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Synthesis, Characterization, Molecular Docking, and Preliminary Antimicrobial Evaluation of Thiazolidinone Derivatives

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ABSTRACT

Several derivatives carrying thiazolidine-4-one pharmacophore were prepared to evaluate their antimicrobial activities. The set of compounds were shown to possess potential activities as determined by molecular docking studies for both candidal (14-alpha demethylase) and bacterial enzymes (Penicillin binding protein of *E. coli*). *In vitro* antimicrobial activities were also performed to confirm the molecular docking results. Molecular characterization by spectral techniques (FT-IR, ^{13}C NMR and ^{1}H NMR) was carried out to confirm the identity of the synthesized compounds. The synthesized compounds were evaluated for antibacterial and anticandidal activity by comparing them with the reference drugs (positive controls) ceftriaxone and fluconazole respectively. Four bacterial species (*Klebsiella pneumonia, Escherichia coli, Staphylococcus epidermis, Staphylococcus aureus*) and one fungal species (*Candida albicans*) were inoculated into petri dishes and were expose to the synthesized compounds by well diffusion method. The series of the proposed compounds were successfully synthesized and some of them were proven to have antibacterial activities comparable to the reference drug. Particularly, the compounds 2c and 2a posessed activities against *K. pneumomia* being higher than ceftriaxone with average inhibition zone diameters of 17 mm and 16 mm at highest concentration respectively. Compound 2b was effective against *E. Coli* also yielding higher activity than ceftriaxone achieving an average diameter of 17 mm at the highest concentration.

Keywords: Thiazolidine-4-One, Molecular docking, antimicrobial agents, antimicrobial resistance, Computer-aided drug design, Drug discovery.

INTRODUCTION

Drug resistant pathogens are becoming an increasing danger that threatens the availability of treatment options available to be chosen. The choices of antibacterial drugs are becoming increasingly limited. An increasing numbers of multi-drug resistant pathogens are emerging due to inappropriate use of antimicrobial drugs. Novel antimicrobial agents are required in order to overcome these treatment-resistant pathogens [1].

Antimicrobial agents are agents that fight infectious diseases caused either by bacteria or fungi. The term antibiotic itself is derived from Greek word “Anti” which translates to against, and bios (life). This term usually refers to naturally produced products which are derived from soil bacteria or fungi [2]. With the advent of synthetic agents, the term antimicrobial was introduced which encompasses broader meaning that includes natural, synthetic, or semi-synthetic agents that act as antifungals, antibiotics, antivirals, and antiparasitics [3]. The use of antibiotics by humans is not a new phenomenon. There is a documented use of antibiotics that dates to 2,500 years ago by the ancient Chinese civilization in which moldy soybeans were used to treat certain infectious diseases. Other civilizations such as Egyptians and Greeks also followed similar method for treatment of infectious diseases. The true microbial origin of such ailments was not established back then; however, the medicinal properties of molds were utilized [4].

Microorganisms were one of the earliest life forms that emerged in the earth. They evolved to cope in living with each other but also, they compete for nutrition. This competition was manifested by their production of antibiotics to destroy their neighboring colo-

nies. As an evolutionary defensive mechanism, microorganism developed methods to overcome such competitors. There is evidence today, made through sampling of ancient bacteria that are frozen in the arctic, proves that microorganism resistance predates the modern-day antibiotic era[5,6].

As a consequence, through billions of years of evolution, both bacteria and fungi have evolved unique methods of acquiring resistance. Resistance can occur due to mutations in their genome or through horizontal gene transfer, which enables these microorganisms to convey drug resistant genes to other strains of microorganisms [7].

In addition to the above methods of resistance, a specific genus of certain microbial agent may be inherently resistant to the microbial agent. This type of resistance is known as "intrinsic resistance". This occurs for example, when the antimicrobial target is not found in the organism. For example, mycobacteria lack the cell wall that covers the cell. As a result, these genera are resistant to antibacterial agents targeting cell wall (e.g., β-lactams and glycopeptides) [8].

The discovery of novel antimicrobial agents has come to halt in the last decades. When antibiotics were first discovered, there was big pool of soil actinomycetes which can be mined for new therapeutically active molecules. However, this pool has long been overmined. Conventional approaches such as combinatorial synthesis and high-throughput screening HTS are limited by penetration of the antimicrobial agent to the cell of the pathogen [9].

Permeation of antimicrobial agents into gram negative bacterium is especially difficult compared to that of gram positive. The reason behind this fact lies in the biochemistry of the cell wall of a gram-negative bacterium. It consists of an outer membrane that is lined by anionic lipopolysaccharides (LPS). This described structure is not found in gram positive cell wall [10].

The *in-silico* molecular docking studies are well established methods for prediction of affinity of ligand to its binding site [11–13]. Today, with the rapid advances in machine learning and artificial intelligence (AI), we can find growing use of such methods for drug discovery. Several algorithms were developed for carrying out the task of virtual screening which speeds up the drug discovery process significantly [14]. A recent example of a successful use of such approach is the discovery of a new AI-derived antibiotic named halicin which was found to possess activities against notable bacteria such Acinetobacter baumannii, Mycobacterium tuberculosis, Clostridioides difficile and carbapenem-resistant species of Enterobacteriaceae [15].

Thiazolidine (TZO) moiety is a heterocyclic compound with 2 heteroatoms; nitrogen and sulfur, such moieties are established scaffold for many drugs with various pharmacological activities. Thiazolidine-4-one moiety has a carbonyl group on the 4 position of the heterocyclic ring. Many synthetic compounds containing thiazolidine-4-one moiety were found to possess anticancer [16], antimicrobial [17,18], antidiabetic [19], antiparasitic [20], anti-inflammatory [21], antitubercular [22], antiviral [23], antioxidant [24], anticonvulsant [25], and analgesic activity [26,27].

The Antimicrobial activity particularly that of antifungal and antibacterial activity of thiazolidine-4-one moiety is a well-researched subject in the literature. Nashaan *et al.* have synthesized couple of derivatives containing both thiazolidine-4-one and triazolo ring which showed a higher antibacterial activity on both gram-positive and gram-negative strains when compared to the reference drug ampicillin. A lower antifungal activity than the reference fluconazole was observed [28].

With the low supply of new antimicrobial agents by the pharmaceutical companies, and rising resistance rates, it is crucial that efforts be focused on synthesizing compounds with antimicrobial properties to be further tested. And so, this work aims to perform *in-silico* experimentation of novel thiazolidine-4-one derivatives and study their suitability as drug candidates, carry out organic synthesis of the proposed molecules and further evaluate their potential antimicrobial properties by susceptibility tests.

EXPERIMENTAL SECTION

Materials

The starting materials p-Formylphenylboronic acid, p-Methoxybenzenesulfonohydrazide, 2,4,6-Trimethylbenzenesulfonyl hydrazide, p-toluenesulfonyl hydrazide, Benzenesulfonyl hydrazide, and Thioglycolic acid were purchased from Sigma Aldrich (Germany).

Instruments

Stuart SMP30 (Germany) was used for uncorrected melting point determinations using capillary method. TLC silica gel plates in ethanol mobile phase were used to monitor the completion of reaction using UV light for spot detection. Spectral analysis was done using Bruker VERTEX 70 FT-IR and Bruker Avance II 400 MHz NMR for both IR and NMR analyses respectively. Acetone-d_6 was used as the solvent medium for NMR analysis.

Molecular docking

Molecular docking studies were performed using The Cambridge Crystallographic Data Centre (CCDC) GOLD 2022 software. The target proteins were obtained from Protein Data Bank (PDB). Penicillin binding proteins of Escherichia coli (PDB: 2ZC4) was used as targets for the synthesized compounds and Ceftriaxone was used as reference drug. Candida albicans enzyme of 14-alpha demethylase (PDB: 5FSA) was used for antifungal in silico determination. Antifungal drug Fluconazole was used as reference ligand. The docking procedure was followed according to the official GOLD user guide as published by the CCDC [29]. The final compounds and the reference drugs were drawn in Chem3D software, energy minimized using Avogadro software using UFF force field as the minimization algorithm. The target protein was loaded in Hermes visualizer (one of CCDC-Discovery assets). Hydrogens were added to the protein and the active site residues were checked for tautomerism and ionization states. Unnecessary chains, ligands, water molecules and cofactors were deleted. The original ligand of the protein was extracted. The active site of the protein was loaded with the reference drug and the final compounds to generate docking solutions. An area of 10 Å was selected as the pocket for the active site. The docked compounds were expressed in terms of PLP fitness score. The intermolecular interaction of each docked compound was visualized and recorded.

ADME studies

The ADME properties of the synthesized molecules were elucidated using SWISS ADME online tool developed by Swiss institute of bioinformatics [30].

Chemical Synthesis

Synthesis of Schiff base intermediates (1a-d)

The p-formylphenyl boronic acid (5 mmol) was dissolved in 20 mL absolute ethanol then an equimolar amount of the hydrazide was added to the solution. 2 drops of concentrated sulfuric acid were added as catalyst. The reaction mixture was placed on reflux for 3 hours as the end of reaction was indicated by thin layer chromatography (TLC) paper. The solution was cooled on refrigeration overnight. The filtrate was obtained washed with distilled water and dried [31].

(4-((2-(phenylsulfonyl)hydrazineylidene)methyl)phenyl)boronic acid (1a)

Obtained as off-white crystals (89% yield), melting point (mp): 187-191 ºC. FT-IR: 3348 cm^{-1} (O-H of boronic acid), 3205 cm^{-1} (sulfonamide NH), 1610 cm^{-1} (imine C=N), 1448 cm^{-1} (Aromatic C=C), 1261cm^{-1} (sulfonamide S=O)

(4-((2-((4-methoxyphenyl)sulfonyl)hydrazineylidene)methyl)phenyl)boronic acid (1b)

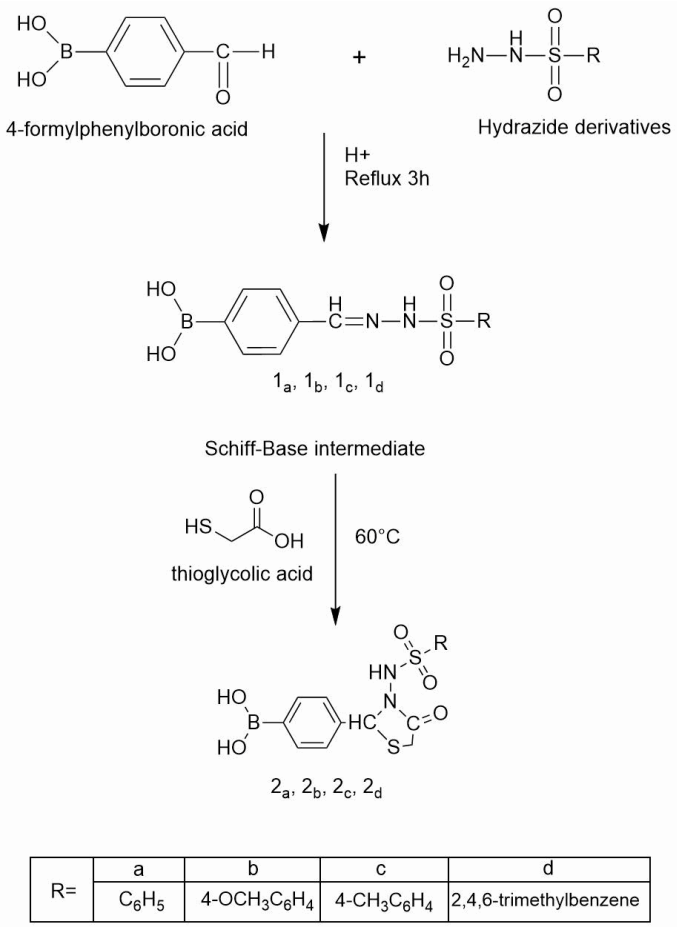
Obtained as off-white crystals (85% yield), mp: 157-161 ºC. FT-IR: 3439 cm^{-1} (O-H of boronic acid), 2985 cm^{-1} (Asymmetric stretch of CH_3), 3188 cm^{-1} (sulfonamide NH), 1600 cm^{-1} (imine C=N), 1504 cm^{-1} (Aromatic C=C), 1271cm^{-1} (sulfonamide S=O)

(4-((2-tosylhydrazineylidene)methyl)phenyl)boronic acid (1c)

Obtained as off-white crystals (80% yield), mp: 143-146 ºC. FT-IR: 3446 cm^{-1} (O-H of boronic acid), 2924 cm^{-1} (Asymmetric stretch of CH_3), 3200 cm^{-1} (sulfonamide NH), 1610 cm^{-1} (imine C=N), 1512 cm^{-1} (Aromatic C=C), 1309 cm^{-1} (sulfonamide S=O)

(4-((2-(mesitylsulfonyl)hydrazineylidene)methyl)phenyl)boronic acid (1d)

Obtained as off-white crystals (90% yield), mp: 165-167 ºC. FT-IR: 3553 cm^{-1} (O-H of boronic acid), 2995 cm^{-1} (Asymmetric stretch of CH_3), 3244 cm^{-1} (sulfonamide NH), 1606 cm^{-1} (imine C=N), 1511 cm^{-1} (Aromatic C=C), 1280 cm^{-1} (sulfonamide S=O)



R=	a	b	c	d
	C_6H_5	4-$OCH_3C_6H_4$	4-$CH_3C_6H_4$	2,4,6-trimethylbenzene

Figure (1): The overall reactions scheme.

Synthesis of thiazolidine-4-ones derivatives (2- a,b,c,d)

A 3 mL of thioglycolic acid was added to 1 mmol of (1_{a-d}) the mixture was stirred for 3 hours at (60 °C). 5 mL of ethyl acetate was added to the mixture, then transferred to separatory funnel and the upper layer was washed with 3 fractions of 20 mL saturated solution of sodium bicarbonate and further with one fraction of 10 mL distilled water. The separated upper layer was dehydrated by magnesium sulfate. The solvent was removed under reduced pressure to yield the desired compounds (2a-d) [32].

(4-(4-oxo-3-(phenylsulfonamido)thiazolidin-2-yl)phenyl)boronic acid (2a)

Obtained as white powder (54% yield), mp: 125 – 128 ºC. FT-IR: 3507 cm^{-1} (O-H of boronic acid), 3403 cm^{-1} (sulfonamide NH), 1718 cm^{-1} (C=O of carbonyl), 1290 cm^{-1} (C-N of amide), 1336 cm^{-1} (S=O of sulfonamide). ^{1}H-NMR (Acetone-d_6, 400 MHz), δ (ppm): 3.60 (dd J = 15.8, 4.0 Hz, 2H, CH_2), 6.03 (s, 1H, CH), 7.25 – 7.92 (m, 9H, ArH), 9.10 (s, 2H, $B(OH)_2$), 9.61 (br s, 1H, NH). ^{13}C-NMR (Acetone-d_6, 100 MHz), δ (ppm): (41.04, 62.86, 126.36,128.11, 128.39, 129.13, 133.59, 134.66, 139.20, 141.54, 168.37).

(4-(3-((4-methoxyphenyl)sulfonamido)-4-oxothiazolidin-2-yl)phenyl)boronic acid (2b)

Obtained as white powder (58% yield), 145 – 149 ºC. FT-IR: 3543 cm^{-1} (O-H of boronic acid), 3333 cm^{-1} (sulfonamide NH), 1727 cm^{-1} (C=O of carbonyl), 1266 cm^{-1} (C-N of amide), 1348 cm^{-1} (S=O of sulfonamide). ^{1}H-NMR (Acetone-d_6, 400 MHz), δ (ppm): 3.20 (dd J = 12.5, 6.6 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 5.88 (s, 1H, CH), 6.89 – 7.83 (m, 8H, ArH), 8.92 (s, 2H, $B(OH)_2$), 9.54 (br s, 1H, NH). ^{13}C-NMR (Acetone-d_6, 100 MHz), δ (ppm): 41.05, 48.24, 62.91, 126.26, 128.81, 131.76, 131.88, 134.58, 136.22, 140.46, 140.78, 168.61.

(4-(3-((4-methylphenyl)sulfonamido)-4-oxothiazolidin-2-yl)phenyl)boronic acid (2c)

Obtained as white powder (68% yield), 144 – 148 ºC. FT-IR: 3470 cm^{-1} (O-H of boronic acid), 3210 cm^{-1} (sulfonamide NH), 1731 cm^{-1} (C=O of carbonyl), 1284 cm^{-1} (C-N of amide), 1338 cm^{-1} (S=O of sulfonamide). ^{1}H-NMR (Acetone-d_6, 400 MHz), δ (ppm): 2.91 (s, 3H, CH_3), 3.69 (dd J = 15.5, 4.3 Hz), 2H, CH_2), 6.02, (s, 1H, CH), 7.27 – 7.88 (m, 8H, ArH), 8.52 (s, 2H, $B(OH)_2$), 9.57 (br s, 1H, NH). ^{13}C-NMR (Acetone-d_6, 100 MHz), δ (ppm): 20.75, 41.04, 62.83, 126.32, 128.46,129.46, 134.63, 135.65, 136.29, 141.60, 144.10, 168.45.

(4-(4-oxo-3-((2,4,6-trimethylphenyl)sulfonamido)thiazolidin-2-yl)phenyl)boronic acid (2d)

Obtained off-white powder (64% yield), 133 – 137 ºC. FT-IR: 3491 cm^{-1} (O-H of boronic acid), 3290 cm^{-1} (sulfonamide NH), 1731 cm^{-1} (C=O of carbonyl), 1288 cm^{-1} (C-N of amide), 1337 cm^{-1} (S=O of sulfonamide). ^{1}H-NMR (Acetone-d_6, 400 MHz), δ (ppm): 2.47 (s, 6H, $(CH_3)_2$), 2.65 (s, 3H, CH_3), 3.14 (dd J = 9.1, 4.7 Hz, 2H, CH_2), 5.58 (s, 1H, CH), 6.77 – 7.39 (m, 6H, ArH), 8.45 (s, 2H, $B(OH)_2$), 9.11 (br s, 1H, NH). ^{13}C-NMR (Acetone-d_6, 100 MHz), δ (ppm): 24.82, 27.59, 54.96, 62.32, 125.84, 129.36, 129.88, 129.98, 130.20, 134.19, 141.27, 167.99.

Antimicrobial activity

The synthesized compounds were tested for antibacterial and anticandidal activity by comparing them with the reference drugs (positive controls) ceftriaxone and fluconazole respectively. Four bacterial species (*Klebsiella pneumonia, Escherichia coli, Staphylococcus epidermis, Staphylococcus aureus*) and one fungal species (*Candida albicans*) were cultured into petri dishes and were expose to the synthesized compounds by well diffusion method. A total of four serial dilutions were made (500, 250, 125, 62.5 µg/ml) and a 100 µL of each dilution was placed into the well. The solvent dimethyl sulfoxide (DMSO) was used as negative control. The dishes were incubated at 37°C for 24 hours. Finally, the inhibition zones expressed as diameter (in mm) of each inoculated agent were measured. Statistical analysis was made using ANOVA tests carried out by IBM ® SPSS ® using 99% as our confidence interval.

RESULTS

Molecular Docking results

The obtained docking results are tabulated in (table 1 and 2) in which the scoring function is based on Piecewise Linear Potential Fitness (PLP Fitness) which models the steric and clash interactions between the ligand and the protein [29].

Table (1): Molecular docking score of the synthesized compounds with PBP of *Escherichia coli* (PDB: 2ZC4) in comparison to reference drug ceftriaxone.

Compound name	PLP Fitness Score	Amino acids involved in interactions
2a	75.6	Ser 337, Lys 340, Ser 395, Asn 397, Thr 550
2b	65.3	Ser 395, Asn 397, Thr 550, Gln 452
2c	67.7	Ser 337, Lys 340, Ser 395, Asn 397, Thr 550
2d	75.5	Ser 337, Lys 340, Ser 395, Asn 397, Thr 550, Ser 548
Ceftriaxone	66.4	Asn 397, Gly 459, Ser 571

Table (2): Molecular docking score of the synthesized compounds with 14-alpha demethylase of Candida albicans (PDB: 5FSA) in comparison to reference drug Fluconazole.

Compound name	PLP Fitness Score	Amino acids involved in interactions
2a	78.8	Tyr 132, Ser 378, Met 508
2b	83.4	Tyr 132, Ser 378, Met 508
2c	89.4	Hem 580, Tyr 132, Ser 378, Met 508
2d	82.4	Tyr 132, Ser 378
Fluconazole	75.2	Hem 580

Antimicrobial activity

The results of bacterial inhibition against *Klebsiella Pneumonia* showed that the compounds (2_{a-d}) demonstrated a similar effect to the standard drug ceftriaxone with no statistical difference except at concentration 500 µg/ml where compounds 2a and 2c exhibited statistically significant higher effect ($p<0.01$) (Figure 2A). The most active compound was found to be 2c followed by 2a with average diameter of 17 and 16 mm respectively (at concentration 500 µg/ml).

The other gram-negative bacteria examined was *Escherichia coli*. The result showed higher activity when compared to the standard in concentration 500 µg/ml among all compounds except for compound 2c ($p=0.144$). at concentrations of 250 µg/ml, all compounds were statistically comparable to the reference except for compound 2b which was higher when compared to the reference ($p<0.01$). At concentration of 125 µg/ml, 2d was statistically higher than the reference in this respective concentration group. Among this bacterial species compound 2b was highest in activity (Figure 2B).

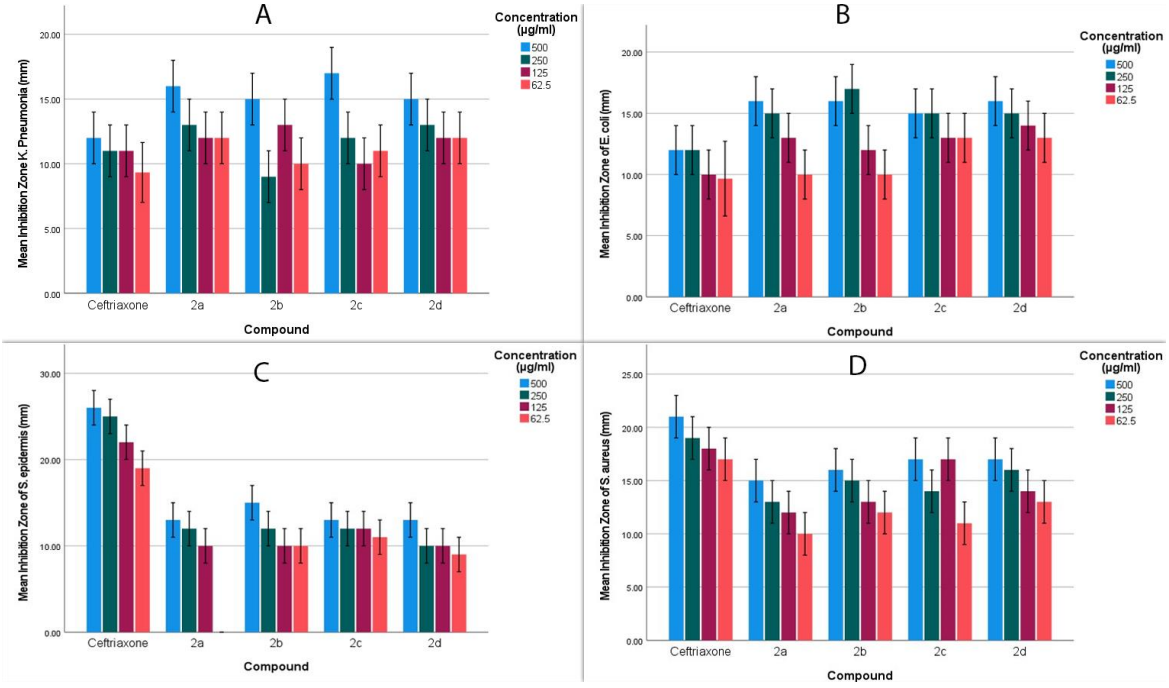


Figure (2): Mean inhibition zone of various concentrations of the synthesized compounds vs. Ceftriaxone for: (A) *K. Pneumonia. (B) E. Coli. (C) S. epidermis (D) S. aureus.*

For the gram-positive bacteria *Staphylococcus epidermis*, the reference drug ceftriaxone was significantly higher than the synthesized compounds indicating a lack of activity against this type of bacterial species (Figure 2C).

In case of *Staphylococcus aureus*, at concentration of 500 µg/ml the positive control ceftriaxone was significantly higher than the compounds ($p<0.01$). Similarly in concentrations of 250 µg/ml ceftriaxone was significantly higher except in compound 2d which showed similar effects to the reference ($p=0.122$). In the same way at concentrations of 125 µg/ml, ceftriaxone statistically surpassed the compounds except in case of 2c where the mean was comparable ($p=1$). Across 62.5 µg/ml dilutions, the reference drug was statistically higher ($p<0.01$) (Figure 2D).

Anticandidal activity

As for the fungal species *Candida albicans*, fluconazole was higher in all cases across all concentrations $p<0.01$ However, when comparing the synthesized compounds 2a and 2d seem to be the highest (Figure 3).

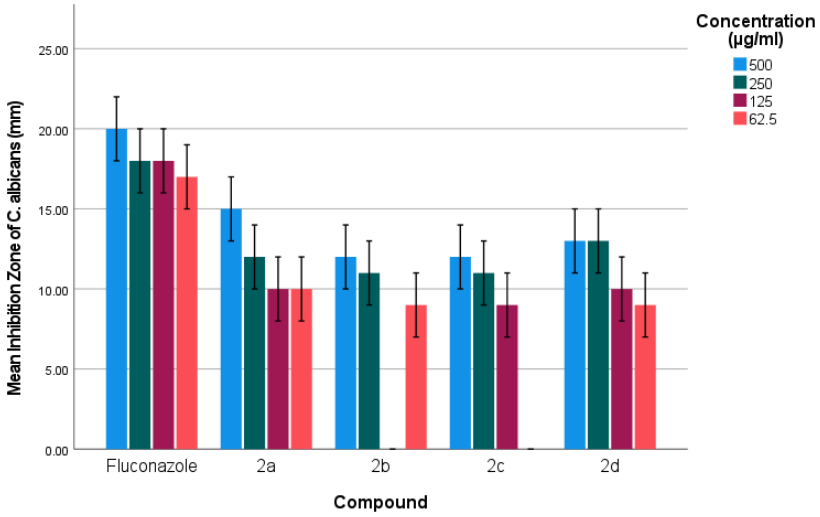


Figure (3): *C. albicans* mean inhibition zone of various concentrations of the synthesized compounds vs. fluconazole.

ADME Studies

SwissADME is an online tool that can be used for in silico ADME prediction. It uses various validated methods for the estimation of pharmacokinetic parameters [33]. The data output for the synthesized compounds is found in table 3.

Table (3): Some general information of the synthesized compounds.

Properties	2a	2b	2c	2d	Standard
M.Wt(g/mol)	378	408	392	420	<500
HBA	6	7	6	6	<10
HBD	3	3	3	3	<5
Log P	0.14	0.09	0.42	1	<5
TPSA (A^2)	140.62	149.85	140.62	140.62	<140
nrotb	5	6	5	5	<10

DISCUSSION

Molecular docking

CCDC's Genetic Optimization for Ligand Docking (GOLD) utilizes genetic algorithm (GA) for the flexible molecular docking simulations. It has been reported in literature that this tool has a high degree of reliability,

and its use is well established in computer automated drug design (CADD) [34,35].

Bacterial PBP are responsible for strengthening the bacterial cell wall by increasing the crosslinks between the peptidoglycan chains [36]. Docking of the synthesized compounds with E. coli PBP showed several hydrogen bond interactions with the protein residues. These interactions may stabilize the ligand-protein complex and may contribute to biological activity. It can be seen from table 1 that binding residues of the synthesized compound differ than that of the reference ligand suggesting different binding mode. This may be due to the different pharmacophoric composition of the synthesized compounds and ceftriaxone. As a result, the compounds would fit differently in the binding cavity and interact with different residues. The active site and ligand interaction of the highest scoring compound (2a) shown in figure 4.

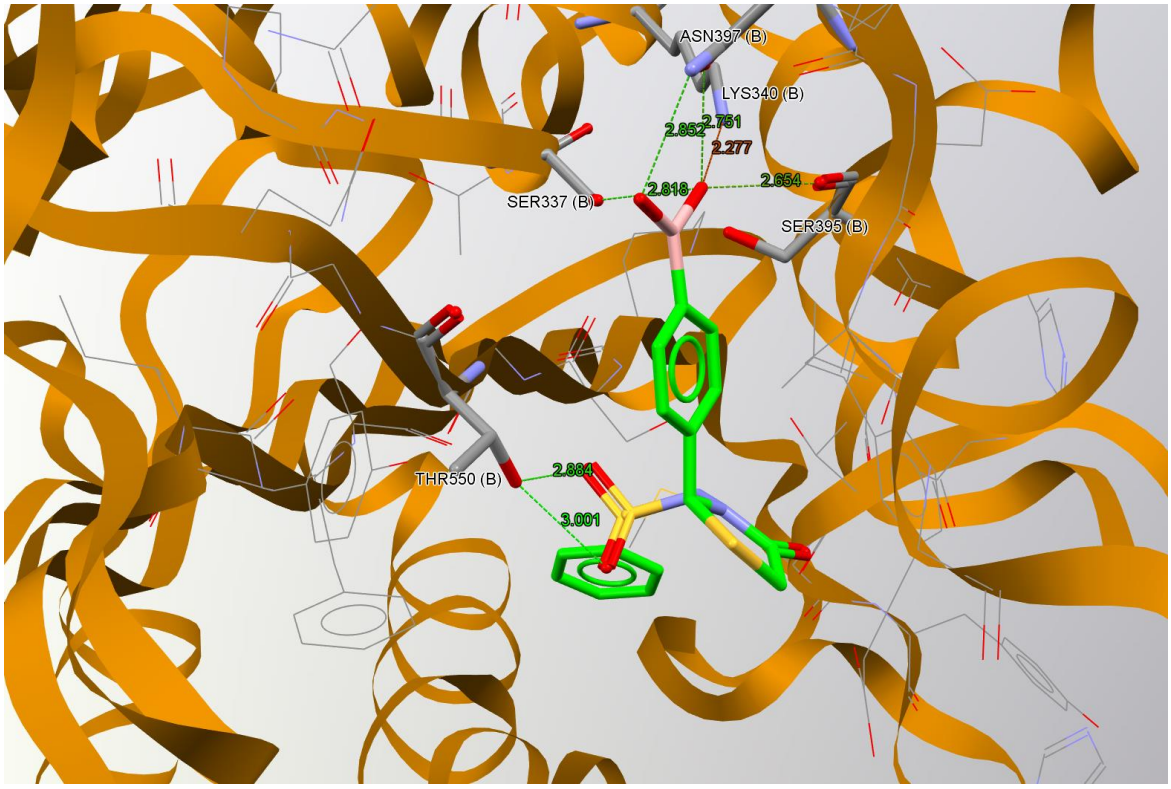


Figure (4): Ligand-Protein interactions between the compound (2a) and PBP of E. coli. Ligand carbon: Green – Protein Amino acid residues carbon: Gray.

The target protein 14-alpha demethylase catalyzes conversion of lanosterol to ergosterol. Inhibition of this enzyme will lead to accumulation of hazardous amounts of sterols [37].Interaction of the synthesized compounds with candidal enzyme 14-alpha demethylase showed both hydrogen bonds and Coordination bond between the ligands and the iron of heme group in the active site of the enzyme. The presence of coordination bond is found in compound 1c and may be explained by the suitable orientation of the sulfonyl oxygen towards the iron of heme group. As can be seen from table 2, methionine 508 was common binding residue for the synthesized compounds except compound 2d. The binding occurred via hydrogen bond between the hydroxyl of the boronic acid which served as the hydrogen bond donor and the carbonyl oxygen of the peptide bond which served as hydrogen bond acceptor. It may be postulated that the hydroxyl groups of the boronic acid moiety are essential for hydrogen binding interactions of the synthesized compounds. Ligand – protein interaction for the highest scoring compound (2c) is shown in figure 5.

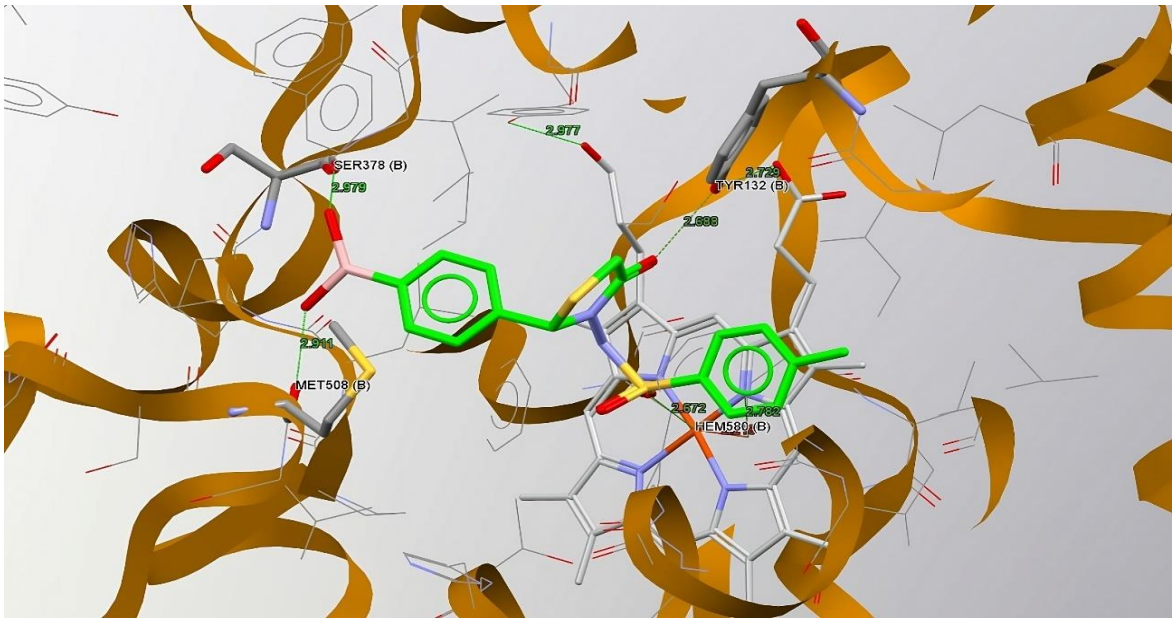


Figure (5): Ligand-Protein interactions between the compound (2c) and 14 alpha-demthylase of *Candida albicans*. Ligand carbon: Green – Protein Amino acid residues carbon: Gray.

Antimicrobial Activity

The result can be summarized that in case of gram-negative bacteria, the synthesized compounds showed either comparable activity or statistically higher than the reference drug. While in the case of gram-positive bacteria, either comparable or lower activity were found. This perhaps can be due to fact that the obtained bacteria were a clinical isolate which may indicate the presence of slight resistance to the reference drug ceftriaxone. While gram positive bacteria are less prone to show resistance.

Highest activity against both *Klebsiella pneumonia* and *staphylococcus aureus* was achieved by the compound 2c which carries a methyl phenyl group which may have contributed into providing a suitable stable conformation that's able to orient the complementary functional groups to suitably interact with the target protein. For *Escherichia coli* and *staphylococcus epidermis* the highest activity was attained by 2b which carries a polar methoxy group. This attribute may have given it an advantage to other derivatives in the series. In case of *candida albicans*, the compound 2a have been the leading among the derivatives. This compound carries no substituents at the terminal benzene ring which leads us to speculate that interaction with the target favors no special substituents at the designated position.

ADME studies

The synthesized compounds were considered to have high gastrointestinal absorption, except for 2b which was predicted to have a low absorption. This prediction is due to them having a polar methoxy group which increases the topological polar surface area (TPSA) resulting in shifting of the compounds outside of the absorbable area within the boiled egg diagram (Figure 6).

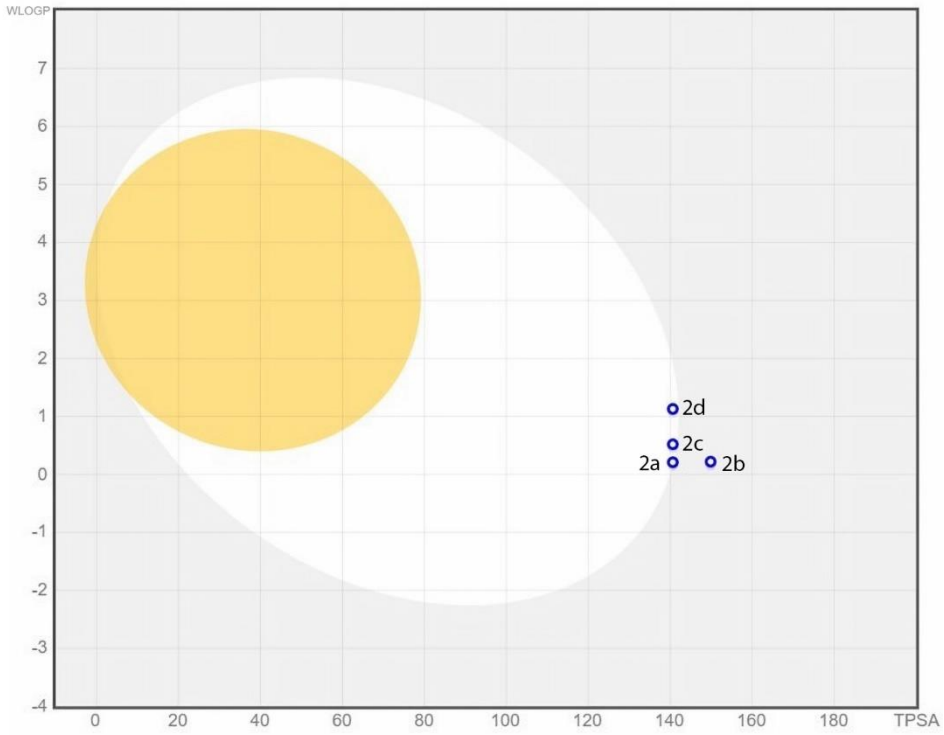


Figure (6): Boiled egg diagram for the synthesized compounds. Compounds that are within the yellow circle have both blood-brain barrier passage and GI absorption. Drugs within the white circle are expected to have high GI absorption.

The compounds were adherent to Lipinski rule of five with acceptable molecular weight and number of hydrogen bond donors and acceptors (table 3).

CONCLUSION

The synthesized compounds were found to interact with their bacterial and fungal target via molecular docking studies. Antimicrobial susceptibility testing showed antibacterial properties particularly in 2c against *K. pneumonia* and via compound 2b against *E. coli*. Candida albicans did show a moderate form of inhibition which was greatly surpassed by the reference drug fluconazole. Further evaluation of these compounds is necessary in order to determine their safety and potential effects *in vivo*.

Conflict of Interests. None to declare

Ethics Approval. None to declare

Author Contribution. All Authors contributed equally to this work

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