

PREPARATION, SPECTRAL CHARACTERIZATION, MOLECULAR DOCKING, AND ANTIOXIDANT ACTIVITY OF NEW SYMMETRICAL DIMERS DERIVATIVES OF OXAZEPINE STARTING FROM PYRIDINE-5,7-DIONE ANHYDRIDE

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Abstract: This study reports the synthesis of a series of oxazepine derivatives via a condensation reaction between amines and various benzaldehyde derivatives, using benzene as the solvent. The resulting intermediates were subsequently reacted with pyridine-5,7-dione anhydride in dry benzene to afford oxazepine derivatives (H₁–H₆). The synthesized compounds were characterized by Fourier-transform infrared (FT-IR) spectroscopy, proton nuclear magnetic resonance (¹H-NMR) spectroscopy, and mass spectrometry. Reaction progress was monitored using thin-layer chromatography (TLC).

The antioxidant activity of compounds H₁–H₆ was evaluated and compared with that of vitamin C. In addition, molecular docking studies were performed for selected compounds (H₁, H₄, and H₆) against tyrosinase (PDB ID: 3NM8) to identify optimal binding sites and evaluate interactions with neighboring residues. The docked complexes exhibited RMSD values of 1.16, 1.40, and 1.30 Å for H₁, H₄, and H₆, respectively. Among the tested compounds, H₄ showed the highest binding affinity, in good agreement with the experimental results.

Overall, the synthesized oxazepine derivatives demonstrated moderate antioxidant activity, warranting further in vivo investigation.

Keywords: Pyridine-5,7-dione anhydride, Antioxidant activity, Oxazepine derivatives, docked protein.

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1. Introduction

Oxazepine derivatives represent a great class of heterocyclic compounds that can be illustrated by a seven-membered ring involving both nitrogen and oxygen atoms [1–4]. The particular chemical structures with unique functional groups of oxazepine have been

established to develop new biologically active molecules (Fig. 1). Structural modifications of the oxazepine that can involve a lactam ring with other sulfur substituents fused within oxazepine rings have exhibited more biologically active compounds [5–8].

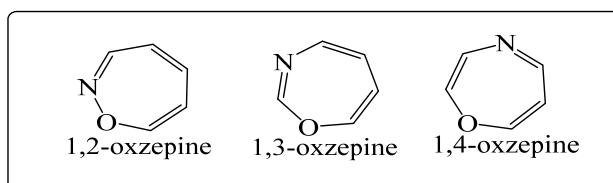


Fig. 1. Oxazepine derivatives

Oxazepine derivatives exhibit stability due to conjugation between the double bonds within the ring structure. Some oxazepine derivatives were previously prepared through the Schiff base

reaction with cyclic anhydrides. Oxazepine derivatives have garnered significant attention from researchers due to their biological activity against various viruses, bacteria, fungi, and

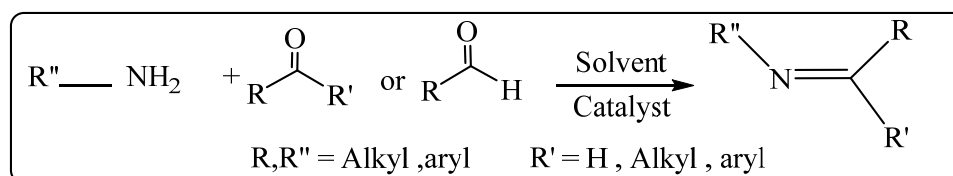
cancerous tumors [5, 9, 10]. They have also demonstrated pharmaceutical potential, including antimicrobial, anticonvulsant, anxiolytic, and analgesic activities [11, 12].

Recent studies have reported innovative techniques for the synthesis and functionalization of oxazepine derivatives. For example, about five compounds have been recently reported involving bicyclic δ -lactam-oxazepine compounds containing a sulfur substituent prepared using an economical synthetic route, showing remarkable biological activity as an antibacterial agent [13]. Another current study reported the preparation, spectral characterization, in silico ADME profiling, molecular docking, and antioxidant activity of

multiple symmetrical dimeric oxazepine derivatives, showing insights into their pharmacokinetic features and antioxidant activity [14].

Schiff bases serve as a fundamental material in the synthesis of numerous organic, biological, and industrial compounds [15, 16].

Including non-homogeneous cyclic compounds through ring-closure reactions, ring addition, and substitution reactions [17, 18]. Schiff bases were first synthesized by the German scientist Hugo Schiff in 1864 [19], through the condensation of a carbonyl group with an aldehyde or a ketone with a primary amine [18]. They were renamed as imine or azomethine compounds [19–22].



Scheme 1. Proposed mechanism for the formation of Azomethine compounds

The general structural formula of Schiff bases is ($\text{R}''\text{N}=\text{CR}'\text{R}$), where (R'' , R' , R) can be aryl, alkyl, hydrogen, or non-homogeneous rings [26–23]. Schiff bases receive alternative names due to variations in the groups (R'' , R' , R) attached to the carbon and nitrogen atoms forming the ($\text{C}=\text{N}$) bond [25]. They are called benzoylates when prepared from aniline and benzaldehyde exclusively [23], as well as anilines when derived from anilines and their

derivatives [27]. They are also known as ketimines when synthesized from ketones and amines and aldimines when prepared from aldehydes and amines [28]. Schiff bases have two geometric isomers depending on the type of groups attached to the nitrogen and carbon atoms, denoted by the symbols (*Z*, *E*), derived from the German words "Entgegen", meaning opposite sides and "Zusammen", meaning same side (Fig. 2) [19].

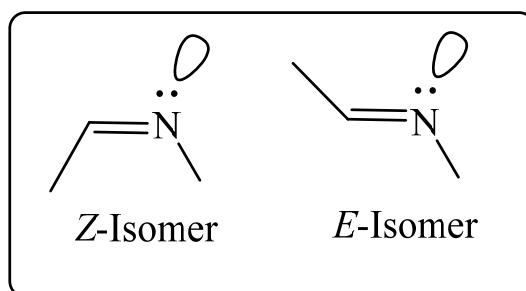


Fig. 2. Geometric isomers of azomethine compounds

The extensive biological activities of oxazepine derivatives, which have demonstrated valuable applications in the medical field, have attracted considerable research interest toward understanding their mechanisms of action. These mechanisms can be explored through advanced computational chemistry approaches, including

molecular docking studies, as well as through the systematic substitution of functional groups to elucidate the influence of structural modifications on binding affinity and bioavailability, thereby facilitating rational drug design. Schiff base reactions provide an effective synthetic route for the preparation of such

compounds. In this study, we aimed to synthesize new oxazepine derivatives from pyridine-5,7-

dione anhydride via Schiff bases and to investigate selected biological activities.

2. Experimental part

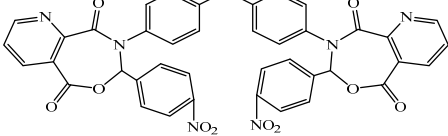
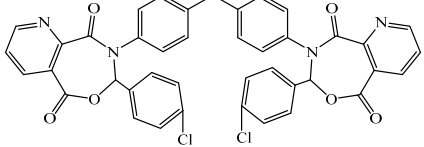
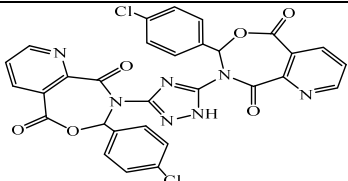
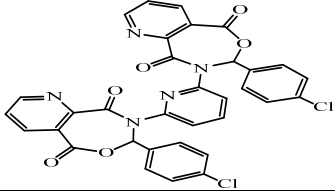
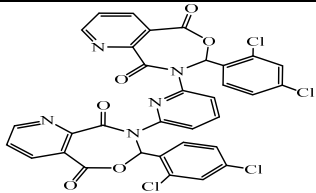
2.1. The chemicals and solvents. All compounds of 4,4'-methylenedianiline, 1,2,4-triazole-3,5-diamine, pyridine-2,6-diamine, 4-nitrobenzaldehyde, 2,4-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-aminophenol, terephthalaldehyde, pyridine-5,7-dione anhydride, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) (99%) from Sigma Aldrich Company. Absolute ethanol (99.9%) from Scharlau Company. Benzene (99.9%) from Merck Company.

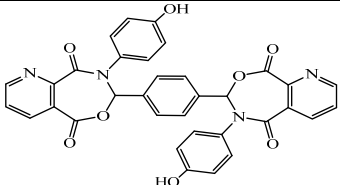
2.2. General procedure for Synthesis of 7,8-dihydropyrido [1,3] oxazepine-5,9-dione [H₁-H₆]. The work method was adopted following references with some modifications [29, 30]. A quantity of 0.01 mole (1.5 gm) of 4-nitrobenzaldehyde was dissolved in 30 ml of dry benzene at the same time. A quantity of 0.005 mole (1 gm) of 4,4'-methylenedianiline was dissolved in 20 ml of the same solvent, the two

solutions were mixed, the mixture was allowed to react, and the progress of the reaction was monitored by thin-layer chromatography (TLC) using the solvent mixture (methanol: cyclohexane) in a ratio of (2:7) [31].

Once the reaction of azomethine was finished, the product was then confirmed using TLC. For oxazepine synthesis, 0.01 mole (1.49 g) of pyridine-5,7-dione anhydride was added to the last product and then refluxed till the product's color changed. Once the reaction was finished, the products were confirmed using TLC using the solvent mixture (benzene:acetone) with a ratio of 6:2. The formed precipitate was collected, and it was recrystallized using absolute ethanol to obtain the H₁ compound. The remaining derivatives of 7,8-dihydropyrido [1,3] oxazepine-5,9-dione [H₂-H₆] were prepared using the same method [29, 32].

Table 1. Properties of the prepared 7,8-dihydropyrido [1,3] oxazepine-5,9-dione [H₁-H₆]

No.	Structure and nomenclature	Molecular formula	Yield%	R _f
H ₁		C ₄₁ H ₂₆ N ₆ O ₁₀	75	0.71
H ₂		C ₄₁ H ₂₆ Cl ₂ N ₄ O ₆	71	0.62
H ₃		C ₃₀ H ₁₇ Cl ₂ N ₇ O ₆	42	0.59
H ₄		C ₃₃ H ₁₉ Cl ₂ N ₅ O ₆	59	0.73
H ₅		C ₃₃ H ₁₇ Cl ₄ N ₅ O ₆	61	0.71

H₆		$C_{34}H_{22}N_4O_8$	57	0.64
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2.3. Antioxidant activity

2.3.1. DPPH Free radical scavenging activity. The compounds were subjected to in vitro antioxidant activity testing using 2,2-diphenyl-1-picrylhydrazyl (DPPH), a method that assesses the compounds' ability to scavenge free radicals. Different concentrations were prepared by dissolving 4 mg of ascorbic acid in 100 ml of methanol to create a standard solution of 400 µg/ml. Using the standard solution, various concentrations of ascorbic acid (0.5, 0.2, 0.15, 0.1, and 0.05 mM) were prepared and utilized as the typical solution. Sample solutions were prepared by dissolving 1 mg of each sample in 1 ml of dimethyl sulfoxide (DMSO), and following the principles of molarity and dilution laws, the concentrations mentioned above were prepared. Furthermore, 4 mg of 2,2-Diphenyl-1-

Picrylhydrazyl was dissolved in 100 mL of the methanol solvent; the solution was shielded from light [33, 34] [14].

2.3.2. The procedure for valuation of 2,2-Diphenyl-1-Picrylhydrazyl hunting action. The absorption of the 2,2-Diphenyl-1-Picrylhydrazyl reagent was directly measured at 517 nm for the control reading. Upon completion of meditation synthesis, 1.5 mL of the reagent was added to each test tube holding the sample and meditations of the standard solution separately. The samples were gestated in the shadowy for 30 minutes. Subsequently, the absorption was measured at 517 nm using a UV-visible spectrometer after 30 minutes, with methanol serving as the blank solution. The free radical antiradical action % was calculated by:

$$\text{Antiradical activity\%} = (A \text{ Control} - A \text{ Test}) / A \text{ Control} * 100$$

A Control = absorbance of the control reaction (containing all reagents except the sample extract) A Test = absorbance of the sample (oxazepine derivatives).

2.4. Docking of the Synthesized Novel Homo-Oxazepine Dimer Derivatives (H₁, H₄, and H₆) with the 3NM8 Reductase. The H₁, H₄ and H₆ structures were generated using ChemDraw software 2013 and then converted to SDF and MOL formats for docking purposes. The PDB of the 3NM8 of tyrosinase was

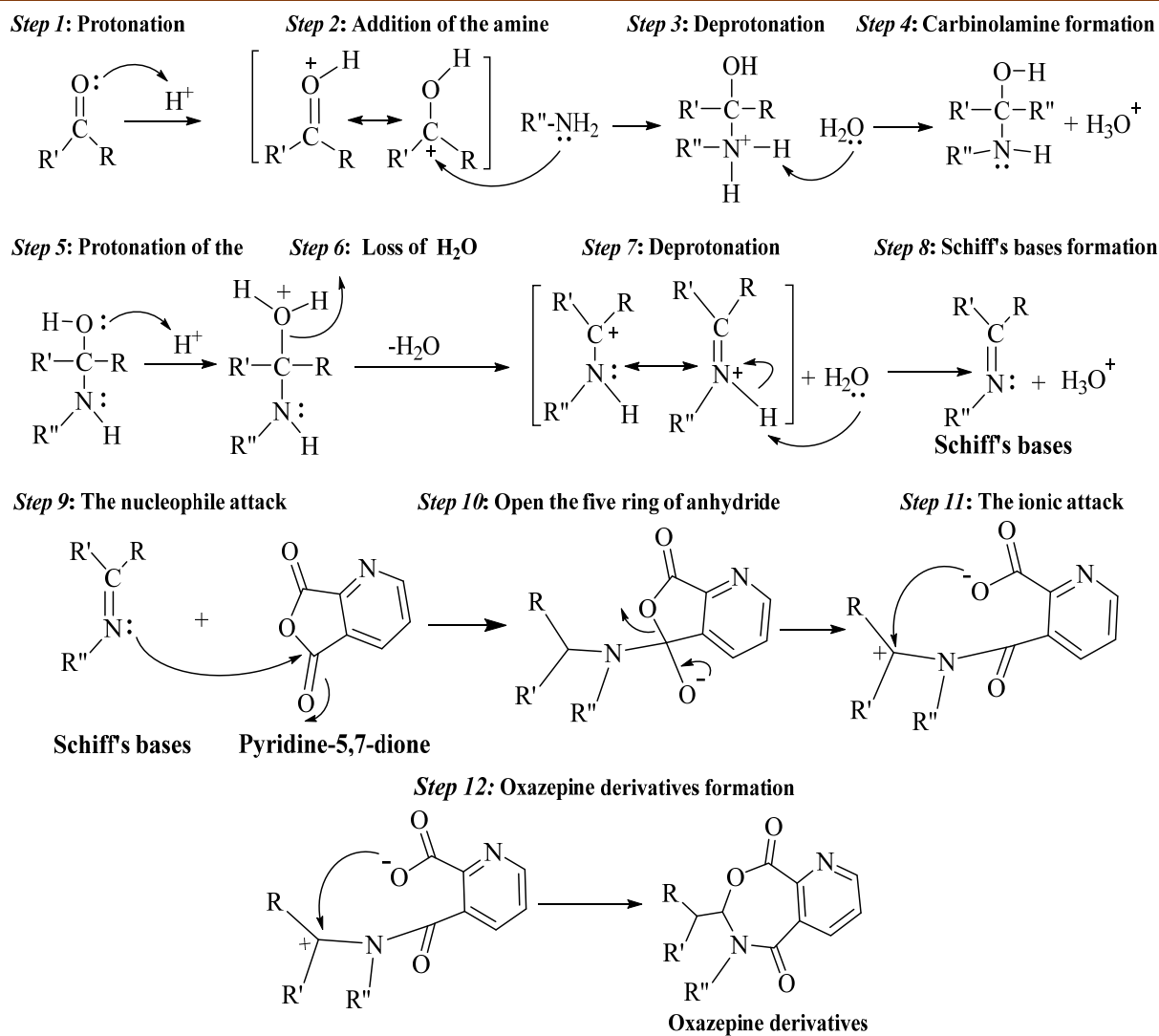
retrieved from the Protein Data Bank (www.rcsb.org) [33]. The MOE Molecular Operating Environment software was used to perform the molecular docking process [35], the PLIP website was used for analysis, and PyMol software was used for visualization [33, 34, 36].

3. Results and discussion

The chemical synthesis of the new oxazepine derivatives compounds (H₁-H₆). The compounds of 7,8-dihydropyrido[1,3]oxazepine-5,9-dione derivatives were obtained by reaction between Schiff's bases and pyridine-5,7-dione anhydride [19]. All the steps of the intermediate in the reaction were confirmed using TLC. The general mechanism of the oxazepine derivatives (H₁-H₆) reactions was suggested as seen in Scheme (2).

3.1. FT-IR spectra of 7,8-

dihydropyrido[1,3]oxazepine-5,9-dione derivatives (H₁-H₆). All 7,8-dihydropyrido[1,3]oxazepine-5,9-dione derivatives were confirmed using infrared spectroscopy, where all spectra showed the disappearance of the absorption band of the C=N groups of the Schiff's bases and the appearance of the lactamic (ν N-C=O) groups in the range (1655-1661 cm⁻¹) and the lactonic (ν O-C=O) groups in the range (1685-1693 cm⁻¹) (Figs 3-8) [37-39].



Scheme 2. The general mechanism for the preparation of the oxazepine derivatives [19]

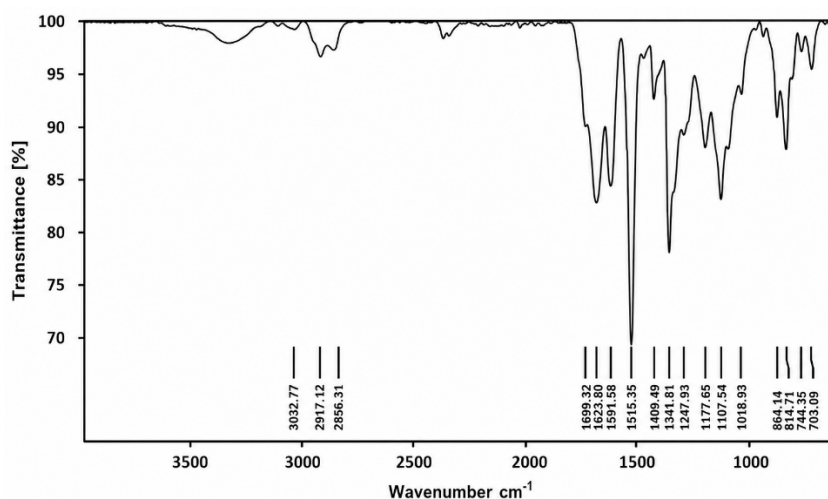
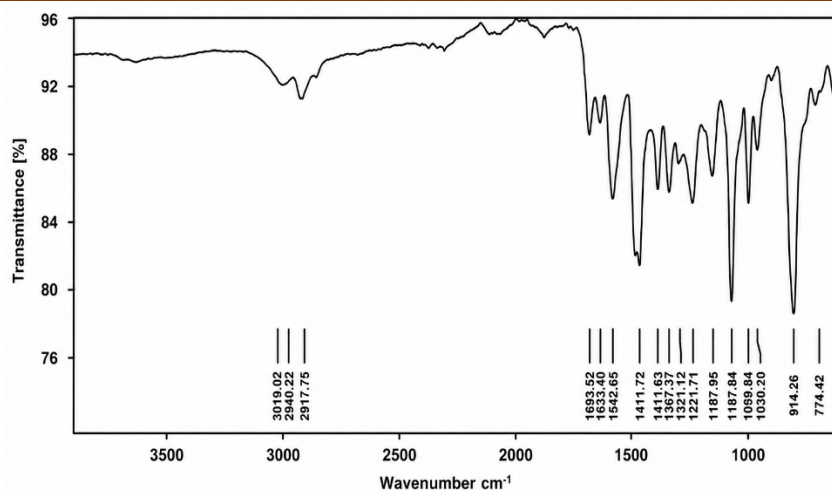
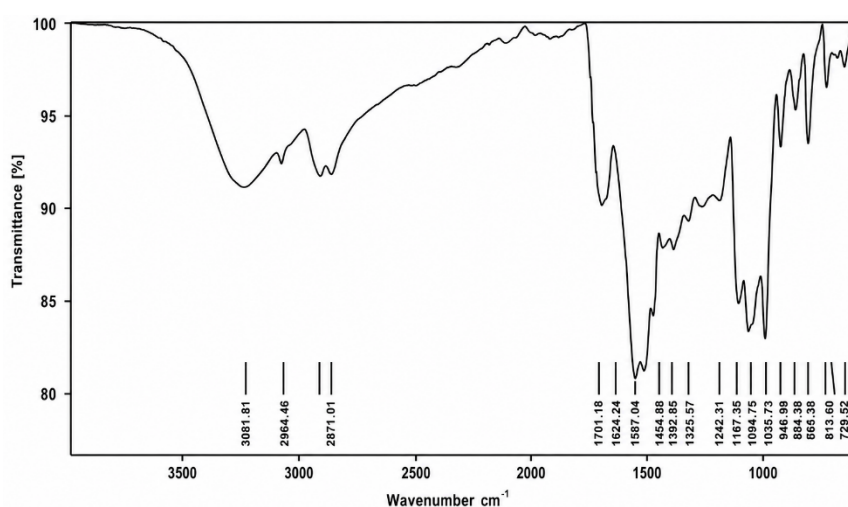
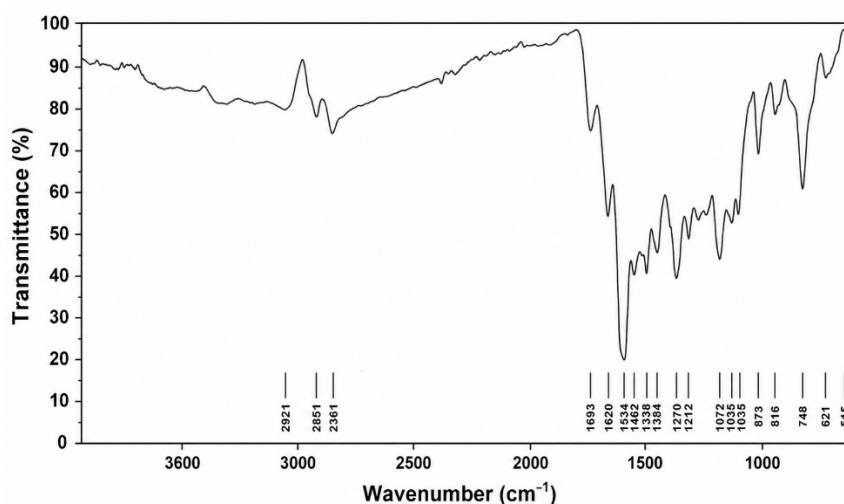


Fig. 3. FT-IR spectrum for H₁ compound

Fig. 4. FT-IR spectrum for H₂ compoundFig. 5. FT-IR spectrum for H₃ compoundFig. 6. FT-IR spectrum for H₄ compound

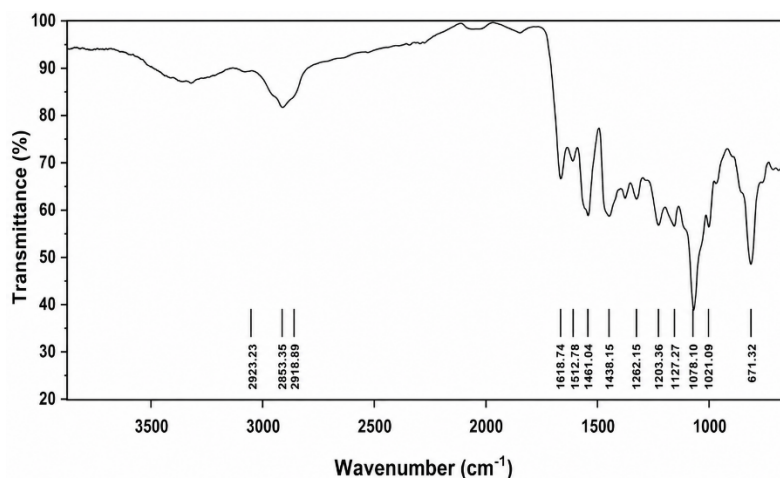
The spectra also showed other absorption bands belonging to the aggregates. Compensation in the synthesis of oxazepine derivatives and aromatic rings was followed in

the FT-IR spectra in each step of the reaction [40, 41]. Table 2 shows the values of absorption bands for derivatives 7, 8-dihydropyridine[1,3] oxazepine-5,9-dione (H₁-H₆) compounds.

Table 2. The FT-IR (cm^{-1}) absorption bands of 7,8-dihydropyrido[1,3]oxazepine-5,9-dione (H_1 - H_6) derivatives (Fig.s 3-8)

No	C-H Aromatic	C=C Aromatic	ν C-H Aliphatic		C=O lactone	C=O lactam	Other
			Asymmetric	Symmetric			
H₁	3032	1605	2917	2865	1718	1669	NO ₂ 1341 and 1511 C-N 1341 C-O 1409
H₂	3006	1608	2984	2911	1707	1661	C-Cl 1011 C-N 1357 C-O 1406
H₃	3085	1571	2920	2871	1718	1643	C-Cl 1012 C-N 1342 C-O 1407 N-H 3248 b
H₄	3059	1587	2913	2862	1714	1660	C-Cl 1014 C-N 1358 C-O 1486
H₅	3057	1583	2921	2852	1729	1654	C-Cl 1010 C-N 1357 C-O 1441
H₆	3037	1593	2923	2874	1729	1676	OH 3368 b C-N 1300 C-O 1413

b= broad

**Fig. 7.** FT-IR spectrum for H_5 compound

3.2. ^1H -NMR spectra. In all Fig. s 9–14, corresponding to the ^1H -NMR spectra of the 7,8-dihydropyrido[1,3]oxazepine-5,9-dione derivatives, three additional signals were observed. The first signal, appearing at 0 ppm, corresponds to the reference compound tetramethylsilane (TMS). The second signal, observed at 2.51 ppm, is attributed to the solvent

dimethyl sulfoxide (DMSO) used to dissolve the samples. The third signal, appearing at approximately 3.50 ppm, arises from residual water commonly present in DMSO [42,43]. All remaining signals were in full agreement with the expected structures of the synthesized products. The assignments of the observed signals for all prepared compounds are summarized in Table 3.

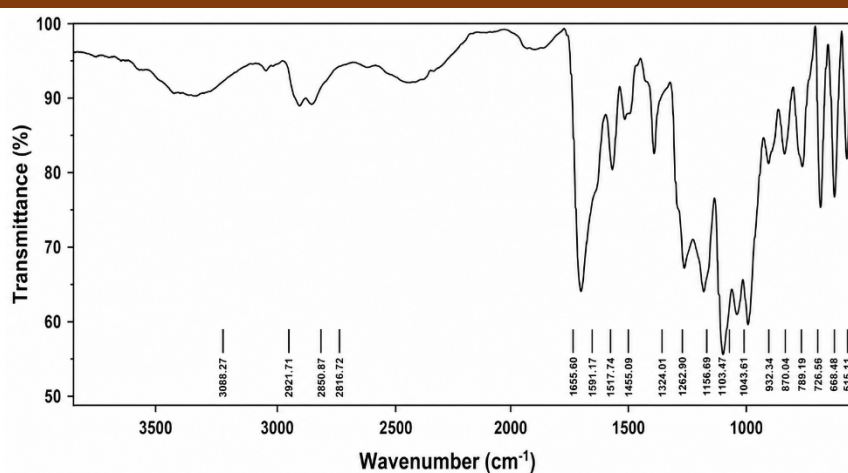
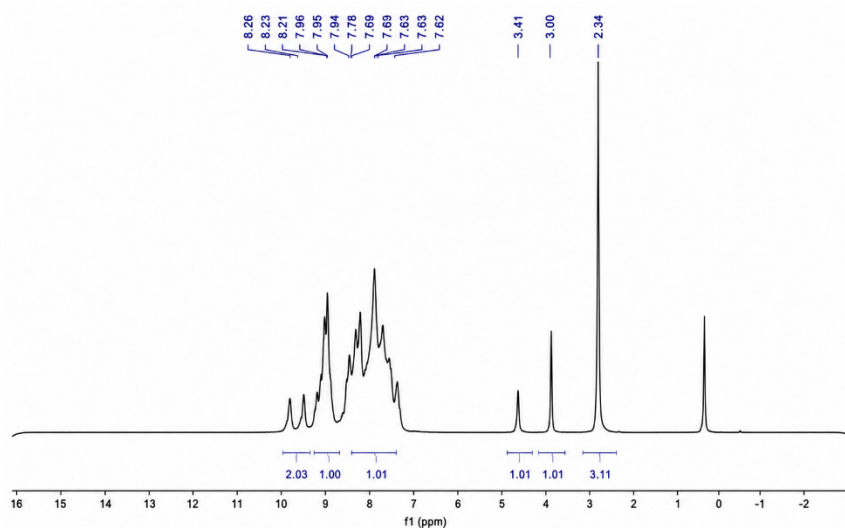
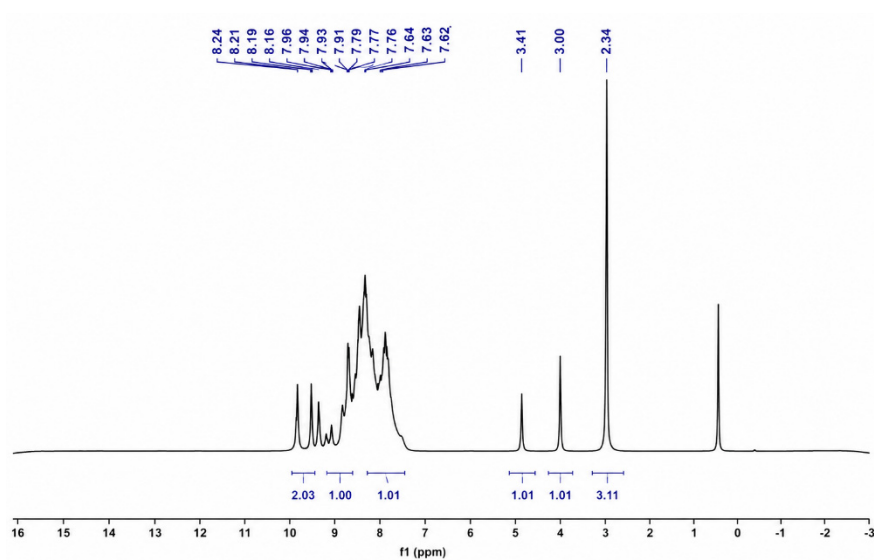
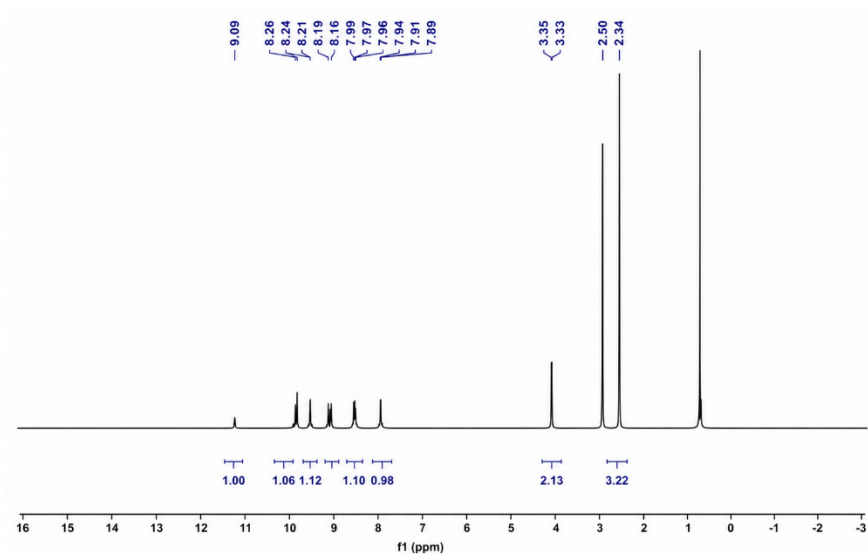


Fig. 8. FT-IR spectrum for H₆ compound

Table 3. ¹H-NMR chemical shift values for selected 7,8-dihydropyrido [1,3] oxazepine-5,9-dione [H₁-H₆]

No	Structure	Number of protons	Type of single	Group	δ Value ppm
H ₁		2	s	Ar-CH ₂ -Ar	4.04
		8	d d	Aromatic protons [A]	6.95-7.79
		8	d d	Aromatic protons [B]	8.17-8.41
		6	m	Pyridine protons [C]	8.76-8.89
		2	s	-N-CH-O heterocycle	9.10
H ₂		2	s	Ar-CH ₂ -Ar	4.03
		8	d d	Aromatic protons [A]	6.77-7.39
		8	d d	Aromatic protons [B]	8.46-8.03
		6	m	Pyridine protons [C]	8.17-8.71
		2	s	-N-CH-O heterocycle	9.08
H ₃		8	d d	Aromatic protons [A]	7.43-7.96
		6	m	Pyridine protons [B]	8.14-8.80
		2	s	-N-CH-O heterocycle	9.08
		1	s	NH of the cycle [C]	10.61
H ₄		8	d d	Aromatic protons [A]	7.40-7.96
		3	m	Pyridine protons [B]	8.16-8.28
		6	m	Pyridine protons [C]	8.40-8.79
		2	s	-N-CH-O heterocycle	9.08
H ₅		8	m	Aromatic protons [A]	7.41-7.61
		3	m	Pyridine protons [B]	7.67-8.01
		6	m	Pyridine protons [C]	8.26-8.78
		2	s	-N-CH-O heterocycle	9.08
H ₆		4	d d	Aromatic protons [A]	7.11-7.18
		8	d d	Aromatic protons [B]	7.51-7.66
		6	m	Pyridine protons [C]	8.79-8.80
		2	s	-N-CH-O heterocycle	9.08
		2	s	-OH	9.66

**Fig. 9.** ^1H -NMR spectrum for H_1 compound**Fig. 10.** ^1H -NMR spectrum for H_2 compound**Fig. 11.** ^1H -NMR spectrum for H_3 compound

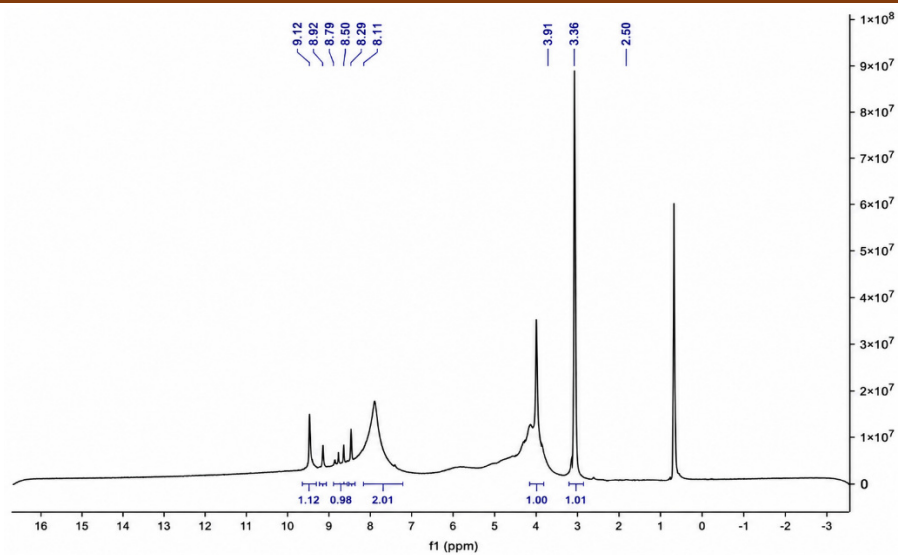


Fig. 12. ^1H -NMR spectrum for H_4 compound

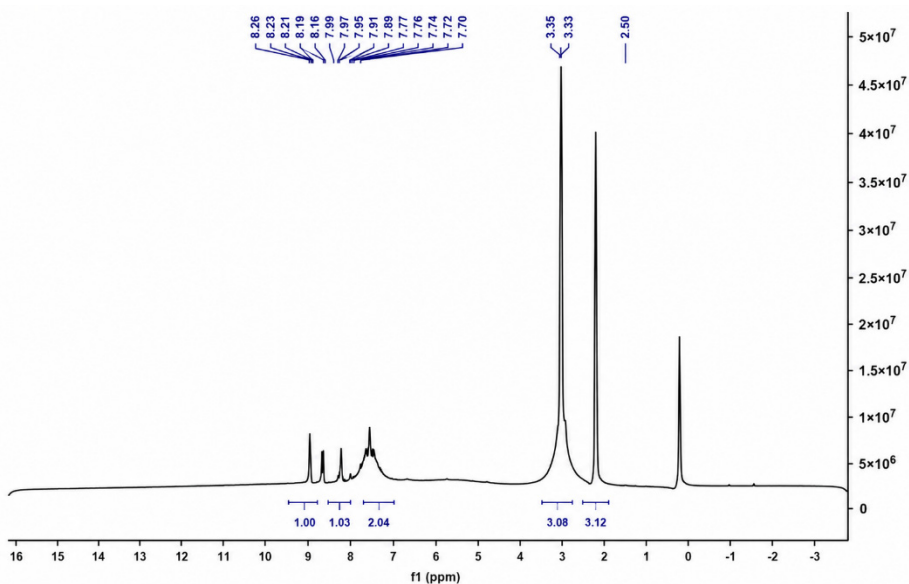


Fig. 13. ^1H -NMR spectrum for H_5 compound

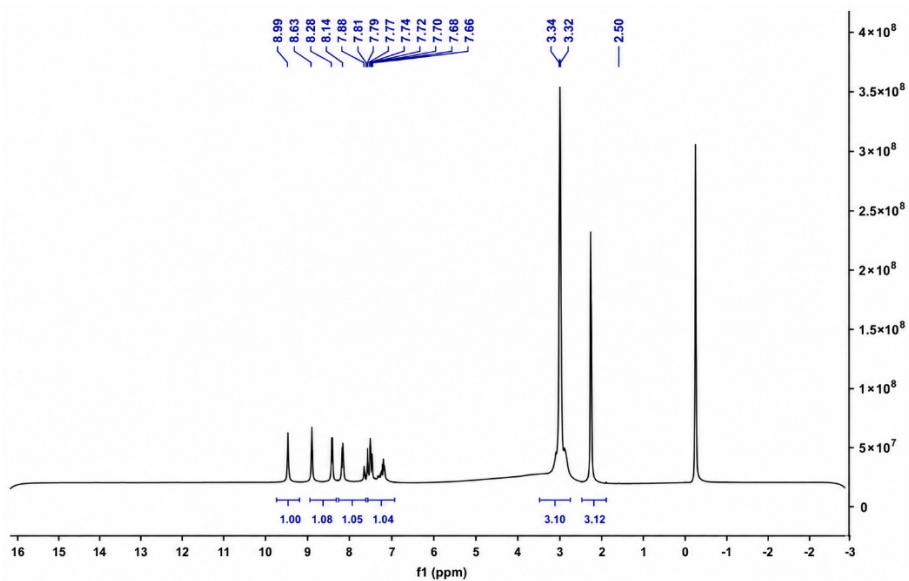


Fig. 14. ^1H -NMR spectrum for H_6 compound

3.3. Mass spectrum. All GC–MS chromatograms of the synthesized products exhibited a single peak with retention times ranging from 0.90 to 0.94 min, indicating the high purity of the newly prepared compounds [44, 45]. The corresponding mass spectra display plots of relative abundance versus m/z , with intense and characteristic peaks observed for all

compounds, confirming that the fragmentation patterns are consistent with the proposed molecular structures. The GC–MS chromatograms and mass spectra are presented below (Fig.s 15-20), while detailed fragmentation analyses are summarized in Tables 4–9.

Table 4. Molecular fragmentations of H₁ compound

Fragments	Mass fragment to Charge formed (m / z)
M ⁺ : C ₄₁ H ₂₆ N ₆ O ₁₀	762.69
C ₃₇ H ₂₆ N ₅ O ₉ ⁺	683.22
C ₃₄ H ₂₃ N ₅ O ₇ ⁺	614.8
C ₃₀ H ₂₇ N ₄ O ₆ ⁺	540.56
C ₂₅ H ₂₁ N ₃ O ₅ ⁺	443.15
C ₂₀ H ₁₉ N ₃ O ₅ ⁺	381.01
C ₁₈ H ₁₄ N ₃ O ₅ ⁺	352.99
C ₁₉ H ₁₃ N ₂ O ₃ ⁺	316.07
C ₁₆ H ₂₀ N ₂ O ₃ ⁺	288.05
C ₁₅ H ₁₈ N ₂ O ₃ ⁺	Base peak 274.05
C ₁₂ H ₁₀ N ₂ O ₃ ⁺	230.05
C ₁₀ H ₅ N ₂ O ₃ ⁺	201.96
C ₈ H ₆ NO ₂ ⁺	148.04
C ₇ H ₉ NO ⁺	123.95
⁺ C ₅ H ₅ N	79.05

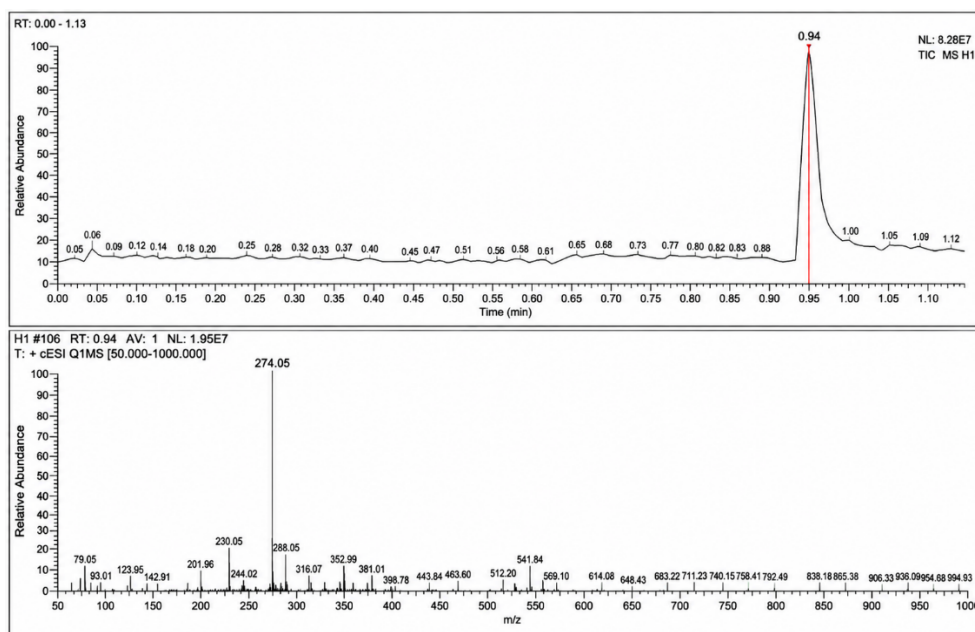


Fig. 15. GC-MS and Mass spectra of H₁ compound

Table 5. Molecular fragmentations of H₂ compound

Fragments	Mass fragment to Charge formed (m / z)
M ⁺ : C ₄₁ H ₂₆ Cl ₂ N ₄ O ₆	741.58
C ₃₈ H ₂₃ Cl ₂ N ₄ O ₄ ⁺	702.79
C ₃₈ H ₃₀ Cl ₂ N ₃ O ₄ ⁺	662.85

$C_{32}H_{26}Cl_2 N_2O_3^+$	558.78
$C_{31}H_{26}Cl_2N_3O_4^+$	540.88
$C_{28}H_{23}ClN_3O_4^+$	500.89
$C_{25}H_{20}ClN_2O_3^+$	431.96
$C_{21}H_{15}Cl N_2O_3^{\bullet+}$	378.83
$C_{19}H_{14}ClN_2O_3^{\bullet+}$	352.95
$C_{19}H_{14}N_2O_3^{\bullet+}$	318.02
$C_{16}H_{18}N_2O_3^+$	287.99
$C_{15}H_{18}N_2O_3^+$	Base peak 274.04
$C_{14}H_{14}N_2O_3^{\bullet+}$	258.89
$C_{12}H_{10}N_2O_3^+$	230.03
$C_{13}H_{14}N_2^+$	198.95
$C_8H_8N_2O_3^+$	180.09
$C_5H_5N^+$	79.02
$C_4H_4N^+$	65.14

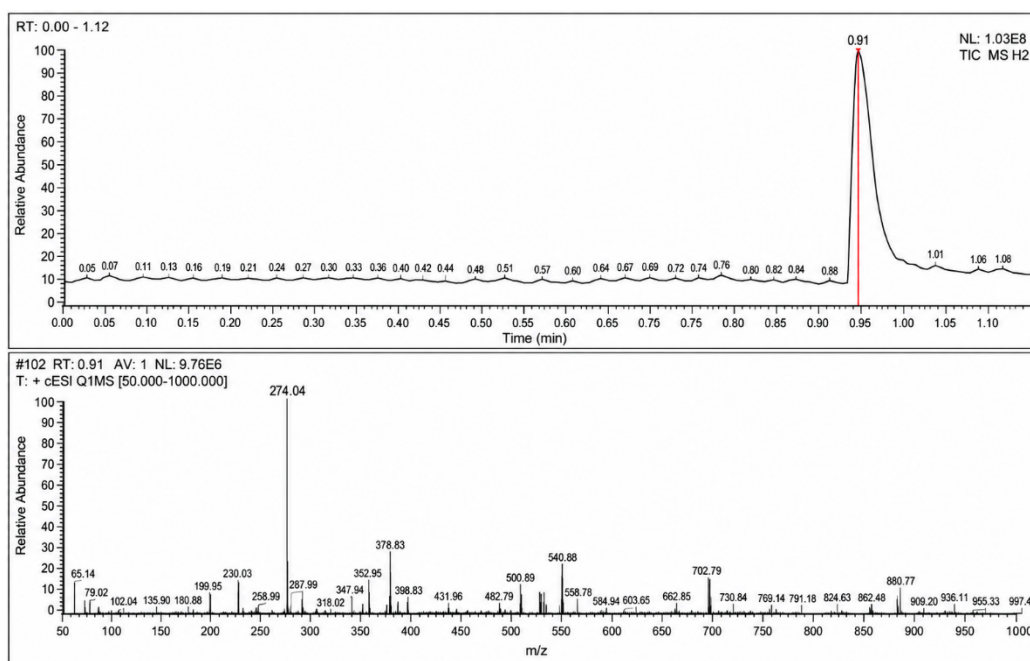
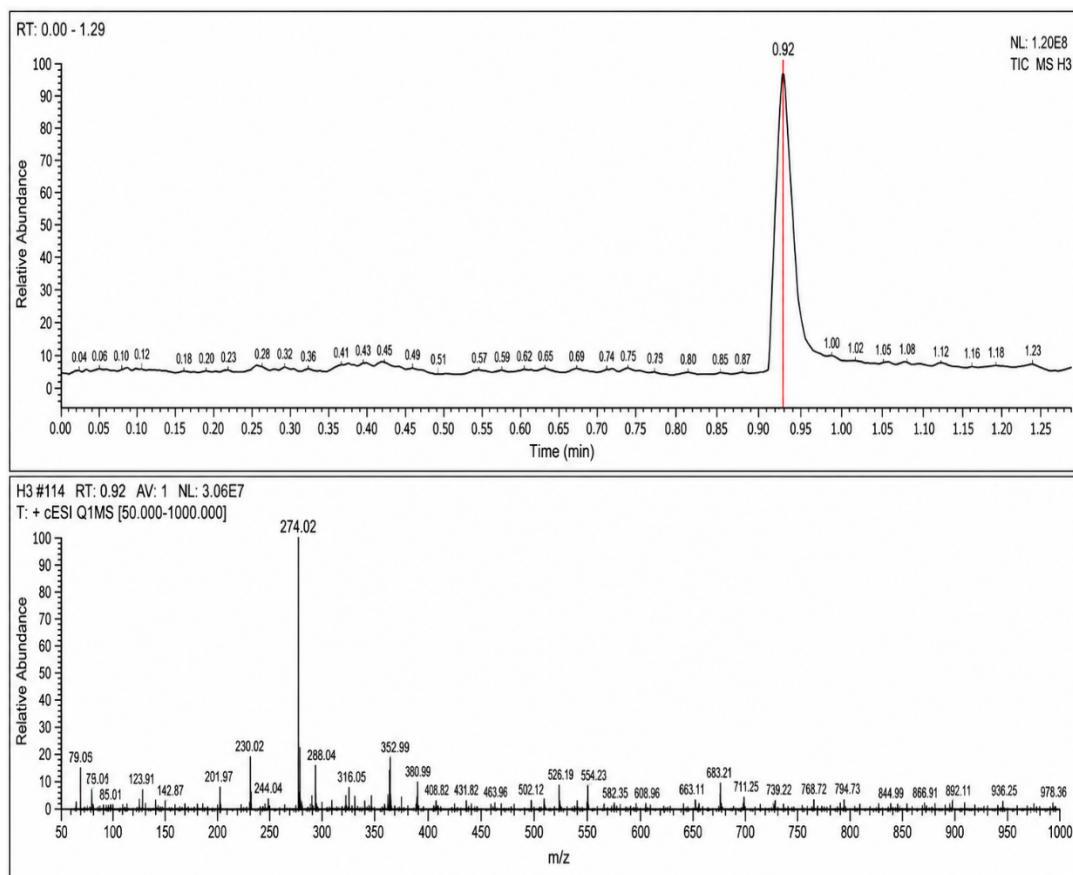


Fig. 16. GC-MS and Mass spectra of H₂ compound

Table 6. Molecular fragmentations of H₃ compound

Fragments	Mass fragment to Charge formed (m / z)
$M^+ = C_{30}H_{17}Cl_2N_7O_6$	642.06
$C_{27}H_{17}Cl_2N_7O_6^+$	606.96
$C_{26}H_{19}Cl_2N_6O_6^+$	582.35
$C_{25}H_{20}Cl_2N_6O_5^+$	554.23
$C_{19}H_{19}ClN_6O_4^+$	431.82
$C_{17}H_{10}ClN_6O_3^{\bullet+}$	380.99
$C_{16}H_8ClN_5O_3^{\bullet+}$	352.99
$C_{15}H_{11}ClN_3O_3^{\bullet+}$	316.05
$C_{14}H_9ClN_2O_3^+$	288.04
$C_{14}H_9ClNO_3^+$	Base peak 274.04
$C_{12}H_{10}N_2O_3^+$	230.02

$C_{10}H_5N_2O_3^{*+}$	201.97
$C_7H_9NO^+$	123.91
$C_5H_5N^+$	79.05
$C_4H_4N^+$	65.14

Fig. 17. GC-MS and Mass spectra of H₃ compoundTable 7. Molecular fragmentations of H₄ compound.

Fragments	Mass fragment to Charge formed (m / z)
$M^{*+} = C_{33}H_{19}Cl_2N_5O_6$	651.07
$C_{32}H_{25}Cl_2N_5O_4^+$	614.10
$C_{28}H_{23}Cl_2N_4O_6^+$	582.19
$C_{27}H_{23}Cl_2N_4O_5^+$	554.13
$C_{26}H_{22}Cl_2N_4O_4^+$	526.02
$C_{23}H_{23}ClN_4O_4^+$	455.70
$C_{19}H_{13}ClN_4O_3^{*+}$	380.98
$C_{18}H_{11}ClN_3O_3^{*+}$	352.96
$C_{17}H_{17}ClN_3O_3^+$	348.01
$C_{15}H_{11}ClN_3O_3^+$	316.06
$C_{14}H_9ClN_2O_3^+$	288.02
$C_{14}H_9ClNO_3^{*+}$	Base peak 274.04
$^+C_{12}H_{10}N_2O_3$	230.04
$C_{10}H_5N_2O_3^{*+}$	201.94
$C_9H_{10}N_2O^+$	162.92
$C_5H_5N^+$	79.05
$C_4H_4N^+$	65.13

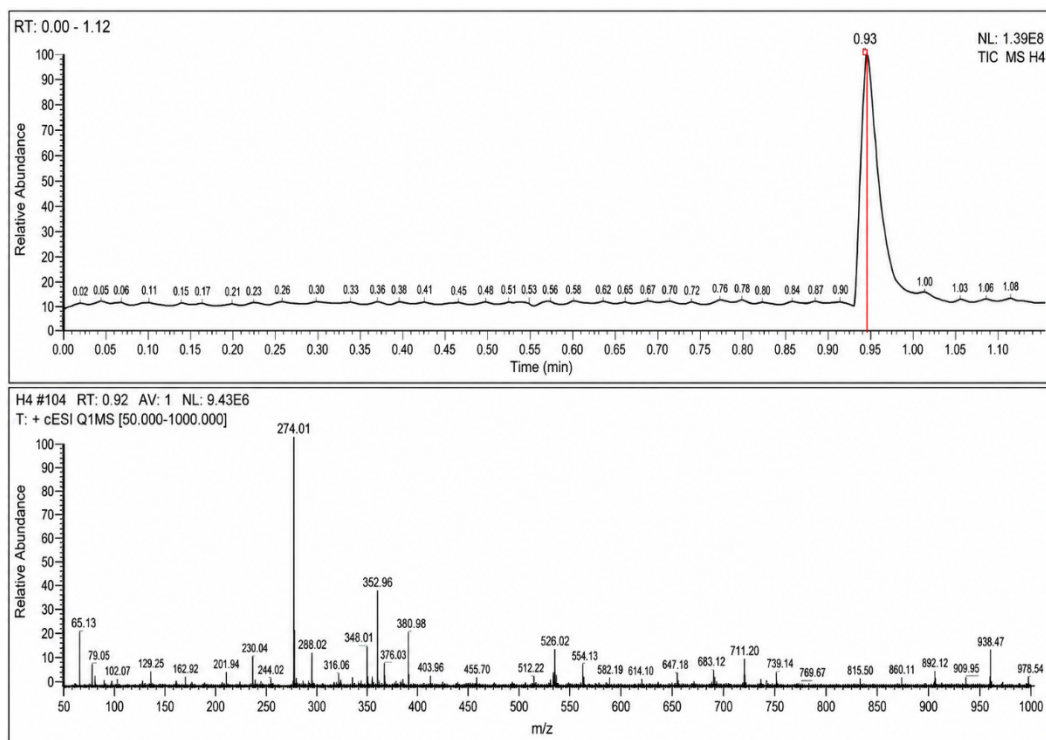


Fig. 18. GC-MS and Mass spectra of H₄ compound

Table 8. Molecular fragmentations of H₅ compound

Fragments	Mass fragment to Charge formed (m / z)
M ⁺ = C ₃₃ H ₁₇ Cl ₄ N ₅ O ₆	721.56
C ₃₁ H ₁₆ Cl ₄ N ₄ O ₆ ⁺	681.77
C ₂₉ H ₂₁ Cl ₃ N ₄ O ₄ ⁺	595.68
C ₂₇ H ₁₉ Cl ₃ N ₄ O ₃ ⁺	554.22
C ₂₇ H ₂₄ Cl ₃ N ₄ O ⁺	526.18
C ₂₁ H ₂₁ Cl ₃ N ₃ O ⁺	437.79
C ₁₈ H ₁₃ Cl ₂ N ₃ O ₃ ⁺	390.78
C ₁₅ H ₁₂ Cl ₂ N ₃ O ₃ ⁺	352.94
C ₁₆ H ₁₃ ClN ₂ O ₃ ⁺	316.02
C ₁₄ H ₉ ClN ₂ O ₃ ⁺	288.02
C ₁₄ H ₉ ClNO ₃ ⁺	Base peak 274.04
C ₁₂ H ₉ N ₂ O ₃ ⁺	299.98
C ₈ H ₉ N ₂ O ₃ ⁺	181.91
C ₆ H ₇ N ₂ O ⁺	123.91
C ₅ H ₅ N ⁺	79.07
C ₄ H ₄ N ⁺	65.12

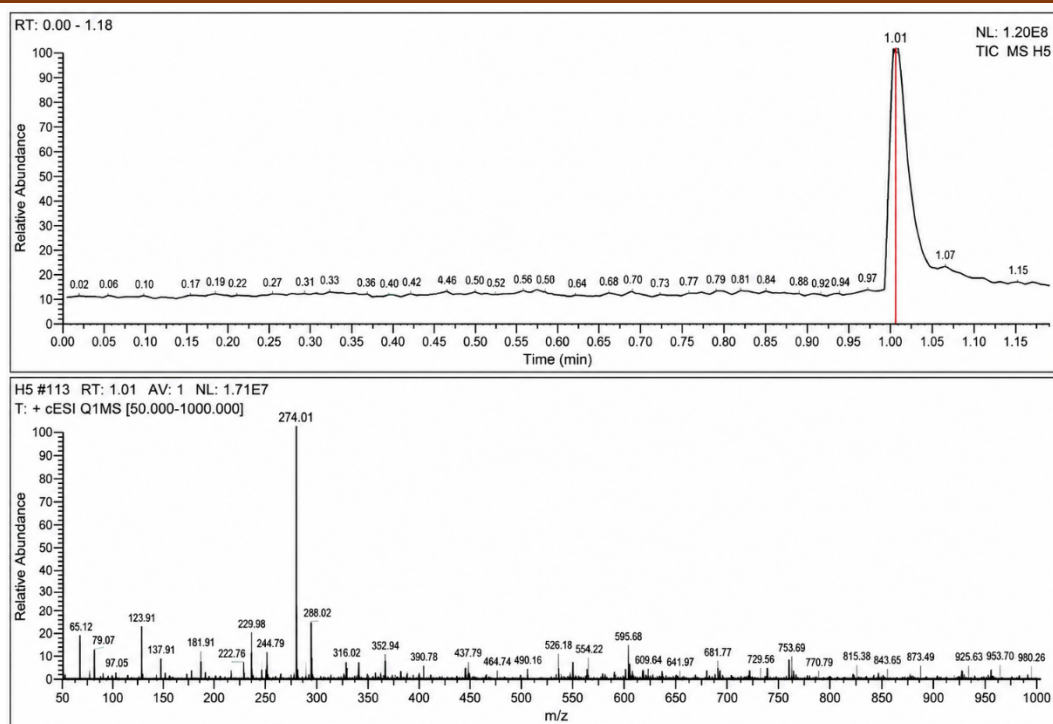


Fig. 19. GC-MS and Mass spectra of H₅ compound

Table 9. Molecular fragmentations of H₆ compound

Fragments	Mass fragment to Charge formed (m / z)
M ⁺ = C ₃₄ H ₂₂ N ₄ O ₈	614.57
C ₃₃ H ₂₂ N ₃ O ₈ ⁺	588.14
C ₃₀ H ₂₄ N ₃ O ₈ ⁺	554.15
C ₂₅ H ₂₁ N ₃ O ₅ ⁺	443.86
C ₂₄ H ₁₇ N ₃ O ₃ ⁺	426.86
C ₂₀ H ₁₄ N ₂ O ₄ ⁺	346.78
C ₁₈ H ₂₀ N ₂ O ₃ ⁺	312.15
C ₁₇ H ₂₀ N ₂ O ₂ ⁺	284.15
C ₁₅ H ₁₇ N ₂ O ₃ ⁺	Base peak 274.04
C ₁₃ H ₁₄ N ₂ O ₂ ⁺	230.11
C ₁₂ H ₁₁ N ₂ O ₂ ⁺	215.08
C ₉ H ₁₁ NO ₂ ⁺	165.08
C ₇ H ₉ NO ⁺	123.07
C ₆ H ₄ ⁺	75.04
C ₄ H ₄ N ⁺	65.12

3.4. Antioxidant activity of the new oxazepine derivatives compounds (H₁-H₆). The activity of the compounds was indicated by a color change of the reagent from purple to yellow, with a more intense yellow coloration signifying higher efficiency. Compounds H₁, H₄, and H₆ exhibited stronger antioxidant activity

than vitamin C [46], indicating their superior potential as antioxidant agents. The present results show the free-radical scavenging activity of the efficiency compounds compared to vitamin C. The results in table 10 confirm the H₆ compound has the best capability of free-radical hunting.

$$\% \text{ Antiradical activity} = \frac{A_{\text{Control}} - A_{\text{Test}}}{A_{\text{Control}}} * 100$$

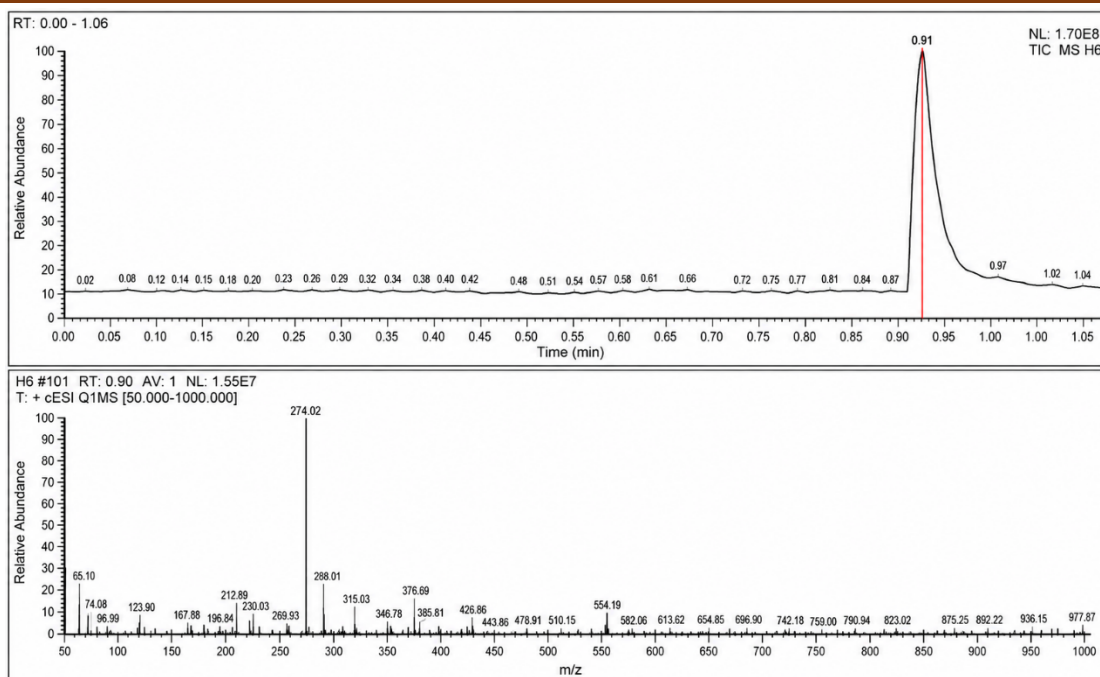


Fig. 20. GC-MS and Mass spectra of H₆ compound

Table 10. Activity of H₁, H₂, and H₆ compounds as anti-oxidant

Concentration (Mm)	Percentage of antioxidant activity (%)			
	H ₁	H ₄	H ₆	Standard (Vitamin C)
0.05	21.8	14.8	37.4	63
0.1	23	17.5	44.3	65.7
0.15	26.7	22.6	51	69
0.2	34	29.4	57.6	76.8
0.5	41.3	32	66.5	87.6

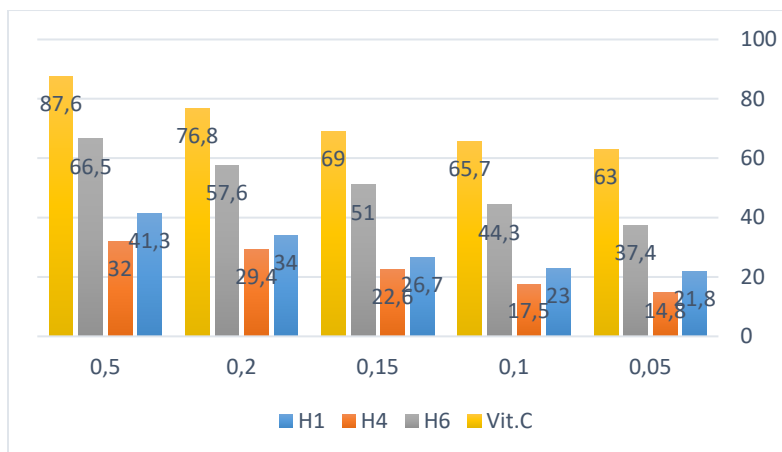


Fig. 21. Antioxidant activity of the H₁ H₄, and H₆ compounds

The IC₅₀ for each compound were particular and display in the Table 11 and Fig.s 22 and 23.

Table 11. IC₅₀ values of antioxidant activity of H₁, H₄ and H₆ compounds [48].

Compound	IC ₅₀ Mm
H ₁	0.4600
H ₄	0.5800
H ₆	0.2700
Vitamin C	0.2049

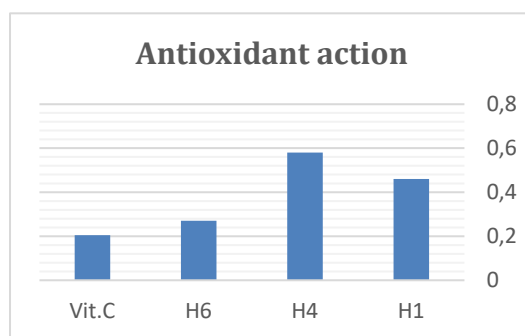


Fig. 22. IC₅₀ antioxidant activity of H₁, H₄ and H₆ compounds (the statistics were performed using Microsoft Excel)

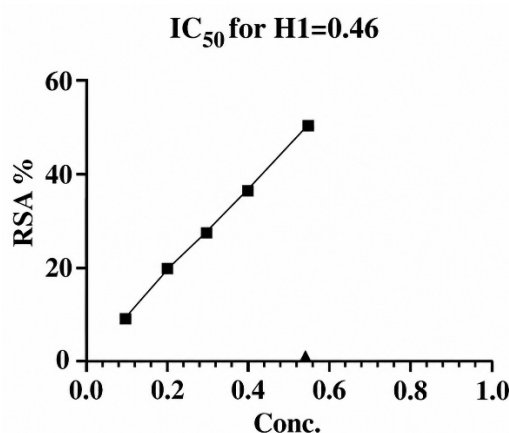


Fig. 23. The IC₅₀ for H₁ (the graph was performed using Prism Graph Pad software 9.0)

3.5. The molecular docking and computational simulation of the new oxazepine derivatives compounds (H₁-H₆) as antioxidant agents. In order to determine the optimal binding locations and the length of the bonds to neighboring residues in the protein, molecular docking of H₁, H₄, and H₆ with Tyrosinase (PDB ID: 3NM8) was performed [33]. With the Tyrosinase enzyme, several binding sites displayed varying binding energies. Nonetheless, the Tyrosinase enzyme with the lowest binding energy among the produced compounds was chosen for more examination and visualization. Molecular docking of H₁, H₄, and H₆ with Tyrosinase (PDB ID: 3NM8) was performed to find the best binding sites and the length of the bonds to nearby residues in the protein [33]. A number of binding sites showed different binding energies with the Tyrosinase enzyme. However, out of all the compounds that were created, the Tyrosinase enzyme with the lowest binding energy was selected for further analysis and visualization, as stated in the previous studies [13, 14].

The docking results for H₁ with Tyrosinase

(PDB ID: 3NM8) showed six hydrogen bonds with the following residues: Arg 6A, Arg 75A, Arg 75A, Arg 78A, Arg 78A, and Asn 270B. However, π cation interactions were shown with Arg 78A. Also, the H₁ compound showed a reasonable binding affinity with approximately -6.4 kcal/mol with Tyrosinase.

The docking results for H₄ with Tyrosinase (PDB ID: 3NM8) showed only two hydrogen bonds with the following residues: Thr 137B and Phe 258A. However, three hydrophobic interactions were found to bind to the prepared compounds with bond lengths less than 3.5 angstroms with Tyrosinase enzyme at Pro 51A, Thr 137B, and Phe 258A. Also, the H₄ compound showed a reasonable binding affinity with approximately -6.7 kcal/mol with Tyrosinase.

On the other hand, the docking results for compound H₆ with tyrosinase (PDB ID: 3NM8) revealed the formation of only two hydrogen bonds involving residues Asp55A and Asn57A. However, three hydrophobic interactions were shown with bond lengths less than 3.5 angstroms with Tyrosinase enzyme at Pro 201A and Val 218A at two sites. Also, H₄ compound showed a

reasonable binding affinity with approximately -6.7 kcal/mol with Tyrosinase. However, π cation interactions were shown with Arg 209A and also a salt bridge at Arg 209°A. All selected docked proteins with prepared compounds H₁, H₄, and H₆ have shown RMSD scores of 1.16,

1.4, and 1.3, respectively. H₄ compound has also shown the best binding affinity, fairly similar to the experimental assessment. Collectively, it can be clearly seen that the prepared compounds have shown fair antioxidant activity, which needs further in vivo investigations.

Table 12. Selected specific interactions between protein residues and the prepared compounds, with bond lengths measured in angstroms (Å)

PDB	Specific interactions	Residue	Amino acid	Distance H-A
H ₁	Hydrogen Bond	6A	Arg	2.8
		75A	Arg	2.8
		75A	Arg	2.2
		78A	Arg	2.8
		78A	Arg	2.0
		270B	Asn	3.0
	π -stacking	78A	Arg	3.0
H ₄	Hydrophobic Interaction	51A	Pro	3.4
		137B	Thr	3.4
		258A	Phe	3.8
	Hydrogen Bond	137B	Thr	2.2
		258A	Phe	2.5
H ₆	Hydrophobic Interaction	210A	Pro	3.8
		218A	Val	3.6
		218A	Val	3.6
	Hydrogen Bond	55A	Asp	2.1
		57A	Asn	2.1
	π -stacking	209A	Arg	4.2
	Salt bridge	209A	Arg	5.0

In silico molecular docking and simulation methods are widely used in pharmaceutical research, particularly in combination with artificial intelligence techniques [47–54]. Typically, the binding affinity of newly

synthesized biomolecules toward target proteins is evaluated through computational simulations prior to experimental investigation [13].

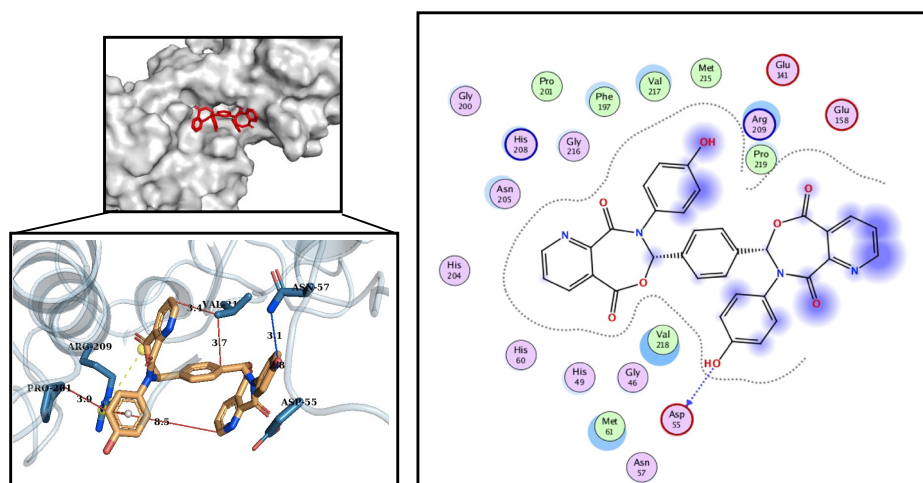


Fig. 24. Molecular docking representation of the synthesized compound H₁ (shown in red and orange) bound to tyrosinase (reductase enzyme, PDB ID: 3NM8), displayed in grey. The docking pose was visualized using PyMOL based on the MOE-generated PDB file

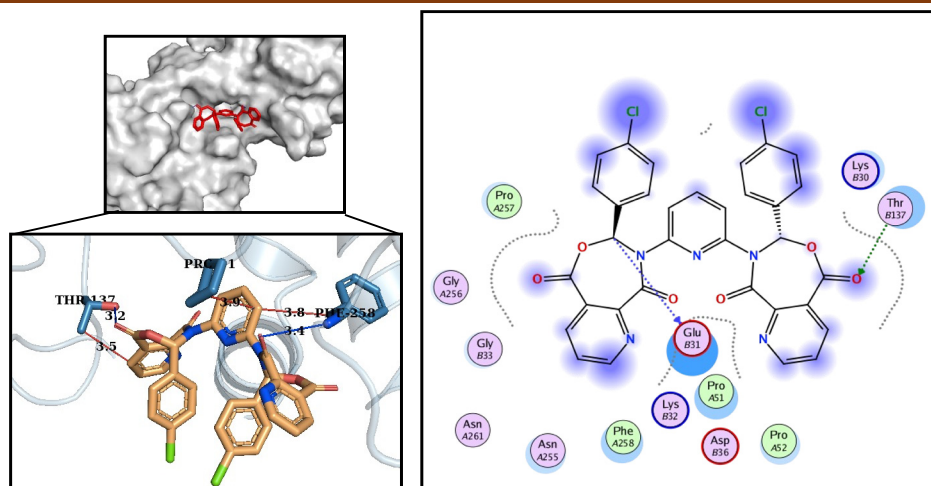


Fig. 25. Molecular docking representation of the synthesized compound H₄ (shown in red and orange) bound to tyrosinase (reductase enzyme, PDB ID: 3NM8), displayed in grey. The docking pose was visualized using PyMOL based on the MOE-generated PDB file

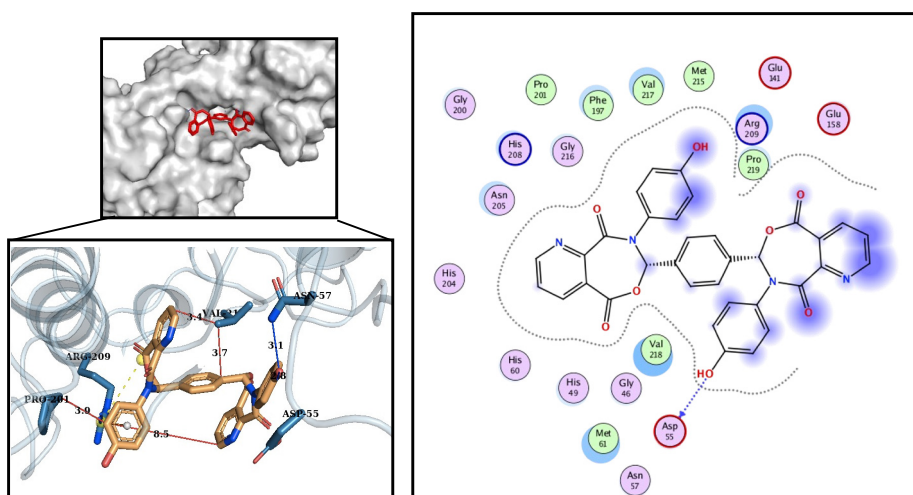


Fig. 26. Molecular docking representation of the synthesized compound H₆ (shown in red and orange) bound to tyrosinase (reductase enzyme, PDB ID: 3NM8), displayed in grey. The docking pose was visualized using PyMOL based on the MOE-generated PDB file

In this study, the binding affinity of novel homo-oxazepine dimer derivatives, designated H₁, H₄, and H₆, toward the reductase enzyme (PDB ID: 3NM8) was investigated using molecular docking in order to evaluate their antioxidant potential (Figs 23-26). Consistent with the docking results, experimental antioxidant assays revealed that compound H₄ exhibited the highest antioxidant activity. Compound H₁ showed lower activity than both H₄ and H₆ and displayed the weakest antioxidant performance among the studied derivatives. Nevertheless, all prepared compounds demonstrated superior antioxidant activity compared with the control (vitamin C). Docking analysis indicated that compound H₄ formed two hydrogen bonds with residues Thr137B and

Thr258A, with favorable bond lengths of approximately 2.0 Å. In addition, three hydrophobic interactions involving Pro51A, Thr137B, and Thr258A were observed, which may contribute to the enhanced binding affinity of this compound. In contrast, compound H₁ formed six hydrogen bonds and only one π - π stacking interaction, a binding mode that may account for its lower affinity relative to H₄. Compound H₆ exhibited intermediate antioxidant activity, which can be attributed to the formation of two hydrogen bonds with Asp55A and Asp57A, along with three relatively weaker hydrophobic interactions (~ 3.0 Å), π - π stacking interactions with Arg209A, and a salt bridge at the same residue with a bond length of approximately 5.0 Å.

Overall, the experimental antioxidant activities showed good agreement with the *in silico* docking results. These findings clearly indicate that variations in binding-site geometry

and functional group interactions significantly influence the biological activity of homo-oxazepine dimers [35].

Conclusion

The aim of this study was to synthesize a series of oxazepine derivatives via the condensation of amines with various benzaldehyde derivatives using benzene as the solvent. The resulting intermediates were subsequently reacted with pyridine-5,7-dione anhydride in dry benzene to afford oxazepine derivatives (H₁–H₆). The synthesized compounds were structurally characterized by Fourier-transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (¹H-NMR) spectroscopy, and mass spectrometry, confirming the successful formation of the target structures. Reaction progress at each stage was monitored by thin-layer chromatography (TLC).

The antioxidant activity of compounds H₁–H₆ was evaluated in comparison with vitamin C, and all synthesized derivatives exhibited superior antioxidant performance relative to the control.

In addition, molecular docking studies of selected compounds (H₁, H₄, and H₆) with tyrosinase (PDB ID: 3NM8) were conducted to identify optimal binding modes and interactions with neighboring amino acid residues. The docked complexes showed RMSD values of 1.16, 1.40, and 1.30 for H₁, H₄, and H₆, respectively, indicating reliable docking poses. Among the studied compounds, H₄ demonstrated the most favorable binding affinity, in good agreement with the experimental antioxidant results.

Overall, the combined experimental and *in silico* findings suggest that the synthesized oxazepine derivatives possess promising antioxidant activity. Nevertheless, further *in vivo* investigations are required to fully assess their biological potential.

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Conflict of interest

The authors announced that there are no conflicts of interest regarding this current work.

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