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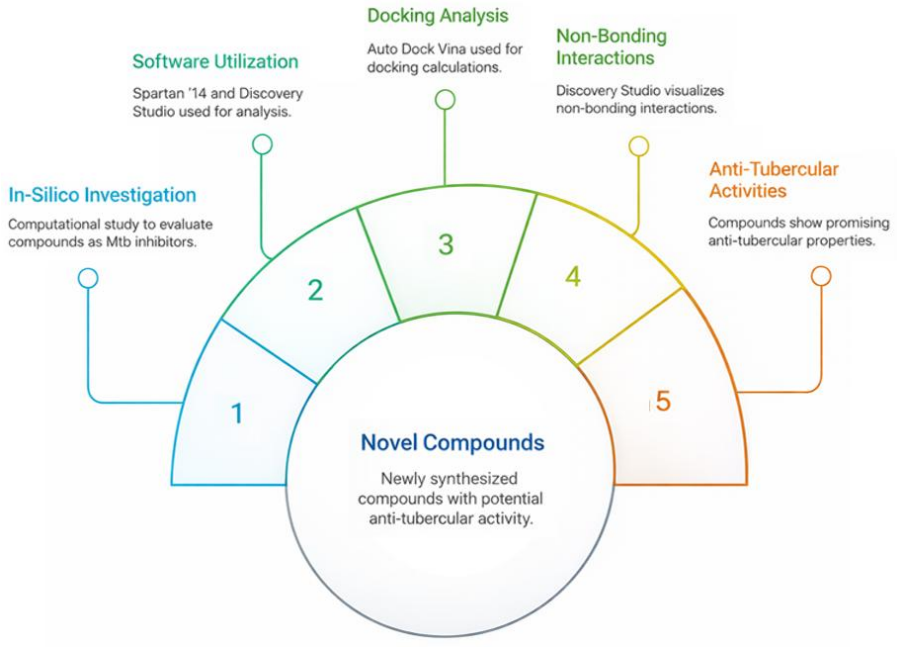
Theoretical bio-investigation of 3-(benzo[d]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one derivatives as potential *Mycobacterium tuberculosis* H37Rv inhibitors

David Gbenga **Oke**[1,2+], Olamide Adetunji **Olalekan**[3], Eniola Faith **Olujinmi**[1], Juliana Oluwasayo **Aworinde**[4], Abel Kolawole **Oyebamiji**[5]

Abstract

3-(Benzo[d]thiazol-2-yl)-2-((substituted aryl) thiazolidin-4-one derivatives were recently synthesized with thioglycolic acid and evaluated for *in vitro* anti-tubercular activity. Two of the derivatives have good anti-tubercular activity. The present study evaluated an in-silico investigation of these ten novel compounds as potential *Mycobacterium tuberculosis* H37Rv inhibitors. The non-bonding interactions between the derivatives and the receptor were studied. Spartan '14 software was used for optimization. Discovery Studio software was used for the receptor treatment. The binding site in the downloaded protein was located using Autodock Tool software. Auto Dock Vina was used to calculate the docking, and Discovery Studio was used to view the non-bonding interactions between the docked complexes. Different other parameters were calculated to describe anti-tubercular activities of 3-(benzo[d]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one derivatives. The findings demonstrated the potential anti-tubercular properties of all the substances under study and inhibited *Mycobacterium tuberculosis* (H37Rv). The calculated binding affinity of the docked compound showed improved inhibition against *Mycobacterium tuberculosis* (H37Rv) better than the standard drugs (Streptomycin and Pyrazinamide), with compound 6 being the best.



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Highlights

- Ten 3-(benzo[d]thiazol-2-yl)-2-((substituted aryl) thiazolidin-4-one was docked.
- The compounds were docked with a protein (PDB ID: 5zhv).
- The potential anti-tubercular properties of all docked substances were studied.
- All the docked compounds have significant anti-tubercular activities.
- Compound 6 activities inhibit *Mycobacterium tuberculosis* (H37RV) the most.

[1]Bowen University, College of Agricultural, Engineering and Science, Iwo, Nigeria. [2]University of Salento, Department of Engineering for Innovation, Lecce, Italy. [3]Redeemer's University, Department of Chemical Sciences, Ede, Nigeria. [4]University of Jos, Department of Medical Laboratory Sciences, Jos, Nigeria. [5]University of Ilesa, Department of Industrial Chemistry, Osun State, Nigeria. **+Corresponding author:** David Gbenga Oke, **Phone:** 08063165709, **Email address:** oke.david@bowen.edu.ng

1. Introduction

Tuberculosis (TB) has been described as a leading cause of mortality and a substantial cause of ill health (WHO, 2021). According to Trajman *et al.* (2022), TB has surpassed HIV/AIDS as the most common infectious disease that caused mortality before the coronavirus (COVID-19) pandemic. *Mycobacterium tuberculosis* is an infectious agent that causes tuberculosis, an illness primarily affecting the lungs (Moule and Cirillo, 2020). When infected individuals sneeze, spit or cough (Swalehe and Obeagu, 2024) the virus disperses through aerosolized particles. The illness has a significant worldwide economic and health impact. As one of the oldest infectious illnesses that may affect humans, research on the *Mycobacterium tuberculosis* (*M. tuberculosis*) complex is ongoing worldwide (WHO, 2022). The development of therapy regimens has shown progress in the ongoing struggle to prevent and control TB (Dookie *et al.*, 2002). The worldwide health threat of *Mycobacterium tuberculosis* infections persists despite a lengthy history and ongoing efforts (Chandra *et al.*, 2022). Since its creation precisely a century ago, the Bacillus Calmette-Guérin (BCG) vaccine has been the most widely used globally and remains the sole approved treatment for tuberculosis. Tuberculosis is still quite high in areas where vaccination campaigns are widespread (Setiabudiawan *et al.*, 2022).

Human illnesses are caused by about 50 different mycobacterial species. The *Mycobacteriaceae* family contains *M. tuberculosis*, *M. canettii*, *M. africanum*, and other members that can infect other animal species with illness. All bacteria in the *Mycobacteriaceae* family have lipid-rich cell walls that provide them resistance to chemotherapeutic drugs but not to physical ones like heat and UV light (Behr *et al.*, 2019; Lerner *et al.*, 2020; Menzies *et al.*, 2018; WHO, 2021). Complex lipids make up almost 60% of the mycobacterium bulk, which makes it extremely hydrophobic. The strongly cross-linked peptidoglycan (PG) layer enveloping the plasma membrane forms covalent compounds with arabinogalactan. To drastically lower the number of new cases each year research breakthroughs are required, such as new medications, drugs and vaccines.

The prevalence of antibiotic-resistant, multidrug and extensively drug-resistant (MDR and XDR) strains as well as the co-occurrence of the HIV and diabetes epidemics, raise the risk of TB and make it an extreme concern (Ferrer *et al.*, 2009; Moule and Cirillo, 2020). The pathogen's capacity to produce cords and the bacteria's propensity for mutation have boosted both the pathogen's virulence and medication resistance (Behr *et al.*, 2019; Chandra *et al.*, 2022; Dookie *et al.*, 2002; Ferrer *et al.*, 2009; Lerner *et al.*, 2020; Menzies *et al.*, 2018; Setiabudiawan *et al.*, 2022; WHO, 2021). Apart from the respiratory complications of the disease, extrapulmonary TB and drug-resistant forms have emerged due to the changeable nature of the causative agent. Approximately 25% of the world's population currently has latent or active TB, with 1.2 million fatalities and 10 million new infections per year (WHO, 2022). A small percentage of tuberculosis cases, about 15%, take the extrapulmonary infections form, which can spread through organ or blood transfusions and affect organs other than lungs, such as the lymph nodes, kidneys, brain, bones, and joints. Such conditions are reportedly very challenging to identify and cure, and they spread quickly through organ transplants (Moule and Cirillo, 2020). However, its adverse effects are more obvious in middle-class and lower-class countries (WHO. Global Tuberculosis, 2021). The United Nation is trying to reduce TB fatalities by 90% by 2030, making the disease one of the key issues of the Sustainable Development Goals (SDGs).

An estimated 590,000 new cases of TB are reported each year in Nigeria, of which over 245,000 are HIV-positive. In Nigeria, more than 10% of fatalities are attributable to tuberculosis. Although there are effective treatments for the disease, around 30 people die from it every hour (Haider *et al.*, 2022). According to the data, around 181.1 million people were living in Nigeria as of 2015; however, six years later (2021), that number rose to 213, translating to a 17.8% rise. The prevalence of TB is rising along with the country's population. For instance, Nigeria, with its estimated 4.3% multidrug resistance in new cases, has the sixth-largest worldwide incidence of TB. Later research reveals that Nigeria rose from sixth to seventh place globally and to second place in Africa relative to 30 nations with a high TB burden (Fadare *et al.*, 2020; Umeokonkwo *et al.*, 2020).

A 1,3-thiazole ring is fused to a benzene ring to form the heterocyclic aromatic chemical class known as benzothiazoles (BTs). Drug developers are interested in benzothiazoles because of their extensive biological and pharmacological actions (Froes *et al.*, 2021). Benzothiazole (BTH), 2-hydroxy-BTH, 2-amino-BTH, 2-methyl benzothiazole (2-Me-BTH), 2-methylthio-BTH (2-Me-S-BTH), 2-mercapto-BTH (2-SH-BTH), 2-thiocyanomethylthio-BTH (2-SCNMeS-BTH), and 2-benzothiazole-sulfonic acid (2-SO_3H-BTH) are among the most frequently studied BHTs (Froes *et al.*, 2021; Shainyan *et al.*, 2022; Stremski *et al.*, 2021; Zhilitskaya *et al.*, 2021). Additionally, benzothiazoles are used as the main component of many different medications, including Zopolrestat and Viozan. The biological activities of benzothiazole derivatives include anticancer (Fadare *et al.*, 2020; Moule and Cirillo, 2020), antibacterial, tubercular (Haider *et al.*, 2022; Taghour *et al.*, 2022), antifungal (Haider *et al.*, 2021), antimicrobial (Levshin *et al.*, 2022), anti-inflammatory (Nasr *et al.*, 2022), antidiabetic (Dernovšek *et al.*, 2021), anticancer, analgesic, anticonvulsant, antimalarial, and anti-inflammatory properties (Dernovšek *et al.*, 2021; Kumar *et al.*, 2017), among others. Many different medicinal compounds are made using the benzothiazole nucleus. Due to these substances' exceptional pharmacological potentials, medicinal chemistry has a key function for them. Benzothiazole derivatives: production, structures, and biological activity have long been of interest to researchers in the medical field (Kumar *et al.*, 2017; Sucheta and Verma, 2017). There are recognized natural sources for BHTs, and tea leaves, and tobacco smoke are natural sources of BTH (Moodley *et al.*, 2022).

Mainly because of the function of benzothiazole in medicinal chemistry, where this moiety offers a more stable metabolic replacement for carboxylic acid functions as well as a more complimentary pharmacokinetic profile, interest in benzothiazole chemistry has been growing rapidly in recent decades. Excellent biological, pharmacological, and therapeutic applications can be achieved when the heterocyclic benzothiazole and thiazolidinedione are combined in a single molecular framework (Aziz, M. *et al.*, 2022a; Aziz, N. *et al.*, 2022b; Salina *et al.*, 2022; Shainyan *et al.*, 2022; Trotsko *et al.*, 2020; Zhilitskaya and Yarosh, 2021). The synthesis of benzothiazole derivatives has been performed using a few different synthetic routes. Condensation of 2-aminobenzenethiol with cyano or carbonyl is the most used technique for creating benzothiazole compounds (Lončarić *et al.*, 2022).

In drug development, docking is used as a screening method to find substances with higher inhibitory affinities. Molecular docking studies have been linked to several difficulties, including the flexibility of proteins and the protein-protein interface. This is because it can improve the interaction between any investigated pharmacophore and enzyme by locating the appropriate binding sites inside the investigated enzyme (receptor)

(Bahrami *et al.*, 2008). Additionally, the docking score aids in predicting the strength of the non-covalent interactions that occur between complexes after docking, the computed binding affinity between the investigated complexes might be given as a dock score (Abdullahi *et al.*, 2020). Furthermore, it reveals the position of the ligand in the active region of the receptor, which is crucial for optimization (Olasupo *et al.*, 2021; Oladipo *et al.*, 2021; Oyebamiji *et al.*, 2021). To design and develop a trustworthy anti-*Mycobacterium tuberculosis* (H37Rv) agent, it is expedient to investigate the roles of the derivatives attached to the parent compounds studied as potential anti-*Mycobacterium tuberculosis* (H37Rv) agents with efficient biological activities. This is the focus of this research.

2. Theoretical methodology

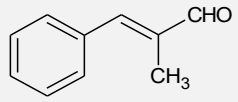
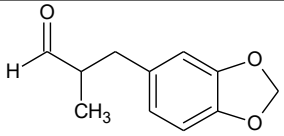
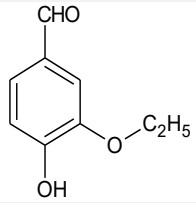
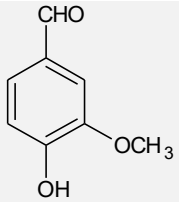
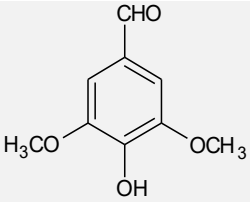
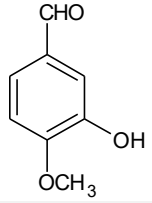
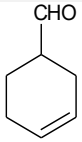
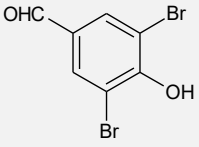
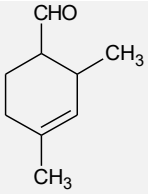
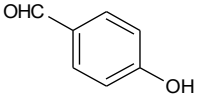
2.1. Studies on docking and optimization

Two-dimensional (2D) structures of ten derivatives of 3-(benzo[d]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one (**Table 1**) were sketched using ChemDraw Professional version 16.0 (Olujinmi *et al.*, 2024; Oyebamiji *et al.*, 2024). Spartan '14 software was used to open the structures and save them as Spartan documents. The setting '6-31G* (B3LYP)' was used as the basis set to express the exchange correlation in the Density Functional Theory (DFT) energy equation. DFT was used to optimize all the derivatives (Oyebamiji *et al.*, 2024). The optimization generated descriptors that describe mycobacterium tuberculosis (H37RV) activities. In this work, a series of molecular descriptors were calculated, and eleven electronic descriptors were selected and used to describe the biological activities of the study compounds.

Protein with PDB ID: 5zhv was downloaded from the PDB bank, treated (cleaned) using Discovery Studio 2019 software (which was also used for viewing the non-bonding interaction between the docked complexes) and was resaved as '.pdbqt' file using Autodock tool software. The grid boxes (dimension and center) were centered (X = –11.899, Y = –6.275, Z = –17.836) and size (X = 30, Y = 30, Z = 30). The spacing was set to be 1.00 Å. The docking calculations (including binding affinities) were achieved using Autodock Vina (command tool) (Trott and Olson, 2010).

Molecular docking of the optimized compounds with the cleaned protein was carried out to calculate binding affinity for individual studied compounds and to observe the non-bonding interaction existing between the complexes. The Autodock Tool was also used for locating binding sites in the downloaded protein and for converting ligands and receptors to '.pdbqt' format from '.pdb' format (Olujinmi *et al.*, 2024).

Table 1. 2-Dimensional structures and IUPAC name of the studied compounds.

S/N	Ar	Molecular Formular/Name	S/N	Ar	Molecular Formular/Name
1		$C_{19}H_{16}N_2OS_2$ (2*E*)-2-methyl-3-phenylprop-2-enal	6		$C_{20}H_{18}N_2O_3S_2$ 3-(1,3-benzodioxol-5-yl)-2-methylpropanal
2		$C_{18}H_{16}N_2O_3S_2$ 3-ethoxy-4-hydroxybenzaldehyde	7		$C_{17}H_{14}N_2O_3S_2$ 4-hydroxy-3-methoxybenzaldehyde
3		$C_{18}H_{16}N_2O_4S_2$ 4-hydroxy-3,5-dimethoxybenzaldehyde	8		$C_{17}H_{14}N_2O_3S_2$ 3-hydroxy-4-methoxybenzaldehyde
4		$C_{16}H_{16}N_2OS_2$ cyclohex-3-ene-1-carbaldehyde	9		$C_{16}H_{10}Br_2N_2O_2S_2$ 3,5-dibromo-4-hydroxybenzaldehyde
5		$C_{18}H_{20}N_2OS_2$ 2,4-dimethylcyclohex-3-ene-1-carbaldehyde	10		$C_{16}H_{12}N_2O_2S_2$ 4-hydroxybenzaldehyde

Source: Elaborated by the authors.

3. Results and discussion

3.1. Molecular descriptors

The calculated molecular descriptors obtained from optimized studied compounds are the highest occupied molecular orbital energy (E_{HOMO}) and the lowest unoccupied molecular orbital energy (E_{LUMO}). The lowest energy orbital that is empty is denoted by LUMO, whereas the highest energy orbital that contains electrons is represented by HOMO. The HOMO-LUMO gap is the energy differential between HOMO and LUMO. A molecule's capacity to take and give electrons is correlated with its LUMO energy. A smaller HOMO-LUMO gap makes molecules more reactive, whereas a greater gap makes molecules more stable. The HOMO-LUMO energies can be used to anticipate how a chemical will interact with biological targets such as proteins or deoxyribonucleic acid (DNA), since many drug-target interactions entail electron transfer or sharing. Additionally, HOMO-LUMO energies have been linked to lipophilicity, which influences a drug's capacity to cross Bruch's membrane in terms of membrane permeability and lipophilicity.

Molecular parameters such as polarizability, dipole moment, hydrogen bond acceptor (HBA), energy band gap, area, volume, polar surface area (PSA), partition coefficient (log P), and hydrogen bond donor (HBD) are calculated and presented in **Table 2**. Higher membrane permeability, which can enhance drug absorption, is frequently correlated with higher polarizability (Tian *et al.*, 2021). On the other hand, very high polarizability could result in nonspecific binding and adverse effects. The dipole moment influences a molecule's solubility and protein binding, which are essential for therapeutic distribution and efficacy, as well as how well it interacts with polar environments like water and proteins. According to Lipinski's Rule of Five (Oyebamiji *et al.,* 2025), an excess of HBAs can impair membrane permeability and be detrimental to drug-target interactions and solubility.

Table 2. Calculated molecular parameters from 3-(benzo[d]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one derivatives.

Compound	E_{HOMO}	E_{LUMO}	BG	MW/amu	log P	Vol/Å^3	PSA	Pol	HBD	HBA	NOR
1	−6.19	−1.27	−4.92	352.48	2.46	343.21	21.173	68.05	0	4	4
2	−5.68	−1.12	−4.56	372.47	0.05	346.51	44.272	68.41	1	6	4
3	−5.69	−1.19	−4.50	388.47	−1.27	355.24	50.223	69.13	1	7	4
4	−6.09	−1.15	−4.94	316.45	2.41	302.48	20.063	64.74	0	4	4
5	−6.11	−1.17	−4.94	344.50	2.91	338.81	19.133	67.69	0	4	4
6	−5.59	−1.17	−4.42	398.51	0.86	373.67	36.276	70.64	0	6	5
7	−5.69	−1.19	−4.50	388.47	−1.27	355.25	50.219	69.3	1	7	4
8	−5.98	−1.22	−4.76	358.44	−0.29	328.49	45.846	66.90	1	6	4
9	−6.26	−1.34	−4.92	486.21	0.96	336.96	37.831	67.55	1	5	4
10	−6.05	−1.15	−5.90	328.42	0.69	301.08	39.901	64.64	1	5	4
P	−7.24	−2.03	−5.21	123.12	−0.96	117.30	51.175	49.66	1	4	4
S	−5.90	−1.08	−4.82	581.58	−6.99	519.83	271.89	82.40	7	15	6

Note: **BG:** band gap, **MW:** molecular weight, **log P:** lipophilicity, **PSA:** polar surface area, **HBD:** hydrogen bond donor, **HBA:** hydrogen bond acceptor, **NOR:** number of rings, **P:** Pyrazinamide, **S:** Streptomycin.
Source: Elaborated by the authors.

The energy band gap is important for several drug classes, especially those that involve electron transport, and it can affect the stability and reactivity of a molecule. A compound's stability, reactivity, and capacity to engage in redox processes or function as a prodrug can all be impacted by its energy band gap.

A drug's ability to bind to target protein binding sites, as well as its ability to traverse membranes and distribute throughout the body, is influenced by its area and volume (Lawson *et al.*, 2021). The capacity of a drug to penetrate cell membranes is correlated with its PSA. Lower PSA frequently indicates better membrane permeability and oral bioavailability. Lipophilicity, which influences solubility, absorption, and distribution, is measured by the log P. For oral drugs, the ideal log P values are normally between 1 and 5 (Lipinski's Rule of Five). HBD is crucial for drug-target interactions and solubility, just as HBAs. Membrane permeability is limited to ≤ 5 by Lipinski's Rule of Five and can be decreased by excess HBDs.

The role of the dipole moment as one of the molecular non-bonded interactions in drug design cannot be over-emphasized (Lewis and Broughton, 2002; Shen *et al.*, 2010). As reported by Oyewole *et al.* (2020) and Oyebamiji *et al.* (2016), a molecular compound with a high dipole moment value is expected to have anomalous properties. As shown in **Table 2**, all the compounds studied have the potential to act as antifungal and antibacterial agents. 3-(1,3-benzodioxol-5-yl)-2-methyl propanal (Compound 6) showed the best ability to release electrons to the adjoining compounds, which are expected to translate into more inhibition than other derivatives, including the standard drugs. Also, the calculated E_{LUMO} obtained from the studied molecules reveal their tendency to receive electrons from the adjacent molecules (Abdul-Hammed *et al.*, 2020; Oyebamiji and Semire, 2020); thus, compound 9 possesses a higher ability to receive electrons from adjacent compounds than other studied ligands. This agrees with the *in vitro* assay (Bhoge *et al.*, 2024).

Other descriptors obtained are molecular weight, HBDs, HBA and log P; all these descriptors were found to fall within the standard range (molecular weight < 400 except for compound 9 (> 400), Streptomycin (> 500), HBD < 2, HBA ≤ 7 except for Streptomycin which is 15 and log P < 3). This showed that all the compounds studied possess drug potential.

3.2. Binding affinity

The degree of interaction between a ligand, like a drug molecule, and its target, usually a protein or receptor, is called binding affinity (Ren *et al.*, 2021). It measures the degree to which the ligand binds to its intended target.

It is commonly measured in molar concentrations (mol/L), with lower values indicating stronger binding. It is generally represented as the inhibition constant (Ki) or the dissociation constant (Kd). The ligand binds more firmly and remains bound for a longer period when it has a high binding affinity (low Kd or Ki). In this work, all the compounds studied show higher binding strengths (–24.3 to –31.0 kJ/mol) to inhibit *Mycobacterium tuberculosis* H37Rv better than Streptomycin (–20.9 kJ/mol) and Pyrazinamide (–16.3 kJ/mol) (which were used as standards), as shown in **Table 3**.

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Since binding affinity frequently corresponds to a medicine's potency and efficacy, it is essential to drug research and influenced by several chemical interactions, including hydrophobic interactions, van der Waals forces, and hydrogen bonds.

Table 3. Calculated binding affinity.

Compound	Binding Affinity (kJ/mol)
1	−29.3
2	−25.1
3	−25.1
4	−25.5
5	−25.5
6	−31.0
7	−24.7
8	−27.6
9	−24.3
10	−25.1
Streptomycin	−20.9
Pyrazinamide	−16.3

Source: Elaborated by the authors.

3.3. Molecular docking results

The optimized compounds were subjected to docking studies (with a suitable receptor that has anti-tuberculosis inhibition activities (**Fig. 1**), via Discovery Studio, autodocking tool and autodocking vina software. Docking studies were carried out on the compounds studied to observe the non-bonding interaction present between 3-(benzo[d]thiazol-2-yl)-2-(substituted aryl) thiazolidin-4-one derivatives and a protein (PDB ID: 5zhv). According to Lewis and Broughton (2002), the compound with the lowest binding affinity value has the highest tendency to inhibit the target the most; thus, compound 6 (2D structure shown in **Fig. 2**) with –31.0 kJ/mol proved to be better than other studied compounds as an anti-tubercular agent, even than the standard drugs that were used.

The standard drugs i.e. Streptomycin and Pyrazinamide have a lower binding affinity compared to the binding affinity obtained for each of the studied 3-(benzo[d]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one derivatives. The compounds under study showed different interactions with the protein studied (**Fig. 1**) and compound 6 (**Fig. 2**). The 2D structure of the docked 'compound 6' with receptor '5zhv' is displayed in **Fig. 3**.

4. Conclusions

The increasing knowledge of computational chemistry and its usage in the design and development of drugs and disease treatment has had a significant positive influence on mortality and morbidity globally. The study of anti-tuberculosis properties of 3-(benzo[d]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one derivatives was observed in this work using density functional theory as well as molecular docking software (Autodock Tool, Auto dock vina and discovery studio). All the studied compounds can act as antifungal and antibacterial agents. The calculated E_{LUMO} obtained from the studied molecules reveals their tendency to receive electrons from the adjacent molecules, thus, compound 9 possesses a higher ability to receive electrons from adjacent compounds than other studied ligands. Other descriptors obtained are molecular weight, HBDs, HBA and log P; all these descriptors were found to fall within the standard range (molecular weight < 400 except for compound 9 (> 400) Streptomycin (> 500), HBD (< 2), HBA (≤ 7) except for Streptomycin which is 15 and log P (< 3)). This showed that all the compounds studied possess drug potential.

While all the docked compounds showed better anti-tubercular activities than the standard drugs, compound 6 was outstanding in its result. This *in silico* approach agrees with the *in vitro* assay earlier carried out by Bhoge *et al.* (2024). This research further strengthens the call that these derivatives could lead the path to the discovery of better anti-tubercular agents.

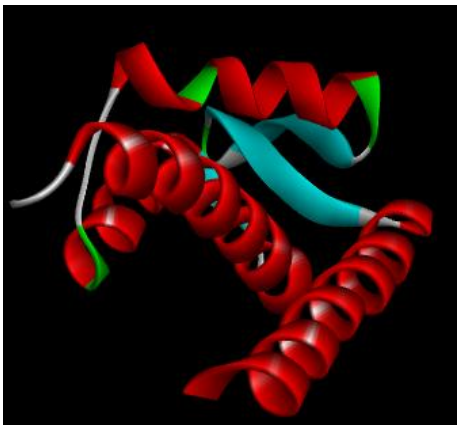

Figure 1. Receptor (5zhv) used for docking.
Source: Elaborated by the authors.

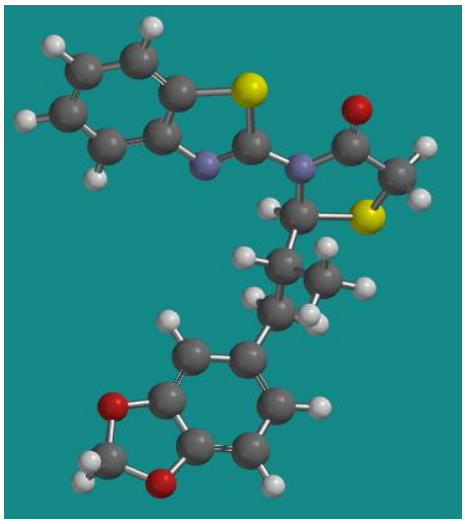

Figure 2. 2D structure of compound 6.
Source: Elaborated by the authors.

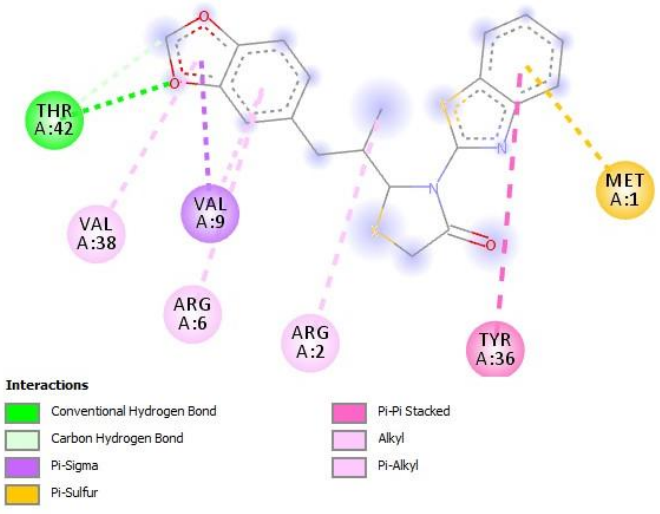

Figure 3. 2D structure of docked compound 6 with receptor 5zhv.
Source: Elaborated by the authors.

Authors' contribution

Conceptualization: Abel Kolawole Oyebamiji; **Data curation**: David Gbenga Oke; **Formal Analysis**: Faith Eniola Olujinmi; **Funding acquisition**: Juliana Oluwasayo Aworinde; **Investigation**: Olamide Adetunji Olalekan; **Methodology**: Abel Kolawole Oyebamiji, David Gbenga Oke; **Project administration**: Abel Kolawole Oyebamiji; **Resources**: David Gbenga Oke; **Software**: Abel Kolawole Oyebamiji; **Supervision**: Abel Kolawole Oyebamiji; **Validation**: Juliana Oluwasayo Aworinde; **Visualization**: Faith Eniola Olujinmi; Olamide Adetunji Olalekan; **Writing – original draft**: David Gbenga Oke; **Writing – review & editing**: David Gbenga Oke; Abel Kolawole Oyebamiji.

Data availability statement

All data sets were generated or analyzed in the current study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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