $C_{16}H_{12}BrN_3OS$ | 374.3 | 138 | Butter | 0.72 | 62.1 |
| MVI | $C_{16}H_{13}BrN_4O$ | 357.2 | 161 | golden yellow | 0.64 | 72 |

**Analysis of FT-IR Spectra**

The FT-IR spectrum of the compound 2-aminobenzimidazole showed two bands of asymmetric and symmetric vibrations of the (NH2) group at (3386-3293 cm-1) of the substrate as in Figure 1 when this amino compound reacts with an aldehyde to form a Schiff (M) base indicative of this compound Through the spectrum as in Figure 1, where he noticed the disappearance of the vibration of the amine group NH2. The appearance of a bundle at (1689 cm-1) this bundle represents the group (C = N) for a compound (M). As for the rest of the compounds (MI, MII, MIV MV, MVI), their interpretation depended on the appearance of the main beam (C=O) to know the compound in the following range in order(1710, 1691, 1687, 1681, 1721 cm-1). As for the rest of the other spectroscopic data of the compounds in Table (2)(Pavia, et al. 2014).

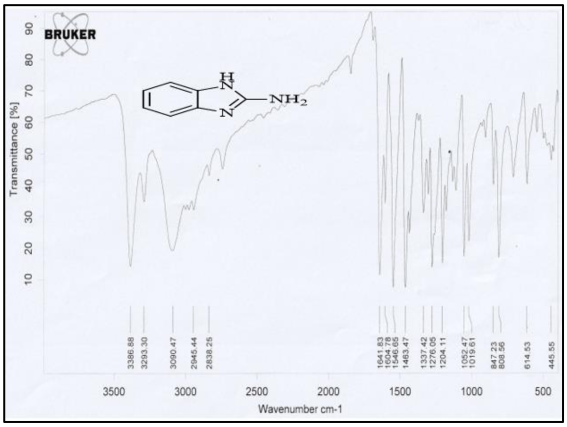


Figure 8. FT-IR spectrum of the compound 2-aminobenzimidazole

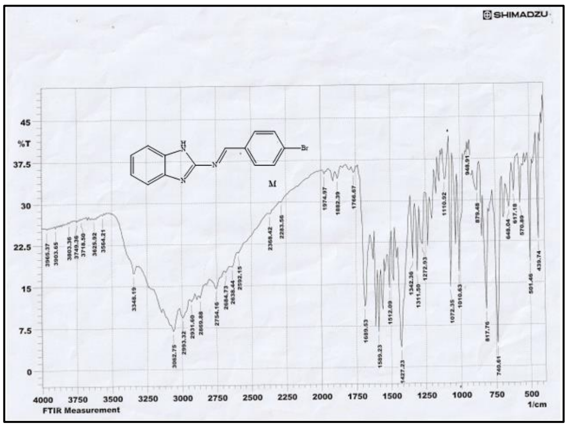


Figure 9. FT-IR spectrum of the compound (M)

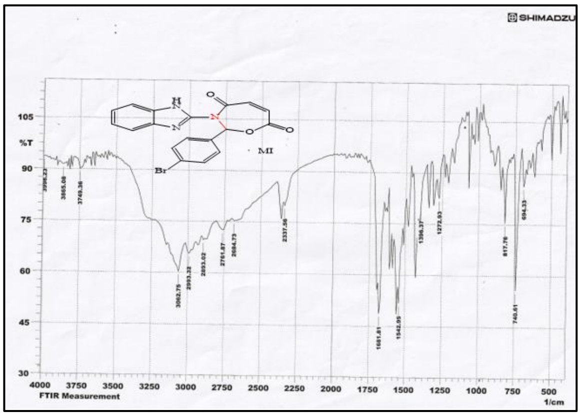


Figure 10. FT-IR spectrum of the compound (MI)

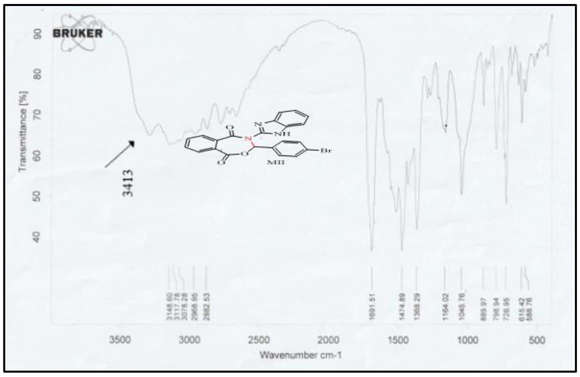


Figure 11. FT-IR spectrum of the compound (MII)

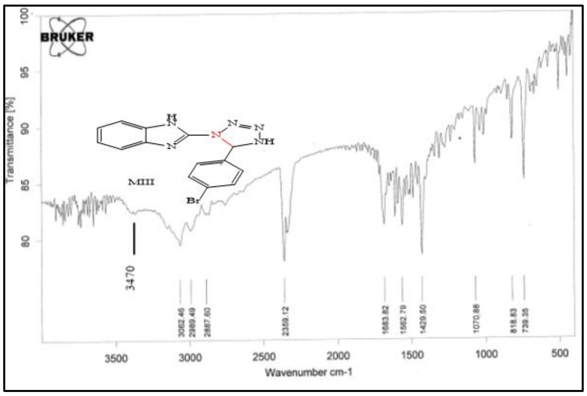


Figure 12. FT-IR spectrum of the compound (MIII)

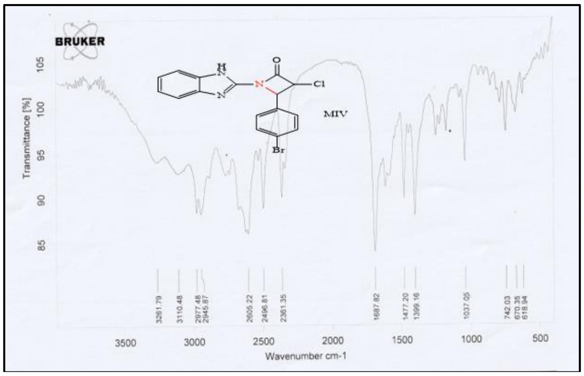


Figure 13. FT-IR spectrum of the compound (MIV)

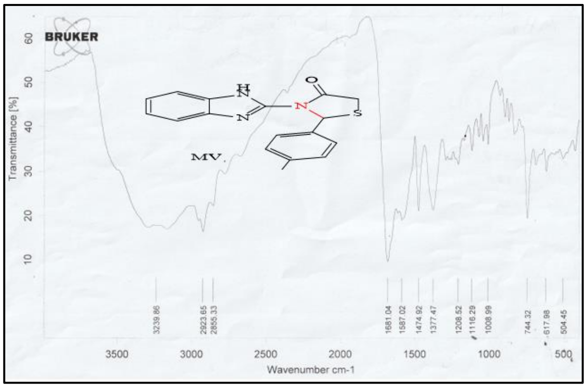


Figure 14. FT-IR spectrum of the compound (V)

Table 2
describe bands in the infrared data (max cm-1) (KBr disc).for prepared derivatives(Pavia DL, et al . 2014)

| Deriv. | υ(N-H) imidazole St. | υ(C-H) arom. St. | υ(C-H) aliph. St. | υ(C=N) St. | υ(C=C) arom. St. | υ(C-N) St. | υ(C-Br) | Other |
|---|---|---|---|---|---|---|---|---|
| M | 3348 | 3062 | 2993, 2931 | 1689 | 1600, 1427 | 1072 | 570 | — |
| MI | 3250 | 3062 | 2993, 2289 | imidazol 1681 | 1600, 1420 | 1272 | 694 | υ (C-O) St. 1100 |
| MII | 3413 | 3070 | 3968,2882 | — | 1593, 1474 | 1368 | 650 | υ (C-O) St. 1045 |
| MIII | 3470 | 3061 | 2989,2887 | imidazol 1683 | 1607, 1429 | 1070 | 620 | υ (N=N) St. 1562 |
| MIV | 3261 | 3092 | 2945 | — | 1610, 1477 | 1037 | 590 | (C-Cl) 742 |
| MV | 3239 | — | 2923,2855 | — | 1587,1474 | 1308 | 617 | — |
| MVI | 3450 | 3062 | 2926,2867 | — | 1610,1461 | 1283 | 622 | υ (N-H) St. 3300 |

**$^{1}$HMNR and $^{13}$C NMR spectrum**

Compound [MI]: through the use (of DMSO-d6) as a solvent. The proton signal (Ar-H) appeared in δ (6.9 - 8.01 ppm), (CH=CH) bond in Oxazepine ring δ (3.3 – 3.5 ppm), (N-H Benzimidazole) δ (9.4 ppm), (1H, (HC-N)) δ 6 ppm. Compound[MII]: Through the use (of DMSO-d6) as a solvent.The proton signal (Ar-H) appeared in δ (7.15 – 8 ppm), (N-H Benzimidazole) δ (8.24 ppm), (1H, (HC-N)) δ 4.24 ppm. The $^{13}$C NMR spectrum was used by (DMSO-d6), showing the signal δ : 78 ppm (C5), 171 ppm (C7), 192 ppm (C10), 139 ppm (C27), 122 ppm (C20), 112-156 ppm(Carom.).

Compound[MIII]: Through the use (of DMSO-d6) as a solvent. The proton signal (Ar-H) appeared in δ (6.8 - 8 ppm), (N-H Benzimidazole) δ (9.4 ppm), (N-H) bond in Tetrazole ring δ (6.1 ppm), (HC-N) in δ (3.5ppm) . The $^{13}$C NMR spectrum was used by (DMSO-d6), showing the signal δ: 66 ppm (C18), 157 ppm (C5), 116-156 ppm(Carom.). Compound[MIV]: Through the use (of DMSO-d6) as a solvent. The proton signal (Ar-H) appeared in δ(6.7 - 8 ppm), (CH-Cl) bond in β-lactam ring (3.36 ppm), (N-H Benzimidazole) δ (10.1 ppm), (1H, (HC-N)) δ 4.7 ppm.

Compound[MV]: Through the use (of DMSO-d6) as a solvent. The proton signal (Ar-H) appeared in δ (6.2 – 6.8 ppm), (S-CH2) bond in thiazolidinedione ring δ (3.56-3.66 ppm), (N-H Benzimidazole) δ (9.9 ppm), (1H, (N-CH)) δ (5.29) ppm. Compound[MVI]: Through the use of Uses(DMSO-d6) as a solvent. The proton signal (Ar-H) appeared in δ (6.2 – 8.26 ppm), (N-H) bond in imidazoline ring (6.4 ppm), (N-H Benzimidazole) δ (9.44 ppm), (1H, (N-HC-N)) δ 4.27 ppm, (CH2) bond in imidazoline ring δ 1.25 ppm. The $^{13}$C NMR spectrum was used by (DMSO-d6), showing the signal δ: 50 ppm (C7), 82 ppm (C4), 171 ppm (C6), 142 ppm (C17), 116-157 ppm(Carom.) (Pavia, et al. 2014).

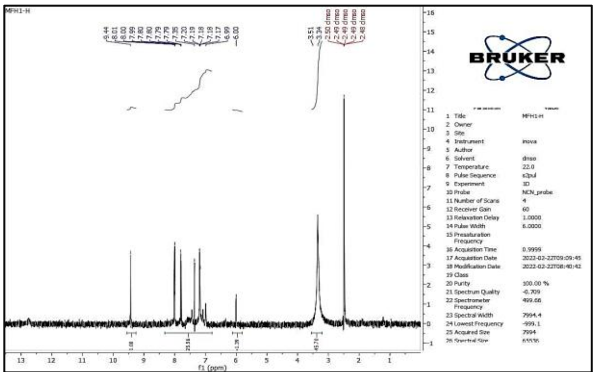

Figure 16. $^{1}$ H-NMR for Compound (MI)

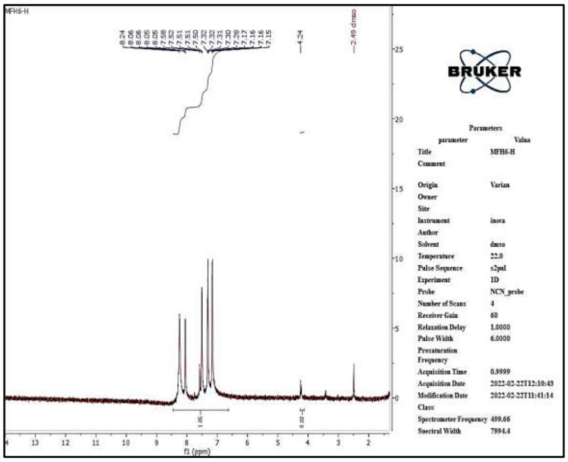


Figure 17. [1] H-NMR for Compound (MII)

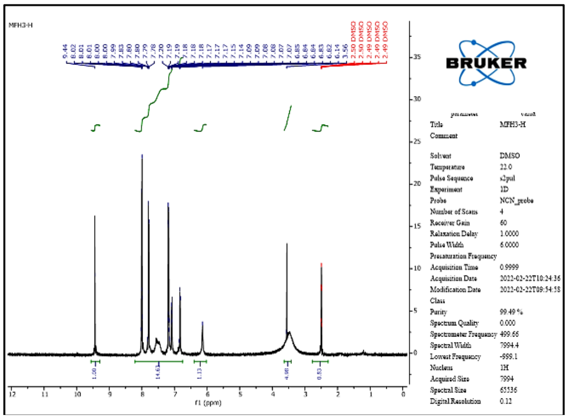


Figure 18. [1] H-NMR for Compound (MIII)

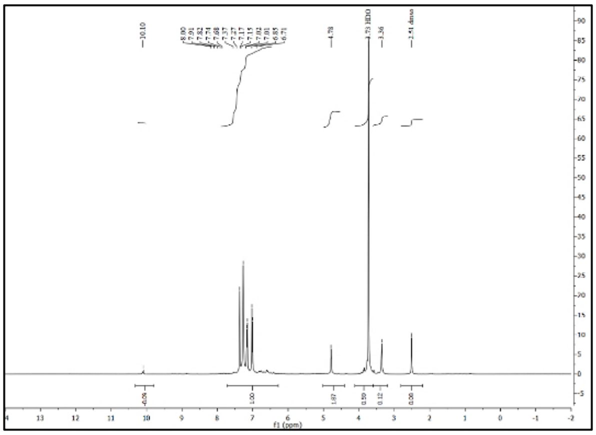


Figure 19. [1] H-NMR for Compound (MIV)

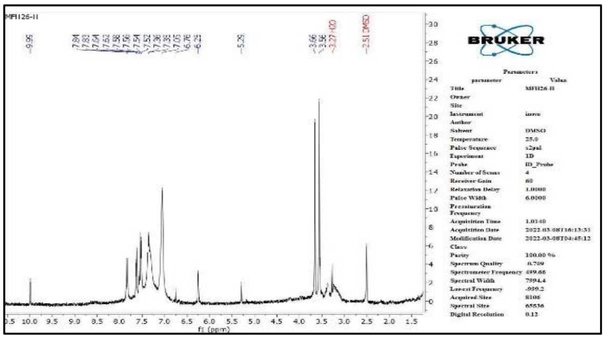


Figure 20. [1] H-NMR Compound (MV)

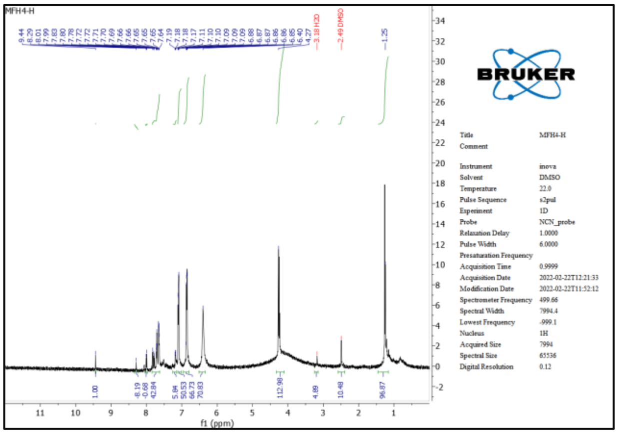


Figure 21. [1] H-NMR for Compound (MVI)

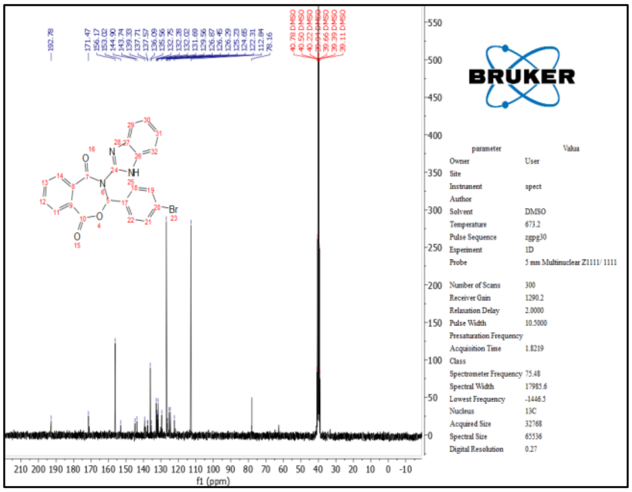


Figure 22. [13]C-NMR for Compound (MII)

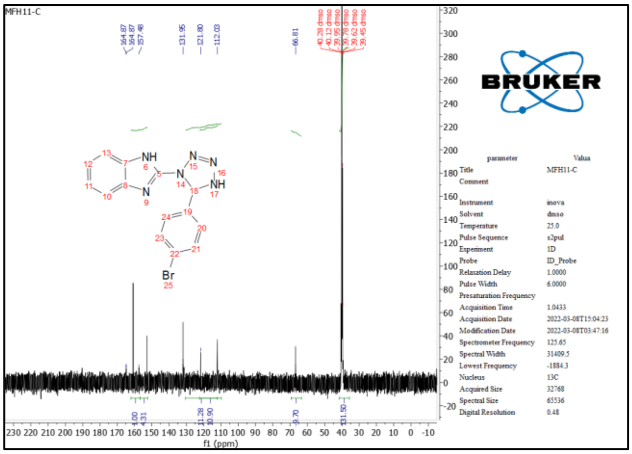

Figure. 23. $^{13}$C-NMR for Compound (MIII)

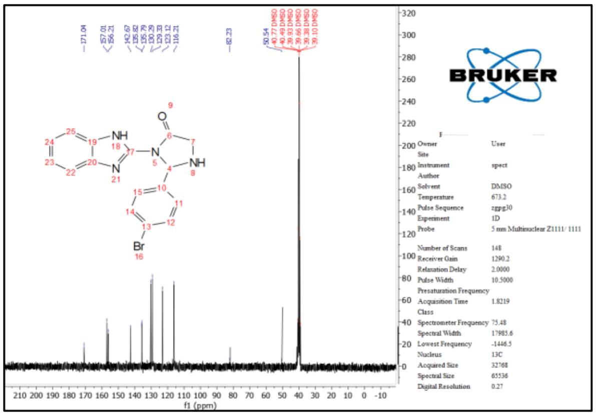

Figure 24. $^{13}$C-NMR for Compound (MVI)

**Biological Activity**

The biological activity in this work was studied against two types of Gram-negative bacteria (Escherichia coli) and Gram-positive bacteria (Staphylococcus aureus) at a concentration (500 ppm) in media prepared for bacteria culture. Used a DMSO solvent with a volume of 5 mL with 0.0025 g from prepared derivatives. This study was carried out in the biology laboratory at the College of the Science / University of Al-Qadisiyah(Yusof, et al. 2019).

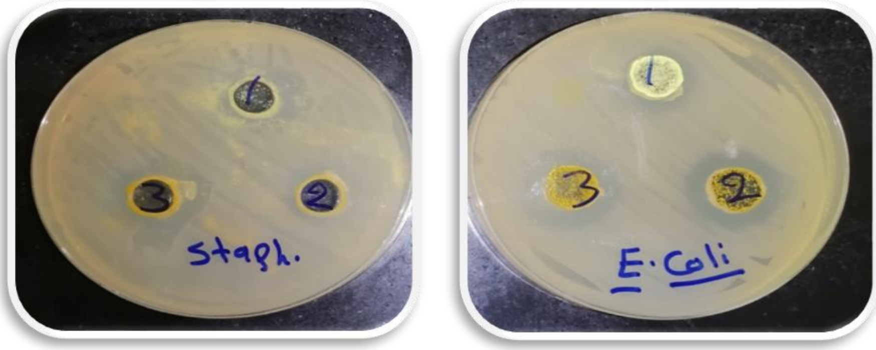


Figure. 25. Shows the effect of the compounds on the(Staphylococcus aureus, Escherichia coli

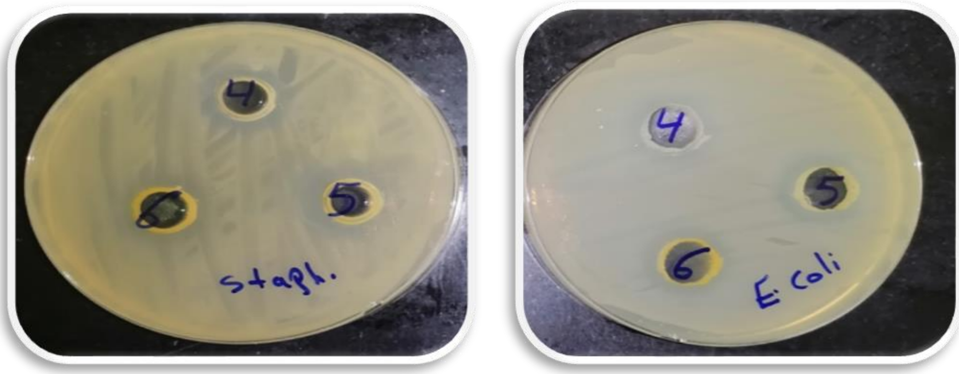


Figure 26. Shows the effect of the compounds on the(Staphylococcus aureus, Escherichia coli

Table 3
The effectiveness of the prepared compounds on two different types of bacteria (*Staphylococcus aureus and Escherichia coli)*

| NO. Sample | Derivative | Antibacterial Activity | | | |
|---|---|---|---|---|---|
| | | Diameter mm | Staphylococcus aureus | Diameter mm | Escherichia Coli |
| 4 | MI | - | - | 8 | + |
| 1 | MII | 10 | + | 20 | ++ |
| 2 | MIII | 15 | + + | 20 | ++ |
| 3 | MIV | 17 | + + | 15 | ++ |
| 5 | MV | 23 | + + + | 18 | ++ |
| 6 | MVI | 25 | + + + | 20 | + + |

"- =Inactive, + = (5-10) mm =slightly active, + + = (11-20) mm middling, +++ = More than 20, active good "

The fungicidal activity of the prepared compounds was studied on two types of fungi that were isolated and identified, and their characteristics were proven. The first type of used species is (Pencellium)(Ghanghas, et al. 2021).

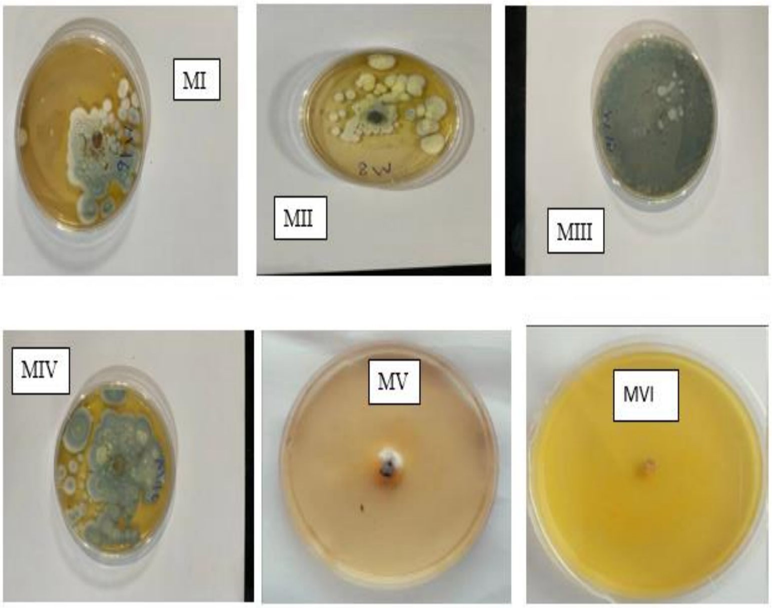


Figure. 27. Shows the biological activity of Penicillium fungus with the prepared compounds

Table 4
Effectiveness of the prepared compounds on *Penicillium* fungi

| Derivative | Penicillium fungi |
|---|---|
| MI | + + |
| MII | + + |
| MIII | - |
| MIV | + |
| MV | + + + |
| MVI | + + + |

**Conclusion**

The study mentioned above shows that heterocyclic compounds were prepared from 2-Aminobenzimidazol by the reflux method successfully, and are represented by Oxazepine, β -lactam thiazolidine, imidazolidine, and tetrazole. The biological activity of the compounds studied with the bacteria used is shown in Table (3). It also showed biological activity against Penicillium fungus, As shown in Table (4).

**Acknowledgments**

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