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Synthesis, antimicrobial activity and Molecular docking study of some novel thiazolidine-2,4-dione derivatives

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Abstract

A series of novel thiazolidine-2,4-diones was synthesized and investigated for antimicrobial activity. The structures of all synthesized compounds were confirmed by means of elemental analysis, IR, ^{1}H NMR, and LCMS. All compounds were evaluated for antimicrobial activity cup plate method against *S. aureus, B. anthracis, P. aeruginosa, E. coli, C. albicans* and *A. niger*. Compounds **2d and 2l** showed significant activity against gram positive and gram negative bacteria. In case of antifungal activity, the zone of inhibition was ranging from 10 to 23 mm and the compounds **2c** and **2e** showed significant activity against the fungal strains as compared with fluconazole.

Keywords: thiazolidine-2,4-diones, antimicrobial activity, synthesis, molecular docking

INTRODUCTION

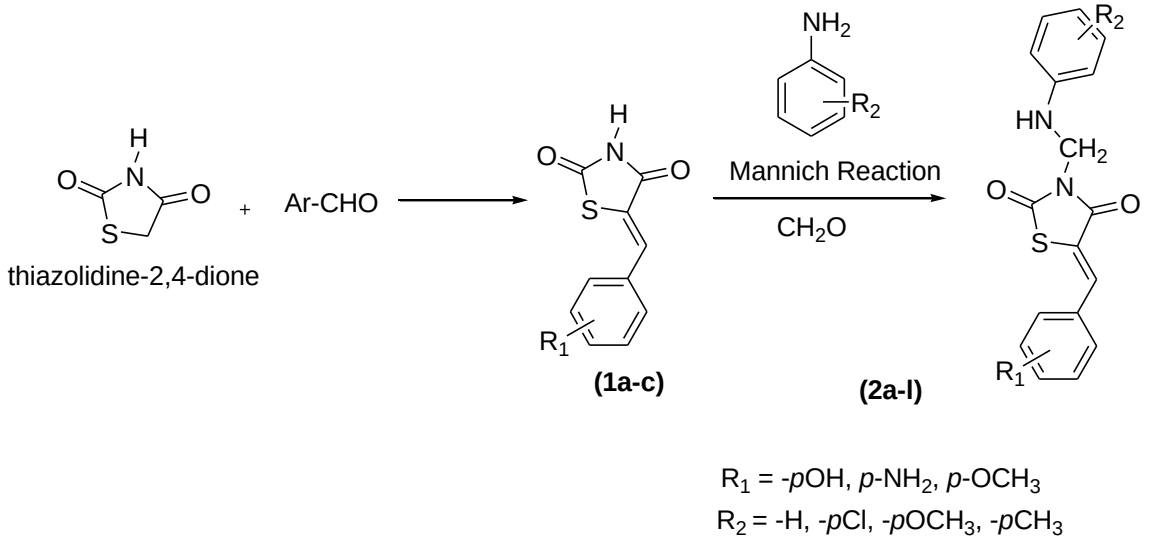
The Centers for Disease Control (CDC) estimates that 19 million new illnesses start each year [1-6]. The use of antimicrobial medications can lead to a few major issues, including local irritation, systemic toxicity, drug resistance, hypersensitivity, suprinfection, nutritional inadequacy, and infection masking [7-16]. Drug resistance is often acquired by bacteria and fungi in one of three ways: by creating metabolising enzymes that break down the medications, by altering the targets of the drugs to render them useless, or by overexpressing efflux proteins that 'pump' the drug out to reduce its concentration [17-28]. The scientific community is extremely concerned about the rising incidences of microbial resistance, which have started to endanger human life everywhere [29-34]. Furthermore, it is challenging to identify and treat invasive microbial infections brought on by multi-drug resistant Gram-positive bacteria and microorganisms. Particularly in immunosuppressed and hospital-acquired patients, they are the main cause of morbidity and death [36-40].

To address these issues, new, stable antimicrobial agents with increased efficacy must be developed.

The thiazolidine-2,4-dione moiety is a flexible lead molecule used in the creation of pharmaceuticals and has a variety of biological functions [41-42]. Thiazolidine-2,4-diones derivatives are of great importance in medicinal chemistry and can be used for the synthesis

of numerous heterocyclic compounds with different biological activities such as anticonvulsant [43-44], antidepressant [45-46], antituberculosis [47-48], anti-inflammatory [49-50], antibacterial [51-52], antiviral [53], antifungal [54-55] and anticancer [56] activities etc.

In the present work, we planned to develop novel thiazolidine-2,4-dione derivatives and screen for antibacterial and antifungal activity.



Scheme 1: Synthesis of thiazolidine-2,4-diones

MATERIAL AND METHODS

All the melting points reported were determined by open capillary tube method and are uncorrected. The synthesis and analytical studies of the compounds were carried out using laboratory grade and analytical grade reagents as the case may be standard procedure or reported method were followed with or without modification appropriately as and when required. Elemental analysis (C, H and N) was undertaken with a Perkin-Elmer model 240C analyzer, and all analyses were consistent with theoretical values (within 0.4%) unless indicated. IR absorption spectra were recorded on Bruker alpha. ^{1}H NMR spectra were recorded on the Bruker DPX-400 instrument at 400 MHz. The ^{1}H chemical shifts are reported as parts per million (ppm) downfield from TMS (Me4Si). The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer. The homogeneity of the compounds was monitored by ascending thin-layer chromatography (TLC) on silica gel G (Merck)-coated aluminum plates, visualized by iodine vapor.

5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (1a)

A mixture of 2.44 g of 4-hydroxybenzaldehyde and 2.32 g of thiazolidin-2,4-dione in 20 mL of toluene was treated with 0.5 g of benzoic acid and 0.5 mL of piperidine. The reaction mixture was refluxed for 2 h. The Dean-Stark water separator was used for continuous removal of water. The mixture was cooled to room temperature and the resulting precipitate was filtered and washed with dichloromethane and diethyl ether.

Melting Point: 298-302 ºC; Yield: 81 %; R_f value: 0.62; Solvent system: Benzene: Methanol (8.5:1.5); IR (υ_{max}, cm^{-1}): 3426, 3312 (N−H), 3077, 3061 (Ar. C−H), 1727 (C=O), 1521, 1490 (Ar. C=C).

Similar procedure was used to synthesize **1b** and **1c** by using appropriate aldehydes.

5-(4-aminobenzylidene)thiazolidine-2,4-dione (1b)

Melting Point: 226-230 ºC; Yield: 72 %; R_f value: 0.84; Solvent system: Benzene: Methanol (8.5:1.5); IR (υ_{max}, cm^{-1}): 3435, 3384 (N−H), 3070, 3054 (Ar. C−H), 1733 (C=O), 1513, 1497 (Ar. C=C).

5-(4-methoxybenzylidene)thiazolidine-2,4-dione (1c)

Melting Point: 216-220 ºC; Yield: 81 %; R_f value: 0.78; Solvent system: Benzene: Methanol (8.5:1.5); IR (υ_{max}, cm^{-1}): 3448, 3375 (N−H), 3094, 3056 (Ar. C−H), 1739 (C=O), 1561, 1511 (Ar. C=C), 1410, 1383 (−CH_3).

5-(4-hydroxybenzylidene)-3-((phenylamino)methyl)thiazolidine-2,4-dione (2a)

5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (1a) (1 mmol) was dissolved in sufficient quantity of ethanol and 2-3 drops of conc. HCl was added drop wise. The reaction mixture was kept for stirring with help of magnetic stirrer. To the stirring reaction mixture formaldehyde (1 mmol) was added drop wise and stirring was kept continuously for some time. Then added aniline (1 mmol) dissolved in ethanol. Further stirring was continued for 15-20 mins followed by reflux for 12 hrs. After completion of the reaction, it was allowed to cool at room temperature and the separated solid was filtered and dried. The obtained product was re-crystallized from ethanol.

Melting Point: 230-234 ºC; Yield: 77 %; R_f value: 0.68; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{17}H_{14}N_2O_3S$ (326.37): C, 62.56; H, 4.32; N, 8.58. Found: C, 62.32; H, 4.38; N, 8.83; IR (υ_{max}, cm^{-1}): 3465, 3343 (N−H), 3063 (Ar. C−H), 1463 (−CH_2−), 1722 (C=O), 1123 (C−N), 1536, 1493 (Ar. C=C), 3460 (O−H); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.91 (s, 1H, OH), 5.18-5.26 (d, 2H, CH_2), 5.66 (s, 1H, NH), 6.66-7.34 (m, 9H, Ar-H), 7.94 (s, 1H, CH).

LCMS (m/z): $[M]^+$; 326.07

The similar procedure was adopted to synthesize derivatives (**2b**-**2l**) by using corresponding aniline.

5-(4-hydroxybenzylidene)-3-((4-chlorophenylamino)methyl)thiazolidine-2,4-dione (2b)

Melting Point: 242-246 ºC; Yield: 81 %; R_f value: 0.72; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{17}H_{13}ClN_2O_3S$ (360.81): C, 56.59; H, 3.63; N, 7.76. Found: C, 56.45; H, 3.81; N, 7.88; IR (υ_{max}, cm^{-1}): 3386, 3265 (N−H), 3077 (Ar. C−H), 1462 (−CH_2−), 1738 (C=O), 1216 (C−N), 1545, 1488 (Ar. C=C), 3634 (O−H), 689 (C−Cl); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.87 (s, 1H, OH), 5.26-5.31 (d, 2H, CH_2), 5.78 (s, 1H, NH), 6.71-7.40 (m, 8H, Ar-H), 7.99 (s, 1H, CH); LCMS (m/z): $[M]^+$; 360.03

5-(4-hydroxybenzylidene)-3-((4-methoxyphenylamino)methyl)thiazolidine-2,4-dione (2c)

Melting Point: 262-266 ºC; Yield: 67 %; R_f value: 0.82; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{18}H_{16}N_2O_4S$ (356.4): C, 60.66; H, 4.53; N, 7.86. Found: C, 61.05; H, 4.87; N, 8.21; IR (υ_{max}, cm^{-1}): 3445, 3389 (N−H), 3079 (Ar. C−H), 1456 (−CH_2−), 1738 (C=O), 1134 (C−N), 1576, 1456 (Ar. C=C), 3468 (O−H), 761 (O−CH_3); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.53 (s, 3H, OCH_3), 3.92 (s, 1H, OH), 5.21-5.27 (d, 2H, CH_2), 5.69 (s, 1H, NH), 6.82-7.39 (m, 8H, Ar-H), 7.89 (s, 1H, CH); LCMS (m/z): $[M]^+$; 356.08

5-(4-hydroxybenzylidene)-3-((*p*-toluidino)methyl)thiazolidine-2,4-dione (2d)

Melting Point: 238-242 ºC; Yield: 78 %; R_f value: 0.74; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{18}H_{16}N_2O_3S$ (340.4): C, 63.51; H, 4.74; N, 8.23; Found: C, 63.74; H, 4.72; N, 8.35; IR (υ_{max}, cm^{-1}): 3459, 3313 (N−H), 3091 (Ar. C−H), 1464 (−CH_2−), 1738 (C=O), 1128 (C−N), 1515, 1484 (Ar. C=C), 3606 (O−H), 1432 (CH_3); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.39 (s, 3H, CH_3), 3.75 (s, 1H, OH), 5.28-5.34 (d, 2H, CH_2), 5.64 (s, 1H, NH), 6.68-7.35 (m, 8H, Ar-H), 7.94 (s, 1H, CH); LCMS (m/z): $[M]^+$; 340.09

5-(4-aminobenzylidene)-3-((phenylamino)methyl)thiazolidine-2,4-dione (2e)

Melting Point: 210-214 ºC; Yield: 85 %; R_f value: 0.83; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{17}H_{15}N_3O_2S$ (325.38): C, 62.75; H, 4.65; N, 12.91. Found: C, 62.42; H, 4.37; N, 13.23; IR (υ_{max}, cm^{-1}): 3465, 3343 (N−H), 3063 (Ar. C−H), 1463 (−CH_2−), 1722 (C=O), 1123 (C−N), 1536, 1493 (Ar. C=C); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 4.03 (s, 2H, NH_2), 5.24-5.29 (d, 2H, CH_2), 5.79 (s, 1H, NH), 6.59-7.32 (m, 9H, Ar-H), 7.79 (s, 1H, CH); LCMS (m/z): $[M]^+$; 325.09

5-(4-aminobenzylidene)-3-((4-chlorophenylamino)methyl)thiazolidine-2,4-dione (2f)

Melting Point: 234-236 ºC; Yield: 73 %; R_f value: 0.69; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{17}H_{14}ClN_3O_2S$ (359.83): C, 56.74; H, 3.92; N, 11.68. Found: C, 56.45; H, 4.18; N, 11.95; IR (υ_{max}, cm^{-1}): 3486, 3435 (N−H), 3084 (Ar. C−H), 1468 (−CH_2−), 1722 (C=O), 1123 (C−N), 1536, 1493 (Ar. C=C), 724 (C−Cl). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 4.11 (s, 2H, NH_2), 5.27-5.35 (d, 2H, CH_2), 5.63 (s, 1H, NH), 6.66-7.45 (m, 8H, Ar-H), 7.92 (s, 1H, CH); LCMS (m/z): $[M]^+$; 359.05

5-(4-aminobenzylidene)-3-((4-methoxyphenylamino)methyl)thiazolidine-2,4-dione (2g)

Melting Point: 262-266 ºC; Yield: 69 %; R_f value: 0.75; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{18}H_{17}N_3O_3S$ (355.41): C, 60.83; H, 4.82; N, 11.82. Found: C, 60.71; H, 4.68; N, 11.95; IR (υ_{max}, cm^{-1}): 3424, 3294 (N−H), 3054 (Ar. C−H), 1457 (−CH_2−), 1738 (C=O), 1142 (C−N), 1576, 1478 (Ar. C=C), 1178 (C−O); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.76 (s, 3H, OCH_3), 4.04 (s, 2H, NH_2), 5.24-5.34 (d, 2H, CH_2), 5.69 (s, 1H, NH), 6.61-7.32 (m, 8H, Ar-H), 7.78 (s, 1H, CH); LCMS (m/z): $[M]^+$; 355.10.

5-(4-aminobenzylidene)-3-((*p*-toluidino)methyl)thiazolidine-2,4-dione (2h)

Melting Point: 234-238 ºC; Yield: 71 %; R_f value: 0.83; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H, 5.05; N, 12.38. Found: C, 63.84; H, 4.88; N, 12.15; IR (υ_{max}, cm^{-1}): 3346, 3299 (N−H), 3067 (Ar. C−H), 1460 (−CH_2−), 1731 (C=O), 1146 (C−N), 1576, 1481 (Ar. C=C), 2945 (C−H); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.34 (s, 3H, CH_3), 4.07 (s, 2H, NH_2), 5.23-5.29 (d, 2H, CH_2), 5.74 (s, 1H, NH), 6.73-7.52 (m, 8H, Ar-H), 7.93 (s, 1H, CH); LCMS (m/z): $[M]^+$; 339.10

5-(4-methoxybenzylidene)-3-((phenylamino)methyl)thiazolidine-2,4-dione (2i)

Melting Point: 202-206 ºC; Yield: 83 %; R_f value: 0.65; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{18}H_{16}N_2O_3S$ (340.4): C, 63.51; H, 4.74; N, 8.23. Found: C, 63.84; H, 4.78; N, 8.36; IR (υ_{max}, cm^{-1}): 3349, 3254 (N−H), 3079 (Ar. C−H), 1467 (−CH_2−), 1733 (C=O), 1123 (C−N), 1543, 1468 (Ar. C=C), 1198 (C−O); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.79 (s, 3H, OCH_3), 5.24-5.27 (d, 2H, CH_2), 5.68 (s, 1H, NH), 6.69-7.48 (m, 9H, Ar-H), 7.94 (s, 1H, CH); LCMS (m/z): $[M]^+$; 340.09

5-(4-methoxybenzylidene)-3-((4-chlorophenylamino)methyl)thiazolidine-2,4-dione (2j)

Melting Point: 194-198 ºC; Yield: 74 %; R_f value: 0.81; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{18}H_{15}ClN_2O_3S$ (374.84): C, 57.68; H, 4.03; N, 7.47.

Found: C, 57.35; H, 4.43; N, 7.58; IR (υ_{max}, cm^{-1}): 3248, 3199 (N−H), 3053 (Ar. C−H), 1456 (−CH_2−), 1729 (C=O), 1095 (C−N), 1576, 1486 (Ar. C=C), 1248 (C−O) 715 (C−Cl); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.83 (s, 3H, OCH_3), 5.29-5.36 (d, 2H, CH_2), 5.74 (s, 1H, NH), 6.71-7.43 (m, 8H, Ar-H), 7.83 (s, 1H, CH); LCMS (m/z): $[M]^+$; 374.05

5-(4-methoxybenzylidene)-3-((4-methoxyphenylamino)methyl)thiazolidine-2,4-dione (2k)

Melting Point: 216-220 ºC; Yield: 69 %; R_f value: 0.66; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{19}H_{18}N_2O_4S$ (370.42): C, 61.61; H, 4.90; N, 7.56. Found: C, 61.53; H, 4.68; N, 7.75; IR (υ_{max}, cm^{-1}): 3387, 3284 (N−H), 3089 (Ar. C−H), 1465 (−CH_2−), 1739 (C=O), 1184 (C−N), 1548 (Ar. C=C), 1249 (C−O); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.23-5.26 (d, 2H, CH_2), 5.79 (s, 1H, NH), 6.64-7.38 (m, 8H, Ar-H), 7.87 (s, 1H, CH); LCMS (m/z): $[M]^+$; 370.10

5-(4-methoxybenzylidene)-3-((*p*-toluidino)methyl)thiazolidine-2,4-dione (2l)

Melting Point: 246-250 ºC; Yield: 89 %; R_f value: 0.79; Solvent system: Benzene: Ethylacetate (8:2); Anal. Calcd. for $C_{19}H_{18}N_2O_3S$ (354.42): C, 64.39; H, 5.12; N, 7.90. Found: C, 64.45; H, 5.32; N, 8.21; IR (υ_{max}, cm^{-1}): 3346, 3254 (N−H), 3056 (Ar. C−H), 1453 (−CH_2−), 1738 (C=O), 1049 (C−N), 1536, 1488 (Ar. C=C), 1187 (C−O); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.49 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.27-5.32 (d, 2H, CH_2), 5.85 (s, 1H, NH), 6.73-7.45 (m, 8H, Ar-H), 7.97 (s, 1H, CH); LCMS (m/z): $[M]^+$; 354.10.

In-silico prediction of absorption and drug likeness

The calculation of molecular properties like drug likeliness and bioactivity were predicted by Molinspiration property engine v2009.01 program.

The Molinspiration home page was opened online, in which free on-line cheminformatics services link option was opened. The molecule to be analyzed was pasted, whose structure was already saved in smile format (through any chemistry software) then with the help of calculate properties or predict bioactivity options, calculations were obtained and saved [57-59].

"Lipinski rule or rule of five is like that to be drug-like, a candidate should have less than five hydrogen bond donors (HBD), less than 10 hydrogen bond acceptors (HBA), a molecular weight of less than 500 Da, and a partition coefficient log P of less than 5. The aim of the *rule of five* is to highlight possible bioavailability problems if two or more properties are violated" [57-59].

"Absorption (%ABS) was calculated by %ABS = 109-(0.345 X TPSA)" [57-59].

Molecular Docking Study

Hardware and Software

Windows 10 (64-bit) operating systems with 4 GB RAM and 2.50 GHz Intel(R) Core(TM) i5-7200U processor was used for executing the docking process. PyRx version 0.8, available at https://pyrx.sourceforge.io/ was used to perform the docking in Auto Dock Vina Wizard [60]. Autodock Tools 4.2.6 which is made accessible by the Scripps Research Institute at https://autodock.scripps.edu/, was used for preparing the proteins and for grid generation, Ligands were processed using Open babel [61] and PyRx 0.8 and interaction poses of ligands were visualized and analysed using Discovery Studio Visualizer.

Selection of Target Proteins: The molecular docking studies were carried out on two microbial proteins for assessing antimicrobial potential. PDB ID 2EG7-*E. coli*

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Dihydrorootase in complex with HDDP and PDB ID 5D6P-ATP Binding domain of GyrB of *S. aureus* in complex with 57U were chosen [62].

Protein and ligand processing for docking

Protein Preparation

The crystal structures of target protein (PDB ID 2EG7- *E. coli* Dihydrorootase in complex with HDDP [62] was downloaded from the RCSB-Protein Data Bank and the proteins were prepared using Autodock Tools 4.2.6. In this step, attached water molecules and bound heteroatoms/ligand were removed, polar hydrogens and Kollman charges were added, the charge was spread equally over all atoms and residues were checked for missing atoms if any. The prepared PDB files were then converted to the PDBQT format for executing the next step.

Ligand Processing

Ligands in smiles format were converted to sdf files and 3D coordinates for all ligands were generated using Open Babel using command line. The 3D structure data files were processed in PyRx using UFF energy minimization and then converted to PDBQT format (autodock detectable format).

Grid Generation

The grid box was first set over attached ligands using AutoDock Tools and then manually adjusted to desired dimensions in PyRx. The grid dimensions were set as 30.329 x 40.334 x 80.415 $Å^3$ keeping number of points as 25 in X, Y, Z direction for PDB ID:2EG7.

Docking and visualization of results:

The docking was implemented in Vina Wizard of PyRx Tool, using exhaustiveness of 8 and the resultant out files were split into individual pose files. These files and the protein structure were then taken for visualization of interactions using Discovery Studio Visualizer.

RESULTS AND DISCUSSION

The title compounds (**2a-2l**) were synthesized as per scheme 1. As per scheme 1, in the first step, 5-(4-substituted benzylidene)thiazolidine-2,4-diones (**1a-1c**) were synthesized by reaction of thiazolidin-2,4-dione with 4-substituted benzaldehydes. In the second step, Compounds (**2a-2l**) was synthesized from 5-(4-substituted benzylidene)thiazolidine-2,4-diones (**1a-1c**) by Mannich reaction with aldehydes.

All the title compounds synthesized were tested against two gram positive bacterial strains *Staphylococcus aureus*, *Bacillus anthracis*, two gram negative bacterial strains *Pseudomonas aeruginosa*, *Escherichia coli* and two fungal strain (*C. albicans*, *A. niger*) by cup-plate method for antimicrobial activity.

For the study, the solutions of 1000 μg/ml concentration of test compounds were prepared in dimethylsulphoxide (solvent). Streptomycin and Fluconazole were used as standard for antibacterial and antifungal activity respectively. Both standard drug control and solvent control were maintained for the study [63].

In case of antibacterial activity, the zone of inhibition was ranging from 09 to 28 mm and 10 to 26 mm for gram positive bacterial and gram negative bacterial strains respectively.

At the same time, it was noted that compounds 2d and 2l showed significant activity against gram positive and gram negative bacteria.

In case of antifungal activity, the zone of inhibition was ranging from 10 to 23 mm and the compounds 2c and 2e showed significant activity against the fungal strains as compared with fluconazole.

Table 1: Antimicrobial Activity of Title compounds

Compound (1000 µg/ml)	**Zone of Inhibition (mm)**					
	S. aureus	***B. anthracis***	***P. aeruginosa***	***E. coli***	***C. albicans***	***A. niger***
Streptomycin	**34**	**35**	**30**	**31**	**-**	**-**
Fluconazole	**-**	**-**	**-**	**-**	**27**	**29**
2a	15	19	10	18	10	11
2b	19	20	10	19	10	15
2c	23	18	18	23	20	21
2d	28	29	26	26	16	18
2e	21	19	16	21	22	23
2f	25	16	15	21	18	18
2g	23	17	19	16	15	16
2h	20	18	13	14	12	10
2i	24	16	9	18	13	16
2j	22	14	12	9	15	16
2k	21	13	12	21	18	19
2l	26	28	25	26	20	22

The calculation of molecular properties like drug likeliness and bioactivity were predicted by Molinspiration property engine v2009.01 program. It was observed that all the compounds (**2a-2l**) exhibited a great % Absorbance ranging from 79.21 to 88.18 % and none of the compound showed any violation of Lipinski rules

Table 2: Drug likeliness and *in-silico* prediction of % absorption

Compounds	**LogP**	**TPSA**	**MW**	**nON**	**nOHNH**	**nviolation**	**nrotb**	**Vol**	**% abs**
2a	2.54	71.33	326.38	5	2	0	4	278.13	84.39
2b	3.22	71.33	360.82	5	2	0	4	291.66	84.39
2c	2.60	80.56	356.4	6	2	0	5	303.67	81.21
2d	2.99	71.33	340.40	5	2	0	4	294.69	84.39
2e	2.10	77.13	325.39	5	3	0	4	281.40	82.39
2f	2.77	77.13	359.84	5	3	0	4	294.94	82.39
2g	2.15	86.36	355.42	6	3	0	5	306.94	79.21

2h	2.54	77.13	339.42	5	3	0	4	297.96	82.39
2i	3.08	60.34	340.40	5	1	0	5	295.66	88.18
2j	3.75	60.34	374.85	5	1	0	5	309.19	88.18
2k	3.13	69.57	370.43	6	1	0	6	321.20	85.00
2l	3.52	60.34	354.43	5	1	0	5	312.22	88.18

The molecular docking studies were carried out for assessing antimicrobial potential. PDB ID 2EG7-*E. coli* Dihydrorootase in complex with was chosen.

On the basis of the interaction energy criterion, compound **2c** showed the best docking interactions equal to (-7.1) and the residues of binding site regions are following. Compound **2c** showed two hydrogen bond interactions with ASN:44 and HIS:177 and forms a carbon-hydrogen bond with HIS:254. It formed a π- π T-shaped interactions with ALA252.

Table 3: Molecular Docking of Compounds (2a-2l) with PDB 2EG7

S. No.	Compound	Binding Energy (Kcal/mol)	Hydrogen Bonding Interactions (Conventional)	Receptor Ligand Interactions
1.	2a	-6.9	ASN A:44, HIS A:18	ALA A:252, ALA A:46, ALA A:266, HIS A:254
2.	2b	-6.1	ARG A:20	HIS A:18, ASN A:44, ALA A:46, HIS A:254, GLY A:267, ALA A:252, ALA A:266, CYS A:221, LEU A:222
3.	2c	-7.1	ASN A:44, HIS A:177	HIS A:18, LEU A:45, ARG A:20, HIS A:254, ALA A:266, ALA A:252
4.	2d	-6.9	ASN A:44, ARG A:20, HIS A:254, ASP A:250, LEU A:222, HIS A:177	ALA A:46, ALA A:252
5.	2e	-6.2	LEU A:222, ASN A:44	ALA A:266, HIS A:18, ALA A:252, HIS A:254, ARG A:20
6.	2f	-6.5	ASN A:54, LEU A: 222	HIS A:18, HIS A:254, ALA A:252, ALA A:266, MET A:24, ARG A:20
7.	2g	-6.7	ASP A:21, ASN A:44, LEU A:222	MET A:24, ARG A:20, HIS A:254, ALA A:252, HIS A:18, ALA A:266
8.	2h	-6.6	ASN A:44, LEU A:222	LEU A:45, ALA A:46, ARG A:20, HIS A:254, ALA A:252,

				HIS A:18, ALA A:266,
9.	2i	-6.2	HIS A:254, ARG A:20	GLY A:267, ALA A:266, LEU A:222, ALA A:252, ALA A:46, LEU A:45
10.	2j	-6.4	ARG A:20, ASN A:44	HIS A:254, ALA A:266, ALA A:252, CYS A:221, LEU A:222, ALA A:46, LEU A:45
11.	2k	-6.4	ASN A:44, ASP A:21	MET A:24, LEU A:45, ALA A:46, ARG A:20, HIS A:254, HIS A:18, ALA A:252, ALA A:266, MIS A:177, LEU A:222, ASP A:250, HIS A:139
12.	2l	-6.7	ARG A:20 ASN A:44, HIS A:254	LEU A:222, MIS A:139, PRO A:105
23	Streptomycin	-6.0	ASP A:21, HIS A:254, ALA A:266	ARG A:258

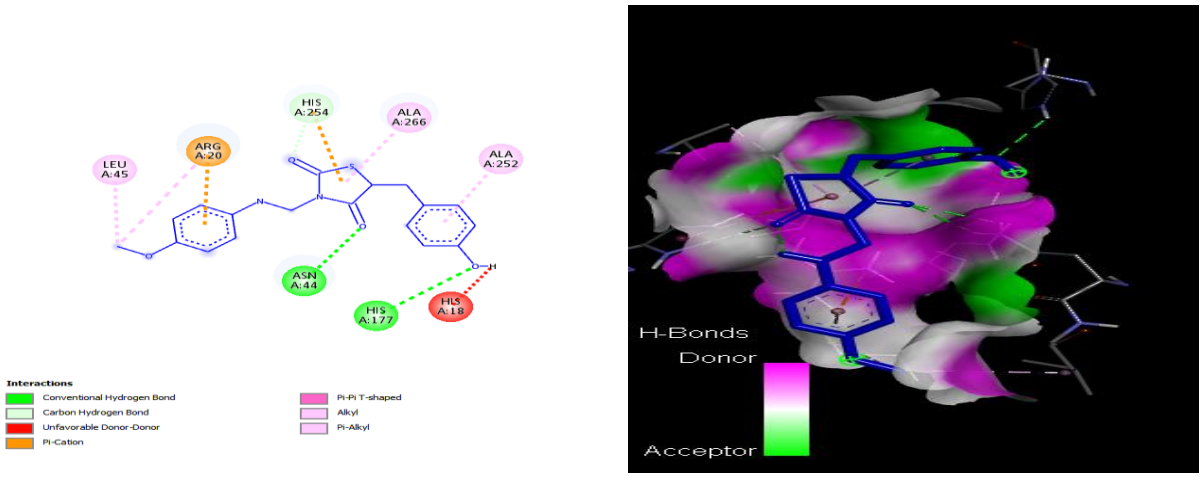

*Figure 1: 2D and 3D binding conformation of Compound **2c** at HDDP binding site of E. coli Dihydrorootase (PDB ID: 2EG7)*

CONCLUSION

Thiazolidin-2,4-dione derivatives constitute an important class of heterocycles with analgesic-anti-inflammatory, antimicrobial, anticonvulsant, antimalarial, anticancer, antioxidant, anti-depressant, anti-leishmanial, neuroprotective and other pharmacological activities. All the title compounds synthesized (**2a-2l**) were tested against 2 gram +ve bacterial strains *S. aureus, B. anthracis*, 2 gram -ve bacterial strains *P. aeruginosa, E. coli*, and 2 fungal strains (*A. niger and C. albicans*) by cup-plate method for antimicrobial activity. It was noted that compounds **2d** and **2l** showed significant activity against gram positive and gram negative bacteria.

In case of antifungal activity, the zone of inhibition was ranging from 10 to 23 mm and the compounds **2c** and **2e** showed significant activity against the fungal strains as compared with fluconazole. It was observed that all the compounds (**2a-2l**) exhibited a great % Absorbance

ranging from **79.21** to **88.18 %** and none of the compound showed any violation of Lipinski rules

REFERENCES

[1]. Cates Jr W, American Social Health Association Panel. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. Sexually transmitted diseases. 1999; S2-S7.

[2]. Workowski KA, Levine WC, Wasserheit JN. US Centers for Disease Control and Prevention guidelines for the treatment of sexually transmitted diseases: an opportunity to unify clinical and public health practice. Annals of Internal Medicine. 2002;137(4):255-262.

[3]. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, Griffin PM, Tauxe RV. Food-related illness and death in the United States. Emerging infectious diseases. 1999; 5(5): 607-625.

[4]. Coustasse A, Kimble C, Maxik K. COVID-19 and vaccine hesitancy: a challenge the United States must overcome. The Journal of ambulatory care management. 2021; 44(1): 71-75.

[5]. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945–1965: recommendations from the Centers for Disease Control and Prevention. Annals of internal medicine. 2012; 157(11): 817-822.

[6]. Holtgrave, DR. Costs and consequences of the US Centers for Disease Control and Prevention's recommendations for opt-out HIV testing. *PLoS medicine*, 2007; *4*(6), 1011-1018.

[7]. Bodey GP. Infection in cancer patients: a continuing association. The American journal of medicine. 1986; 81(1): 11-26.

[8]. Chambers HF. General principles of antimicrobial therapy. Goodman Gilman's the pharmacological basis of therapeutics. McGraw-Hill, USA. 2006: 1095-10111.

[9]. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surgical infections. 2013; 14(1): 73-156.

[10]. Schlossberg D. Clinical approach to antibiotic failure. Medical Clinics. 2006; 90(6): 1265-1277.

[11]. Vento S, Cainelli F. Infections in patients with cancer undergoing chemotherapy: aetiology, prevention, and treatment. The lancet oncology. 2003; 4(10): 595-604.

[12]. Gallagher JJ, Williams-Bouyer N, Villarreal C, Heggers JP, Herndon DN. Treatment of infection in burns. Total Burn Care. Philadelphia: Elsevier, Inc. 2007; 136-176.

[13]. Eales L. The dangers of antibiotics. South African Medical Journal. 1962; 36(7): 121-126.

[14]. Arendsen LP, Thakar R, Sultan AH. The use of copper as an antimicrobial agent in health care, including obstetrics and gynecology. Clinical Microbiology Reviews. 2019; 32(4): e00125-18.

[15]. Mishra H, Dikshit H. Antimicrobials Resistance: Need for A Rational Approach. Journal of Indira Gandhi Institute of Medical Sciences. 2015; 1(1): 1-8.

[16]. Altemeier WA, Wulsin JH. Antimicrobial therapy in injured patients. Journal of the American Medical Association. 1960; 173(5): 527-533.
[17]. Berman J, Krysan DJ. Drug resistance and tolerance in fungi. Nature Reviews Microbiology. 2020; 18(6): 319-331.
[18]. Cowen LE. The evolution of fungal drug resistance: modulating the trajectory from genotype to phenotype. Nature Reviews Microbiology. 2008; 6(3): 187-198.
[19]. Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. The American journal of medicine. 2012; 125(1): S3-13.
[20]. Anderson JB. Evolution of antifungal-drug resistance: mechanisms and pathogen fitness. Nature Reviews Microbiology. 2005; 3(7): 547-556.
[21]. Cowen LE, Sanglard D, Howard SJ, Rogers PD, Perlin DS. Mechanisms of antifungal drug resistance. Cold Spring Harbor perspectives in medicine. 2015; 5(7): a019752.
[22]. Cannon RD, Lamping E, Holmes AR, Niimi K, Baret PV, Keniya MV, Tanabe K, Niimi M, Goffeau A, Monk BC. Efflux-mediated antifungal drug resistance. Clinical microbiology reviews. 2009; 22(2): 291-321.
[23]. Gold HS, Moellering Jr RC. Antimicrobial-drug resistance. New England journal of medicine. 1996; 335(19): 1445-1453.
[24]. Hooper DC, Jacoby GA. Mechanisms of drug resistance: quinolone resistance. Annals of the New York academy of sciences. 2015; 1354(1): 12-31.
[25]. Fernández J, Bert F, Nicolas-Chanoine MH. The challenges of multi-drug-resistance in hepatology. Journal of hepatology. 2016; 65(5): 1043-1054.
[26]. Anderson ES. Drug resistance in Salmonella typhimurium and its implications. Br Med J. 1968; 3(5614): 333-339.
[27]. Barbosa TM, Levy SB. The impact of antibiotic use on resistance development and persistence. Drug resistance updates. 2000; 3(5): 303-311.
[28]. MacPherson DW, Gushulak BD, Baine WB, Bala S, Gubbins PO, Holtom P, Segarra-Newnham M. Population mobility, globalization, and antimicrobial drug resistance. Emerging infectious diseases. 2009; 15(11): 1727-1731.
[29]. Vincent JL. Microbial resistance: lessons from the EPIC study. Intensive care medicine. 2000; 26(1): S003-S008.
[30]. Gunawan C, Marquis CP, Amal R, Sotiriou GA, Rice SA, Harry EJ. Widespread and indiscriminate nanosilver use: genuine potential for microbial resistance. ACS nano. 2017; 11(4): 3438-3445.
[31]. Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. Annals of intensive care. 2011; 1(1): 1-7.
[32]. Dadgostar P. Antimicrobial resistance: implications and costs. Infection and drug resistance. 2019; 12: 3903-3910.
[33]. Van Duin D, Paterson DL. Multidrug-resistant bacteria in the community: trends and lessons learned. Infectious disease clinics. 2016; 30(2): 377-390.
[34]. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Guerin PJ, Piddock LJ. Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet. 2016; 387(10014): 176-187.
[35]. Verweij PE, Meis JF. Microbiological diagnosis of invasive fungal infections in transplant recipients. Transplant Infectious Disease: Review article. 2000; 2(2): 80-87.

[36]. Tarrand JJ, Lichterfeld M, Warraich I, Luna M, Han XY, May GS, Kontoyiannis DP. Diagnosis of invasive septate mold infections: a correlation of microbiological culture and histologic or cytologic examination. American journal of clinical pathology. 2003; 119(6): 854-858.

[37]. Sheng WS, Hsueh PR, Hung CC, Teng LJ, Chen YC, Luh KT. Clinical features of patients with invasive Eikenella corrodens infections and microbiological characteristics of the causative isolates. European Journal of Clinical Microbiology and Infectious Diseases. 2001; 20(4): 231-236.

[38]. Rao SD. Invasive fungal infections: a comprehensive review. Am J Infect Dis. 2013; 1(4): 64-69.

[39]. Spitzer M, Robbins N, Wright GD. Combinatorial strategies for combating invasive fungal infections. Virulence. 2017; 8(2): 169-185.

[40]. Ioanas M, Ferrer R, Angrill J, Ferrer M, Torres A. Microbial investigation in ventilator-associated pneumonia. European Respiratory Journal. 2001; 17(4): 791-801.

[41]. Chadha N, Bahia MS, Kaur M, Silakari O. Thiazolidine-2, 4-dione derivatives: programmed chemical weapons for key protein targets of various pathological conditions. Bioorganic & Medicinal Chemistry. 2015; 23(13): 2953-2974.

[42]. Ha YM, Park YJ, Kim JA, Park D, Park JY, Lee HJ, Lee JY, Moon HR, Chung HY. Design and synthesis of 5-(substituted benzylidene) thiazolidine-2, 4-dione derivatives as novel tyrosinase inhibitors. European journal of medicinal chemistry. 2012; 49: 245-252.

[43]. Zaher AF, Khalil NA, Ahmed EM. Synthesis and anticonvulsant activity of new 3'-aryl-7-bromo-spiro [[1] benzothiophene-3, 2'-[1, 3] thiazolidine]-2, 4'-dione derivatives. Oriental Journal of Chemistry. 2010; 26(4): 1241-1248.

[44]. Rajopadhye M, Popp FD. Potential anticonvulsants. VII. Synthesis of 5′- methylspiro [3H- indole- 3, 2′- thiazolidine]- 2, 4′(1H)- diones. Journal of heterocyclic chemistry. 1984; 21(2):289-291.

[45]. Laxmi SV, Anil P, Rajitha G, Rao AJ, Crooks PA, Rajitha B. Synthesis of thiazolidine-2, 4-dione derivatives: anticancer, antimicrobial and DNA cleavage studies. Journal of chemical biology. 2016; 9(4): 97-106.

[46]. Bajpai P, Jain S, Choubey A. Thiazolidine, a versatile ring in the treatment of various diseases: A systematic review. Asian Journal of Research in Chemistry. 2020; 13(4): 283-286.

[47]. Shaikh FM, Patel NB, Rajani D. Synthesis of new thiazolidine-2, 4-dione derivatives and their antimicrobial and antitubercular activity. Indian Journal of Research in Pharmacy and Biotechnology. 2013; 1(4): 496-503.

[48]. Aziz HA, El-Saghier AM, Badr M, Abuo-Rahma GE, Shoman ME. Thiazolidine-2, 4-dione-linked ciprofloxacin derivatives with broad-spectrum antibacterial, MRSA and topoisomerase inhibitory activities. Molecular Diversity. 2022; 26(3): 1743-1759.

[49]. Barros CD, Amato AA, de Oliveira TB, Iannini KB, da Silva AL, da Silva TG, Leite ES, Hernandes MZ, de Lima MD, Galdino SL, Neves FD. Synthesis and anti-inflammatory activity of new arylidene-thiazolidine-2, 4-diones as PPARγ ligands. Bioorganic & medicinal chemistry. 2010; 18(11): 3805-3811.

[50]. Santos LC, Uchoa FT, Canas AR, Sousa IA, Moura RO, Lima MC, Galdino SL, Pitta IR, Barbe J. Synthesis and Anti-inflammatory Activity of New Thiazolidine-2, 4-diones, 4-thioxothiazolidinones and 2-thioxoimidazolidinones. Heterocyclic communications. 2005; 11(2): 121-128.

[51]. Trotsko N, Przekora A, Zalewska J, Ginalska G, Paneth A, Wujec M. Synthesis and *in vitro* antiproliferative and antibacterial activity of new thiazolidine-2, 4-dione derivatives. Journal of enzyme inhibition and medicinal chemistry. 2018; 33(1): 17-24.

[52]. Aziz HA, El-Saghier AM, Badr M, Abuo-Rahma GE, Shoman ME. Thiazolidine-2, 4-dione-linked ciprofloxacin derivatives with broad-spectrum antibacterial, MRSA and topoisomerase inhibitory activities. Molecular Diversity. 2022; 26(3): 1743-1759.

[53]. Jain VS, Vora DK, Ramaa CS. Thiazolidine-2, 4-diones: Progress towards multifarious applications. Bioorganic & medicinal chemistry. 2013 Apr 1;21(7):1599-1620.

[54]. Marc G, Ionuț IO, Pirnau A, Vlase LA, Vodnar DC, Duma M, Tiperciuc BR, Oniga O. Microwave assisted synthesis of 3, 5-disubstituted thiazolidine-2, 4-diones with antifungal activity. Design, synthesis, virtual and in vitro antifungal screening. Farmacia. 2017; 65(3): 414-22.

[55]. Rajput S, Sisodia D, Badwaik H, Thakur D, Nagori K. Synthesis, characterization and antimicrobial activity of a 5 (4-(4-Substituted) Aminobenzylidine) Thiazolidine-2, 4-dione derivatives. Asian Journal of Research in Chemistry. 2011; 4(1): 40-43.

[56]. Azizmohammadi M, Khoobi M, Ramazani A, Emami S, Zarrin A, Firuzi O, Miri R, Shafiee A. 2H-chromene derivatives bearing thiazolidine-2, 4-dione, rhodanine or hydantoin moieties as potential anticancer agents. European journal of medicinal chemistry. 2013; 59: 15-22.

[57]. Pallas 3.1.1.2, ADME-Tox software, CompuDrug International Inc., U.S.A., 2000

[58]. http://www.molinspiration.com/cgi-bin/properties (Retrieved on 11/5/2020)

[59]. Zhao YH, Abraham MH, Le J, Hersey A, Luscombe CN, Beck G, Sherborne B, Cooper I. Rate-limited steps of human oral absorption and QSAR studies. Pharmaceutical research. 2002; 19(10): 1446-57.

[60]. Trott O, Olson AJ. Software news and update AutoDock Vina: improving the speed and accuracy of docking with a new scoring function. Efficient Optimization, and Multithreading. 2010; 31(2): 455-461.

[61]. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. *J Cheminform*. 2011; 3: 33.

[62]. Alegaon SG, Alagawadi KR, Kumar D, Kavalapure RS, Ranade SD, Priya AS, Jalalpure SS. Synthesis, molecular docking and ADME studies of thiazole-thiazolidinedione hybrids as antimicrobial agents. Journal of Biomolecular Structure and Dynamics. 2021; 1-7.

[63]. Moorthy NSHN, Singh RJ, Singh HP, Gupta SD. Synthesis, biological evaluation and in silico metabolic and toxicity prediction of some flavanone derivatives. Chemical and Pharmaceutical Bulletin, 2006; 54(10): 1384-1390.