# SYNTHESIS, CHARACTERIZATION OF A NEW COMPOUND 22-(3,5-BIS(3,5,5,6-TETRAMETHYL-1,1-DIOXIDO-5,6-DIHYDRO-2H-1,2-THIAZIN-2-YL)PHENYL)-3,5,5,6-TETRAMETHYL-5,6-DIHYDRO-2H-1,2-THIAZINE 1,1-DIOXIDE, AND STUDY OF ITS BACTERIAL AND FUNGAL ACTIVITY AND MOLECULAR DOCKING

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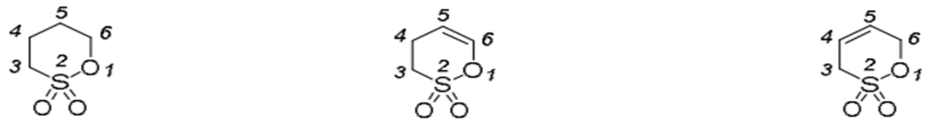
*Received 17.01.2025*
*Accepted 11.02.2025*

***Abstract:*** *A synthesis of a new compound (II) with three groups of 1,2-thiazine 1,1-dioxide, called (2-(3,5-bis(3,5,5,6-tetramethyl-1,1-dioxido-5,6-dihydro-2H-1,2-thiazin-2-yl)phenyl)-3,5,5,6-tetramethyl-5,6-dihydro-2H-1,2-thiazine 1,1-dioxide ), was synthesized by reacting moles (1:3) of each of benzene-1,3,5-triamine with 3,4,4,6-tetramethyl-3,4-dihydro-1,2-oxathiine 2,2-dioxide (I), respectively. The last compound (I) was prepared by equal moles of each of (4-methylpent-3-en-2-one) with (sulfonylethane). The structural formula of the resulting compounds was confirmed by their spectroscopic identification (FT-IR, $^1$H-NMR, $^{13}$C-NMR). The effect of these two compounds at different concentrations (0.01, 0.1, 1.0, and 10 mg/ml) on the growth of six types of Gram-negative and positive bacteria (Protans vulgarisginosa, Staphylococcus aureus, Pseudonas aeruginosa, Bacillus subtillus, and Enterbacter sp.) was studied. Compared with the pharmaceutical compound Chloramphenicol, it shows high inhibition values at concentrations (1.0 and 10 mg/ml) and exceeds the reference's inhibition limit. It is also noted that the concentrations of the acid compound (0.01 and 0.1 mg/ml) are acceptable. The effect of these two compounds was also measured using concentrations (10, 25, and 30 mg/ml) on the growth of fungi A. fumigates, T.mentagrophytes, C.albicans and M. canis zone (killing). For the concentrations of the prepared compounds, the killing range of compound (II) is much higher compared to compound (I). Furthermore, molecular docking studies have revealed many correlations with amino acid residues in active sites, so these results have the potential to stimulate further research on heterocyclic compounds.*

***Keywords:*** *Synthesis, new compound, -1,2-thiazine 1,1-dioxide, Dugong, fungi, bacteria*

## Introduction

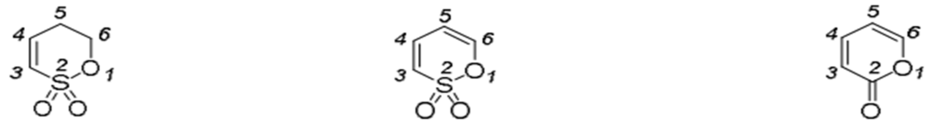
Old, the name 1,4-sultones, 1,4-butanesultone, or δ-sultones was given to the compounds 1,2-oxathiine 2,2-dioxides [1], which are relatively rare compounds and are heterocyclic compounds of which there are multiple isomers at the positions (1,2,3) [2-4]. The least discovered of which is 1,2-oxathiine. A review of the literature shows, that compounds with hexagonal rings containing one or two heteroatoms were prepared (Fig. 1): tetrahydro-1 (1,2-oxathiane 2,2-dioxide), three dihydro-2, 3, 4 isomers, and the completely unsaturated 1,2-oxathiine 2,2-dioxide systems that can be considered as SO₂ analogues of the pyran-2-one system that has been studied in detail and is distinguished by its great biological effect [5-7].



1,2-oxathiane 2,2-dioxide
**1**

3,4-dihydro-1,2-oxathiine 2,2-dioxide
**2**

3,6-dihydro-1,2-oxathiine 2,2-dioxide
**3**



5,6-dihydro-1,2-oxathiine 2,2-dioxide
**4**

1,2-oxathiine 2,2-dioxide
**5**

2*H*-pyran-2-one
**6**

**Fig. 1.** Structure and nomenclature of 1,2-oxathiine derivatives

A review of the scientific literature on the reactions, synthesis, structure, and applications of the 1,2-oxathiine 2,2-dioxide ring system [8] suggests that this heterogeneous ring, which has rarely been studied, can be studied, for example, following traditional and modern synthetic chemistry, as this ring provides great potential as it is considered a basic building block for building many heterogeneous and non-cyclic compounds. Furthermore, δ-sultone is an invaluable reagent, as it is easily soluble in water, as well as in a variety of materials including polymers and dyes [9-13].

These compounds, as well as those containing nitrogen atoms, are also heterogeneous, play an important role in the effect of biological activity, and the use of these compounds appears to be of great importance in many applications in the field of medicinal chemistry, pharmaceuticals, and agricultural pesticides [14-15].

They are used in various compounds with biological properties, including antibacterial [16], anticonvulsant [17], herbicide [18], activity against Gram-positive bacteria [19, 20], anti-HIV [21], anti-inflammatory effects [22], anti-allergic [23], antifungal, and antiviral [24, 25].

They also have pharmaceutical applications due to their stability towards moisture, light, oxygen, and metabolism in the body [26]. They also have wide applications in industry [27], can be used as photosensitizing materials [28], dyes, and agricultural chemicals [29]. They have a benefit as synthetic aids [30-31] and are used as anti-corrosion agents commercially and in drug discovery [32], materials science [26], and synthetic chemistry [33-35].

The purpose of this study was the synthesis and characterization of a new compound, 22-(3,5-bis(3,5,5,6-tetramethyl-1,1-dioxido-5,6-dihydro-2H-1,2-thiazin-2-yl)phenyl)-3,5,5,6-tetramethyl-5,6-dihydro-2H-1,2-thiazine 1,1-dioxide, and the study of its bacterial and fungal activity and molecular docking.

## Experimental part

**Synthesis of 3,4,4,6-tetramethyl-3,4-dihydro-1,2-oxathiine 2,2-dioxide (I)** [36-38].

The reaction was carried out using the method previously described by Brain [38], with some modifications. 4-Methylpent-3-en-2-one (3.93 g, 0.04 mol) is added gradually to acetic anhydride (45 g), and the mixture is cooled to 0 degrees Celsius. Then, sulfonyl ethane acid (3.68 g, 0.04 mol) is added drop by drop while the reaction temperature remains at 0 degrees Celsius, using an ice bath with salt. The reaction is stirred for two hours, then placed in the refrigerator for 24 hours. Then we separate the reaction mixture by pouring it into an equal amount of water and ice with vigorous stirring. The resulting light yellow precipitate is then separated. A solvent consisting of 80% water and ethanol was used to purify the precipitate by recrystallization. The reaction was followed using the TLC technique. It gave a product (3,4,4,6-tetramethyl-3,4-dihydro-1,2-oxathiine 2,2-dioxide (I)), which has a prismatic shape and is colorless, and its melting point is m.p. 77-79°C, and yield is 78%. The identity of the resulting compound was confirmed by spectroscopic methods.

**Synthesis of 2-(3,5-bis(3,5,5,6-tetramethyl-1,1-dioxido-5,6-dihydro-2H-1,2-thiazin-2-yl)phenyl)-3,5,5,6-tetramethyl-5,6-dihydro-2H-1,2-thiazine 1,1-dioxide (II)** [36-38]

Benzene-1,3,5-triamine (0.5 g, 0.004 mol) is gradually added to the compound 3,4,4,6-tetramethyl-3,4-dihydro-1,2-oxathiine 2,2-dioxide (I) (2.28 g, 0.012 mol). In a circular flask equipped with a reflux condenser at a temperature not exceeding 120°C for a period ranging from 40 to 48 hours. After the reaction is over, the mixture is added to dilute hydrochloric acid (1%), then the precipitate is filtered, washed with water, dried, and recrystallized from absolute methanol to give bright white crystal blades with m.p. 122-124 °C and yields of 84%. The identity of the resulting compound was confirmed by spectroscopic methods.

## Results and discussion

The derivative of the oxathiine compound was prepared by reacting an equal number of moles of (4-methylpent-3-en-2-one) with (sulfonylethane) using a catalyst (acetic anhydride) to obtain a heterogeneous cyclic compound with 6-membered ring (I) (Fig. 2).

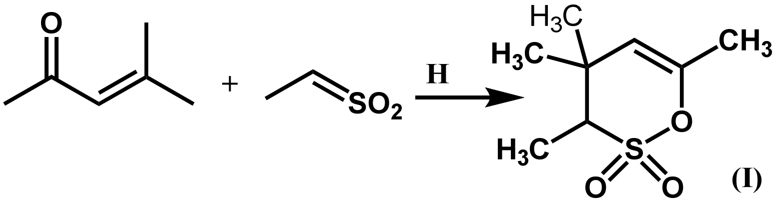


**Fig. 2.** Synthesis of compound (I)

Using spectrometers (FT-IR, $^1$H-NMR and $^{13}$C-NMR), the nature of the prepared compound was confirmed.

The FT-IR of compound (I) shows a double stretching absorption band of the $SO_2$ group at 1420 and 1032 cm$^{-1}$. The appearance of a band at the range 3065 cm$^{-1}$ is due to the (=C-H) group, a band at the range 2450 and 725 cm$^{-1}$ is (C-H), and at the range 2655 cm$^{-1}$ is due to the (-C-H) group -CH3, and the functional group (C=C) appears at the range 1654 cm$^{-1}$ and the appearance of a stretching band for the (C-O) group at the range 1266 cm$^{-1}$. The absence of a stretching band for the (C=O) group at the range 1740-1720 cm$^{-1}$.

The $^1$H-NMR spectrum of compound (I) gave a signal for the $CH_3$–CO group at (2.81 s)δ ppm, and for $(CH_3)_2$–C- at (2.05, 2.14 s) δ ppm, while the olefinic proton C=C-H showed a signal at (6.91s) δ ppm, and a signal at (6.01-6.11 m) δ ppm. is due to the S-C-H group.

$^{13}$C-NMR spectrum of compound (I) and chemical shifts d6-DMSO. The appearance of the $CH_3$-C-$SO_2$ frequency at δ 19.98 ppm, and the methyl groups show two carbon atoms $(CH_3)_2$-C- frequencies at 39.37-39.80 and 40.20-40.62 δ ppm, while the carbon atoms =C-$CH_3$ appear at 21.37 δ ppm. The frequency at 100.24 δ ppm, belongs to the carbon $(CH_3)_2$-C- as well as the frequency of 113.96 δ ppm for the carbon $CH_3$-C-$SO_2$ and also the appearance of a frequency at position 147.09 δ ppm belongs to the carbon $CH_3$-C=C- and also the frequency at 156.71 belongs to the carbon $CH_3$-C=C.

One of the most important reactions that these compounds (thiazines) undergo is the replacement of the ether oxygen atom in the 6-membered ring with the substituted nitrogen atom, via the ANRORC (nucleophilic ring addition-opening-ring-closing) reaction to produce it.

Then, to produce the last compound (II), 3 moles of 3,4,4,6-tetramethyl-3,4-dihydro-1,2-oxathiine 2,2-dioxide (I) react with one mole of benzene-1,3,5-triamine to obtain 2-(3,5-bis(3,5,5,6-tetramethyl-1,1-dioxido-5,6-dihydro-2H-1,2-thiazin-2-yl)phenyl)-3,5,5,6-tetramethyl-5,6-dihydro-2H-1,2-thiazine1,1-dioxide (II) (Fig. 2).

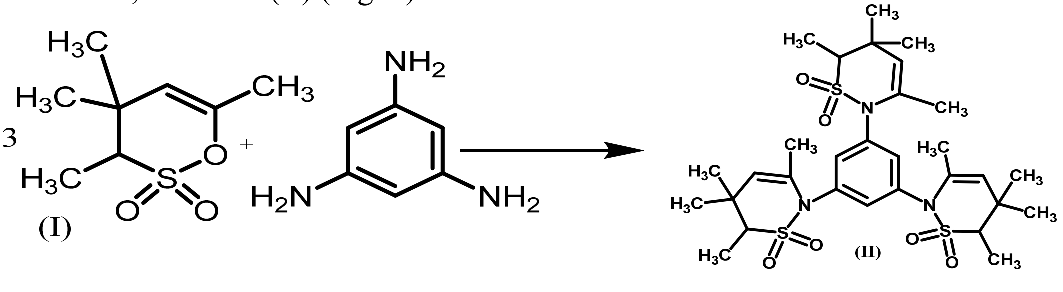


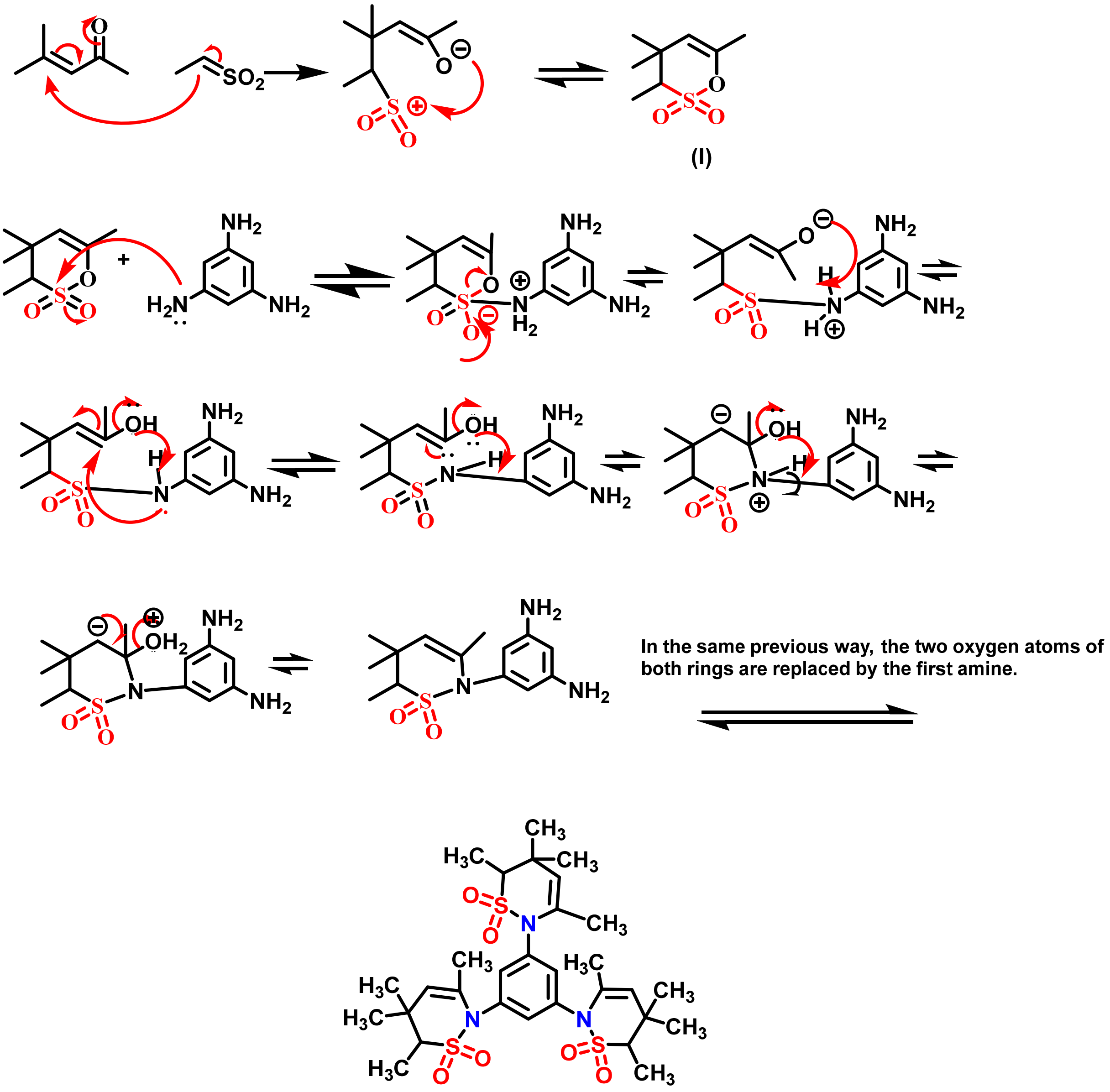
**Fig. 3.** **S**ynthesis of compound **(**II**)**

The FT-IR of compound (II) shows a double stretching absorption band for the $SO_2$ group at 1431 and 1023 cm$^{-1}$. A two bands at the range 2966 cm$^{-1}$ and 750 cm$^{-1}$ are due to (C-H); the appearance of a band at the range 3063 cm$^{-1}$ is due to the (=C-H) group; a band at the range 2961 cm$^{-1}$ is due to the (-C-H) to -$CH_3$ group; and the functional group (C=C) appears at the range 1645 cm$^{-1}$, as well as two bands at positions 1317 and 1243 cm$^{-1}$ due to the (C-N) group, and the absence of a stretching band for the (C-O) group at the range 1266-1420 cm$^{-1}$, as well as the disappearance of a double band due to (-$NH_2$) between the range 3000-3300 cm$^{-1}$.

The $^1$H-NMR spectrum of compound (II) gave signals for the $CH_3$–CN group at (1.98 s) δ ppm and for $(CH_3)_2$–C = at (5.01, 5.71 s) δ ppm, while the olefinic proton C=C-H showed a signal at (7.54

s) δ ppm. Also, a signal at (7.31–7.42 M) δ ppm is due to the S-C-H group, and a signal (7.58 s) δ ppm is due to the protons of the aromatic ring.

$^{13}$C-NMR spectrum of compound (II) and characteristic chemical shifts (d6- DMSO). The appearance of the $CH_3$-C-$SO_2$ frequency at 21.65 δ ppm, and the methyl groups show two carbon atoms $(CH_3)_2$-C- frequencies at 77.74, 77.36 δ ppm, while the carbon atoms =C-$CH_3$ appear at 29.37 δ ppm. as well as the frequency of 110.67 δ ppm for the carbon $CH_3$-C-$SO_2$ and also the appearance of a frequency at positions 129.54-129.74 and 129.86-129.64 δ ppm, which belongs to the olefinic carbon $CH_3$-C=C-; also the frequency at 141.61 δ ppm which belongs to the cyclo-olefinic carbon $CH_3$-C-N-; the frequency at 116.18 and 144.24 δ ppm is due to the aromatic ring carbons C=C-C and C=C-N, respectively.



In the same previous way, the two oxygen atoms of both rings are replaced by the first amine.

**Fig. 4.** Mechanism of synthesis of the two compounds (I) and (II)

**Bioactivity.** Using the cup agar plate diffusion method [39-42], the new synthesized compounds of 3,4,4,6-tetramethyl-3,4-dihydro-1,2-oxathiine-2,2-dioxide (I) and 2-(3,5-bis(3,5,5,6-tetramethyl-1,1-dioxido-5,6-dihydro-2H-1,2-thiazin-2-yl) phenyl)-3,5,5,6-tetramethyl-5,6-dihydro-2H-1,2-thiazine-1,1-dioxide (II) were evaluated at concentrations (0.01, 0.1, 1.0, and 10 mg/ml) in the growth of six types of Gram-negative and positive bacteria (*Protans vulgarisginosa, Staphylococcus aureus, Pseudonas aeruginosa, Bacillus subtillus, and Enterbacter sp.*), using the drug compound (Chloramphenicol) as a reference. The inhibition of compound (II) is observed to be greater than that of compound (I), in general, and for almost all concentrations. This is due to the increase in the number of faction groups when comparing the first and second synthesized compounds. A Table 1 shows high inhibition values at concentrations (1.0 and 10 mg/ml) and also exceeds the inhibition limit of the reference. It is also noted that the concentrations of the acid compound (0.01 and 0.1 mg/ml) are acceptable. This is done by measuring the inhibition values of the tablets (saturated with concentrations of the compound II) and embedded in bacteria dishes for 24 hours at a temperature of 37°C.

**Table 1.** The Diameter of Inhibition zone (mm)of Some Synthesized Compound Against Some *Gram$^{+ve}$ and Gram$^{-ve}$ Bacteria*

| *Comp. No.* | *Con. (mg/ml)* | *Protans vulgarisginosa* | *Staphylococcus aureus* | *Escherichia coli* | *Bacillus subtillus* | *Enterbacter sp.* | *Pseudonas aeruginosa* |
|---|---|---|---|---|---|---|---|
| I | 0.01 | - | - | 8 | 4 | - | 12 |
| | 0.1 | 4 | - | 9 | 12 | 5 | 13 |
| | 1.0 | - | 15 | 10 | - | 14 | 9 |
| | 10 | 10 | 9 | 11 | 20 | 17 | 15 |
| II | 0.01 | 2 | 14 | - | 10 | 24 | 14 |
| | 0.1 | 6 | - | 20 | 15 | 12 | 17 |
| | 1.0 | 10 | 27 | 19 | 16 | 25 | 24 |
| | 10 | 27 | 18 | 15 | 24 | 27 | 23 |
| Chloramphenicol (30/µgm)disk | control | 22 | 21 | 25 | 26 | 23 | 22 |

By observing the Table 2, which shows the effect of concentrations (10, 25, and 30 mg/ml) respectively for the synthetic compounds (I) and (II) against the types of fungi *A. fumigates, T.mentagrophytes, C.albicans and M. canis*. by measuring the inhibition zone (killing) for the concentrations of the prepared compounds, the killing range of compound (II) is much higher compared to compound (I), due to the previous reason, which is the presence of a number of functional groups for compound (II) more than compound (I), and it is noted for all types of fungi with a very good evaluation except against *A. fumigates*, as it is noted that its resistance to killing is high.

**Table 2.** The diameter of inhibition zone (mm) for organic compounds at (10, 20, and 40 mg/ml) against some fungal species [43]

| **Fungal types** | **Diameter of inhibition zone (mm) for synthesizes of organic comp.** | | | | | |
|---|---|---|---|---|---|---|
| | **Cons. comp. (I)** | | | **Cons. comp. (II)** | | |
| | 10 | 25 | 30 | 10 | 25 | 30 |
| *T.mentagrophytes* | 21 | 22 | 21 | 22 | 21 | 21 |
| *C.albicans* | 30 | 28 | 31 | 34 | 33 | 30 |
| *A. fumigates* | 16 | 13 | 14 | 17 | 15 | 10 |
| *M. canis* | 25 | 27 | 24 | 28 | 29 | 25 |

**Molecular docking.** Molecular docking studies were carried out for compounds (I) and (II) to identify the target enzymes under investigation and to assess the possible interactions of the heterocyclic rings, which have chemical affinities, indicating possible similarities in their chemical properties or methods, and amino acids as potential sources of importance in ligand binding. Docking studies of the present acidic residues ARG158 is an experimental compound with potential applications in medicine. Preliminary studies suggest that ARG158 may target biological pathways specifically associated with diseases [44-45]. Basic enzyme receptor studies influence how it works, making it promising for further clinical research. Current research focuses on evaluating its efficacy, safety, and outcomes [46-48].

The study showed that compound (I) interacts with the protective residue at the site by forming various interactions: the hydrogen bonding ARG158 protective tank is located at the formation site with an oxygen pair of electrons for the sulfate complex in the vessel, and three alkyl bonds remain on security beads ILE254, MET160, and PRO98 located at the site of production with methyl groups in the mixture (Table 2, Fig. 5).

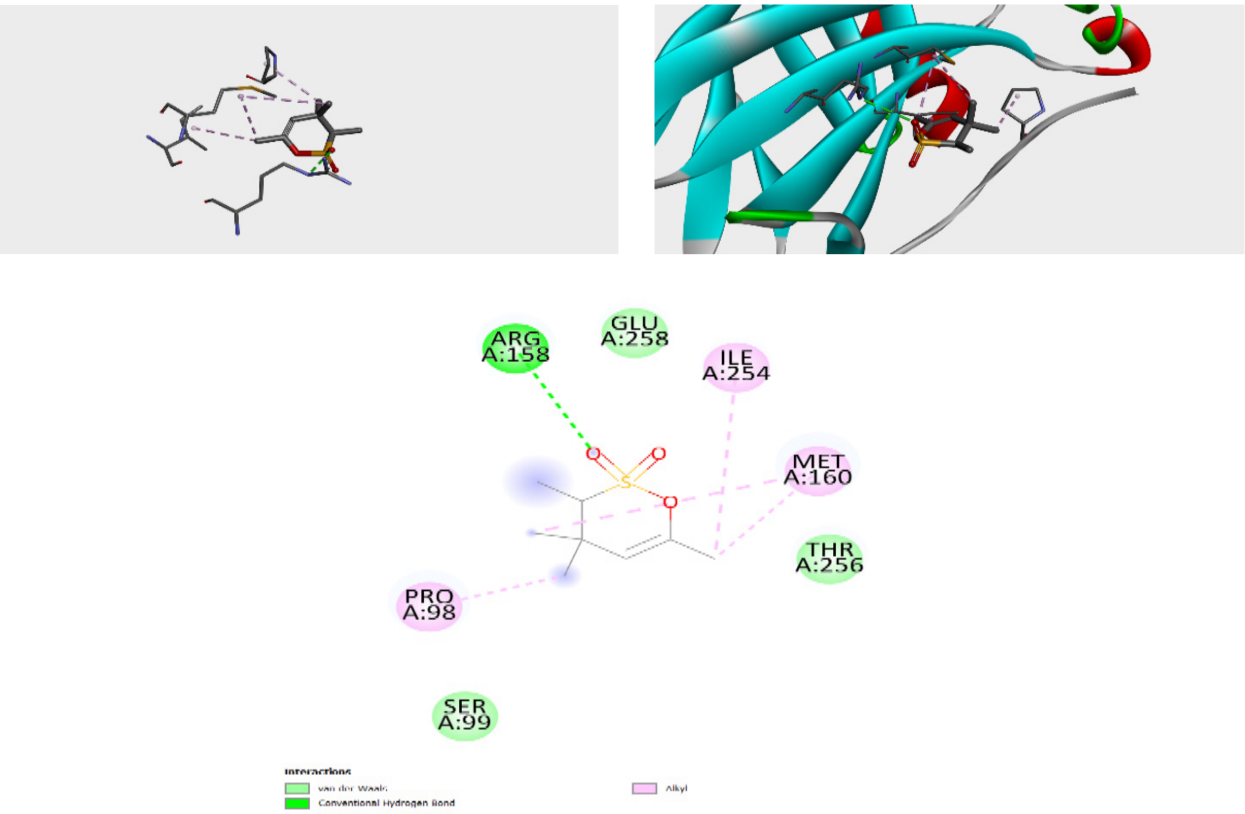
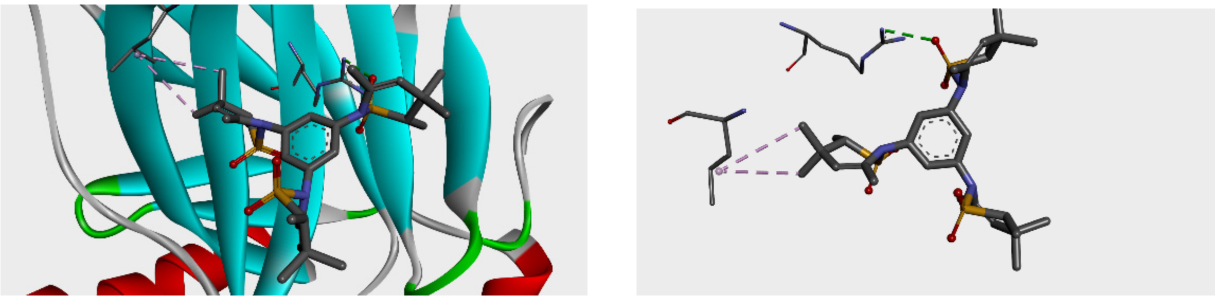


**Fig. 5.** The interaction between the compound (I) and Gastric cancer

Molecular docking studies of the prepared organic derivatives revealed the quantitative and qualitative interactions with amino acid residues in the active site, as the study identified compound (II) interacting with double bonds of amino acid residues ARG158, linking the sulfate group of the compound to the two electrons of the oxygen atom, and double alkyl bonds linking amino acid residues in the active site with methyl groups of the compound LEU264 [49-51] (Tab. 3, Fig. 6).



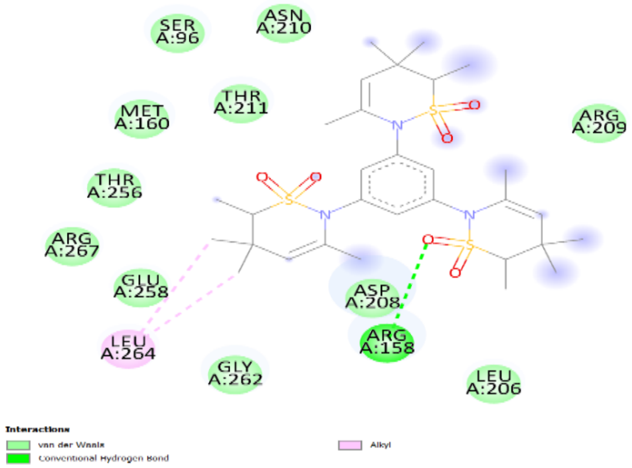


**Fig. 6.** The interaction between the compound II and Gastric cancer

**Table 3.** Values of binding energies for the compound **I and II**

| **Comp. Symb.** | **RMSD** | **Docking Score** |
|---|---|---|
| **I** | 0.042 | -7.7 |
| **II** | 0.046 | -7.1 |

## Conclusion

High-value heterocyclic compounds were synthesized for target compounds (I) and (II). Purified compounds were studied for effects on various bacteria (Gram-negative and Gram-positive) and were determined using spectroscopic techniques such as FT-IR, 13C NMR, and 1H-NMR, and structures were analyzed and discussed. The biological interactions of the formulations were compared with those of conventional antibiotics. Our new compounds clearly showed inhibition of a variety of bacteria, as well as effects on fungi, some of which showed higher biological activity than the selected compounds in the two studies. A molecular docking study revealed several interactions involving amino acid residues in the active site.

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