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Article

Synthesis of Diazepine Derivatives and its Potential Antibacterial Characteristics

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ABSTRACT

Diazepines are a class of nitrogen-containing heterocycles that have a seven-membered ring structure that includes two atoms of nitrogen. Chalcone-based diazepine moieties have attracted significant interest from researchers due to their increased pharmacological, biological, and therapeutic abilities. The present research included the synthesis of three new diazepine derivatives by the reaction between 1,2-diaminobenzene and three distinct chalcone derivatives. The produced compounds underwent characterization using ^{1}HNMR and Fourier-transform infrared spectroscopies. The diazepines that were obtained were subjected to screening for antibacterial activity against *Escherichia coli*, *Pseudomonas*, and *Bacillus subtilis*. The findings revealed that derivative F exhibited the most potent action against *E. coli* and *B. subtilis*, while derivative D showed the greatest activity specifically against *B. subtilis*.

Key words: Heterocyclic, Diazepine, Antibacterial, Chemistry.

1. INTRODUCTION

In the field of therapeutic applications, some scaffolds are more prevalent than others among the wide variety of natural and synthesized compounds [1]. Barresi *et al*. have the first to introduce favored structure, which refers to a singular molecular framework capable of serving as a ligand for a wide range of receptors [2]. It has been shown that the group of compounds made by fusing a benzene ring with a 1,4-diazepine ring has a wide range of pharmacological effects [3]. The first identification of medicinal compounds containing 1,4-diazepine was made in the late 1950s by American researchers employed by Hoffman-La Roche [4]. Their focus was on investigating compounds that exhibited anxiolytic qualities [4]. The 1,3-diazepine scaffold has become widely accepted as a favored molecule in the field of drug development [5,6]. The chemical is present in both natural and synthetic forms and exhibits an array of biological actions, such as anticancer, antibacterial, and antiviral effects. Pentostatin and coformycin are two adenosine deaminase inhibitors that possess anticancer qualities and have received approval from the FDA. In addition, avibactam, a β-lactamase inhibitor, has also been licensed by the FDA [7]. Several additional 1,3-diazepines, including DMP323, an HIV protease inhibitor, and other medical activities [8-10]. Heterocyclic compounds are an important group of organic compounds [11] that have a ring structure with at least two different types of atoms, such as nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), selenium (Se), silicon (Si), bismuth (Bi), and arsenic (As). The inclusion of heteroatoms inside the ring structure imparts several noteworthy physical and chemical features to heterocyclic compounds [12].

In this work, the diazepine derivatives synthesized through chalcone reaction were used as antibacterials against *Escherichia coli*, *Pseudomonas*, and *Bacillus subtilis.*

2. MATERIALS AND METHODS

The materials in the present research procured from BDH and Merck. The Fourier-transform infrared (FT-IR) spectra had been obtained using a Bruker spectroscopic instrument. The ^{1}HNMR spectra have been recorded using a Bruker 400 MHz spectrometer.

2.1. General Prepare of Compounds (A-F)

2.1.1. Prepare of chalcone derivatives (A-C)

0.01 mol of each 2-hydroxy acetophenone was mixed with 0.01 mol of 4-bromobenzaldehyde, 2-hydroxybenzaldehyde, and 2,4-dihydroxybenzaldehyde, respectively, in 30 mL of absolute ethanol and 10% sodium hydroxide. Stirred the mixture for 8 h at 75°C, filtered off of solution [13].

2.1.2. Prepare of (2E)-3-(4-bromophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (A)

Color: Light brown. Yield: 64%. M.P: 203°C. FT-IR (cm^{-1}): 3339 υ(Hydroxyl), 3042 υ(C-H)$_{Aromatic}$, 2976 and 2886 υ(C-H of aliphatic ring), 1651 υ(carbonyl) [14], 1617 υ(C=C alkene), and 1590 υ(C=C of aromatic ring) [15], as shown in Figure 1.

2.1.3. Synthesis of (2E)-3-(2-hydroxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (B)

Color: Dark yellow. Yield: 69%. M.P: 187°C. FT-IR (cm^{-1}): 3496 υ(Hydroxyl), 3056 υ(C-H of aromatic ring), 2952 and 2886 υ(C-H of aliphatic ring), 1660 υ(C=O), 1626 υ(C=C of alkene) [16], and 1594 υ(C=C)$_{Aromatic}$, as shown in Figure 2.

2.1.4. Prepare of (2E)-3-(2,4-dihydroxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (C)

Color: Light brown. Yield: 72%. M.P: 213°C. FT-IR (cm^{-1}): 3378 υ(Hydroxyl), 3011 υ(C-H)$_{Aromatic}$, 2819 υ(C-H)$_{Aliphatic}$, 1661 υ(C=O), 1628 υ(C=C)$_{Alkene}$, and 1571 υ(C=C)$_{Aromatic}$, as shown in Figure 3.

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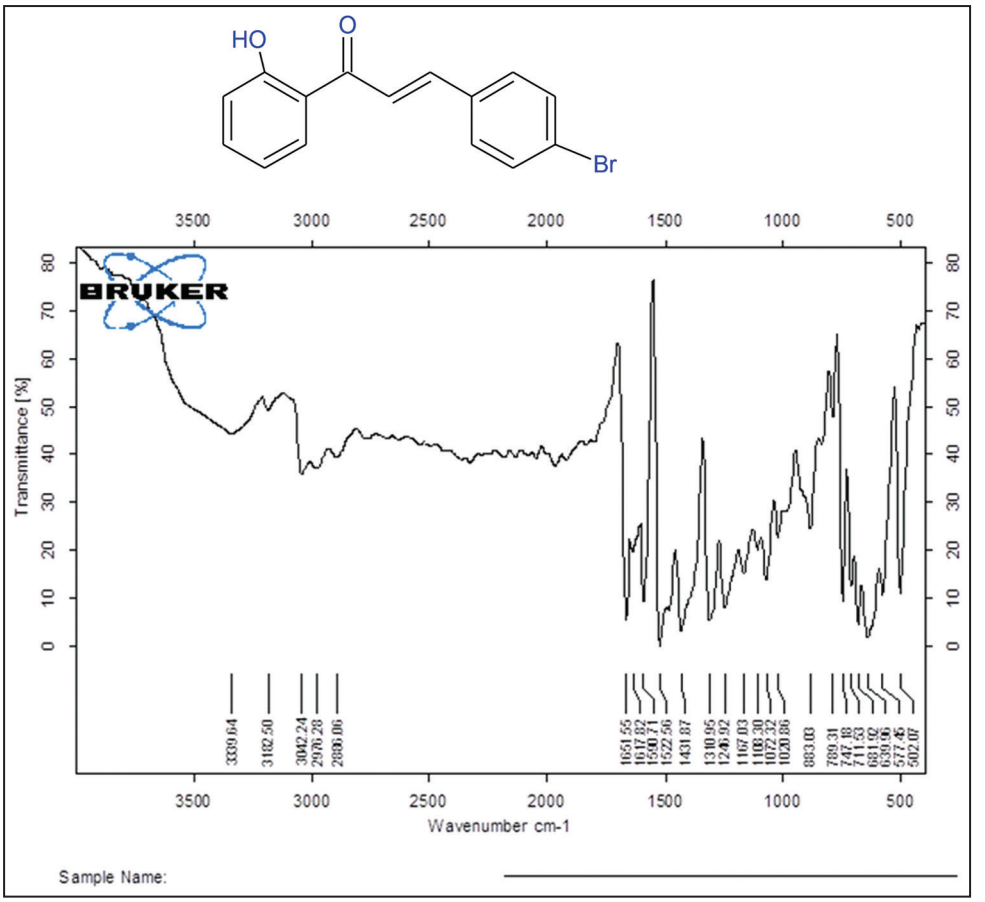

Figure 1: Fourier-transform infrared spectra of derivative A.

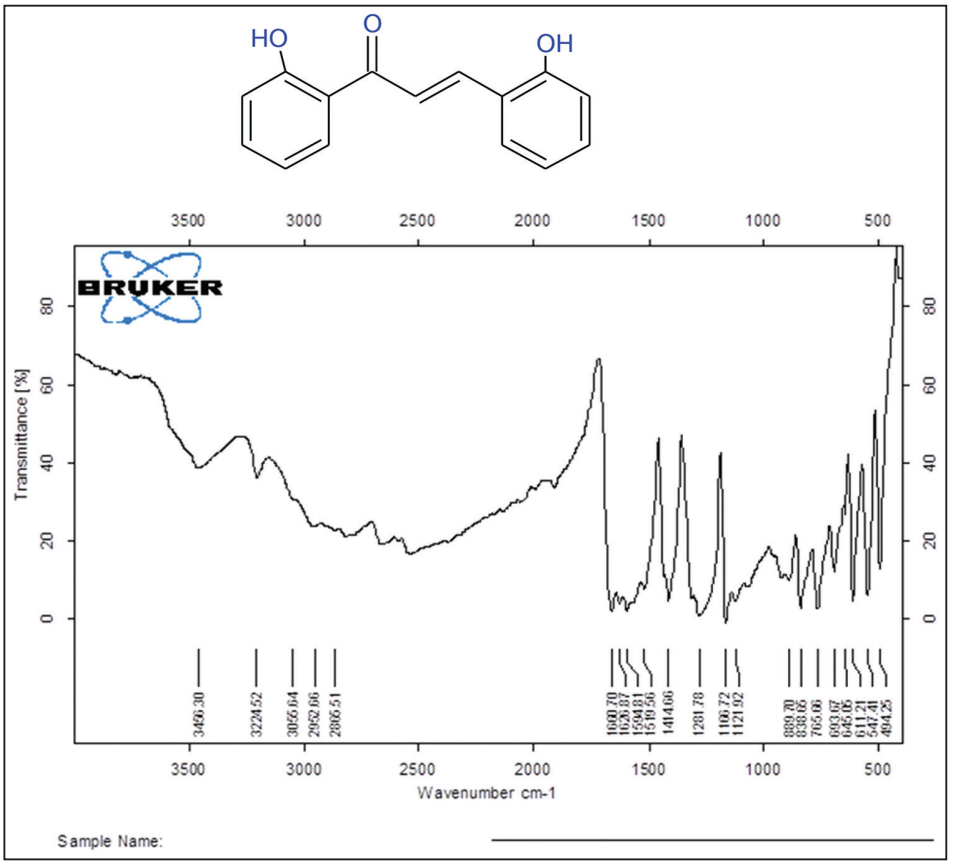

Figure 2: Fourier-transform infrared spectra of derivative B.

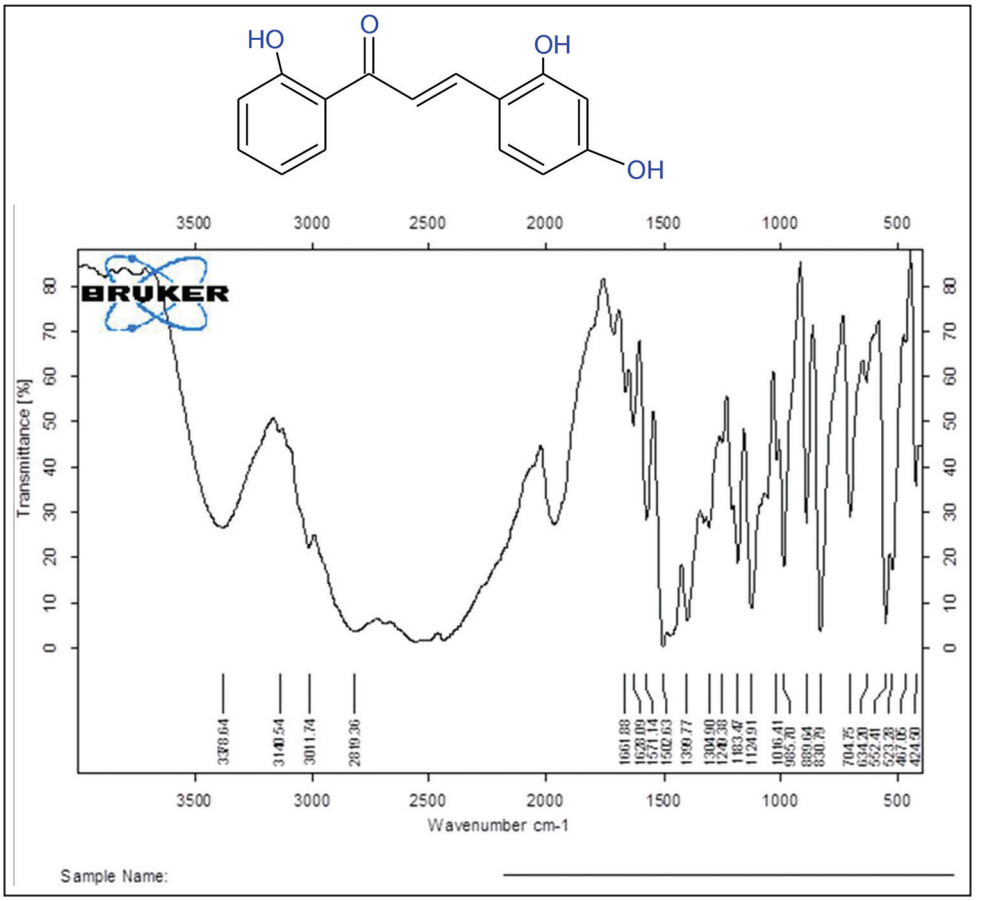

Figure 3: Fourier-transform infrared spectra of derivative C.

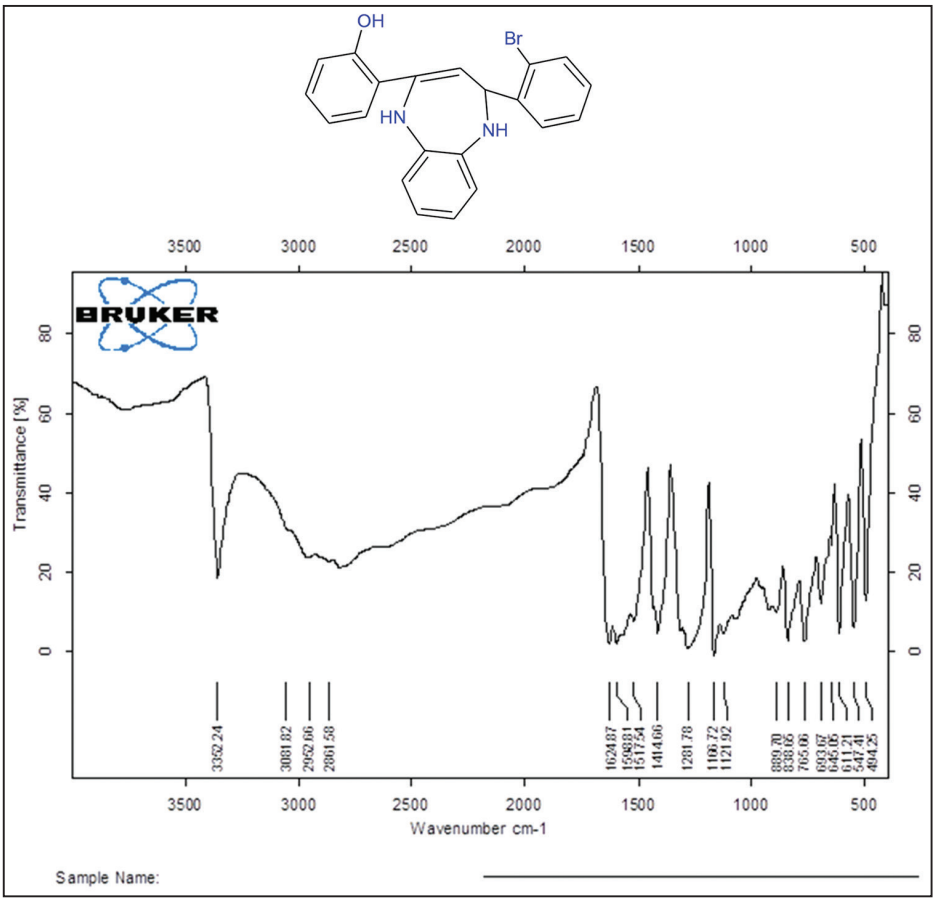

Figure 4: Fourier-transform infrared spectra of diazepine D.

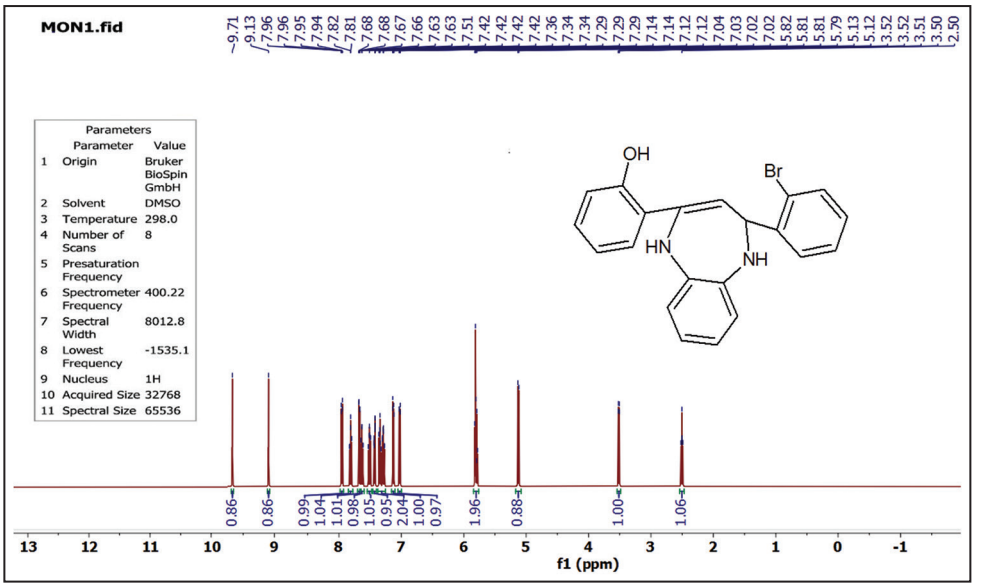

Figure 5: [1]HNMR of diazepine D.

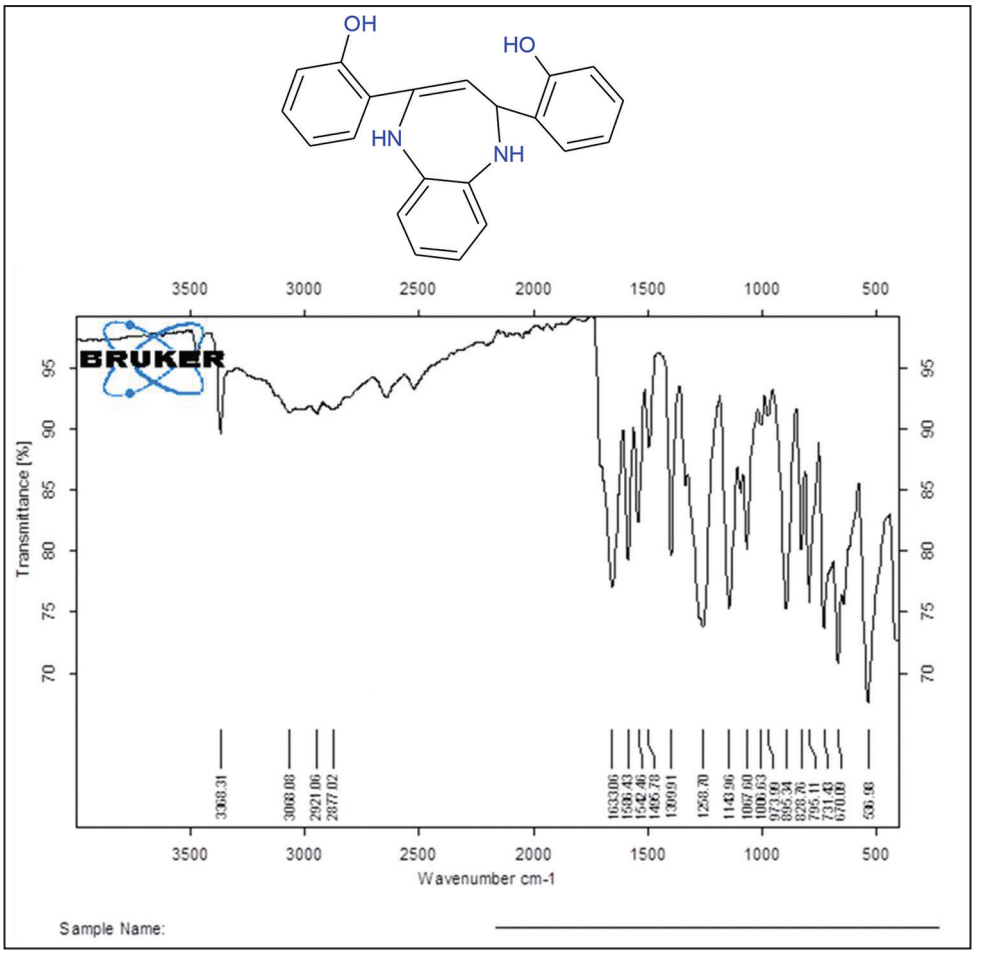

Figure 6: Fourier-transform infrared spectra diazepine E.

2.2. Diazepine Derivatives Preparation (D-F)

As part of the experiment, 0.01 moles of the newly made chalcone derivative (A-C) were mixed with 0.01 moles of O-phenylenediamine. Following that, a solution of NaOH dissolved in absolute ethanol (40 mL, 10%) was introduced to the mixture. After that, the solution underwent reflux for a duration of 6 h. Following this, the resulting mixture from the reaction was introduced into a volume of cold water measuring 300 mL. While being subjected to stirring for a duration of 1 h. Subsequently, the solution was refrigerated for 24 h. Following this, the resulting solid precipitate was subjected to filtration, washing, and subsequent recrystallization using ethanol as the solvent [17] [Figures 4-9].

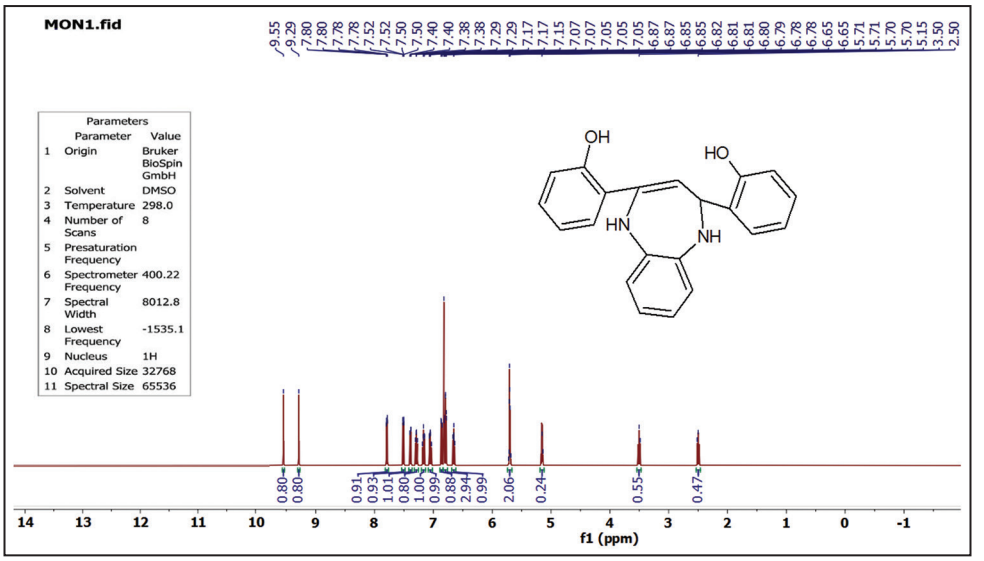

Figure 7: [1]HNMR of diazepine E.

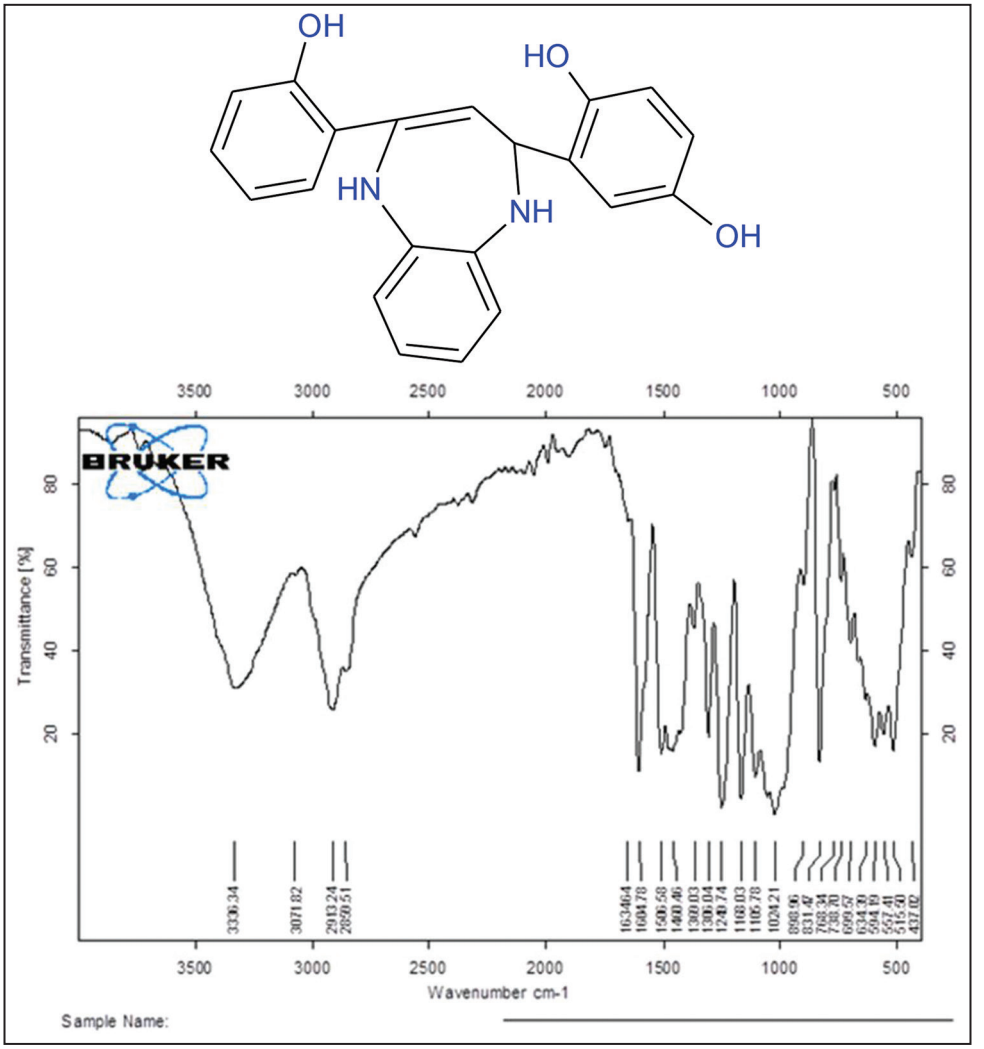

Figure 8: Fourier-transform infrared spectra of diazepine F.

2.2.1. Synthesis of 2-[4-(2-bromophenyl)-4,5-dihydro-1H-1,5-benzodiazepin-2-yl]phenol (D)

Color: Red. Melting point: 171°C, Yield: 74%. FT-IR (cm^{-1}): 3352 υ(primary amine), 3081 $\upsilon(C\text{-}H)_{Aromatic}$, 2952 and 2861 υ(C-H of aliphatic) [18], 1624 υ(C=C), 1598 $\upsilon(C{=}C)_{Aromatic}$. ^1H NMR (Solvent: DMSO-d_6, ppm): 9.13 (2H, s, amino group), 9.71 (1H, s, hydroxyl), 7.02–7.96 (12H, m, aromatic ring), and 5.81 (1H, d, C^{β} of unsaturated) [19].

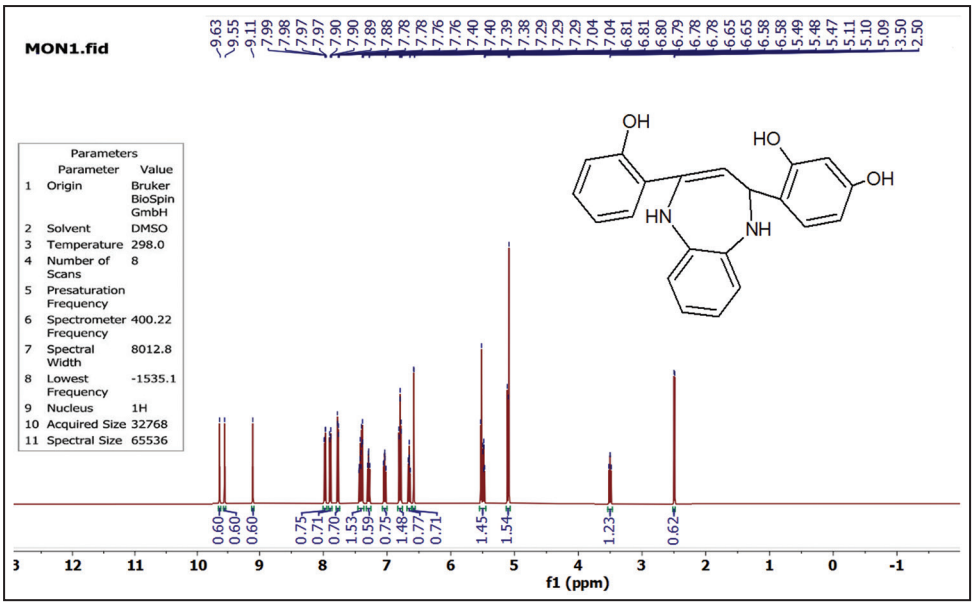

Figure 9: [1]HNMR of diazepine F.

Table 1: Antibacterial activity of the compounds produced, namely, compounds D-F, were evaluated.

Bacteria	Inhibition zone (mm)		
	D	E	F
Escherichia coli	13	11	17
Pseudomonas	15	13	14
Bacillus subtilis	10	13	15

2.2.2. Prepare of 2,2'-(2,5-dihydro-1H-1,5-benzodiazepine-2,4-diyl)diphenol (E)

Color: Dark-Reddish. Melting point: 143°C, Yield: 69%. FT-IR (cm^{-1}): 3368 υ(primary amine), 3068 υ(C-H of Aromatic) [20], 2921 and 2877 υ(C-H of aliphatic) 1633 υ(C=C), 1586 υ(C=C of aromatic). [1]HNMR (Solvent: DMSO-d_6, ppm): 9.29 (2H, s, amino), 9.55 (1H, s, hydroxy), 6.65–7.80 (Aromatic ring as multiplet, 12H) [21], and 5.71 (Carbon of β unsaturated).

2.2.3. Prepare of 2-[4-(2-hydroxyphenyl)-2,5-dihydro-1H-1,5-benzodiazepin-2-yl]benzene-1,4-diol (F)

Color: Dark yellow. Melting point: 187°C, Yield: 68%. FT-IR (cm^{-1}): 3352 υ(primary amine), 3081 υ(C-H of Aromatic), 2962 and 2861 υ(C-H of aliphatic), 1624 υ(C=C), 1598 υ(C=C of Aromatic). [1]H NMR (DMSO-d_6, ppm): 9.11 (2H, s, amino), 9.63 (1H, s, hydroxyl), and 6.58-7.99 (Aromatic ring as multiplet, 12H), 5.49 (Carbon of β unsaturated).

2.3. Antibacterial Activity

The synthesized compounds, at a concentration of 50 mg/mL, were exposed to testing against three microorganisms: *E. coli*, *Pseudomonas*, and *B. subtilis*. This testing was conducted using the inhibition zone process [22]. The results are shown in Table 1.

3. CONCLUSION

In the first step, a series of new diazepine derivatives (D-F) were made and then characterized using two spectroscopic methods: FT-IR spectroscopy (FT-IR) and proton nuclear magnetic resonance spectroscopy ([1]H-NMR). Furthermore, a study was conducted on the synthesized compounds to assess their efficacy as antibacterial agents against various bacterial strains, yielding promising results. Moreover, compound F exhibited superior antibacterial efficacy compared to the other produced derivatives due to the presence of two hydroxyl groups, which serve as active functional groups.

4. REFERENCES

1. A. Kadhim, A. A. Al-Amiery, R. Alazawi, M. K. Al-Ghezi, R. H. Abass, (2021) Corrosion inhibitors. A review, ***International Journal of Corrosion and Scale Inhibition***, **10(1)**: 54-67.
2. E. Barresi, M. Robello, E. Baglini, V. Poggetti, M. Viviano, S. Salerno, F. Da Settimo, S. Taliani, (2023) Indol-3-ylglyoxylamide as privileged scaffold in medicinal chemistry, ***Pharmaceuticals (Basel)***, **16(7)**: 997.
3. Y. Malki, J. Martinez, N. Masurier, (2021) 1,3-Diazepine: A privileged scaffold in medicinal chemistry, ***Medicinal Research Reviews***, **41(4)**: 2247-2315.
4. A. Di Capua, A. Reale, M. Paolino, G. Chemi, S. Brogi, A. Cappelli, G. Giorgi, F. Grande, L. Di Cesare Mannelli, C. Ghelardini, R. Matucci, A. Garofalo, M. Anzini, (2020) Design, synthesis and biological evaluation of 7-substituted 4-phenyl-6H-imidazo[1,5-a]thieno[3,2-f] [1,4]diazepines as safe anxiolytic agents, ***European Journal of Medicinal Chemistry***, **200:** 112405.
5. B. Li, C. Chen, J. Jia, L. He, (2022) Research progress in antineoplastic, antibacterial, and anti-inflammatory activities of seven-membered heterocyclic derivatives, ***Current Medicinal Chemistry***, **29(30)**: 5076-5096.
6. G. C. Brahmbhatt, T. R. Sutariya, H. D. Atara, N. J. Parmar, V. K. Gupta, I. Lagunes, J. M. Padrón, P. R. Murumkar, M. R. Yadav, (2020) New pyrazolyl-dibenzo[b,e][1,4]diazepinones: Room temperature one-pot synthesis and biological evaluation, ***Molecular Diversity***, **24:** 355-377.
7. A. Belal, N. M. Abdel Gawad, A. B. Mehany, M. A. Abourehab, H. Elkady, A. A. Al-Karmalawy, A. S. Ismael, (2022) Design, synthesis and molecular docking of new fused 1 H-pyrroles, pyrrolo[3,2-d]pyrimidines and pyrrolo[3,2-e][1, 4]diazepine derivatives as potent EGFR/CDK2 inhibitors, ***Journal of Enzyme Inhibition and Medicinal Chemistry***, **37(1)**: 1884-1902.

8. A. Ghosh, S. K. Chattopadhyay, (2020) Microwave-mediated synthesis of medium ring-sized heterocyclic compounds, ***Current Microwave Chemistry***, **7(2)**: 123-144.
9. Z. Xu, D. Xu, W. Zhou, X. Zhang, (2022) Therapeutic potential of naturally occurring benzofuran derivatives and hybrids of benzofurans with other pharmacophores as antibacterial agents, ***Current Topics in Medicinal Chemistry***, **22(1)**: 64-82.
10. R. Bardovskyi, O. Grytsai, C. Ronco, R. Benhida, (2020) Synthesis and characterization of new heterocycles related to aryl[e][1,3] diazepinediones. Rearrangement to 2,4-diamino-1,3,5-triazine derivatives, ***New Journal of Chemistry***, **44(20)**: 8171-8175.
11. A. Al-Mulla, (2017) A review: Biological importance of heterocyclic compounds, ***Der Pharma Chemica***, **9(13)**: 141-147.
12. Z. Hosseinzadeh, A. Ramazani, N. Razzaghi-Asl, (2018) Anti-cancer nitrogen-containing heterocyclic compounds, ***Current Organic Chemistry***, **22(23)**: 2256-2279.
13. S. Farooq, Z. Ngaini, (2019) Recent synthetic methodologies for chalcone synthesis (2013-2018), ***Current Organocatalysis***, **6(3)**: 184-192.
14. J. C. Jung, Y. Lee, D. Min, M. Jung, S. Oh, (2017) Practical synthesis of chalcone derivatives and their biological activities, **Molecules**, **22(11)**: 1872.
15. S. Verma, A. K. Srivastava, O. Pandey, (2018) A review on chalcones synthesis and their biological activity, ***PharmaTutor***, **6(2)**: 22-39.
16. V. Ţucureanu, A. Matei, A. M. Avram, (2016) FTIR spectroscopy for carbon family study, ***Critical Reviews in Analytical Chemistry***, **46(6)**: 502-520.
17. A. S. Bhathiwal, A. Bendi, A. Tiwari, (2022) A study on synthesis of benzodiazepine scaffolds using biologically active chalcones as precursors, ***Journal of Molecular Structure***, **1258:** 132649.
18. M.A. Mohamed, J. Jaafar, A. F. Ismail, M. H. Othman, M.A. Rahman, (2017) ***Fourier Transform Infrared (FTIR) Spectroscopy, in Membrane Characterization***, Amsterdam: Elsevier, p3-29.
19. B. Insuasty, J. Ramírez, D. Becerra, C. Echeverry, J. Quiroga, R. Abonia, S. M. Robledo, I. D. Vélez, Y. Upegui, J. A. Muñoz, V. Ospina, M. Nogueras, J. Cobo, (2015) An efficient synthesis of new caffeine-based chalcones, pyrazolines and pyrazolo[3,4-b] [1,4]diazepines as potential antimalarial, antitrypanosomal and antileishmanial agents, ***European Journal of Medicinal Chemistry***, **93:** 401-413.
20. B. Shankar, P. Jalapathi, M. Ramesh, A. K. Kumar, M. Ragavender, G. Bharath, (2016) Synthesis, antimicrobial evaluation, and docking studies of some novel benzofuran based analogues of chalcone and 1,4-benzodiazepine, ***Russian Journal of General Chemistry***, **86:** 1711-1721.
21. N. G. Fahad, N. H. Imran, H. A. Kyhoiesh, M. K. Al-Hussainawy, (2023) Synthesis, anticancer for prostate cancer cells and antibacterial activity of new diazepine derivatives, ***Results in Chemistry***, **6:** 101049.
22. M. A. Rashid, A. Ashraf, S. S. Rehman, S. A. Shahid, A. Mahmood, M. Faruq, (2019) 1,4-diazepines: A review on synthesis, reactions and biological significance, ***Current Organic Synthesis***, **16(5)**: 709-729.