Egypt. J. Chem. **Vol. 65,** No. 8, pp. 133 - 146 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

An efficient One-pot three-component synthesis, Molecular docking, ADME and DFT predictions of new series Thiazolidin-4-one derivatives bearing a Sulfonamide moiety as potential Antimicrobial and Antioxidant agents

Sangar Ali Hassan[a*], Media Noori Abdullah[b], Dara Muhammed Aziz[a]

[a]*Department of Chemistry, College of Science, University of Raparin, Sulaymaniyah, Iraq.*

[b]*Department of Chemistry, College of Science, Salahaddin University-Erbil, Erbil, Iraq.*

Abstract

Thiazolidin-4-ones possess high biological effectiveness, we present various methods for one-pot three-component synthesis. The thiazolidin-4-ones (**4a-i**) with sulfonamide bioactive moieties were synthesized in reasonable yields by reacting sulfadiazine (**1**) with various substituted benzaldehydes (**2a-i**) and mercaptoacetic acid (**3**). The spectral data all agreed on all titled compounds. Assessment of their in vitro antimicrobial activity was employed by a microdilution technique, the newly synthesized compounds screened significant growth suppression against resistant strains. All compounds exhibited acceptable DPPH Radical Scavenging Activity. To investigate possible binding mechanisms for the *Staphylococcus aureus* MurB protein (ID Code: 1HSK), in silico molecular docking was carried out. Furthermore, The Lipinski rule of five was observed in synthesized compounds with good ADME predictions. Lastly, the DFT/B3LYP principle and the 6-31 G (d, p) base set were used to compute HUMO, LUMO, MEP analysis, and quantum parameters.

Keywords: Thiazolidin-4-ones; Antimicrobial; Antioxidant; Molecular docking; ADME and DFT prediction.

1. Introduction

Heterocyclic compounds are a sort of organic compounds in which some or all of the atoms within the molecule are linked together in rings that contain at least one atom of an element other than carbon, utilized as intermediates in the production of other important heterocyclic rings which are normally distributed in nature [1]. Many heterocyclic rings, including sulfur, and nitrogen, have long been significant in the pharmaceutical field due to their varied biological activities [2] for example, anti-tumor, anti-inflammatory [3], and antibacterial [4].

4-Thiazolidinone, a five-member circle comprising sulfur and nitrogen with a carbonyl group on the fourth position, is one of the most important thiazolidine derivatives. It belongs to a key category of heterocyclic compounds [5]. Thiazolidin-4-one derivatives were synthesized from the reaction of Schiff bases with thioglycolic acid and some different techniques were used as conventional, sonication, and microwave techniques [6-10]. 4-Thiazolidinone derivatives possess a broad variety of biological and pharmaceutical properties, including antimicrobial [11], antioxidant, anti-candida [12], anticancer effect [13], antiproliferative [14], antihyperglycemic [15], antitoxoplasmaa gondii [16], anti-urease [17], antischistosomal [18], cytotoxicity [19], antimalarial [20], herbicidal [21], antihyperlipidemic [22], antidiabetic [23], anti-HIV [24], anticonvulsant [25], analgesic [26], antiparasitic [27], and antihypertensive [28]. Thiazolidin-4-ones combined with other chemical compounds produce significant biologically potent derivatives like sulfadiazine and sulfamethazine, often known as sulfonamide moiety and sulfa drugs [29]. They have been found to possess anticancer [30], antibacterial [31], anti-inflammatory [32], antiviral [33], and antifungal [34] activities. One-pot synthesis is becoming a more valuable and interesting field of research in organic synthesis because it provides high levels of efficiency by combining various operational steps, can comply with green chemistry protocols, delivers high levels of atom economy, is easy to handle, has short reaction time [35]. Because of the biological significance of thiazolidin-4-ones a bearing sulfonamide moiety, Herein, new series 4-thiazolidinone derivatives were synthesized as

*Corresponding author e-mail: sangar.ali@uor.edu.krd; (Sangar Ali Hassan).

Received Date: 04 November 2021, Received date: 15 December 2021, Accepted date: 04 January 2022

DOI: 10.21608/ejchem.2022.104381.4819

effective antimicrobial agents and antioxidant activity with computational studies.

2. Experimental

2.1. *Materials*

Chemical materials were purchased and utilized without additional purification from Merck, and Fluka. The melting points were measured in open capillaries with digital electrothermal 9100, and were uncorrected. The reactions' progress was checked by a TLC aluminum plate (HF254, 200 mesh) with an eluent of diethyl ether: methanol: ethyl acetate (70:15:15). UV light (CSL-MDOCBASIC) was used to visualize the TLC plates. Sonication was carried out with the help of an intelligent ultrasonic processor (Drawell, serial number: 201805517, and a standard power of 950 W). Hot Sale Laboratory Microwave Chemical Reaction Oven was used (Model Number: WBFY-205). A Thermo Scientific spectrometer was used to record FT-IR spectra (Model: Nicolet iS 10). Bruckner (400 MHz) was used to record the ^{13}C, and ^{1}H-NMR (DMSO-d_6) spectrum. Electron impact ionization was used to measure mass spectra using a JEOL-SX-102 device. A Shimadzu FLASHEA 112 analyzer was used to perform the elemental analysis. The chemical terms are abbreviated as written in the bracket (Hertz = Hz, coupling constant = *J*, broad = br, triplet = t, doublet = d, and singlet = s). The antimicrobial activity of the products was detected using a microplate reader (BioTek-ELx808). The absorbances were measured using a spectrophotometer (JENWAY Model: 6705).

2.2. Synthetic Methods

2.2.1. Synthesis of thiazolidin-4-ones (4a-i) using conventional in a one-pot three-component method

An appropriate synthetic conventional pathway was used with minor modifications [6-8]. Equimolar quantities of Sulfadiazine (1) (1 mmol), a series of substituted benzaldehydes (2a–i) (1 mmol), and mercaptoacetic acid (3) (1 mmol) were refluxed 8.5–14.5 hours, using 20 mL of DMF and 4–5 drops of acetic acid. TLC was utilized to monitor the reactions' progress. The solution was poured into chilled water, filtration of the precipitate. Column chromatography was used to purify the products using diethyl ether: methanol: ethyl acetate (70:15:15) as eluent.

2.2.2. Synthesis of thiazolidin-4-ones (4a-i) using sonication in a one-pot three-component technique

A proposed synthetic Ultrasound pathway was used with slight revisions [8, 9]. A mixture of an equimolar amount of Sulfadiazine (1) (1 mmol), a series of substituted benzaldehydes (2a–i) (1 mmol), and mercaptoacetic acid (3) (1 mmol) were irritated inside an ultrasonicator acoustic chamber at 80℃ for 125-220 minutes, using 10 mL of DMF and 3–4 drops of acetic acid. TLC was utilized to monitor the reactions' progress. The solution was poured to chilled water, filtration of precipitate. Column chromatography was used to purify the products using diethyl ether: methanol: ethyl acetate (70:15:15) as eluent.

2.2.3. Synthesis of thiazolidin-4-ones (4a-i) using a microwave-assisted in a one-pot three-component technique

plausible synthetic Microwave method was used with slight modifications [8, 10] Sulfadiazine (1) (1 mmol), a series of substituted benzaldehydes (2a–i) (1 mmol), and mercaptoacetic acid (3) (1 mmol) were mixed inside an open container, 5 mL of DMF and 2–3 drops of acetic acid were added, and irradiated in a domestic microwave oven at 700 W for 6.5-11 minutes. TLC was utilized to monitor the reactions' progress. The solution was poured into chilled water, filtration of the precipitate. Column chromatography was used to purify the products using diethyl ether: methanol: ethyl acetate (70:15:15) as eluent.

2.3. Characterization of synthesized compounds

4-(4-oxo-2-phenylthiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4a)

Yellow color solid, MP=298-299℃, FT-IR cm^{-1}: 3312 (N-H $_{str.}$), 3041 (C-H $_{Ar.}$), 2941, 2876 (C-H $_{aliphatic}$), 1676 (C=O $_{sy.str.}$), 1578 (C=C $_{sy.str.}$), 1334 (SO_2 $_{asy. str.}$), 1156 (SO_2 $_{sy. str.}$). ^{1}H-NMR δ: 11.439 (s, 1H (N-H)), 8.516 (d, 2H ($H_{4''}$, $H_{6''}$), *J*= 8.4 Hz), 7.727 (d, 2H ($H_{2'}$, $H_{6'}$), *J*= 8 Hz), 7.544 (d, 2H ($H_{3'}$, $H_{5'}$), *J*= 7.6 Hz), 7.397 (d, 2H (H_2, H_6), *J*= 8 Hz), 7.341 (t, 2H (H_3, H_5) , *J*= 5.2, 5.2 Hz), 7.257 (t, 1H (H_4) , *J*= 5.6, 5.6 Hz), 7.068 (t, 1H ($H_{5''}$), *J*= 4.8, 4.8 Hz), 6.384 (s, 1H (C-$H_{thiazolidin-4-one}$)), 4.051 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.2 Hz), 3.937 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.2 Hz). ^{13}C-NMR δ: 170.39 (C=$O_{thiazolidin-4-one}$), 168.95 ($C_{2''}$), 157.73 ($C_{4''}$, $C_{6''}$), 143.97 ($C_{4'}$), 137.61 (C_1), 135.06 ($C_{1'}$), 129.37 ($C_{2'}$, $C_{6'}$), 127.61 (C_3, C_5), 126.81 (C_4), 126.63 (C_2, C_6), 121.65 ($C_{3'}$, $C_{5'}$), 115.98 ($C_{5''}$), 74.03 (C-$H_{thiazolidin-4-one}$), 32.84 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{19}H_{16}N_4O_3S_2$: C, 55.33 (55.35); H, 3.91 (3.90); N, 13.58 (13.60); S, 15.54 (15.56). EI-MS: *m/z* Found: 412.53 $[M]^+$.

4-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4b)

Light-yellow color solid, MP= 352-353℃, FT-IR cm^{-1}: 3315 (N-H $_{str.}$), 3036 (C-H $_{Ar.}$), 2938, 2865 (C-H $_{aliphatic}$), 1685 (C=O $_{sy.str.}$), 1578 (C=C $_{sy.str.}$), 1532 (NO_2 $_{asy. str.}$), 1351 (NO_2 $_{sy. str.}$), 1331 (SO_2 $_{asy. str.}$), 1157 (SO_2 $_{sy. str.}$). ^{1}H-NMR δ: 11.236 (s, 1H (N-H)), 8.519

(d, 2H ($H_{4''}$, $H_{6''}$), *J*= 8 Hz), 8.300 (d, 2H (H_3, H_5), *J*=8.8 Hz), 7.767 (d, 2H ($H_{2'}$, $H_{6'}$), *J*= 7.6 Hz), 7.543 (d, 2H (H_2, H_6), *J*=8 Hz), 7.479 (d, 2H ($H_{3'}$, $H_{5'}$), *J*= 8.8 Hz), 7.030 (t, 1H ($H_{5''}$), *J*= 4.8, 4.8 Hz), 6.318 (s, 1H (C-$H_{thiazolidin-4-one}$)), 4.126 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 16.8 Hz), 4.042 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 16.8 Hz). ^{13}C-NMR *δ*: 170.45 (C=$O_{thiazolidin-4-one}$), 167.91 ($C_{2''}$), 157.60 ($C_{4''}$, $C_{6''}$), 147.82 (C_4), 146.94 (C_1), 145.80 ($C_{4'}$), 136.40 ($C_{1'}$), 129.96 (C_2, C_6), 129.54 ($C_{2'}$, $C_{6'}$), 124.51 (C_3, C_5), 121.82 ($C_{3'}$, $C_{5'}$), 116.18 ($C_{5''}$), 73.41 (C-$H_{thiazolidin-4-one}$), 34.23 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{19}H_{15}N_5O_5S_2$: C, 49.88 (49.81); H, 3.31 (3.32); N, 15.31 (15.34); S, 14.02 (14.03). MS (ESI): *m/z* Found: 457.20 $[M]^+$.

4-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4c)

Peach color solid, MP= 345-346℃, FT-IR cm^{-1}: 3407 (O-H $_{str.}$), 3273 (N-H $_{str.}$), 3041 (C-H $_{Ar.}$), 2964, 2873 (C-H $_{aliphatic}$), 1692 (C=O $_{sy.str.}$), 1577 (C=C $_{sy.str.}$), 1359 (SO_2 $_{asy. str.}$), 1155 (SO_2 $_{sy. str.}$). ^{1}H-NMR *δ*: 11.821 (s, 1H (O-H)), 11.634 (s, 1H (N-H)), 8.551 (d, 2H ($H_{4''}$, $H_{6''}$), *J*= 8.8 Hz), 7.721 (d, 2H ($H_{2'}$, $H_{6'}$), *J*= 8 Hz), 7.585 (d, 2H (H_2, H_6), *J*= 8.4 Hz), 7.462 (d, 2H ($H_{3'}$, $H_{5'}$) , *J*= 7.6 Hz), 7.063 (t, 1H ($H_{5''}$), *J*= 4.8, 4.8 Hz), 6.818 (d, 2H (H_3, H_5), *J*= 8 Hz), 6.312 (s, 1H (C-$H_{thiazolidin-4-one}$)), 4.071 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.4 Hz), 3.963 (d, 1H (CH_{2} $_{Thiazolidin-4-one}$), *J*= 15.4 Hz). ^{13}C-NMR *δ*: 171.52 (C=$O_{thiazolidin-4-one}$), 169.73 ($C_{2''}$), 159.18 ($C_{4''}$, $C_{6''}$), 155.87 (C_4), 143.69 ($C_{4'}$), 136.46 ($C_{1'}$), 132.13 (C_1), 131.27 (C_2, C_6), 130.05 ($C_{2'}$, $C_{6'}$), 122.21 ($C_{3'}$, $C_{5'}$), 116.69 (C_3, C_5), 114.96 ($C_{5''}$), 74.07 (C-$H_{thiazolidin-4-one}$), 32.83 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{19}H_{16}N_4O_4S_2$: C, 53.26 (53.25); H, 3.76 (3.77); N, 13.08 (13.06); S, 14.96 (14.97). EI-MS: *m/z* Found: 428.10 $[M]^+$.

4-(2-(2-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4d)

Brown color solid, MP= 327-328℃, FT-IR cm^{-1}: 3417 (O-H $_{str.}$), 3228 (N-H $_{str.}$), 3039 (C-H $_{Ar.}$), 2940, 2834 (C-H $_{aliphatic}$), 1689 (C=O $_{sy.str.}$), 1584 (C=C $_{sy.str.}$), 1332 (SO_2 $_{asy. str.}$), 1153 (SO_2 $_{sy. str.}$). ^{1}H-NMR *δ*: 12.442 (s, 1H (O-H)), 11.739 (s, 1H (N-H)), 8.544 (d, 2H ($H_{4''}$, $H_{6''}$), *J*= 8 Hz), 8.094 (d, 2H ($H_{2'}$, $H_{6'}$), *J*= 8.4 Hz), 7.560 (d, 2H ($H_{3'}$, $H_{5'}$), *J*= 7.6 Hz), 7.138 (t, 1H ($H_{5''}$), *J*= 4.4, 4.4 Hz), 7.069 (t, 1H (H_5) , *J*= 5.2, *J*= 5.2 Hz), 6.931 (d, 1H (H_6), *J*= 8 Hz), 6.845 (d, 1H (H_4), *J*= 7.6 Hz), 6.370 (s, 1H (C-$H_{thiazolidin-4-one}$)), 4.171 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.2 Hz), 4.033 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.2 Hz), 3.781 (s, 3H (OCH_3)). ^{13}C-NMR *δ*: 170.74 (C=$O_{thiazolidin-4-one}$), 168.01 ($C_{2''}$), 157.25 ($C_{4''}$, $C_{6''}$), 148.41 (C_3), 146.08 (C_2), 145.89 ($C_{4'}$), 136.16 ($C_{1'}$), 130.43 ($C_{2'}$, $C_{6'}$), 124.27 (C_5), 122.20 ($C_{3'}$, $C_{5'}$),120.61 (C_6), 119.68 (C_1), 115.98 ($C_{5''}$), 112.64 (C_4), 68.03 (C-$H_{thiazolidin-4-one}$), 56.50 (OCH_3), 34.37 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{20}H_{18}N_4O_5S_2$: C, 52.39 (52.40); H, 3.96 (3.97); N, 12.22 (12.21); S, 13.98 (13.96). EI-MS: *m/z* Found: 458.32 $[M]^+$.

4-(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4e)

Maroon color solid, MP= 317-318℃, FT-IR cm^{-1}: 3423 (O-H $_{str.}$), 3234 (N-H $_{str.}$), 3035 (C-H $_{Ar.}$), 2943, 2831 (C-H $_{aliphatic}$), 1693 (C=O $_{sy.str.}$), 1581 (C=C $_{sy.str.}$), 1336 (SO_2 $_{asy. str.}$), 1161 (SO_2 $_{sy. str.}$). ^{1}H-NMR *δ*: 12.364 (s, 1H (O-H)), 11.780 (s, 1H (N-H)), 8.495 (d, 2H ($H_{4''}$, $H_{6''}$), *J*= 8.4 Hz), 7.933 (d, 2H ($H_{2'}$, $H_{6'}$), *J*= 8 Hz), 7.468 (d, 2H ($H_{3'}$, $H_{5'}$), *J*= 8.8 Hz), 7.391 (s, 1H (H_2), 7.213 (d, 1H (H_6), *J*= 7.6 Hz), 7.083 (t, 1H ($H_{5''}$), *J*= 4.8, 4.8 Hz), 6.847 (d, 1H (H_5) , *J*= 8.4 Hz), 6.296 (s, 1H (C-$H_{thiazolidin-4-one}$)), 4.136 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.6 Hz), 4.074 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.6 Hz), 3.803 (s, 3H (OCH_3)). ^{13}C-NMR *δ*: 171.49 (C=$O_{thiazolidin-4-one}$), 167.32 ($C_{2''}$), 158.84 ($C_{4''}$, $C_{6''}$), 147.09 (C_3), 146.90 (C_4), 145.42 ($C_{4'}$), 134.08 ($C_{1'}$), 133.43 (C_1), 130.16 ($C_{2'}$, $C_{6'}$), 121.13 (C_6), 120.74 ($C_{3'}$, $C_{5'}$), 116.34 (C_5), 115.49 ($C_{5''}$), 113.17 (C_2), 69.46 (C-$H_{thiazolidin-4-one}$), 57.76 (OCH_3), 32.86 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated for (Found) $C_{20}H_{18}N_4O_5S_2$: C, 52.39 (52.41); H, 3.96 (3.96); N, 12.22 (12.19); S, 13.98 (13.96). EI-MS: *m/z* Found: 458.47 $[M]^+$.

4-(2-(4-iodophenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4f)

Yellow color solid, MP= 360-361℃, FT-IR cm^{-1}: 3387 (N-H $_{str.}$), 3036 (C-H $_{Ar.}$), 2963, 2879 (C-H $_{aliphatic}$), 1690 (C=O $_{sy.str.}$), 1573 (C=C $_{sy.str.}$), 1357 (SO_2 $_{asy. str.}$), 1139 (SO_2 $_{sy. str.}$). ^{1}H-NMR *δ*: 11.696 (s, 1H (N-H)), 8.473 (d, 2H ($H_{4''}$, $H_{6''}$), *J*= 8.4 Hz), 8.059 (d, 2H (H_3, H_5), *J*=8 Hz), 7.771 (d, 2H ($H_{2'}$, $H_{6'}$), *J*= 7.6 Hz), 7.534 (d, 2H ($H_{3'}$, $H_{5'}$), *J*= 8.4 Hz), 7.206 (d, 2H (H_2, H_6), *J*=7.2 Hz), 7.055 (t, 1H ($H_{5''}$), *J*= 4.4, 4.4 Hz), 5.991 (s, 1H (C-$H_{thiazolidin-4-one}$)), 3.838 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.2 Hz), 3.753 (d, 1H ($CH_{2thiazolidin-4-one}$), *J*= 15.2 Hz). ^{13}C-NMR *δ*: 169.15 (C=$O_{thiazolidin-4-one}$), 166.89 ($C_{2''}$), 155.93 ($C_{4''}$, $C_{6''}$), 143.81 ($C_{4'}$), 139.36 (C_1), 134.80 ($C_{1'}$), 130.95 (C_3, C_5), 130.15 (C_2, C_6), 128.32 ($C_{2'}$, $C_{6'}$), 122.06 ($C_{3'}$, $C_{5'}$), 120.94 (C_4), 114.87 ($C_{5''}$), 69.91 (C-$H_{thiazolidin-4-one}$), 31.75 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{19}H_{15}IN_4O_3S_2$: C, 42.39 (42.40); H, 2.81 (2.80); N, 10.41 (10.42); S, 11.91 (11.90). EI-MS: *m/z* Found: 537.79 $[M]^+$.

4-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4g)

Moccasin color solid, MP= 276-277℃, FT-IR cm^{-1}: 3325 (N-H $_{str.}$), 3033 (C-H $_{Ar.}$), 2942, 2875 (C-H $_{aliphatic}$), 1683 (C=O $_{sy.str.}$), 1572 (C=C $_{sy.str.}$), 1335 (SO_2

asy. str.), 1162 (SO_2 sy. str.). ^{1}H-NMR δ: 11.435 (s, 1H (N-H)), 8.563 (d, 2H ($H_{4''}$, $H_{6''}$), J= 8 Hz), 7.836 (d, 2H ($H_{2'}$, $H_{6'}$), J= 8 Hz), 7.561 (d, 2H ($H_{3'}$, $H_{5'}$), J= 7.2 Hz), 8.426 (d, 2H (H_3, H_5), J=8.4 Hz), 7.343 (d, 2H (H_2, H_6), J=8 Hz), 7.091 (t, 1H ($H_{5''}$), J= 4.8, 4.8 Hz), 6.382 (s, 1H (C-$H_{thiazolidin-4-one}$)), 3.926 (d, 1H ($CH_{2thiazolidin-4-one}$), J= 14.8 Hz), 3.837 (d, 1H ($CH_{2thiazolidin-4-one}$), J= 14.8 Hz). ^{13}C-NMR δ: (ppm) δ 172.21 (C=$O_{thiazolidin-4-one}$), 169.92 ($C_{2''}$), 156.76 ($C_{4''}$, $C_{6''}$), 147.04 ($C_{4'}$), 138.46 (C_1), 136.74 ($C_{1'}$), 131.79 (C_4), 130.87 (C_2, C_6), 130.08 ($C_{2'}$, $C_{6'}$), 129.31 (C_3, C_5), 120.84 ($C_{3'}$, $C_{5'}$), 115.76 ($C_{5''}$), 68.59 (C-$H_{thiazolidin-4-one}$), 32.99 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{19}H_{15}ClN_4O_3S_2$: C, 51.06 (51.03); H, 3.38 (3.39); N, 12.54 (12.55); S, 14.35 (14.34). EI-MS: *m/z* Found: 446.11[M]$^+$.

4-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4h)

Wheat color solid, MP= 315-316℃, FT-IR cm^{-1}: 3268 (N-H str.), 3035 (C-H Ar.), 2944, 2870 (C-H aliphatic), 1673 (C=O sy.str.), 1581 (C=C sy.str.), 1332 (SO_2 asy. str.), 1156 (SO_2 sy. str.). ^{1}H-NMR δ: 11.476 (s, 1H (N-H)), 8.428 (d, 2H ($H_{4''}$, $H_{6''}$), J= 8.8 Hz), 7.985 (d, 2H ($H_{2'}$, $H_{6'}$), J= 8.8 Hz), 7.765 (d, 2H ($H_{3'}$, $H_{5'}$), J= 8 Hz), 7.326 (d, 2H (H_2, H_6), J=8.8 Hz), 7.076 (t, 1H ($H_{5''}$), J= 4.8, 4.8 Hz), 6.797 (d, 2H (H_3, H_5), J=8 Hz), 6.121 (s, 1H (C-$H_{thiazolidin-4-one}$)), 4.038 (d, 1H ($CH_{2thiazolidin-4-one}$), J= 16.4 Hz), 3.961 (d, 1H ($CH_{2thiazolidin-4-one}$), J= 16.4 Hz), 3.033 (s, 3H (OCH_3)). ^{13}C-NMR δ: 170.90 (C=$O_{thiazolidin-4-one}$), 168.89 ($C_{2''}$), 157.53 ($C_{4''}$, $C_{6''}$), 150.83 (C_4), 144.14 ($C_{4'}$), 136.35 ($C_{1'}$), 131.21 ($C_{2'}$, $C_{6'}$), 130.20 (C_1), 129.53 (C_2, C_6), 121.55 ($C_{3'}$, $C_{5'}$), 116.22 ($C_{5''}$), 112.63 (C_3, C_5), 69.35 (C-$H_{thiazolidin-4-one}$), 54.61 (OCH_3), 35.41 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{20}H_{18}N_4O_4S_2$: C, 54.29 (54.30); H, 4.10 (4.11); N, 12.66 (12.67); S, 14.49 (14.49). EI-MS: *m/z* Found: 442.10 [M]$^+$.

4-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (4i)

Golden color solid, 308-309℃, FT-IR (υ cm^{-1}): 3350 (NH str.), 3043 (CH Ar.), 2945, 2877 (C-H aliphatic), 1671 (C=O str.), 1579 (C=C str.), 1344 (SO_2 asy. str.), 1152 (SO_2 sy. str.). ^{1}H-NMR δ: 11.813 (s, 1H (N-H)), 8.523 (d, 2H ($H_{4''}$, $H_{6''}$), J= 8.4 Hz), 8.016 (d, 2H ($H_{2'}$, $H_{6'}$), J= 8 Hz), 7.543 (d, 2H ($H_{3'}$, $H_{5'}$), J= 8.4 Hz), 7.377 (d, 2H (H_2, H_6), J=8.4 Hz), 7.215 (d, 2H (H_3, H_5), J=8 Hz), 7.076 (t, 1H ($H_{5''}$), J= 4.4, 4.4 Hz), 6.193 (s, 1H (C-$H_{thiazolidin-4-one}$)), 4.076 (d, 1H ($CH_{2thiazolidin-4-one}$), J= 15.4 Hz), 3.959 (d, 1H ($CH_{2thiazolidin-4-one}$), J= 15.4 Hz). ^{13}C-NMR δ: 172.32 (C=$O_{thiazolidin-4-one}$), 166.07 ($C_{2''}$), 162.13 (C_4), 157.70 ($C_{4''}$, $C_{6''}$), 143.94 ($C_{4'}$), 136.25 ($C_{1'}$), 134.98 (C_1), 130.38 (C_2, C_6), 129.94 ($C_{2'}$, $C_{6'}$), 121.66 ($C_{3'}$, $C_{5'}$), 116.29 (C_3, C_5), 115.97 ($C_{5''}$), 69.88 (C-$H_{thiazolidin-4-one}$), 31.93 ($CH_{2thiazolidin-4-one}$). CHNS-analysis; Calculated (Found) for $C_{19}H_{15}FN_4O_3S_2$: C, 53.01(52.99); H, 3.51(3.52); N, 13.02 (13.01); S, 14.90 (14.91). EI-MS: *m/z* Found: 430.01 [M]$^+$.

2.4. *In vitro Antimicrobial assay*

Thiazolidin-4-ones (**4a-i**) were evaluated against *Escherichia coli*, and *Staphylococcus aureus* bacterial strains, *Aspergillus niger*, and *Trichophyton mentagrophytes* fungal strains. The two-fold microdilution technique was used to estimate the MIC as recommended by the CLSI, EUCAST, and NCCLS [12, 36-38]. The bacterial and fungal strains were inoculated in the nutrient broth media for 24 h at 37 °C, fungal and bacterial strains' cultures medium were diluted to a final concentration of 10^6 and 10^{-4} colony forming unit (CFU)/mL, respectively. For the preparation of stock solutions (50 µg/mL) of the products (**4a-i**), dimethylsulfoxide (DMSO) was used as the solvent. Nystatin and Penicillin G were used as references for antifungal and antibacterial drugs, respectively. In a 96-well microplate, series dilutions (25, 20, 15, 10, 5, 1, 0.5, and 0.1 µg/mL) from the stock solution were prepared to get of 100 µL in all well, 100 µL of the strains were added and the microplate was incubated about 48 h at 24 °C and 24 h at 37℃ for antifungal and antibacterial microorganisms, respectively. The medium was utilized as a negative control, whereas the culture without the chemicals was used as a positive control. MIC values were calculated by measuring the optical density at 600 and 530 nm for antifungal and antibacterial strains using a spectroscopic technique using a BioTek-ELx808 microplate reader [39, 40].

2.5 Antioxidant Assay

The antioxidant ability of the products (**4a-i**) was evaluated via utilizing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) [41]. The serial concentrations (20, 40, 60, 80, 100, and 120 µg/mL) of the products (**4a-i**), Ascorbic acid (VIT C), and butylated hydroxytoluene (BHT) were prepared in ethanol [42-44]. An equal quantity of each of the abovementioned solutions was additional to an equivalent quantity of 0.1 mM methanolic DPPH solution, and vortexed extensively. The resulting mixtures were kept at room temperature for 30 minutes in a dark place. After that, each mixture's absorbance value was observed at 517 nm.

2.6. Molecular docking study

Protein Data Bank (PDB) (https://www.rcsb.org) was utilized to download the *Staphylococcus aureus's* crystal structure murb protein receptor (ID Code: 1HSK) [45]. Water molecules in the protein structure have been deleted during the docking process by using Discovery Studio 2020 Client. Later, the target protein was saved in PDB format, which was then imported into

Pyrx (https://pyrx.sourceforge.io) program and converted to macromolecules. Spartan software was used to prepare the ligands and save them in a PDB format. The PyRx program was utilized to carry out docking of ligand-receptor interactions. The docked results were visualized by using the Discovery Studio 2020 Client [46].

2.7. ADME prediction

Parameters of bioavailability in conformity with Lipinski's rule of five, the absorption, distribution, metabolism, and excretion (ADME) prediction of biocompatibility has been calculated for all products (4a-i) using the http://www.swissadme.ch/index.php, https://www.molinspiration.com, and https://www.cbligand.org/BBB/predictor.php. Topological polar surface area (TPSA) was used to measure the absorption's percentage by the following equation [47, 48]:

$$\%\,\mathrm{Abs} = 109 - [0.345 \times \mathrm{TPSA}] \quad (1)$$

2.8. DFT prediction

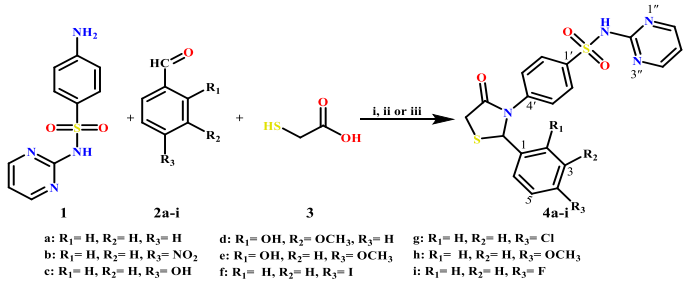
The current study focuses on the application of DFT. DFT technique at the B3LYP/6-31G (d, p) has been used in the vast majority of computing investigations. The Gaussian 09W program and the Gauss-View molecular visualization software package were used in the DFT study [49]. Chem3D Professional 16.0 was used for the designed 3D input Gaussian file.

3. Results and Discussion

3.1. Chemistry

According to scheme 1, the titled products (**4a-i**) were prepared through a one-pot synthesis between sulfadiazine (**1**), different substituted benzaldehyde (**2a-i**), and mercaptoacetic acid (3). Acetic acid has been utilized as a catalyst [8]. Herein three different synthetic methods were used (conventional, ultrasonic, and microwave), the yield of the products have been improved and the reactions time have been significantly reduced [50]. The reaction time required was 8.5-14.5 hours, 125-220 minutes, and 6.5-11 minutes for conventional, ultrasonic, and microwave methods, respectively. The product yield of the microwave method is higher than the ultrasonic method and it is higher than the conventional method as illustrated in Table 1.

FT-IR, ^{1}H, ^{13}C-NMR, Mass spectroscopy, and CHNS-analysis had been utilized to depict all of the synthesized scaffolds (**4a-i**). The presence of a strong band at around 1671-1693 cm^{-1}, which was attributed to vibrations stretching of the 4-thiazolidinone's carbonyl groups and the disappearance of NH_2 vibration bands, confirmed the synthesis of the thiazolidin-4-ones (**4a-i**) [6, 51]. A broad single vibration band appeared for all synthesized compounds around 3387-3228 cm^{-1}, which belong to the N-H stretching of sulfadiazine [52]. The absorption bands around 3407, 3417, and 3423 cm^{-1} for compounds 4c-e, respectively, were assigned to stretching vibrations of the hydroxyl [53]. Two bands, related to (SO_2) asymmetric stretching and (SO_2) symmetric stretching, appear at around 1331-1359 cm^{-1} and 1139-1162 cm^{-1}, individually [54]. The NO_2 asymmetric and symmetric stretching bands for compound **4b** appeared at around 1532 and 1351cm^{-1}, respectively [55].



Scheme 1. Plausible reaction synthesis of 4-Thiazolidinone derivatives (**4a-i**), i: DMF, AcOH, and refluxed 8.5-14.5 hours. ii: DMF, AcOH, and Ultrasonic for 125-220 minutes. iii: DMF, AcOH, and MW for 6.5-11 minutes

Table 1. The time required and yield productions of thiazolidin-4-ones (**4a-i**).

Compounds	Conventional		Ultrasonic		Microwave	
	Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
4a	11	68	160	70	8	75
4b	8.5	75	125	79	6.5	84
4c	14.5	67	220	74	11	78
4d	12.5	66	190	73	9.5	76
4e	12	62	180	65	9	69
4f	9.5	68	145	75	7.5	78
4g	10.5	64	155	75	8	78
4h	13	66	195	69	10	74
4i	11.5	61	170	65	8.5	69

The synthesis of thiazolidin-4-ones (4a–o) was confirmed by ^{1}H-NMR spectral data. A single signal equivalent to one proton was observed at 6.384-5.991 ppm for C-H of thiazolidin-4-one rings, and tow doublet signal for CH_2 of thiazolidin-4-one rings has been observed at 4.171-3.838 ppm; 4.074-3.753 ppm, which were considered a strong confirmation for the formation of the thiazolidin-4-one ring closure [56]. The singlet signals appeared for NH protons of sulfadiazine around 11.813-11.236 ppm [43]. The signals of aromatic protons appeared around δ 8.554-6.797 ppm, single signals showed up for the proton of OH groups at δ 11.821, 12.442, and 12.364 for compounds 4c, 4d, and 4e, respectively [57]. Single signals were appeared for the protons of CH_3 groups at δ 3.781, 3.803, and 3.033 for compounds 4d, 4e, and 4h, respectively [58].

^{13}C-NMR spectrum confirmed the appearance of the deshielding signals for C=O of thiazolidin-4-ones, which appeared at δ 172.32-169.15 ppm [59]. The two shielding signal carbons of ($CH_{\text{thiazolidin-4-ones}}$) and ($CH_{2\ \text{thiazolidin-4-ones}}$) showed up around δ 74.07-68.03 ppm and δ 35.41-31.75 ppm, respectively [45]. The sp^2 aromatic carbons signals showed up at δ 169.92-112.63 ppm and the signals' carbons of methoxy (OCH_3) groups appeared at δ 56.50, 57.76, and 54.61 ppm for compounds 4d, 4e, and 4h, respectively [43]. Finally, mass spectroscopy and CHNS-analysis were performed to support the FT-IR, ^{1}H, and ^{13}C-NMR spectrum. The mass spectrum and CHNS ratio agreed with thaiazolidin-4-ones (**4a-i**) scaffolds.

3.2. *In vitro* Antimicrobial assay

The synthesized compounds (**4a-i**) were assessed for their antimicrobial ability against *E. coli*, *S. aureus*, *A. niger*, and *T. mentagrophytes* resistant strains. The results are shown in Table 2, with Nystatin and Penicillin G standard drugs, the results revealed that the products exhibited varying inhibitory effects on resistant strains. Among all the derivatives screened, particularly compound **4e** displayed promising activity (MIC value is equal to 2.3 µg/mL), and against *Staphylococcus aureus*. Compound **4e** also displayed 2.1 µg/mL against *E. coli*. Compounds 4e exhibited the best activity (MIC value is equal to 3.3 and 3.9 µg/mL) against *A. niger* and *T. mentagrophytes*, respectively. Compound **4f** screened the lowest ability, the MIC value is equal to 5.5, 4.0, 9.0, and 8.7 µg/mL against *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger*, and *Trichophyton mentagrophytes* respectively. According to the results, the compounds possess antibacterial activity in descending order: 4e>4d>4b>4c>4h>4a>4i>4g>4f against *Staphylococcus aureus* and 4e>4d>4b>4c>4h>4a>4i>4g>4f against *Escherichia coli*. The antifungal activity of compounds in descending order were found to be: 4e>4d>4b>4h, 4c>4a>4i>4g>4f against *Aspergillus niger* and 4e>4d>4b>4c> 4h>4a>4i>4g>4f against *Trichophyton mentagrophytes*.

Table 2. *In vitro* antimicrobial activity of thiazolidin-4-ones (4a-i).

compounds	MIC values (µg/mL)			
	S.aureus	*E.coli*	*A. niger*	*T. mentagrophytes*
4a	4.0	3.4	7.0	7.7
4b	2.6	2.5	4.4	5.0
4c	3.0	2.9	6.0	6.1
4d	2.4	2.3	3.5	4.5
4e	2.3	2.1	3.3	3.9
4f	5.5	4.0	9.0	8.7
4g	5.1	3.7	8.6	8.5
4h	3.6	3.1	6.0	6.5
4i	4.5	3.5	7.1	8.1
Penicillin G	1.5	1.2	-	-
Nystatin	-	-	3.0	3.5

3.3. Antioxidant Assay

4-thiazolidinone derivatives (**4a-i**) were evaluated for their antioxidant activity with butylated hydroxytoluene (BHT) and Ascorbic acid as standards. The IC_{50} values for the products were determined and summarized in Table 3. DPPH has a nitrogen-centered free radical that quickly receives hydrogen radicals or an electron to form a stable diamagnetic compound. Whenever DPPH radicals interact with appropriate reducing agents, the electrons are coupled together, leading to the formation of the equivalent hydrazine. Depending on the number of electrons previously occupied, the solution changes color from purple to yellow. With increasing concentrations of the products, the radical scavenging activity increased, and lowering IC_{50} values were observed. According to the results, synthesized compounds (**4a-i**) exhibited antioxidant activity in the descending order: 4e> 4d>4c>4b>4h>4i>5g>4f>4a. Irrespective of the type of heterocyclic nucleus, it was observed that compound **4e** exhibited the highest (IC_{50} value is equal to 27 µg/ml) and compound **4a** screened the lowest (IC_{50} value is equal to 67 µg/ml) antioxidant activity among compounds in the respective series. The following expression has been utilized to measure the free radical scavenging of thiazolidin-4-ones, BHT, and (VIT C) solutions:

$$\text{Radical Scavenging } \% = \frac{\text{Ac}-\text{As}}{\text{Ac}} * 100 \qquad (2)$$

Where: As= Absorbance of thiazolidin-4-ones, BHT, and Ascorbic acid solutions. Ac= control's absorbance (including methanol and DPPH).

3.4. Molecular docking study

Theoretical studies are widespread. The interaction of the target protein with the ligands was studied using molecular docking predictions [60, 61]. The molecules with the strongest interaction with the protein are more stable. Up-to-date drug computational studies have significance role to the

screen of drug-drug and drug-receptor interaction [62]. All docked compounds (**4a-i)** and Penicillin G have been shown to have comparable binding orientations from around binding sites of the protease 1HSK [45], with varied interacts with the residues within a binding affinity range of -6.50 to -8.30 (Table 4). The binding affinity and the residues interactions are illustrated in fig. 1-6, and Table 4. The compounds **4e,** and **4d** displayed the maximum binding affinity value -8.30 and -8.20 kcal/mol, correspondingly. For results comparison, Penicillin G was used as a reference drug. It is worth noting that hydroxyl and methoxy group substitutions improve binding ability more than the other groups. The positions of methoxy moiety play a key role in the biological activities as well as binding interactions [17]. Furthermore, nitro and halogen groups exhibited a wide range of orientations and interacted with the active sites of key residues [63]. From results, the binding affinity of synthesized compounds **4a-i** in the descending order: 4e>4d>4b>4c>4g>4b>4i>4f>4a. Lastly, in silico computational studies were used for further support, design, and analysis of all newly synthesized compounds, likewise theoretical results close to the experimental values with minimum differences. The reason for the differences between theoretical and experimental studies is that the theoretical studies are conducted in a pure and isolated environment [60].

Table 3: Antioxidant activity of thiazolidin-4-ones (**4a-i**)

Compounds	IC_{50} (µg/ml)
4a	67
4b	44
4c	32
4d	29
4e	27
4f	64
4g	57
4h	50
4i	55
A.A[a]	15
BHT[b]	25

[a]Ascorbic acid
[b]Butylated hydroxytoluene

Table 4. Docking studies results of thiazolidin-4-ones docked into crystal the structure of *Staphylococcus aureus* murb protein receptor (ID Code: 1HSK)

Comp	B.A.[a)]	Interactions type/ Active sites of the protein (amino acids): Residue Positions
4a	-6.50	Conventional HB/ 2(ARG:A^{310}), TYR:A^{149}, GLN:A^{193}, VAL:A^{199}. Pi-sulfur/ HIS:A^{196}, TYR:A^{149}. Pi-Pi T-shaped/ TYR:A^{77}, ILE:A^{84}, TYR:A^{149}. Pi-alkyl/ ILE:A^{84}. Carbon HB/ VAL:A^{198}. vdW/ GLY:A^{79}, LEU:A^{78}, GLY:A^{146}, GLY:A^{145}, LEU:A^{98}, LYS:A^{194}
4b	-7.80	Conventional HB/ TYR:A^{149}, GLN:A^{193}, GLU:A^{308}, ARG:A^{242}. Pi-anion/ 2(GLU:A^{308}). Pi-sulfur/ TYR:A^{187}, MET:A150. Carbon HB/ TYR:A^{187}. Pi-sigma/ ARG:A^{310}. Pi-alkyl/ ARG:A^{188}. vdW/ ASN:A^{189}, ASN:A^{83}, VAL:A^{309}, PHE:A^{240}, GLN:A^{241}
4c	-7.60	Conventional HB/ PHE:A^{240}, ARG:A^{188}. Pi-sigma/ ALA:A^{248}. Pi-alkyl/ ALA:A^{154}, ILE:A^{140}, ARG:A^{242}. Pi-cation/ ARG:A^{225}. Carbon HB/ GLY:A^{249}. Pi-Donor HB/ GLY:A^{153}. vdW/ GLN:A^{241}, PHE:A^{247}, GLY:A^{237}, GLY:A^{273}, LYS:A^{250}, HIS:A^{271}, PHE:A^{274}, GLN:A^{229}, PRO:A^{141}, SER:A^{238}.
4d	-8.20	Conventional HB/ ARG:A^{225}, GLY:A^{153}, SER:A^{238}, TYR:A^{155}. Pi-cation/ 2(ARG:A^{188}). Unfavorable Donor-Donor/ ARG:A^{188}. Pi-alkyl/ ALA:A^{248}, MET:A^{150}. Pi-Donor HB/ GLY:A^{156}. vdW/ GLY:A^{157}, GLN:A^{229}, PHE:A^{274}, PRO:A^{141}, GLY:A^{237}, GLU:A^{308}, ASN:A^{83}, ILE:A^{140}, ALA:A^{152}.
4e	-8.30	Conventional HB/ ASN:A^{83}, SER:A^{82}, ARG:A^{188}, GLU:A^{308}, GLN:A^{229}. Unfavorable Donor-Donor/ ARG:A^{225}. Pi-alkyl/ ARG:A^{188}, PRO:A^{141}. Carbon HB/ SER:A^{235}, TYR:A^{187}, SER:A^{238}. vdW/ ARG:A^{242}, GLN:A^{241}, PHE:A^{240}, GLY:A^{237}, ILE:A^{140}, MET:A^{150}, TYR:A^{42}, PHE:A^{274}.
4f	-6.70	Conventional HB/ ARG:A^{188}, SER:A^{82}. Pi-alkyl/ PHE:A^{274}, PRO^{141}, ALA:A^{152}, TYR:A^{42}. Alkyl/ LEU:A^{231}, PRO:A^{141}. vdW/ MET:A^{150}, GLY:A^{146}, ASN:A^{83}, TYR:A^{149}, GLY:A^{79}, GLY:A^{381}, ASN:A^{80}, ILE:A^{84}, ALA:A^{147}, GLY:A^{142}, SER:A^{143}, GLY:A^{237}, ILE:A^{140}, SER:A^{235}, GLN:A^{229}, ARG:A^{225}, SER:A^{238}.
4g	-7.50	Conventional HB/ ARG:A^{242}, ALA:A^{248}. Pi-Pi T-shaped/ PHE:A^{247}. Pi-Pi Stacked/ HIS:A^{271}. Pi-alkyl/ LYS:A^{228}. Pi-Donor/ HB SER:A^{238}. vdW/ PHE:A^{240}, PHE:A^{274}, ARG:A^{224}, TYR:A^{155}, LYS:A^{250}, GLN:A^{229}.
4h	-6.80	Conventional/ HB 2(THR:A^{76}). Pi-Pi T-shaped/ HIS:A^{196}. Pi-alkyl/ ARG:A^{92}. Carbon HB/ ARG:A^{92}, GLU:A^{171}, VAL:A^{65}. Pi-sigma/ ILE:A^{91}. vdW/ ALA:A^{68}, TYR:A^{69}, ILE:A^{73}, TYR:A^{77}, VAL:A^{75}, PRO:A^{74}, ARG:A^{310}, ILE:A^{312}, GLY:A^{313}, GLU:A^{314}.
4i	-7.30	Conventional HB/ SER:A^{235}, ARG:A^{188}, GLN:A^{229}, 2(TYR:A^{155}). Pi-cation/ ARG:A^{188}, ARG:A^{225}. Pi-alkyl/ ALA:A^{154}, PRO:A^{141}. Pi-Donor/ HB TYR:A^{155}. vdW/ SER:A^{82}, GLY:A^{237}, ASN:A^{83}, MET:A^{150}, ILE:A^{140}, SER:A^{238}, LYS:A^{228}, ARG:A^{224}, GLY:A^{153}, PHE:A^{274}, TYR:A^{42}.
Pen. G	-7.60	Conventional HB/ 2(SER:A^{238}), ARG:A^{188}. Pi-Pi T-shaped/ PHE:A^{274}. Pi-alkyl/ PRO:A^{141}. Carbon HB/ ALA:A^{152}. vdW/ ALA:A^{147}, MET:A^{150}, ILE:A^{140}, ASN:A^{83}, GLY:A^{237}, SER:A^{82}, TYR:A^{42}, SER:A^{235}, LEU:A^{231}, GLN:A^{229}, ARG:A^{225}, GLY:A^{153}

[a]Binding Affinity (kcal/mol)

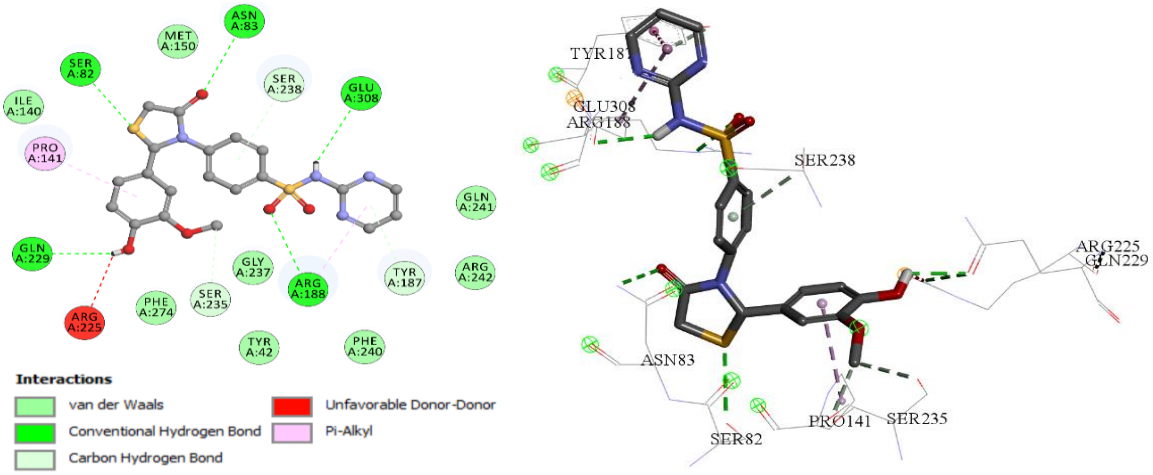


Fig. 1. 2D (left) and 3D (right) molecular interactions of compound 4i with Staphylococcus aureus murb protein receptor (ID Code: 1HSK).

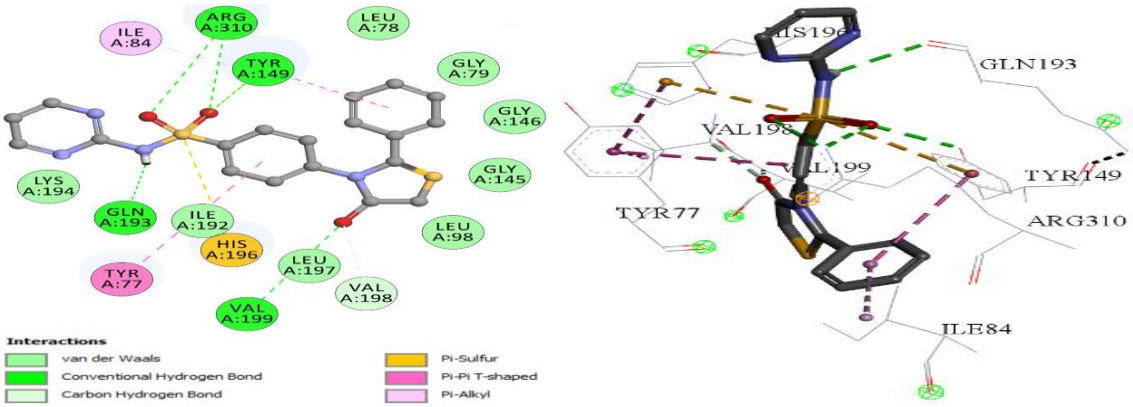


Fig. 2. 2D (left) and 3D (right) molecular interactions of compound 4a with Staphylococcus aureus murb protein receptor (ID Code: 1HSK).

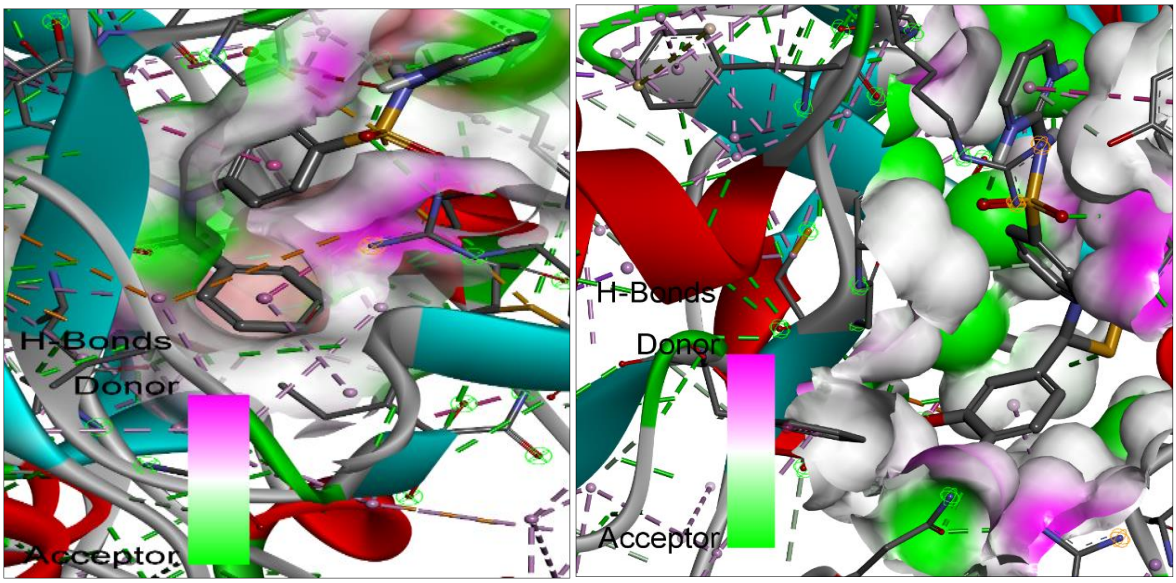


Fig. 3. 3D-molecular interactions of compounds 4a (left) and 4i (right) with Staphylococcus aureus murb protein receptor (ID Code: 1HSK), the active sites of the H-bond donor and acceptor are shown in different colors).

3.5. ADME prediction

ADME was estimated for synthesized compounds (**4a-i**). The evaluation of drug-likeness properties for all compounds is performed using the SwissADME and Molinspiration web-based servers [64, 65]. As said by Lipinski's rule of five should have an MW < 500, H-B donors ≤5, H-B acceptors ≤10, Log P < 5, number of R. bonds ≤10, TPSA ≤160 [47, 66]. The molecular weights of the products are less than 500 g/mole except for compound **4f**. Oral absorption will be challenging for drug candidates that violation over than one [67, 68]. The GI absorption value is a measurement of how much a compound is absorbed from the intestine; if the score is high, the absorption might be excellent, Ciprofloxacin was used as a reference drug [69]. All of the tested compounds had BBB absorption scores that were close to the normal range (0.3 to 1) [70]. According to this overhead rule, all the synthesized compounds (**4a-i**) exhibited very good bioactivity scores (Table 4).

Table 4. Parameters of the pharmacokinetics of thiazolidin-4-ones (**4a-i**)

comp	MW[a)] g/mol	H-B[b)] D.	H-B[c)] A.	Viol[d)]	R.[e)] bond	BBB[f)] permeant	GI[g)] Absorp	TPSA[h)]	% Abs[i)]	LogP[j)]
4a	410.5	1	5	0	5	0.143	High	66.48	86.06	3.26
4b	455.5	1	8	0	6	0.112	High	112.30	70.25	2.70
4c	426.5	2	6	0	5	0.066	High	86.71	79.08	2.82
4d	456.5	2	7	0	6	0.044	High	95.94	75.90	2.97
4e	456.5	2	7	0	6	0.043	High	95.94	75.90	2.91
4f	536.4	1	5	2	5	0.094	High	66.48	86.06	3.95
4g	444.9	1	5	0	5	0.093	High	66.48	86.06	3.82
4h	440.5	1	6	0	6	0.095	High	75.71	82.88	3.31
4i	428.5	1	5	0	5	0.107	High	66.48	86.06	3.60
Cip.	331.3	2	6	0	3	-0.043	High	74.57	83.27	1.10

[a)]molecular weight , [b)] hydrogen bond donor, [c)] hydrogen bond acceptor, [d)] violation , [e)] number of rotatable bonds [f)] Blood–brain barrier, [g)] Gastrointestinal, [h)] Topological polar surface area, [i)] Absorbance, [j)] Octanol-water partition coefficient).

3.6. DFT prediction

To illustrate the theoretical-experimental correlation, quantum chemical measurements were done with comprehensive geometry optimizations using the Gaussian 09W and Gauss-View 6.0 programs. DFT technique at B3LYP/6-31G (d, p) was employed in the computational investigations. The dipole moments of synthesized compounds (4a-i) were computed, which are mostly utilized to examine non-bonded type dipole-dipole interactions, compound **4d** leads to strong intermolecular interactions [71]. The electronic states and energy gaps values of the synthesized compounds (**4a-i**) were demonstrated in Table 5. As illustrated in fig. 4, the decrease of the energy gaps indicates the charge transfer in the molecule. When the value of E_{HOMO} is high, it indicates the ease of donating an electron to the unoccupied orbital of the receptor molecule such as compound **4a**. When the value of E_{LUMO} is small, this means that it has small resistance to accept electrons so it will be more able to accept electrons as compounds **4e** and **4d** [72]. It was discovered that LUMOs have an anti-bonding orbital, whereas HOMOs have both a bonding and a nonbonding orbital. The energy gap was calculated by the following equation [73].

$$\text{Energy gap } (\Delta E) = |EHOMO - ELUMO| \quad (3)$$

The energy gap is a helpful characteristic for determining a molecule's chemical reactivity and kinetic stability. The lowest energy gaps were observed in compounds **4e** and **4d**, making them more reactive and less stable [74, 75]. The electron affinity is equal to $-E_{LUMO}$ and ionization potential is equal to $-E_{HOMO}$. Within the framework of finite differences approximation, the following expressions are based on HOMO and LUMO energy values for complexes at DFT/B3LYP principle and the 6-31 G (d,p) level of calculation as follows [72, 76].

$$\eta = (EHOMO - ELUMO)/2 \quad (4)$$

$$\mu = -(EHOMO + ELUMO)/2 \quad (5)$$

$$\omega = \mu 2/2\eta \quad (6)$$

$$\chi = (EHOMO + ELUMO)/2 \quad (7)$$

$$S = 1/2\eta = \quad (8)$$

The ionization Potential (I) of compound **4a** is lower means that the molecule will be the better electron donor and the electron affinity (A) of compound **4d** is larger the molecule will be the better electron acceptor [72]. The compound **4g** has the highest chemical hardness (η) and lowest global softness, compound **4d** has the lowest chemical hardness (η), highest global softness, and the lowest Chemical potential (μ) but has a highest Chemical potential (μ). Compound **4f** shows the highest Electrophilicity Index (ω) value whereas compound **4f** screened the lowest Electrophilicity Index (ω) value. The compound **4d** has the highest Electronegativity (χ) value and **4a** has the lowest. All the results were presented in Table 5.

Table 5. DFT calculated data of thiazolidin-4-ones (**4a-i**).

Comp	Electronic states HOMO	LUMO	ΔEg[a] (eV)	D[b]	I[c] (eV)	A[d] (eV)	η[e] (eV)	μ[f] (eV)	ω[g] (eV)	χ[h] (eV)	S[i] (eV)
4a	-0.19922	-0.05681	0.14241	7.71	0.1992	0.056	0.0712	-0.2276	0.363	0.2276	7.02
4b	-0.27194	-0.23219	0.03975	10.35	0.2719	0.232	0.0198	-0.3880	3.787	0.3880	25.15
4c	-0.23175	-0.06543	0.16632	7.73	0.2317	0.065	0.0831	-0.2644	0.420	0.2644	6.01
4d	-0.33094	-0.30400	0.02694	8.40	0.2134	0.056	0.0784	-0.2416	0.372	0.2416	6.37
4e	-0.33777	-0.31351	0.02426	8.50	0.2748	0.182	0.0461	-0.3661	1.453	0.3661	10.83
4f	-0.21340	-0.05646	0.15694	8.67	0.3309	0.084	0.2077	-0.2887	0.200	0.2887	2.40
4g	-0.27489	-0.18261	0.09228	9.68	0.3377	0.084	0.2108	-0.2957	0.207	0.2957	2.37
4h	-0.27114	-0.18753	0.08361	6.80	0.2711	0.188	0.0418	-0.3649	1.592	0.3649	11.96
4i	-0.26586	-0.17646	0.08940	7.76	0.2658	0.176	0.0447	-0.3540	1.402	0.3540	11.18

[a] Energy gap, [b] Dipolmoment (Unit= Debye), [c] Ionization Potential, [d] Electron Affinity, [e] Chemical hardness, [f] Chemical potential, [g] Electrophilicity Index, [h] χ= Electronegativity and [i] Global softness

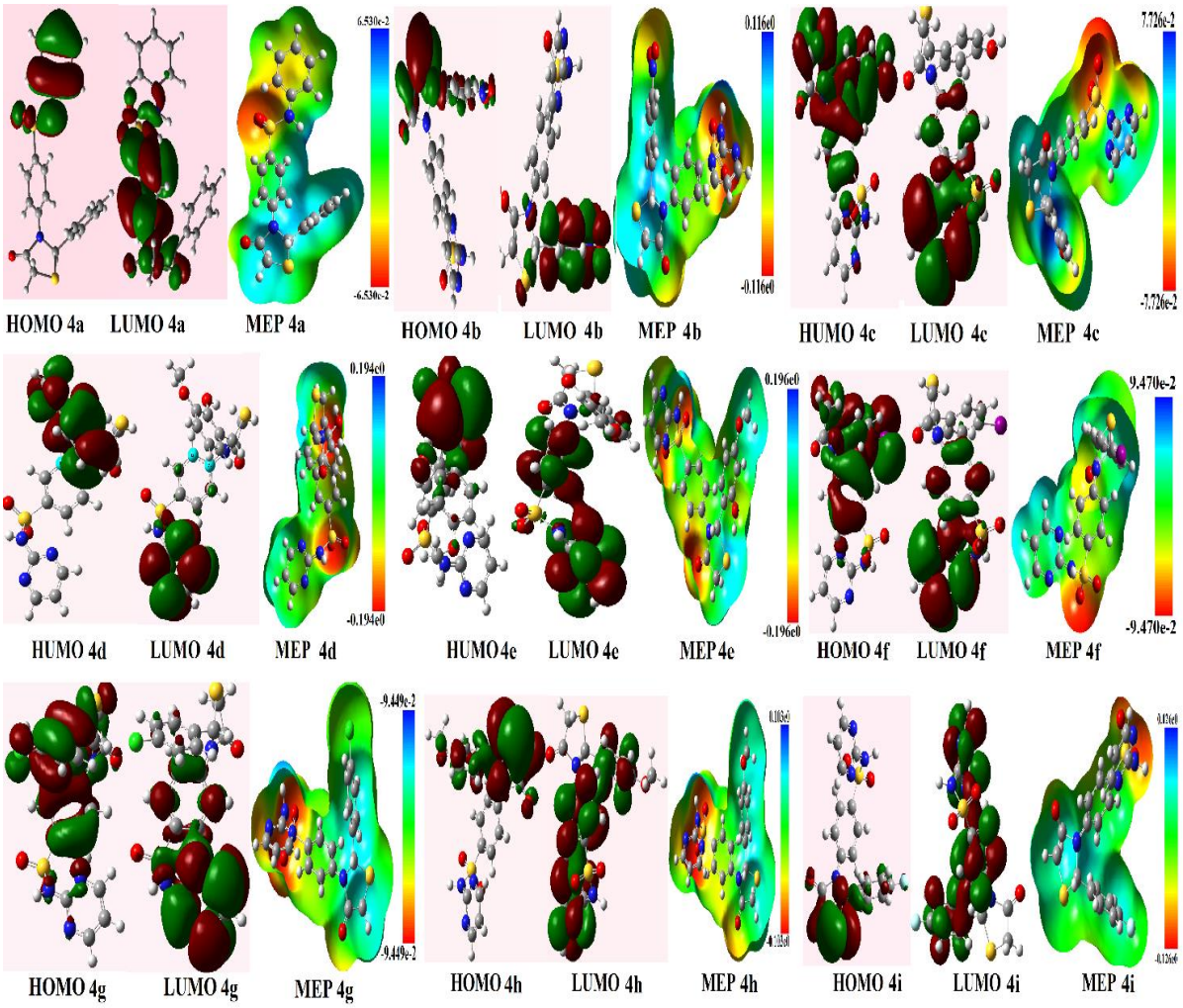
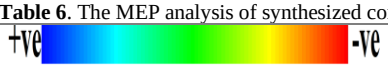


Fig. 4. The HOMO, LUMO orbitals, and MEP surfaces of thiazolidin-4-ones **(4a-i).**

The molecular electrostatic potential (MEP) mapping has been widely utilized to study the electrophilic, and nucleophilic attack reactive sites in the reactions, as well as the study of specific biological activities and hydrogen bonding interactions. MEP provides information on molecular characteristics such as electronegativity, dipole moment, partial charges of molecules, and chemical reactivity because it is correlated to the overall electron density distribution of the molecule. Fig. 4 demonstrates how different colors in MEP maps represent various values at the surface of electrostatic potential. The highest negative electrostatic potential zone is represented in red, the highest positive electrostatic potential zone is represented in blue, and the zero potential zone is represented in green color [77]. Potential of blue > green > yellow > orange > red [78]. The neutral electrostatic potential (green) envelopes over the π-system of the ring. The highest negative electric potential area was mostly found on

the N atoms on the pyridine rings, oxygen atoms of the NO_2, OH, and OCH_3 groups (attached to the benzene ring), oxygen atoms of SO_2, carbonyl of 4-thiazolidinone rings, and as a result this is the preferred site for the electrophilic attack [79]. The highest positive electric potential area surrounds all hydrogen atoms that are involved in nucleophilic reactivity [80]. The negative (-ve) and positive (+ve) potential values of each compound are listed in Table 6. The minimal value was observed for compound **4c** (-0.07726 a.u. to 0.07726 a.u), whereas the highest value was observed for compound **4e** (-0.196 a.u. to 0.196 a.u).

Table 6. The MEP analysis of synthesized compounds (**4a-i**).



Comp	+ve potential	-ve potential
4a	0.0653	-0.0653
4b	0.116	-0.116
4c	0.07726	-0.09319
4d	0.194	-0.07726
4e	0.196	-0.194
4f	0.09470	-0.196
4g	0.09449	-0.09449
4h	0.103	-0.103
4i	0.126	-0.126

4. Conclusion

The thiazolidin-4-one derivatives (**4a-i**) bearing a sulfonamide moiety were synthesized in comparison with the conventional method, ultrasonic sonication, and microwave irradiation techniques. It was seen that microwave irradiation was better than other methods. Compound 4e was the most active compound against *Trichophyton mentagrophytes*, *Aspergillus niger*, *Escherichia coli*, and *Staphylococcus aureus* resistant strain, with MICs of 3.9, 3.3, 2.1, and 2.3 g/mL, respectively. And also compound 4e displayed the highest antioxidant activity, with an IC_{50} of 27 µg/ml. Compound 4e was found to be the most effective ligand, with a binding score of -8.30 Kcal/mole. Most of the synthesized compounds have shown good bioactivity scores as well as drug-like properties, Lipinski's five-point rule applies. The compounds **4e** and **4d** displayed a highly chemical reactivity but less stability with the ΔE values 0.024 and 0.026 eV, respectively. Finally, compounds 4e and 4d have the highest electrostatic potential values (-0.196 a.u. to 0.196 a.u.) and (-0.194 a.u. to 0.194 a.u.) respectively, making them more reactive. In conclusion, we understood that the synergistic effect of both the sulfonamide and the thaiazolidin-4-one ring could explain the targets' superior bioactive profiles.

5. Acknowledgments

The Research Center and Chemistry department at Raparin University supported this work.

5. References

[1] Taylor A.P., Robinson R.P., Fobian Y.M., Blakemore D.C., Jones L.H. and Fadeyi O., Modern advances in heterocyclic chemistry in drug discovery. *Org. Biomol. Chem.*, **14**(28): 6611-6637 (2016).

[2] Kumar A.S., Kudva J., Bharath B., Ananda K., Sadashiva R., Kumar S.M., Revanasiddappa B.C., Kumar V., Rekhah P.D. and Narali D., Synthesis, structural, biological and in silico studies of new 5-arylidene-4-thiazolidinone derivatives as possible anticancer, antimicrobial and antitubercular agents. *NJC.*, **43**(3): 1597-1610 (2019).

[3] Manjal S.K., Kaur R., Bhatia R., Kumar K., Singh V., Shankar R., Kaur R. and Rawal R.K., Synthetic and medicinal perspective of thiazolidinones: a review. *Bioorg. chem.*, **75**: 406-423 (2017).

[4] Singh U.P., Bhat H.R., Kumawat M.K. and Singh R.K., Utilisation of Home Laundry Effluent (HLE) as a catalyst for expeditious one-pot aqueous phase synthesis of highly functionalised 4-thiazolidinones. *SpringerPlus*, **2**(1): 1-11 (2013).

[5] Sahiba N., Sethiya A., Soni J., Agarwal D.K. and Agarwal S., Saturated five-membered thiazolidines and their derivatives: from synthesis to biological applications. *Top. Curr. Chem.* **378**(2): 1-90 (2020).

[6] El Azab I.H. and Abdel-Hafez S.H., One-pot three-component microwave-assisted synthesis of novel thiazolidinone derivatives containing thieno[*d*]pyrimidine-4-one moiety as potential antimicrobial agents. *Russ. J. Bioorg. Chem.*, **41**(3): 315-323 (2015).

[7] Chate A.V., Tathe A.G., Nagtilak P.J., Sangle S.M. and Gill C.H., Efficient approach to thiazolidinones via a one-pot three-component reaction involving 2-amino-1-phenylethanone hydrochloride, aldehyde and mercaptoacetic acid. *Chinese J. Catal.*, **37**(11):1997-2002 (2016).

[8] Rahim F., Taha M., Ullah H., Wadood A., Selvaraj M., Rab A., Sajid M., Shah S.A., Uddin N. and Gollapalli M., Synthesis of new arylhydrazide bearing Schiff bases/thiazolidinone: α-amylase, urease activities and their molecular docking studies. *Bioorg. chem.*, **91**: 103-112 (2019).

[9] Angapelly S., Ramya P.S., SunithaRani R., Kumar C.G., Kamal A. and Arifuddin M., Ultrasound assisted, $VOSO_4$ catalyzed synthesis of 4-thiazolidinones: antimicrobial evaluation of indazole-4-thiazolidinone derivatives. *Tetrahedron Lett.*, **58**(49):4632-4637 (2017).

[10] Das S., Das V.K., Saikia L. and Thakur A.J., Environment-friendly and solvent-free synthesis of symmetrical bis-imines under microwave irradiation. *Green Chem. Lett. Rev.*, **5**(3): 457-574 (2012).

[11] Gouveia F.L., de Oliveira R.M., de Oliveira T.B., da Silva I.M., do Nascimento S.C., de Sena K.X. and Albuquerque J.F., Synthesis, antimicrobial and cytotoxic activities of some 5-arylidene-4-thioxo-thiazolidine-2-ones. *Eur. J. Med. Chem.*, **44**(5): 2038-2043 (2009).

[12] Secci D., Carradori S., Bizzarri B., Chimenti P., De Monte C., Mollica A., Rivanera D., Zicari A., Mari E., Zengin G. and Aktumsek A., Novel 1,3-thiazolidin-4-one derivatives as promising anti-Candida agents endowed with anti-oxidant and

chelating properties. *Eur. J. Med. Chem*., **117**: 144-156 (2016).
[13] Havrylyuk D., Mosula L., Zimenkovsky B., Vasylenko O., Gzella A. and Lesyk R., Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety. *Eur. J. Med. Chem.,* **45**(11): 5012-5021 (2010).
[14] Kumar K.S., Hanumappa A., Vetrivel M., Hegde M., Girish Y.R., Byregowda T.R., Rao S., Raghavan S.C. and Rangappaa K.S., Antiproliferative and tumor inhibitory studies of 2,3 disubstituted 4-thiazolidinone derivatives. *Bioorg. Med. Chem. Lett.,* **25**(17): 3616-3620 (2015).
[15] Bhosle M.R., Mali J.R., Pal S., Srivastava A.K. and Mane R.A., Synthesis and antihyperglycemic evaluation of new 2-hydrazolyl-4-thiazolidinone-5-carboxylic acids having pyrazolyl pharmacophores. *Bioorg. Med. Chem. Lett.,* **24**(12): 2651-2654 (2014).
[16] Tenorio R.P., Carvalho C.S., Pessanha C.S., de Lima J.G., de Faria A.R., Alves A.J., de Melob E.J. and Goes A.J., Synthesis of thiosemicarbazone and 4-thiazolidinone derivatives and their in vitro anti-Toxoplasma gondii activity. *Bioorg. Med. Chem. Lett.,* **15**(10): 2575-2578 (2005).
[17] Rahim F., Zaman K., Ullah H., Taha M., Wadood A., Javed M.T., Rehman W., Ashraf M., Uddin R., Uddin I., Asghar H., Khan A.A. and Khan K.M., Synthesis of 4-thiazolidinone analogs as potent in vitro anti-urease agents. *Bioorg. Chem.,* **63**: 123-131 (2015).
[18] Taha H. and Soliman M., Antischistosomal activity of 3-substituted-5-(2-aryl-2-oxoethyl)-2, 4-dioxo-1, 3-thiazolidine (Ro-354). *Int. J. Agric. Biol*., **9**: 87-93 (2007).
[19] De Monte C., Carradori S., Bizzarri B., Bolasco A., Caprara F., Mollica A., Rivanera D., Mari E., Zicari A., Akdemir A. and Seccia D., Anti-Candida activity and cytotoxicity of a large library of new N-substituted-1, 3-thiazolidin-4-one derivatives. *Eur. J. Med. Chem.,* **107**: 82-96 (2016).
[20] Orrling K.M., Marzahn M.R., Gutiérrez H., Åqvist J., Dunn B.M. and Larhed M., α-Substituted norstatines as the transition-state mimic in inhibitors of multiple digestive vacuole malaria aspartic proteases. *Bioorg. Med. Chem.,* **17**(16): 5933-5949 (2009).
[21] Sanemitsu Y., Kawamura S., Satoh J., Katayama T. and Hashimoto S., Synthesis and herbicidal activity of 2-acylimino-3-phenyl-1,3-thiazolines A new family of bleaching herbicides. *J. Pestic. Sci.,* **31**(3): 305-310 (2006).
[22] Nampurath G.K., Mathew S.P., Khanna V., Zachariah R.T., Kanji S. and Chamallamudi M.R., Assessment of hypolipidaemic activity of three thiazolidin-4-ones in mice given high-fat diet and fructose. *Chem. Biol*., **171**(3): 363-368 (2008).
[23] Murugan R., Anbazhagan S. and Narayanan S.S., Synthesis and in vivo antidiabetic activity of novel dispiropyrrolidines through [3+2] cycloaddition reactions with thiazolidinedione and rhodanine derivatives. *Eur. J. Med. Chem.,* **44**(8): 3272-3279 (2009).
[24] Ravichandran V., Jain A., Kumar K.S., Rajak H. and Agrawal R.K., Design, Synthesis, and Evaluation of Thiazolidinone Derivatives as Antimicrobial and Anti-viral Agents. *Chem Biol Drug Des.,* **78**(3): 464-470 (2011).
[25] Agarwal A., Lata S., Saxena K., Srivastava V. and Kumar A., Synthesis and anticonvulsant activity of some potential thiazolidinonyl 2-oxo/thiobarbituric acids. *Eur. J. Med. Chem.,* **41**(10): 1223-1229 (2006).
[26] Bhati S.K. and Kumar A., Synthesis of new substituted azetidinoyl and thiazolidinoyl-1,3,4-thiadiazino(6,5-b)indoles as promising anti-inflammatory agents. *Eur. J. Med. Chem.,* **43**(11): 2323-2330 (2008).
[27] Pink R., Hudson A., Mouriès M.A. and Bendig M., Opportunities and challenges in antiparasitic drug discovery. *Nat. Rev. Drug Discov.,* **4**(9):727-740 (2005).
[28] Bhandari S.V., Bothara K.G., Patil A.A., Chitre T.S., Sarkate A.P., Gore S.T., Dangre S.C. and Khachane C.V., Design, synthesis and pharmacological screening of novel antihypertensive agents using hybrid approach. *Bioorg. Med. Chem.,* **17**(1): 390-400 (2009).
[29] Zhang Y., Wang S., Wu S., Zhu S., Dong G., Miao Z., Yao J., Zhang W., Sheng C. and Wang W., Facile construction of structurally diverse thiazolidinedione-derived compounds via divergent stereoselective cascade organocatalysis and their biological exploratory studies. *ACS Comb. Sci.,* **15**(6): 298-308 (2013).
[30] Ghorab M.M., Ragab F.A., Heiba H.I., Agha H.M. and Nissan Y.M., Novel 4-(4-substituted-thiazol-2-ylamino)-N-(pyridin-2-yl)-benzenesulfonamides as cytotoxic and radiosensitizing agents. *Arch. Pharm. Res.,* **35**(1):59-68 (2012).
[31] Naaz F., Srivastava R., Singh A., Singh N., Verma R., Singh V.K. and Singh R.K., Molecular modeling, synthesis, antibacterial and cytotoxicity evaluation of sulfonamide derivatives of benzimidazole, indazole, benzothiazole and thiazole. *Bioorg. Med. Chem.,* **26**(12): 3414-3428 (2018).
[32] Abdellatif K.R., Abdelgawad M.A., Elshemy H.A. and Alsayed S.S., Design, synthesis and biological screening of new 4-thiazolidinone derivatives with promising COX-2 selectivity, anti-inflammatory activity and gastric safety profile. *Bioorg. Chem.,* **64**: 1-12 (2016).
[33] Kumar M., Ramasamy K., Mani V., Mishra R.K., Majeed A.B., De Clercq E. and Narasimhana B., Synthesis, antimicrobial, anticancer, antiviral evaluation and QSAR studies of 4-(1-aryl-2-oxo-1, 2-dihydro-indol-3-ylideneamino)-N-substituted benzene sulfonamides. *Arab. J. Chem.,* **7**(4): 396-408 (2014).
[34] Subhedar D.D., Shaikh M.H., Khan F.A., Sangshetti J.N., Khedkar V.M. and Shingate B.B., Facile synthesis of new N-sulfonamidyl-4-thiazolidinone derivatives and their biological evaluation. *NJC.,* **40**(4): 3047-3058 (2016).
[35] Vinoda B., Bodke Y., Vinuth M., Sindhe M., Venkatesh T. and Telkar S., One pot synthesis, antimicrobial and in silico molecular docking study of 1,3-benzoxazole-5-sulfonamide derivatives. *Curr. Org. Chem.,* **5**(2): 1-6 (2016).
[36] Kulkarni P.S., Karale S.N., Khandebharad A.U., Agrawal B.R. and Sarda S.R., Design, Synthesis, and Biological Evaluation of Newer Arylidene Incorporated 4-Thiazolidinones Derivatives as Potential Antimicrobial Agents. *Polycycl Aromat Compd.,* **12**: 1-14 (2020).

[37] Constantin S.M., Buron F., Routier S., Vasincu I.M., Apotrosoaei M., Lupaşcu F., Confederat L., Tuchilus C., Constantin M.T., Sava A. and Profire L., Formulation and characterization of new polymeric systems based on chitosan and xanthine derivatives with thiazolidin-4-one scaffold. *Material*, **12**(4): 1-19 (2019).

[38] Popiołek Ł., Stefańska J., Kiełczykowska M., Musik I., Biernasiuk A., Malm A. and Wujec M., Synthesis, Dissociation Constants, and Antimicrobial Activity of Novel 2, 3-Disubstituted-1, 3-thiazolidin-4-one Derivatives. *J. Heterocycl. Chem.*, **53**(2): 393-402 (2016).

[39] Stana A., Vodnar D.C., Marc G., Benedec D., Tiperciuc B., Tamaian R. and Oniga O., Antioxidant activity and antibacterial evaluation of new thiazolin-4-one derivatives as potential tryptophanyl-tRNA synthetase inhibitors. *J Enzyme Inhib Med Chem.*, **34**(1): 898-908 (2019).

[40] Stana A., Vodnar D.C., Tamaian R., Pîrnău A., Vlase L., Ionuț I., Oniga O. and Tiperciuc B., Design, synthesis and antifungal activity evaluation of new thiazolin-4-ones as potential lanosterol 14α-demethylase inhibitors. *Int. J. Mol. Sci.*, **18**(1):1-25 (2017).

[41] Mishra K., Ojha H. and Chaudhury N.K., Estimation of antiradical properties of antioxidants using DPPH assay: A critical review and results. *Food Chem.*, **130**(4):1036-1043 (2012).

[42] Fathy U., Gouhar R.S., Younis A. and El-Ghonemy D.H., Synthesis of Novel pyrimido [4,5-b]quinoline-4-one Derivatives and Assessment as Antimicrobial and Antioxidant Agents. *Pharmacon. J.*, **13**(2): 550-562 (2021).

[43] Hassan S.A. and Abdullah M.N., Synthesis, Spectroscopic study and Biological activity of some New Heterocyclic compounds derived from Sulfadiazine. *ZJPAS*, **31**(6):92-109 (2019).

[44] Sharifi-Rad M. and Pohl P., Synthesis of Biogenic Silver Nanoparticles (AgCl-NPs) Using a Pulicaria vulgaris Gaertn. Aerial Part Extract and Their Application as Antibacterial, Antifungal and Antioxidant Agents. *Nanomaterials*, **10**(4): 1-17 (2020).

[45] Ahmed S., Zayed M.F., El-Messery S.M., Al-Agamy M.H. and Abdel-Rahman H.M., Design, synthesis, antimicrobial evaluation and molecular modeling study of 1,2,4-triazole-based 4-thiazolidinones. *Molecules*, **21**(5): 4-17 (2016).

[46] Hassan S.A., Abdullah M.N. and Aziz D.M., Synthesis of New Series Bis-3-Chloro-*β*-Lactam Derivatives from Symmetrical Bis-Schiff Bases as Effective Antimicrobial Agents with Molecular Docking Studies. *SJUOZ*, **9**(3):128-137 (2021).

[47] Bhutani R., Pathak D.P., Kapoor G., Husain A. and Iqbal M.A., Novel hybrids of benzothiazole-1,3,4-oxadiazole-4-thiazolidinone: Synthesis, in silico ADME study, molecular docking and in vivo anti-diabetic assessment. *Bioorg. chem.*, **83**: 6-19 (2019).

[48] Domínguez-Villa F.X., Durán-Iturbide N.A. and Ávila-Zárraga J.G., Synthesis, molecular docking, and in silico ADME/Tox profiling studies of new 1-aryl-5-(3-azidopropyl) indol-4-ones: Potential inhibitors of SARS CoV-2 main protease. *Bioorg. chem.*, **106**: 1-5 (2021).

[49] Mohi A.T., Ismail A.H., Weli A. F. and Jassim A.H., Synthesis, Theoretical and antimicrobial activity study of new benzimidazole derivatives. *Egypt. J. Chem.*, **63**(8):2877-2886 (2020).

[50] Ubeid M.T., Thabet H.K. and El-Feky S.A., An efficient, one-pot three-component synthesis of 4H-thiazolo[3,2-a][1,3,5]triazin-6-one derivatives. *Heterocycl Comm.*, **22**(1): 43-47 (2016).

[51] Salehi M., Ghasemi F., Kubicki M., Asadi A., Behzad M., Ghasemi M.H. and Gholizadeh A., Synthesis, characterization, structural study and antibacterial activity of the Schiff bases derived from sulfanilamides and related copper (II) complexes. *Inorganica Chim. Acta.*, **453**:238-246 (2016).

[52] Thangavelu P. and Thangavel S., Design, Synthesis, and Docking of Sulfadiazine Schiff Base Scaffold for their Potential Claim as INHA Enoyl-(Acyl-Carrier-Protein) Reductase Inhibitors. *Asian J. Pharm. Clin. Res.*, **11**(10): 233-237 (2018).

[53] Salehi M., Kubicki M., Galini M., Jafari M. and Malekshah R.E., Synthesis, characterization and crystal structures of two novel sulfa drug Schiff base ligands derived sulfonamide and molecular docking study. *J. Mol. Struct.*, **1180**: 595-602 (2019).

[54] Anacona J., Noriega N. and Camus J., Synthesis, characterization and antibacterial activity of a tridentate Schiff base derived from cephalothin and sulfadiazine, and its transition metal complexes. *Acta A Mol. Biomol. Spectrosc.*, **137**: 16-22 (2015).

[55] Patel N.B. and Shaikh F.M., Synthesis and antimicrobial activity of new 4-thiazolidinone derivatives containing 2-amino-6-methoxybenzothiazole. *SPJ*, **18**(3): 129-136 (2010).

[56] Thomas A.B., Nanda R.K., Kothapalli L.P., Sharma P.A. and Apte K.G., Synthesis, Biological Activity, Molecular Modelling Studies and 3D-QSAR Investigations of N-[2-(aryl/substituted aryl)-4-oxo-1,3-thiazolidin-3-yl] pyridine-4-carboxamides. *The Op. Conf. Proceed. J.*, **4**: 99-112 (2013).

[57] Maurya R., Patel P. and Rajput S., Synthesis and characterization of Mixed-Ligand Complexes of Cu (II), Ni (II), Co (II), Zn (II), Sm (III), and U (VI) O2, with a Schiff Base Derived from the Sulfa Drug Sulfamerazine and 2,2′-Bipyridine. *Synth React Inorg Met Org Chem.*, **33**(5): 801-816 (2003).

[58] Shahid M., Salim M., Khalid M., Tahir M.N., Khan M.U. and Braga A.A., Synthetic, XRD, non-covalent interactions and solvent dependent nonlinear optical studies of Sulfadiazine-Ortho-Vanillin Schiff base:(E)-4-((2-hydroxy-3-methoxy-benzylidene) amino)-N-(pyrimidin-2-yl)benzene-sulfonamide. *J. of Mol. Str.*, **1161**: 66-75 (2018).

[59] Vekariya P.B., Pandya J.R. and Joshi H.S., An efficient and facile synthesis of 1,2,4-Aryl triazoles and 4-thiazolidinones bearing 6-fluorochroman nucleus. *ISRN*, **2014**: 1-7 (2014).

[60] Genç B. H., Taslimi P., Akyuz B., Tuzun B. and Gulcin I., Synthesis, characterization, biological evaluation, and molecular docking studies of some piperonyl-based 4-thiazolidinone derivatives. *Arch. Pharm.* **353**(1): 1-9 (2020).

[61] Morris G.M., Goodsell D.S., Halliday R.S., Huey R., Hart W.E., Belew R.K. and Olson A.J., Automated docking using a Lamarckian genetic algorithm and an

empirical binding free energy function. *J. Comput. Chem.*, **19**(14): 1639-1662 (1998).

[62] Hassan S.A., Abdullah M.N. and Aziz D.M., Synthesis, in vitro Antimicrobial assay and Molecular Docking Studies of some new Symmetrical Bis-Schiff Bases and their 2-Azetidinones. *ZJPAS*, **33**(2): 34-50 (2021).

[63] Yusufzai S.K., Osman H., Khan M.S., Abd Razik B.M., Ezzat M.O., Mohamad S., Sulaiman O., Ganasu J.A. and Parumasivam T., 4-Thiazolidinone coumarin derivatives as two-component NS_2B/NS_3 DENV flavivirus serine protease inhibitors: synthesis, molecular docking, biological evaluation and structure–activity relationship studies. *Chem. Cent., J.*, **12**(1): 1-16 (2018).

[64] Daina A., Michielin O. and Zoete V., SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.,* **7**(1): 1-13 (2017).

[65] El-Maghraby A.M. and Abdelmonsef A.H., Synthesis, characterization and in silico molecular docking studies of novel chromene derivatives as Rab23 inhibitors. *Egypt. J. Chem.,* **63**(4): 1341-1358 (2020).

[66] Lipinski C.A., Lombardo F., Dominy B.W. and Feeney P.J., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev*., **23**(3): 3-25 (1997).

[67] Husain A., Ahmad A., Khan S.A., Asif M., Bhutani R. and Al-Abbasi F.A., Synthesis, molecular properties, toxicity and biological evaluation of some new substituted imidazolidine derivatives in search of potent anti-inflammatory agents. *SPJ*, **24**(1): 104-114 (2016).

[68] Faizi M., Jahani R., Ebadi S.A., Tabatabai S.A., Rezaee E., Lotfaliei M., Amini M. and Almasirad A., Novel 4-thiazolidinone derivatives as agonists of benzodiazepine receptors: design, synthesis and pharmacological evaluation. *Excli J*. **16**: 52-62 (2017).

[69] Taha D.E., Raauf A.M. and Ali K.F., Design, Synthesis, Characterization, Biological Activity and ADME Study of New 5-arylidene-4-Thiazolidinones Derivatives Having. *AJPS*, **19**(4): 77-88 (2019).

[70] Ujan R., Saeed A., Channar P.A., Larik F.A., Abbas Q., Alajmi M.F., El-Seedi H.R., Rind M.A., Hassan M., Raza H. and Seo S., Drug-1,3,4-thiadiazole conjugates as novel mixed-type inhibitors of acetylcholinesterase: synthesis, molecular docking, pharmacokinetics, and ADMET evaluation. *Molecules*, **24(**5): 1-14 (2019).

[71] da Silva F.D., Coropceanu V., Fichou D., Gruhn N.E., Bill T.G., Gierschner J., Cornil J. and Brédas J., Hole-vibronic coupling in oligothiophenes: impact of backbone torsional flexibility on relaxation energies. *Phil. Trans. R. Soc. A*., **365**(1855): 1435-1452 (2007).

[72] Khan S.A., Rizwan K., Shahid S., Noamaan M.A., Rasheed T. and Amjad H., Synthesis, DFT, computational exploration of chemical reactivity, molecular docking studies of novel formazan metal complexes and their biological applications. *Organomet. Chem.*, **34**(3): 1-24 (2020).

[73] Baroudi B., Argoub K., Hadji D., Benkouider A., Toubal K., Yahiaoui A. and Djafri A., Synthesis and DFT calculations of linear and nonlinear optical responses of novel 2-thioxo-3-N,(4-methylphenyl) thiazolidine-4 one. *J. Sulphur Chem*., **41**(3): 310-325 (2020).

[74] Abbas S.S. and Kubba A.M., Synthesis, Characterization and Preliminary Antimicrobial Evaluation with DFT Study of New Thiazole Derivatives. *Iraqi J. Pharm. Sci*., **27**(1): 69-78 (2018).

[75] Mumit M.A., Pal T.K., Alam M.A., Islam M.A., Paul S. and Sheikh M.C., DFT studies on vibrational and electronic spectra, HOMO–LUMO, MEP, HOMA, NBO and molecular docking analysis of benzyl-3-N-(2,4,5-trimethoxyphenylmethylene) hydrazinecarbodithioate. *J. Mol. Struct*., **1220**: 1-34 (2020).

[76] Khanna L., Singhal S., Jain S.C. and Khanna P., Spiro-Indole-Coumarin Hybrids: Synthesis, ADME, DFT, NBO Studies and In Silico Screening through Molecular Docking on DNA G-Quadruplex. *ChemistrySelect*., **5**(11): 3420-3433 (2020).

[77] Ermiş E., Synthesis, spectroscopic characterization and DFT calculations of novel Schiff base containing thiophene ring. *J. Mol. Struct.,* **1156**: 91-104 (2018).

[78] Raj G.J., Jayanthi P. and Sekar M., Synthesis, spectral characterization, molecular structure, HOMO-LUMO, MEP and NLO analysis of some (*E*)-*N*-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines. *Int. J. Adv. Chem.,* **4**(2): 27-35 (2016).

[79] Aman H., Rashid N., Ashraf Z., Bibi A., Chen H.T. and Sathishkumar N., Synthesis, density functional theory (DFT) studies and urease inhibition activity of chiral benzimidazoles. *Heliyon*, **6**(10): 1-8 (2020).

[80] Nadhiya V.D. and Kumaresan R., Combined experimental and computational investigation of 2-(2-hydroxyphenylimino)phenolic derivatives: synthesis, molecular structure and NLO studies. *IJOC*, **7**(2): 185-217 (2017).