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Synthesis, Characterization, Molecular Docking Studies and Biological Evaluation of Oxazolidine-5-one Schiff Base Analogs

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ABSTRACT

In vitro tests were conducted to determine the likely antibacterial activities of a novel class of 2-aminobenzothiazole compounds that had been substituted. Chloroacetic acid and prepared Schiff bases were combined to create new oxazolidin-5-one compounds with dioxane acting as a solvent. The reaction was monitored and described using the melting point, yield, and color during the sublimation method of preparation. Proton and carbon nuclear magnetic resonance (^{1}H&^{13}C-NMR), thin-layer chromatography (TLC), infrared spectroscopy (FT-IR), and quantitative elemental analysis (C.H.N.) were used to determine whether the reaction was completed. Among all the compounds created, W1 was more effective than ampicillin at 0.01 µg/ml against both Gram-positive (Staph. epidermidis) and Gram-negative (K. pneumoniae) bacteria. The compounds W4 and W7 were the most effective against Staphylococcus epidermidis. The produced compounds showed moderate to high antibacterial activity, according to the results. Compound W1, according to molecular docking studies and in vitro antibacterial activity, is a promising drug for the treatment of Staph. epidermidis. W4 and W7 compounds demonstrated antimicrobial properties. According to molecular docking studies, oxazolidin-5-one analogs bonded well to putative receptor binding sites.

Key words: Schiff base, 2-Amino benzothiazoles, oxazolidine-5-one; biological activity;, Molecular Docking

1-Introduction

2-aminobenzothiazole contains one sulfur atom and two nitrogen atoms, and it is a significant compound in medicinal chemistry, associated with various medical activities, including antitumor, antibacterial[1] anti-impaction, and anti-inflammatory effects. Recently, an extraordinary collection of powerful and low-toxicity 2-aminobenzothiazole compounds has been detected as heterocyclic compounds of new cancers.so that a major sign of the search for physical chemistry and medicine is [2] due to different limits for physical function. 2-Synthesis and study of medical properties of amino benzothiazole derivatives have increased

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significantly[3]. Many review items are also dedicated to the subject [4]. Molecules with a leg zothiazol silence have a clear range of biological activity, such as antiviral [2-5], antimicrobial [5], anti-inflammatory [6], acidibitic [7] antioxidant [8], antidant [9], anti-alzheimer's disease[10], antiepileptic[11] hypertension and angina.[12], anticon [13], immunomodulatory effects. In BTA derivatives, there are anthelmintic [14], antimalarial [15], antifungal [16], pesticide [17], and herbicidal properties. Azomythine Group (CH=N[20]). Schiff's bases are extensively studied compounds owing to their chemical efficacy, physical characteristics, and many uses in sectors such as medicinal chemistry and the pharmaceutical industry. The azomethine group is what gives Schiff's bases their biological activity[18]. Antifungal[19], renders them useful as antivirals for numerous diseases[20], including antibacterial applications. antimicrobial [21] anticonvulsant [22] antitumor [23] anti-leishmanial [24] antiviral [25] antioxidant [27] anticancer [28] anti-inflammatory agents [29] COX inhibitory activity, MAO inhibitory activity [30] analgesic [31] antileishmanial [32]. The creation and biological properties of oxazolidin-5-ones are important in medicinal chemistry and chemical biology [33]. Oxazolidin-5-one derivatives are important types of chemical compounds with heterocyclic structure. Many aryl-oxazolidinone compounds have diverse biological properties, including hypoglycemic and strong antibiotic effects against various bacteria. However, Fig. 1 shows the general ring structure of oxazolidin-5-one compounds [34]. Many 5-substituted-1,3-oxazolidindione derivatives with different substituents have been generated, and their anti-inflammatory capabilities have been evaluated [35]. To sum up, this work aims to create new five-ring compounds from oxazolidine-5-one by reacting prepared Schiff bases with chloroacetic acid while dioxane is present as a solvent. The biological activity of these compounds against two different kinds of Gram-positive and Gram-negative bacteria will be assessed.

2. Materials and methods

We measured melting points with a Stuart apparatus and an open capillary, and they didn't change. We used a Shimadzu FTIR-8100 spectrophotometer with KBr and ^{1}H NMR discs to take infrared spectra. We used an MHZ spectrometer and DMSO-d6 as the solvent to measure spectra. We employed thin-layer chromatography (TLC) on metal plates coated in silica gel (type 60 F254 Merck, Darmstadt, Germany) to monitor the reaction and ensure the cleanliness of the chemicals.

2.1. Chemicals

The chemicals and liquids came from Fluka and Aldrich, and they were used without being cleaned first. Table 1 displays the chemicals and materials used in this study.

2.2. . Preparation of substituted 2-Amino benzothiazoles (w_1-w_3): Figure 1 depicts the structure of the nucleus that has been substituted. 2-Amino benzothiazoles: As the temperature was kept below 10°C, A solution of 0.1 mole of substituted aniline and 0.4 moles of potassium thiocyanate was added dropwise while stirring 16 g (0.1 mole) of bromine diluted in 50 ml of glacial acetic acid. Following the addition of each bromine solution, the mixture was agitated for ten hours. In warm water, the combined filtered substances dissolve. Using 10% NaOH, the mixed filtrate was neutralized. A filter was used to collect and dry the precipitate. recrystallization with an appropriate solvent [36].

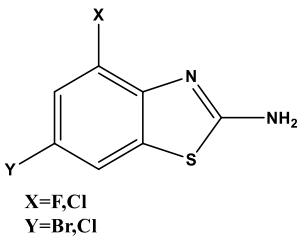


Fig. 1: Nucleus substituted -2-aminobenzothazol

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Table 1: physical properties of compounds (W1-3)

Molecular Formula	colour	Yield (%)	m.p (°C)-	X Y	Compd. No.
$C_7H_4BrFN_2S$	White	76	183-185	4-F 6-Br	W1
$C_7H_4BrClN_2S$	yellow	72	232-235	4-Cl 6-Br	W2
$C_7H_4Cl_2N_2S$	White	83	192-194	4-Cl 6-Cl	W3

2.3. . Preparation of Synthesis of schiff bases (W_{4-6})

Introduce 10 ml of ethanol to 0.001 mol (0.219 g) of modified 2-amino benzothiazole. Subsequently, incorporate 0.001 mol (0.269 g) of one of the 1-(5-fluorothiophen-2-yl)ethan-1-one (W4-6) solutions, which have also been mixed with 10 ml of ethanol. After six hours, strain the mixture and allow it to dry. Table 2 [37] delineates the many qualities of matter.

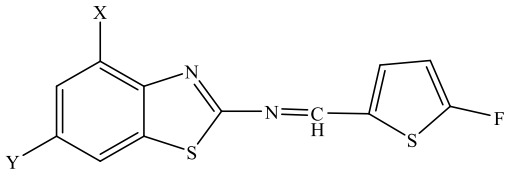


Fig. 2: Nucleus Schiff base

Table 2: Physical characteristics of compounds (W4-6)

Molecular Formula	colour	Yield (%)	m.p (°C)-	X Y	Compd. No.
$C_{12}H_7BrF_2N_2S_2$	Yellow	70	160-162	4-F 6-Br	W4
$C_{12}H_7BrClFN_2S_2$	Yellow	44	148-150	4-Cl 6-Br	W5
$C_{12}H_7Cl_2FN_2S_2$	Brawn	61	170-172	4-Cl 6-Cl	W6

2.4. Preparation of 1,3-Oxazolidine-5-one Derivatives (W7-9)

A total of 0.001 mol of previously prepared Schiff bases and 0.002 mol of chloroacetic acid were combined in a round-bottom flask with dioxane acting as the solvent. After six hours in a water bath, the mixture was recrystallized from ethanol. TLC was used to follow the reaction, as shown in Table 3 [38].

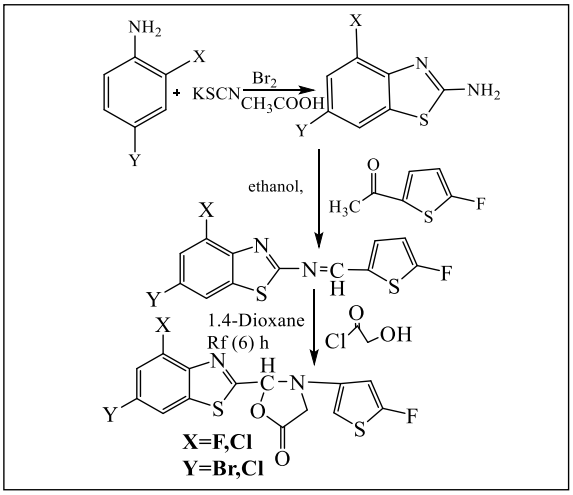


Fig. 3. Route of prepared compounds (W1-9)

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Table 3: Some physical properties of the 1,3-oxazolidine-5-one derivatives (W7-9)

Molecular Formula	colour	Yield (%)	m.p (°C)-	X Y	Compd. No.
$C_{14}H_7BrF_2N_2O_2S_2$	Yellow	70	160-162	4-F 6-Br	W7
$C_{14}H_7BrClFN_2O_2S_2$	Yellow	44	148-150	4-Cl 6-Br	W8
$C_{14}H_7Cl_2FN_2O_2S_2$	Brawn	61	170-172	4-Cl 6-Cl	W9

2.5. Cultivation media

The nutritional broth was made in accordance with the manufacturer's directions and then autoclaved at 121°C for 15 minutes at 15 MPa to kill any bacteria or viruses. Once poured, it was allowed to cool in containers or tubes. The biological activity of medicines and antibiotics was measured in this study using the medium. Inhibition zone diameter measurements are taken using this media.[39]

2.7. Biological activity evaluation

Figure 4 illustrates the journey that the produced compounds (W1–W9) take throughout the body. We tested the effectiveness of the produced compounds against a number of harmful bacteria, such as S. aureus and Proteus species, using the agar well diffusion method [40]. The reference compound used to investigate the possible effects of these compounds was ciprofloxacin. The compounds were evaluated using dimethyl sulfoxide (DMSO) as the solvent and control at various concentrations (0.01, 0.001, and 0.0001 mg/mL) [41]. Utilizing the inhibition zone diameter in millimeters (IZD), we evaluated the antibiotic's effectiveness. We looked at every drug and compared it to the control to find the minimum inhibitory concentration (MIC, g/mL). According to the analysis of the antibacterial screening data, 6-bromo-4-fluoro-2-aminobenzothiazole (W1) [42] has shown a notable level of antibacterial activity. Gram-negative bacteria (K. pneumoniae) were significantly inhibited by compounds W2, W3, W5, W6, W7, and W8 [43]. In contrast to derivatives of ciprofloxacin, compounds W9, W10, and W1 had striking action against all tested pathogens and demonstrated significant antibacterial efficacy against Gram-positive bacteria (Staphylococcus epidermidis). The highest effectiveness of all medications was observed at 12.5 g/mL.

Result & discussion

4.1. Characterization of 6-bromo-4-fluoro 2-amino benzothiazoles (W1) [44].

Spectroscopic techniques like FTIR and 1H-NMR are used to confirm the structure of the produced compounds. To prepare Schiff base, 6-bromo-4-fluoro-2-amino benzothiazoles are needed, as indicated by the compounds' IR spectra (W1). These compounds' infrared spectra revealed a band at (1625 cm^{-1}) for the (C=N) group, at (1446-1581 cm^{-1}) for the (C-C) group, at (1267 cm^{-1}) for the (C-Br) group, a band at (1038 cm^{-1}) for the (C-S-C) group,a band at (3180 cm^{-1}) for the (Ar-H) group, and a band at (3455-3355 cm^{-1}) for the (NH_2) group. IR data was displayed in Figure 5. The H1-NMR spectra of substances (W1) (CDCl3) The H1-NMR is displayed in figure (6). It shows the signal at 2.50 ppm for DMSO, 6.95693 ppm for ArH, and 6.03 ppm for NH_2.. All compounds (W1) have their 13C NMR spectra analyzed (see Experi. Part). The 13C NMR revealed the following resonances: δ = 134 ppm due to carbon thiazole rings (C-A), δ = 116 ppm due to carbon-D, δ = 129 ppm due to carbon-F, and a singlet signal at δ = 39.49-40.49 ppm due to DMSOd6 [45].

Table 4: IR- spectral data of Compounds (**W_{1-3}**)

FTIR cm^{-1} (KBr)					X Y	Compd. No.
Others cm^{-1}	(C=C)	(C=N)	(Ar-H)	C-S-C		
υ(C-F) 1305	1506	1696	3062	620	4-F Br	W1

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υ (C-Br) 1083	1434	1658	3058	712	4-Cl Br	W2
υ (C-Cl) 1100	1444	1624	3023	682	4-Cl Cl	W3

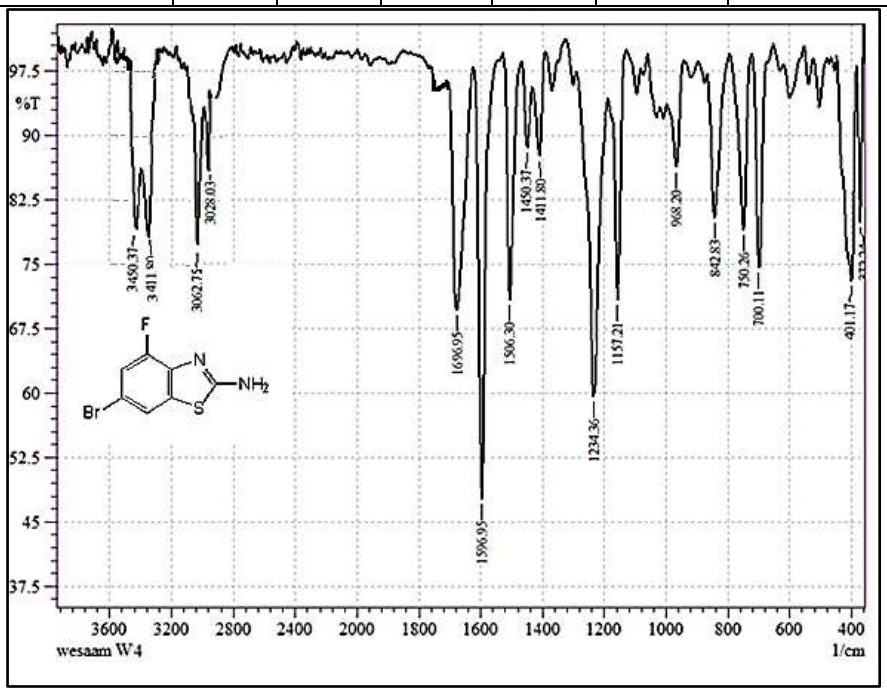


Fig.4. the compound's FT-IR spectra(J1) (W_1)

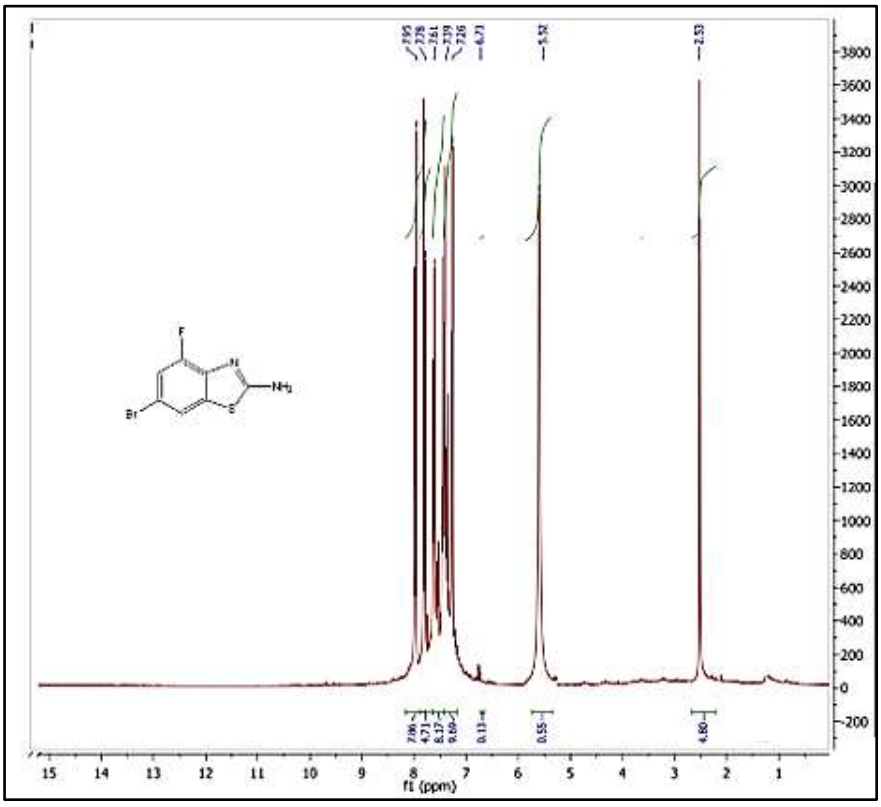


Fig. 5. 1-H NMR spectra of the substance(W_1)

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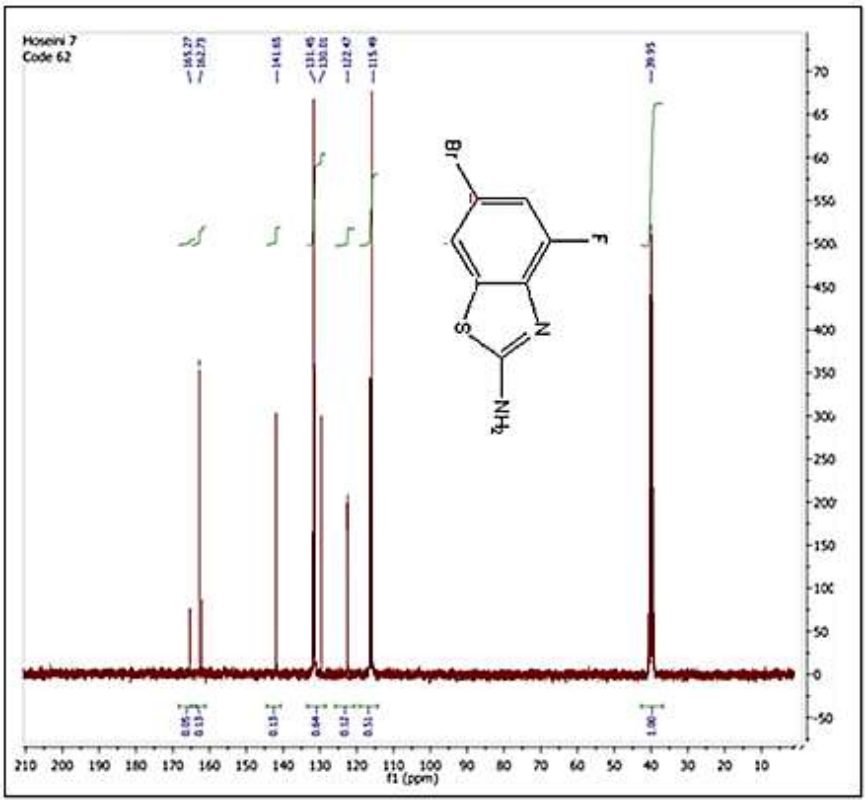


Fig. 6. CNMR spectra of the substance($\mathbf{W_1}$)

4.2. Characterization of Schiff Bases (W4-W6) [46]

Schiff base compounds are produced when 2-amino benzothiazole derivatives interact with 1-(5-fluorothiophen-2-yl)ethan-1-one. The infrared spectrum and resonance spectrum showed peaks at frequencies of 1599-1643 cm^{-1}, which corresponded to imine (C=N) stretching; 1487-1543 cm^{-1}, which corresponded to alkyne (C≡C) stretching; 3097 cm^{-1}, which indicated aromatic C-H stretching (Ar-H); 1033 cm^{-1}, which was related to thioether (C-S-C) stretching; and 813 cm^{-1}, which was related to alkyl chloride (C-Cl) stretching. Protons (F, CH = C) are indicated by a signal at δ = 6.2 ppm in compound W4; H, CH-phenyl are indicated by a signal at 7.4 ppm; phenyl protons (H) are indicated by a signal within the range of δ = 6.7-8 ppm; and CH = C-Cl is indicated by a signal at 7.36 ppm. Carbon (C, CH = CH) is represented by a signal at 115 ppm in the C13-NMR spectrum of chemical W4. This is followed by carbon atoms in benzene rings at δ = 123–130 ppm, carbon in (C = N) at 149 ppm, carbon in (C-F) at 157 ppm, and C2 in benzothiazole at 167 ppm [47].

Table 5: IR- spectral data of Compounds (w4-6)

FTIR cm^{-1} (KBr)					**X Y**	**Compd. No.**
Others cm^{-1}	**(C=C)**	**(C=N)**	**(Ar-H)**	**C-S-C**		
3024 for C-H aliphatic	1587	1649	3060	1022	4-F Br	W4
1339 for - Br	1511	1617	3077	1008	4-Cl Br	W5
784 for Cl	1532	1637	3075	11103	4-Cl Cl	W6

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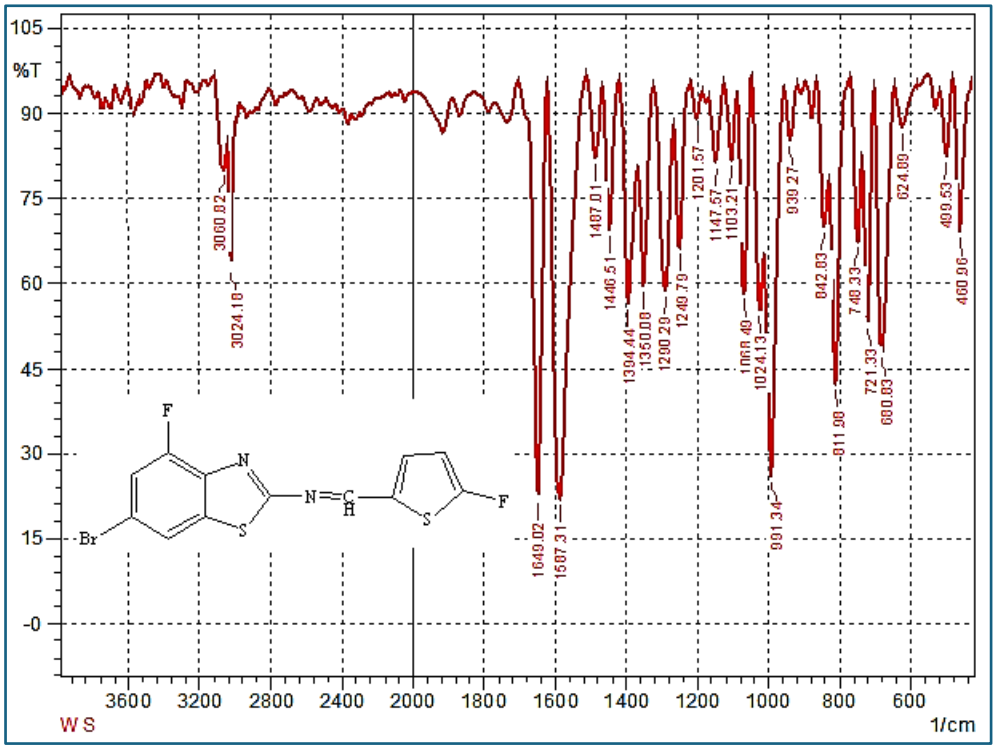


Fig. 7. The compound's FT-IR spectra(W_4)

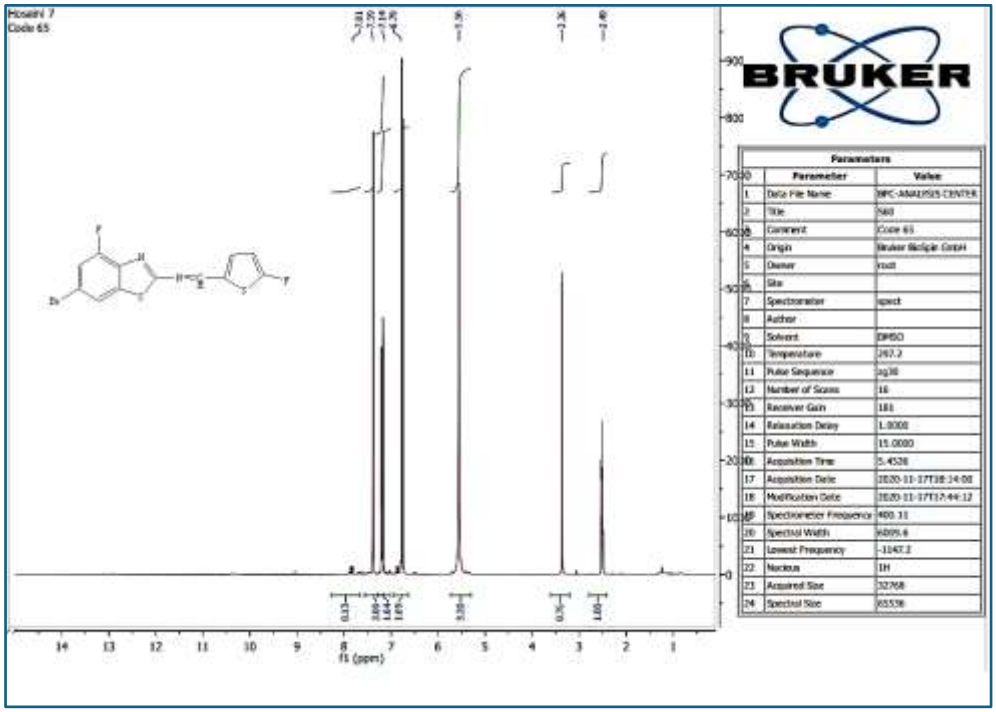


Fig. 8. 1-H NMR spectra of the substance(W_4)

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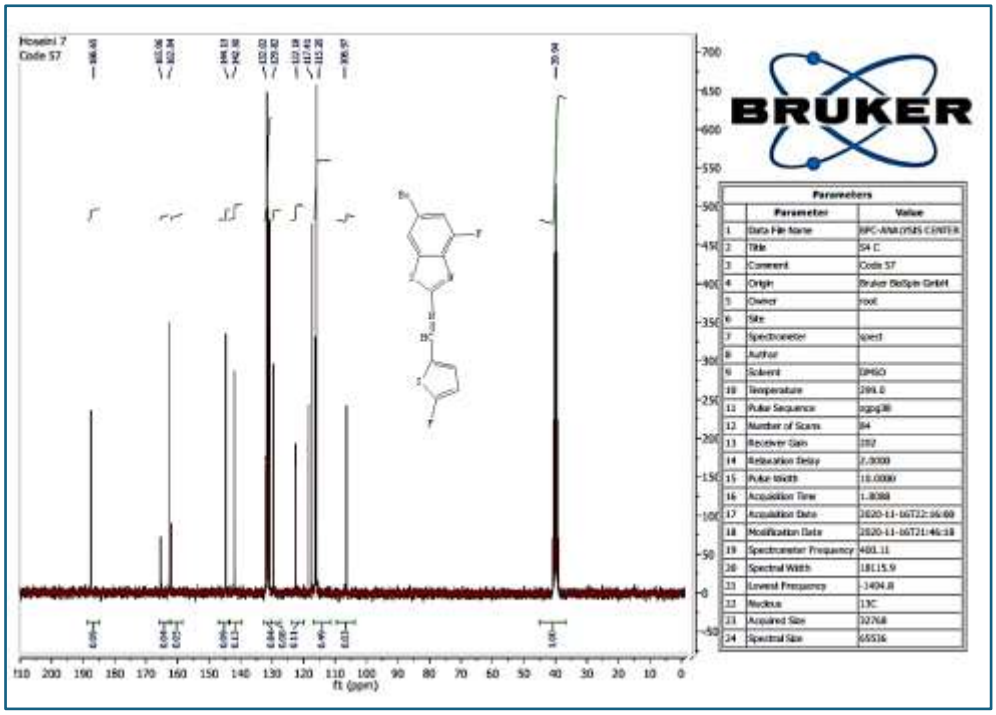


Fig. 9. CNMR spectra of the substance(W_4)

4.3. Characterization of 1,3-Oxazolidine-5 One Derivatives (W7-9)[48]

The FT-IR spectrum of the disordered compounds exhibited a band at 3085-3017 cm^{-1} for aromatic (CH), two bands at 2918-2889 and 2883 cm^{-1} for aliphatic (CH), a band at 1658-1617 cm^{-1} for (C=O), two bands at 1571-1513 and 1508 cm^{-1} for aromatic (C=C), a band at 1336-1371 cm^{-1} for (C-O), and a band at 1096-1076 cm^{-1} for (N-N). Refer to Table 2. Upon analyzing the 1H-NMR spectrum of compound W7, we observed two (C-H-a) signals at 8.72 ppm corresponding to the protons of the aromatic rings, a signal at 7.43 ppm for the (CH-b) proton, a signal at 7.08 ppm for the (CH-c) protons, a signal at 6.22 ppm for the (CH-f), and a signal at 5.79 ppm for the (CH-e). The C13-NMR spectrum of chemical W7 exhibited signals at 128 ppm for C (C-a), 119 ppm for C (C-b), and 116 ppm for C (C-c). The return to C (C-c) indicated a signal at a frequency of 115 ppm. The return to C (C-d) exhibited a signal with a frequency of 157 ppm. The return to C (C-e) exhibited a signal at a frequency of 134 ppm. The return to C (C-f) indicated a signal at a frequency of 168 ppm. The return to C (C-g) displayed a signal with a frequency of 106 ppm, then returned to C (C-h). disclosed a signal with a frequency of 140 ppm returning to C (C-i) exhibited a signal at a frequency of 107 ppm corresponding to C (C-j); displayed a signal at a frequency of 168 ppm corresponding to C (C-k); presented a signal at a frequency of 111 ppm corresponding to C (C-l) A signal at δ = 171 ppm corresponds to carbon (C-M), while a signal at the identical frequency (δ = 171 ppm) pertains to carbon (C-N) .This signal is seen in Figure 9.

Table 6: IR- spectral data of Compounds (w_{7-9})

FTIR cm^{-1} (KBr)					**X Y**	**Compd. No.**
Others cm^{-1}	**(C-O)**	**(C=O)**	**(Ar-H)**	ν(CH)Aliph		
1336 for C-F	1336	1658	3055	2918	4-F Br	W7
1157for C-Br	1491	1617	3085	2889	4-Cl Br	W8
1052 for Cl	1488	1637	3017	2883	4-Cl Cl	W9

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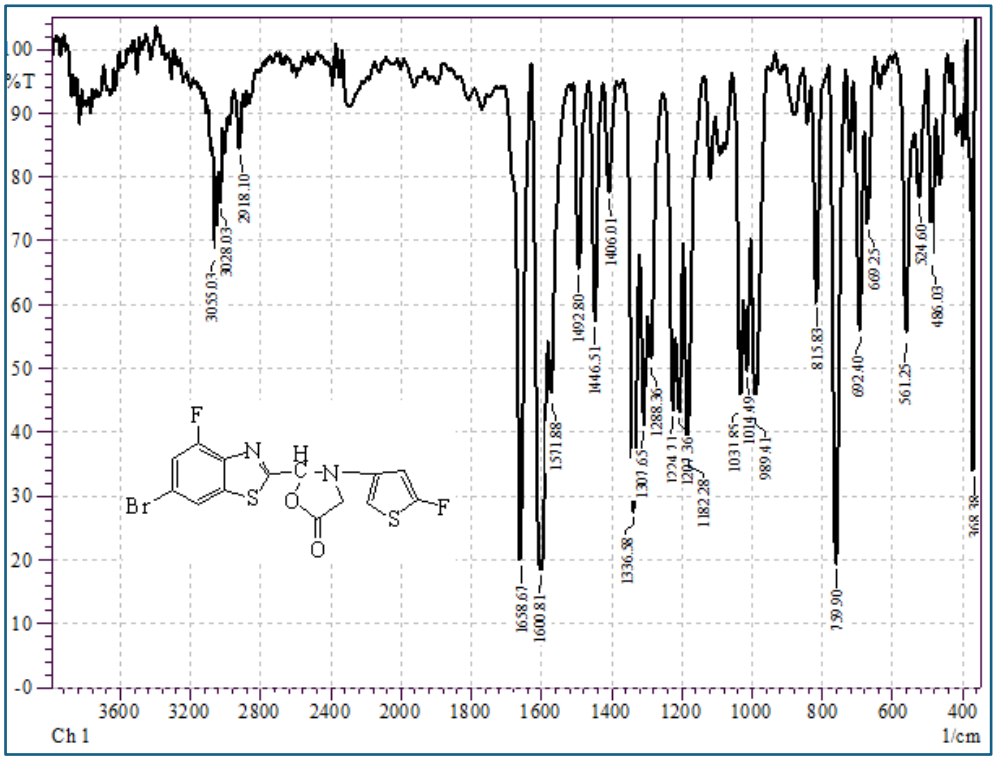


Fig. 10. The compound's FT-IR spectra(W_7)

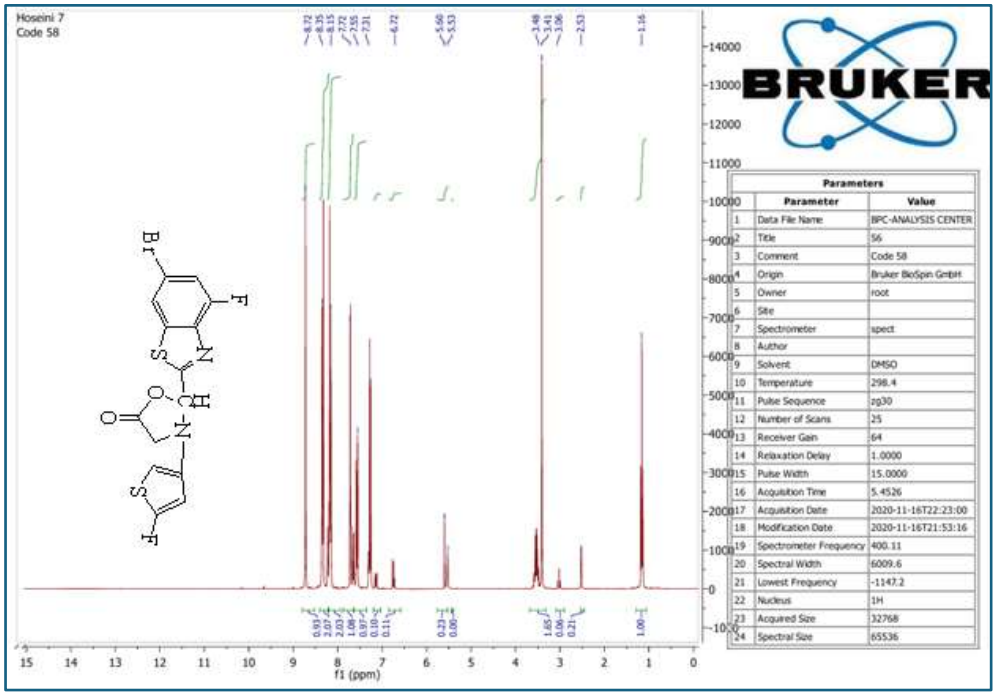


Fig. 11. The substance's 1-H NMR spectrum (W7)

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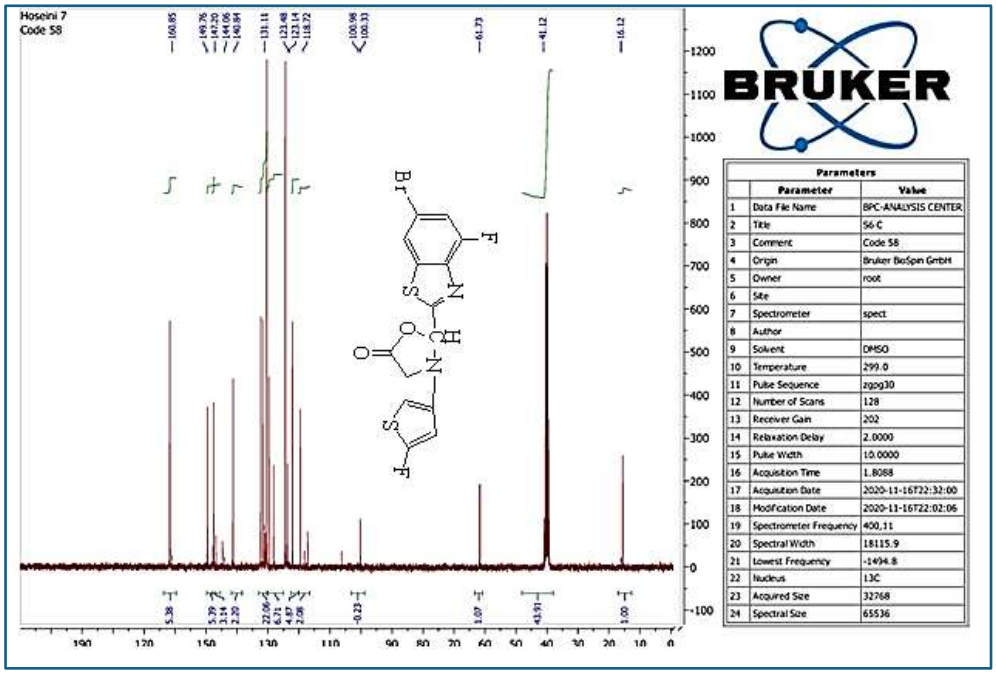


Fig. 12. CNMR spectra of the substance(W_7)

4.4- Results of several synthetic compounds' molecular docking analyses

Pseudomonas aeruginosa microorganisms were tested using the molecular docking[49] of certain chemicals (w1–w3). Using the MOE tool, the compounds' binding energies were determined. Analysis of the generated chemical compounds' molecular docking revealed the number and type of binding connections. The molecules formed several hydrogen bonds, pi-type interactions, and Van der Waals interactions using the amino acid residues in the active site. The table displays the dimensions of the molecule's hydrogen bonds. The table demonstrates this technique.

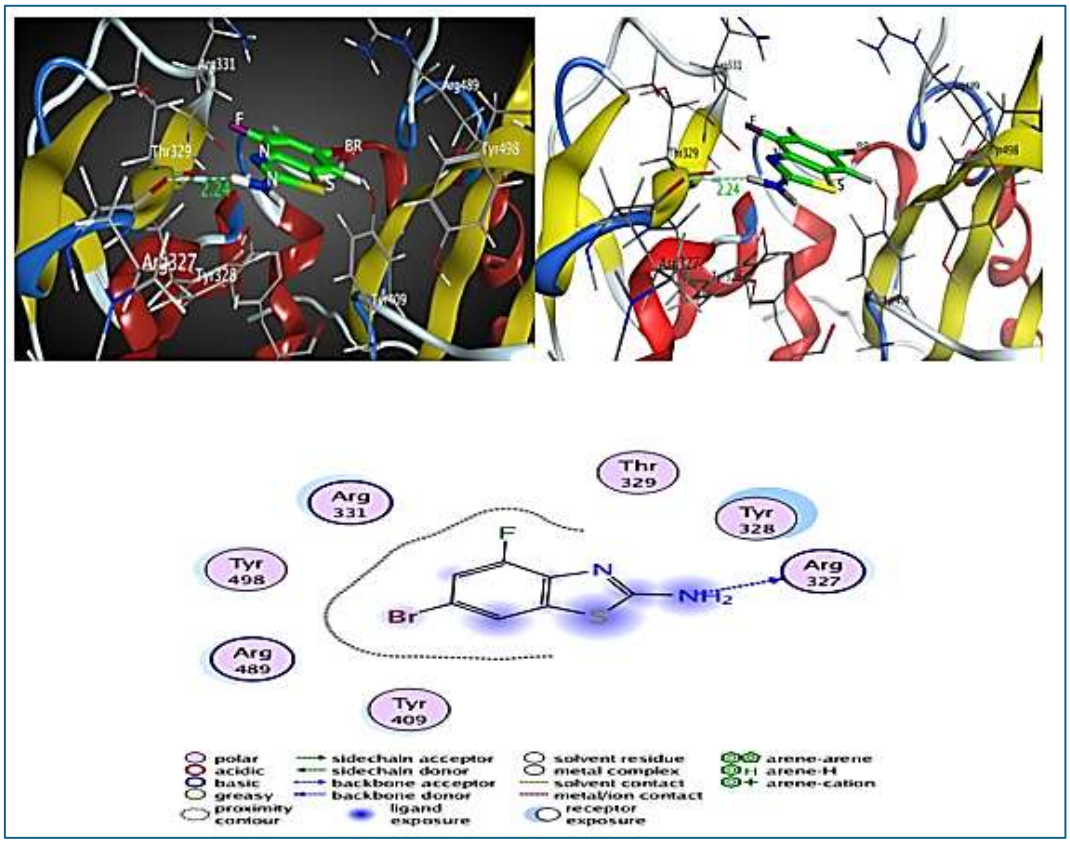
Table 7. Values of binding energy, hydrogen bond lengths, and the influence of amino acids on the interactions between the synthesized chemicals and the receptor (6R3X), a strain of Pseudomonas aeruginosa bacterium.

Number No acids Amino Affected	Other amino acids affected by Van der Waals forces and others	Hydrogen bond			RMDS	**Docking Score**	Complex	Compound
		The length of the B.H	Amino acids Associated	B.H				
6	Arg.489,331,Thr.329, 328, 489,409.	2.24(A)	Arg,327	1	2.45	-3.572	$C_7H_4BrFN_2S$	w_1
9	Phe.359,Lle.325,Gly.326 ,Asp317,Val.320,Trp.31 0Lys.356.,Val.316,Gln3 24	2.20(A) 2.54(A)	Lys,309	2	3.42	-5.874	$C_{22}H_{10}Br_2F_2N_4S_2$	w_1
5	Pro.49,Asp.198Lle.204, Ale.50,Gln47	2.05(A) 2.38(A)	Arg.199 Gln.47	2	1.69	-6.058	$C_{36}H_{20}Br_2F_2N_6O_2S_2$	w_3

Through the creation of two types of hydrogen bonds[50], the study showed how the chemical (w1) interacts with amino acid residues in the active area. Arg327 at the active site is connected to the electronic pair of the nitrogen atom in the amine group by the first type of hydrogen bond. As indicated in Table (7)

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above, it also forms several van der Waals-type connections with the amino acid residues Arg.489, 331, Thr.329, 328, and 409. Moreover, Figure (8).



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