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DESIGN, SYNTHESIS AND *IN-SILICO* STUDY OF NOVEL SERIES OF 2-PHENYL- 3-(5-SULFANYL-1,3,4-THIADIAZOL-2-YL)-1,3-THIAZOLIDIN-4-ONE DERIVATIVES WITH POTENTIAL ANTI-TUBERCULAR ACTIVITY

V. G. Dadlani [*1], R. R. Somani [2] and P. K. Tripathi [3]

Department of Pharmaceutical Chemistry [1], Faculty of Pharmacy, Dr. L. H. Hiranandani College of Pharmacy, Thane - 421003, Maharashtra, India.
Department of Pharmaceutical Chemistry [2], Faculty of Pharmacy, Vivekanand Education Society's College of Pharmacy, Mumbai - 400074, Maharashtra, India.
Department of Pharmacy [3], Faculty of Pharmacy, Rameshwaram Institute of Technology and Management, Lucknow - 227202, Uttar Pradesh, India.

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Shikimate kinase, 5-Amino-1,3,4-thiadiazole-2-thiol, Montmorillonite KSF, 4-thiazolidinones, Anti-tubercular activity, MABA, Docking studies

Correspondence to Author:
Vedika G. Dadlani

Assistant Professor,
Department of Pharmaceutical Chemistry, Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Thane - 421003, Maharashtra, India.

E-mail: vedika.dadlani@dlhhcop.org

ABSTRACT: In an attempt to identify potential new agents active against tuberculosis with Shikimate kinase as the target, a novel series of 2-phenyl- 3-(5-sulfanyl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one derivatives were synthesized by convenient one-pot three-component reaction of amine, aldehyde and mercaptoacetic acid on montmorillonite KSF clay as a solid acidic catalyst in good yields. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H-NMR and elemental analysis and were subjected for anti-tubercular activity by Microplate Alamar Blue Assay (MABA) against *Mycobacterium tuberculosis* H37Rv. Docking and ADMET studies were used to better describe the titled compounds as potential anti-tubercular agents. The compound, 2-(3,4-dimethoxyphenyl)-3-(5-sulfanyl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one(4j), was found to be the most active against *Mycobacterium tuberculosis* H37Rv with MIC of 1.6 µg/ml and good drug likeness and dock scores. Molecular docking study revealed that the molecules fit well into the cavity of Shikimate kinase. Also, the molecular properties and bioactivity scores for the synthesized compounds obtained by *in-silico* studies were found to be within the acceptable range defined for human use revealing their potential as possible drug-like compounds. The anti-tubercular activity of the titled compounds was comparable to that of the standard drug Isoniazid and Ciprofloxacin. The results indicate that the synthesized thiadiazolyl-thiazolidinone derivatives may have an affinity towards Shikimate kinase active site which can be further explored for selective target based studies. Thus these compounds could act as a potential lead for further anti-tubercular studies.

INTRODUCTION: Tuberculosis (TB), an infectious disease resulting from the bacteria *Mycobacterium tuberculosis* (MTB), poses a primary worldwide health problem.

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Recently, the rising numbers of extensively drug-resistant TB (XDR) and multidrug-resistant TB (MDR-TB) have significantly threatened to jeopardize global efforts to control TB, especially in HIV endemic regions. There is a pressing need to broaden effective new antitubercular agents, preferably belonging to new structural classes, to better fight TB, which include MDR-TB and XDR-TB, to shorten the period of contemporary therapy, to improve patient compliance and to provide the effective remedy of latent tuberculosis contamination [1-3].

Cutting-edge anti-tubercular drugs more often target cell approaches concerned in bacterial progression and either inhibit the growth of bacteria or act as bactericidal. These encompass cell wall synthesis inhibitors, nucleic acid synthesis inhibitors, protein synthesis inhibitors, and energy inhibitors. Newer drugs with novel targets are being exploited to cope up with the problems of multidrug tolerance and dormant TB populations [4].

The shikimic acid pathway is essential for the survival of microorganisms and is unique to microorganisms. This pathway is absent in mammals which allows identification of targets that can decrease the toxicity of drug candidates. The evidence that the shikimate pathway is essential for MTB even in the presence of exogenous supplements as p-hydroxybenzoate, p-aminobenzoate and aromatic amino acids highlight its importance as a drug target. Consequently, inhibition of critical enzymes involved in this pathway seems to be an attractive target for the development of new anti-infective agents [3]. One of the most promising enzymes of the shikimic acid pathway is Shikimate kinase (SK), which is involved in the fifth step in the shikimate pathway. The availability of the *M. tuberculosis* shikimate kinase (MtSK) structures complexed with shikimate provides crucial information for the design of SK inhibitors [3].

Reported docking simulations have identified that potential inhibitors had a structural relationship to a triazole or tetrazole hetero-aromatic system which may provide a candidate leads for the discovery of MtSK inhibitors [5]. The presence of sulfur moiety as an electron-rich center can improve lipophilicity and modulate electron density of the triazole ring, as well as its interaction with hydrogen bond donors of the organism. It was reported that the best scoring compounds including ASXE1 contained a mercapto group and a triazole ring in the scaffold [6].

Further, isosterism can be explored as a tool to alter the pharmacological profile of a compound. The bioisosteric replacement of a ring with another ring might lead to compounds with increased lipophilicity and improved biological properties. The thiadiazole ring is a bioisostere of oxadiazole, oxazole, triazole and benzene ring. The thiadiazole derivatives, due to the presence of sulfur atom that gives high liposolubility, show oral absorption and good cell permeability leading to a good bioavailability [7, 8]. Also, the heterocycle, thiazolidinone, a five-membered ring is widely used in medicinal chemistry. Its derivatives show a diverse range of biological activities, for example, antimicrobial [9], antitubercular [10], anticancer [11], anti-inflammatory [12], anti-HIV [13] and antidiabetic [14]. The 4- thiazolidinone scaffold is multi-faceted and forms a structural element of several clinically used drugs.

Kucukguzel *et al*., have reported antimycobacterial activity of substituted 4-thiazolidinones and found that one of the compounds in the series, Compound (a), showed 98% inhibition at 6.25 µg/ml [15]. In this light, molecules were designed by molecular hybridization of 4-thiazolidinones and 1,3,4-thiadiazoles as bioisosteres of 1,2,4-triazoles as depicted in **Fig. 1**. The design principle was aimed at combining the pharmacophores of 4-thiazolidinone derivatives and 1,3,4-thiadiazole moiety to gain synergism and obtain molecules with better antitubercular activity.

The synthesis of 1,3-thiazolidin-4-ones is illustrated by various methods in the literature. Essentially, the three-component reaction involves a primary amine, a carbonyl compound, and the mercapto acetic acid either in a one or two-step process. It is proposed that the reaction involves imine formation in the first step followed by an attack of the sulfur nucleophile on the imine carbon and finally intramolecular cyclization with the elimination of water. The latter step seems to be critical for obtaining high yields of 4-thiazolidinones [16]. Therefore, various methods have been tried to remove water during cyclization. The most common practice is using azeotropic distillation with Dean-Stark trap for removal of water [17]. Besides, other protocols were developed by using dehydrating agents like anhydrous $ZnCl_2$ [18], molecular sieves [19] and 1,3-dicyclohexylcarbodiimide [20], with the purpose to improve the yield of the desired products. Thiazolidinones have also been synthesized using unconventional methods like ultrasound irradiation [21], microwave irradiation [22] or ionic liquid-phase catalysis [23].

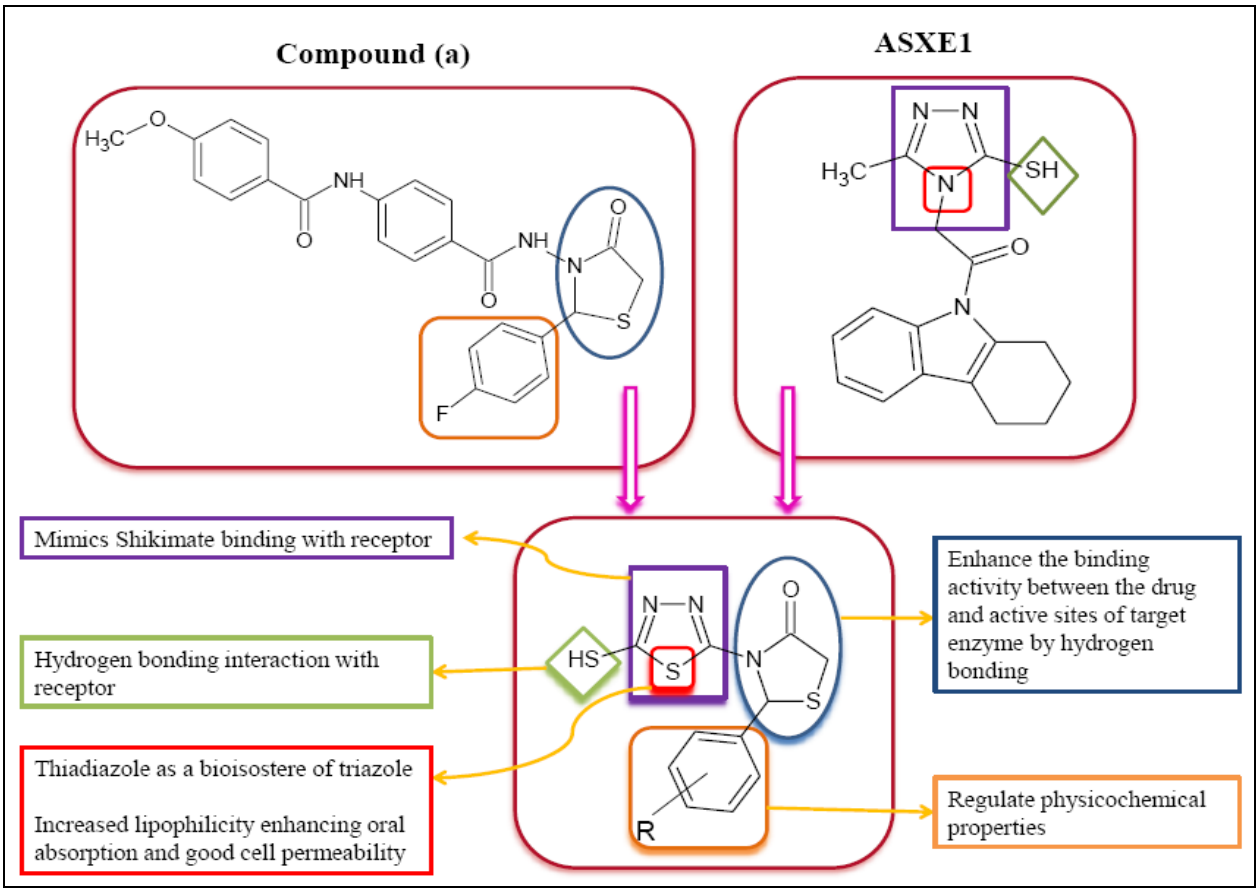


FIG. 1: DESIGN OF HYBRIDS OF THIAZOLIDINONES WITH 1,3,4-THIADIAZOLE MOIETY

Recently, efficient synthesis of such heterocycles by biocatalysis with *Saccharomyces cerevisiae* has also been described [24]. These procedures are limited by yields ranging from moderate to very good depending on the reactants. Multicomponent reactions have gained a great deal of attention as they provide easy and rapid access to a large, complex and diverse library of compounds without isolation of any intermediate and have other advantages such as productivity, simple procedures, time and energy saving, and high product yields. Nosrat O. Mahmoodi *et al.*, have developed a convenient, one-pot three-component reaction for the synthesis of thiazolidinones from aldehydes, thiosemicarbazide, and maleic anhydride in the presence of KSF@Ni as heterogeneous catalyst under microwave irradiation [25]. Bearing this in mind, we surmised that montmorillonite KSF clay could be explored as a dehydrating agent and solid acidic catalyst for the synthesis of different thiadiazolyl-thiazolidin-4-one derivatives by three component reaction from the condensation reaction between an appropriate mixture of amine, aldehyde and thioglycolic acid in good yields.

MATERIAL AND METHODS:

Chemistry: All chemical reagents and solvents were purchased from the commercial suppliers like Merck and Sigma Aldrich companies and used without further purification. The progress of reactions and the purity of compounds were checked by TLC analysis on silica gel 60 F254 plates (Merck), and visualization was done with UV light (254 nm).

Melting points were determined in open glass capillaries using Oswald Precision Melting Point apparatus and are uncorrected. Elemental analyses were performed using Thermo Scientific (FLASH 2000) CHN Elemental Analyser and are expressed in percentage of each element analyzed. The IR spectra were recorded in anhydrous potassium bromide (KBr) disks on "Shimadzu IR Affinity-1" and are reported in cm^{-1}.

1H-NMR spectra were recorded using Avance-II (Bruker) 400 MHz analyzer spectrometer in deuterated solvents, and chemical shifts are expressed as δ (ppm) with tetramethylsilane as an internal standard.

General procedure for the synthesis of 2-phenyl-3-(5-sulfanyl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one derivatives 4a-j: We investigated in this report conventional two-step process using $ZnCl_2$ (Method I) and one-pot three-component synthesis of thiazolidinones catalyzed by KSF (Method II).

Method 1: Conventional Method (Two-Step Process):

Step I: Synthesis of benzylidene 5-amino -1,3,4 thiadiazole-2-thiol derivatives 3a-j: Equimolar quantities of 5-amino-1,3,4-thiadiazole-2-thiol (1) and various aromatic aldehydes (2a-j) in ethanol were refluxed for 6 h. The completion of the reaction was monitored by TLC plates using hexane and ethyl acetate (1:1) as an eluent. The reaction mixture was concentrated and kept overnight below 20 °C for crystallization. The solid separated was filtered under vacuum and recrystallized from 95 % ethanol to yield compound (3a-j).

Step II: Synthesis of 2-phenyl- 3-(5-sulfanyl-1, 3, 4- thiadiazol- 2- yl)- 1, 3-thiazolidin- 4- one derivatives 4a-j: To a solution of compound (3a-j) (1 mmol) in methanol (10 ml) a solution of mercaptoacetic acid (2 mmol) in methanol (10 ml) was added followed by catalytic amount of zinc chloride, and reaction mixture was refluxed for 4 h, mixture was evaporated under vacuum. The residue was then treated by the solution of bicarbonate to remove the excess of mercaptoacetic acid. The compound was extracted with ethyl acetate. The combined ethyl acetate layer was evaporated under vacuum. Compound (4a-j) was then isolated by silica gel column chromatography eluting with ethyl acetate and benzene and then recrystallized from ethanol.

Method 2: One-Pot Synthesis using KSF as a Catalyst: To a solution of 5-amino-2-mercapto-1,3,4-thiadiazole (1) (1 mmol) in ethanol (30 mL), aldehyde (2a-j) (1mmol), montmorillonite KSF in the ratio of 1 g to 1 mole of aldehyde and glacial acetic acid (1 ml) was added. The mixture was refluxed for 3 h. After that, the mercaptoacetic acid (1 mmol) was added and the mixture was refluxed until the reaction was complete, as shown by TLC. The solution was filtered and evaporated under vacuum. Ethyl acetate (20 ml) was added and the mixture was washed with saturated solution of $NaHCO_3$ (3 × 20 mL), sodium bisulfate (3 × 20 mL), and then finally with brine. The organic layer was dried over sodium sulphate anhydrous and solvent was removed under reduced pressure to get a residue that was purified by column chromatography on silica gel using hexane–ethyl acetate as an eluent to afford compounds (4a-j).

2- (4- hydroxyphenyl)- 3- (5-sulfanyl- 1, 3, 4-thiadiazol- 2- yl)- 1, 3-thiazolidin- 4- one (4a): IR (KBr, cm^{-1}) 3456.3, 2916, 2556, 1638.4, 1447.8, 834.7; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.75 (d, J=15.6 Hz, 1H, CH_2-S), 3.91 (d, J=15.6 Hz, 1H, CH2-S), 6.47 (s, 1H, CH-N), 7.16-7.68 (m, 4H, Ar-H), 10.99 (s, 1H, SH), 13.5 (s,1H, 1OH). Anal. Calcd for $C_{11}H_9N_3O_2S_3$: C, 42.43; H, 2.91; N, 13.49; O, 10.28; S, 30.89. Found C, 41.64; H, 2.82; N, 13.07; O, 10.22; S, 30.83.

2- (4- methoxyphenyl)- 3- (5- sulfanyl-1, 3, 4-thiadiazol-2-yl)- 1, 3- thiazolidin-4-one (4b): IR (KBr, cm^{-1}) 2916, 2552, 1674.5, 1410.8, 1187.5, 831.3; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.76 (d, J=15.6 Hz, 1H, CH_2-S), 3.91 (d, J=15.6 Hz, 1H, CH_2-S), 6.29 (s, 1H, CH-N), 6.9-7.84 (m, 4H, Ar-H), 11.56 (s, 1H, SH),2.97 (s, 1H, OCH3). Anal. Calcd for $C_{12}H_{11}N_3O_2S_3$: C, 44.29; H, 3.41; N, 12.91; O, 9.83; S, 29.56; Found C, 43.22; H, 3.21; N, 12.82; O, 9.76; S, 29.42.

2-(4-nitrophenyl)-3- (5-sulfanyl-1, 3,4-thiadiazol-2-yl)-1, 3-thiazolidin-4-one (4c): IR (KBr, cm^{-1}) 2977, 2548, 1641, 1563, 1436, 882; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.75 (d, J=15.7 Hz, 1H, CH_2-S), 3.83 (d, J=15.7 Hz, 1H, CH_2-S), 6.6 (s, 1H, CH-N), 7.5-7.9 (m, 4H, Ar-H), 11.23 (s, 1H, SH). Anal. Calcd for $C_{11}H_8N_4O_3S_3$: C, 38.81; H, 2.37; N, 16.46; O, 14.10; S, 28.26; Found C, 38.73; H, 2.19; N, 16.29; O, 14.03; S, 28.21.

2- (4- chlorophenyl)- 3- (5- sulfanyl- 1, 3, 4-thiadiazol- 2- yl)- 1, 3-thiazolidin- 4- one (4d): IR (KBr, cm^{-1}) 2922.4, 2562, 1685, 1417, 832, 765.2; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.77 (d, J=15.9 Hz, 1H, CH_2-S), 3.89(d, J=15.9 Hz, 1H, CH_2-S), 6.24 (s, 1H, CH-N), 7.00-7.80 (m, 4H, Ar-H), 11.44 (s, 1H, SH). Anal. Calcd for $C_{11}H_8ClN_3OS_3$: C, 40.05; H, 2.44; Cl, 10.75; N, 12.74; O, 4.85; S, 29.16; Found C, 39.02; H, 2.42; Cl, 10.68, N, 12.63; O, 4.82; S, 29.13.

2- (4- bromophenyl)- 3- (5- sulfanyl-1, 3, 4- thiadiazol-2-yl)- 1, 3- thiazolidin-4-one (4e): IR (KBr, cm^{-1}) 2905.7, 2560, 1684.9, 1415.1, 827.9, 765.4; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.77 (d, J=15.7 Hz, 1H, CH_2-S), 3.92 (d, J=15.7 Hz, 1H, CH_2-S), 6.23 (s, 1H, CH-N), 7.00-7.65 (m, 4H, Ar-H), 11.50 (s, 1H, SH). Anal. Calcd for $C_{11}H_8BrN_3OS_3$: C, 35.30; H, 2.15; Br, 21.35; N, 11.23; O, 4.27; S, 25.70; Found C, 34.87; H, 2.1; N, 11.13; Br, 21.29; O, 4.25; S, 25.6.

2-(4-fluorophenyl)-3-(5-sulfanyl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one (4f): IR (KBr, cm^{-1}) 2906, 2547, 1685.9, 1420.4, 837.6, 763.4; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.59 (d, J=15.5 Hz, 1H, CH_2-S), 3.91 (d, J=15.5 Hz, 1H, CH_2-S), 6.92 (s, 1H, CH-N), 7.00-7.87 (m, 4H, Ar-H), 10.58 (s, 1H, SH). Anal. Calcd for $C_{11}H_8FN_3OS_3$: C, 42.16; H, 2.57; F, 6.06; N, 13.41; O, 5.11; S, 30.69; Found C, 42.08; H, 2.54; F, 6.02; N, 13.49; O, 5.03; S, 30.65.

2- (4- methylphenyl)- 3- (5- sulfanyl- 1, 3, 4- thiadiazol-2-yl)-1, 3-thiazolidin-4-one (4g): IR (KBr, cm^{-1}) 2977, 2556, 1651, 1426, 882; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.86 (d, J=15.7 Hz, 1H, CH2-S), 4.0 (d, J=15.7 Hz, 1H, CH_2-S), 6.74 (s, 1H, CH-N), 6.49-7.74 (m, 4H, Ar-H), 11.23 (s, 1H, SH), 2.77 (s, 3H, CH_3). Anal. Calcd for $C_{12}H_{11}N_3OS_3$: C, 46.58; H, 3.58; N, 13.58; O, 5.17; S, 31.09; Found C, 46.51; H, 3.56; N, 13.49; O, 5.10; S, 30.99.

2- (2- chlorophenyl)- 3- (5- sulfanyl- 1, 3, 4- thiadiazol-2-yl)-1, 3-thiazolidin-4-one (4h): IR (KBr, cm^{-1}) 2926.4, 2553, 1684.9, 1415.1, 854.7, 756.1; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.87 (d, J=15.7 Hz, 1H, CH_2-S), 3.98 (d, J=15.7 Hz, 1H, CH_2-S), 6.34 (s, 1H, CH-N), 7.03-7.74 (m, 4H, Ar-H), 11.52 (s, 1H, SH). Anal. Calcd for $C_{11}H_8ClN_3OS_3$: C, 40.05; H, 2.44; Cl, 10.75; N, 12.74; O, 4.85; S, 29.16; Found C, 39.98; H, 2.41; Cl, 10.65; N, 12.69; O, 4.83; S, 29.10.

2-(2-nitrophenyl)-3-(5-sulfanyl-1, 3, 4-thiadiazol-2-yl)-1, 3-thiazolidin-4-one (4i): IR (KBr, cm^{-1}) 2974, 2556, 1641, 1536, 1442, 882; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.59 (d, J=15.5 Hz, 1H, CH_2-S), 3.88 (d, J=15.5 Hz, 1H, CH_2-S), 6.70 (s, 1H, CH-N), 7.00-7.87 (m, 4H, Ar-H), 10.58 (s, 1H, SH). Anal. Calcd for $C_{11}H_8N_4O_3S_3$: C, 38.81; H, 2.37; N, 16.46; O, 14.10; S, 28.26; Found C, 38.81; H, 2.36; N, 16.43, O, 14.07; S, 28.16.

2-(3, 4-dimethoxyphenyl)- 3- (5-sulfanyl-1, 3, 4-thiadiazol-2-yl)-1, 3-thiazolidin-4-one (4j): IR (KBr, cm^{-1}) 2939.5, 2559, 1662, 1449.6, 1209.3, 819.4; 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.51 (d, J=15.2 Hz, 1H, CH_2-S), 3.82 (d, J=15.2 Hz, 1H, CH_2-S), 3.92 (s, 1H, OCH_3), 6.64 (s, 1H, CH-N), 6.82-7.52 (m, 4H, Ar-H), 11.99 (s, 1H, SH). Anal. Calcd for $C_{13}H_{13}N_3O_3S_3$: C, 43.93; H, 3.69; N, 11.82; O, 13.50; S, 27.06; Found C, 44.08; H, 3.65; N, 11.74; O, 13.43; S, 26.98.

Anti-Tubercular Activity: The synthesized compounds (4a-j) were screened against *M. tuberculosis* H37Rv to determine the minimum inhibitory concentration (MIC) with Microplate Alamar Blue Assay (MABA) assay in 96-well microplates [26].

Outer perimeter wells were filled with sterile deionized water to minimize dehydration in test wells during incubation. Homogenous mycobacterial (H37Rv) culture suspension was seeded in microtitre plates in 100 µL of the Middlebrook 7H9 broth (Difco Laboratories, Detroit, MI, USA) and serial dilution of compounds were made directly on plate. Plates were covered and sealed with parafilm and incubated at 37 ºC for seven days. 25 µl of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% Tween 80 was added to the plate and again incubated for 48 h. The blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as the lowest drug concentration which prevented the color change from blue to pink. Isoniazid and Ciprofloxacin were used as the reference drug.

Docking Study: Crystal structure of *M. tuberculosis* Shikimate kinase co-crystallized with shikimate and ADP (PDB ID: 2IYQ) was provided from the Protein Data Bank and prepared for docking calculations using Molecular Design Suite (VLife MDS software package, version 4.4; from VLife Sciences, India) with default settings [27, 28]. Docking was performed using GRIP batch docking method implemented in VLife MDS 4.4 software package and standard parameters were used. Water molecules were not included. The ligand forming

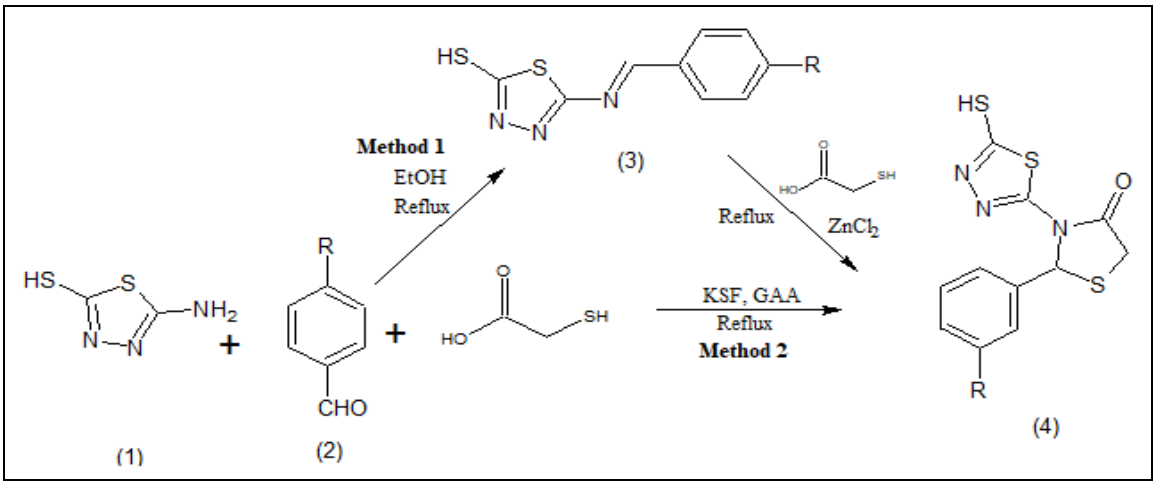
the most stable drug-receptor complex is the one which has minimum dock score (interaction energy) and the scoring interaction energy of the original co-crystallized ligand was used for comparison.

***In-silico* ADMET Properties and Drug Likeness Prediction:** *In-silico* prediction of ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties is very important for lead identification and optimization. admetSAR, a free online server was used to predict ADMET properties.[29] The ADMET properties of 3-(5-sulfanyl- 1, 3, 4- thiadiazol- 2- yl)- 2- (aryl)-1, 3-thiazolidin-4-one derivatives were estimated using admetSAR online database (www.lmmd.ecust. edu.cn, accessed on 21st April 2018). It provides inclusive data for different entities linked with known ADMET profiles.

Chemical structures and SMILES notations of the titled compounds were obtained by using ACD labs Chemsketch version 12.0. SMILES notations of the thiadiazolyl-thiazolidinone derivatives were then fed in the online Molinspiration software version 2011.06 (www.molinspiration.com) to calculate various molecular properties and to predict bioactivity score for drug targets including enzymes and nuclear receptors, kinase inhibitors, glycoprotein coupled receptor (GPCR) ligands, and ion channel modulators [30]. Molecular properties such as partition coefficient (Log P), topological polar surface area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight and violations of Lipinski's rule of five were calculated to evaluate the drug-likeness of the synthesized compounds. The bioactivity score and drug likeliness properties of the thiadiazolyl-thiazolidinone derivatives were compared with the standard drugs Ciprofloxacin and Isoniazid.

RESULTS AND DISCUSSION:

Chemistry: The synthetic route to 2-phenyl-3-(5-sulfanyl-1, 3, 4-thiadiazol-2-yl)-1, 3-thiazolidin-4-one derivatives (4a-j) is illustrated in **Scheme 1**. The titled compounds (4a-j) were successfully synthesized by the three-component reaction in a one-step process. The strategy of using montmorillonite KSF clay as a dehydrating agent afforded strong acidity in mild reaction conditions and effectively resulted in achieving better yields than the conventional two-step process. A comparative data between our applied procedure and the conventional method has been shown in the general procedure section and the yields are presented in **Table 1**. Different types of compounds with electron withdrawing substituents (Cl, Br, F, NO_2) and electron donating substituents (OCH_3, OH) were synthesized to investigate the electronic effects of various moieties.



SCHEME 1: SYNTHETIC ROUTES TO THIAZOLIDINONE DERIVATIVES (4a-j)

The structures of the synthesized compounds were characterized by IR, ^{1}H NMR and elemental analysis. Characteristic peaks were observed for SH stretching, C=O stretching, and CH-N stretching in FTIR. The IR spectra of 5-amino-1,3,4-thiadiazole-2-thiol 2 showed prominent peaks for primary amine at 3338.78, and 3251.98 cm^{-1} and those of aldehydes showed peculiar absorption for C=O at 1740-1720 cm^{-1} which disappeared in compound 3. Compound 3 showed prominent

HC=N stretching at 1539-1573 cm^{-1}. Compound 4 showed peculiar absorption in the range of 1638-1685 cm^{-1} due to C=O lactam amide stretching vibration. The ^1H NMR spectrum of compound 4 showed a singlet for CH of the thiazolidinone ring as at 6.23- 6.92 ppm, a doublet at 3.51 and 4.00 for CH_2-S of thiazolidinone rings, a singlet for SH at 10.58 - 11.99 ppm and aromatic protons related to the phenyl group appeared at 6.9-7.9 ppm. A singlet at 2.77, 2.97 and 3.92 for CH_3 was observed in compounds 4b, 4g, 4j respectively. A singlet at 13.5 ppm for OH was observed in compound 4a. Elemental analysis proved the molecular formula of the compounds.

TABLE 1: PROPERTIES OF SYNTHESIZED COMPOUNDS

Compounds	R	Formula	MW (g/mol)	MP	Yield (%) Method 1	Yield (%) Method 2
4a	4-OH	$C_{11}H_9N_3O_2S_3$	311.4	154	56	70
4b	4-OCH_3	$C_{12}H_{11}N_3O_2S_3$	325.43	165	75	82
4c	4-NO_2	$C_{11}H_8N_4O_3S_3$	340.4	196	59	79
4d	4-Cl	$C_{11}H_8ClN_3OS_3$	329.85	189	68	80
4e	4-Br	$C_{11}H_8BrN_3OS_3$	374.3	184	58	69
4f	4-F	$C_{11}H_8FN_3OS_3$	313.39	187	47	58
4g	4-CH_3	$C_{12}H_{11}N_3OS_3$	309.43	161	65	71
4h	2-Cl	$C_{11}H_8ClN_3OS_3$	329.85	168	52	63
4i	2-NO_2	$C_{11}H_8N_4O_3S_3$	340.4	159	55	63
4j	3,4-di-OCH_3	$C_{13}H_{13}N_3O_3S_3$	355.46	189	57	66

Antitubercular Activity: The synthesized compounds (4a-j) were screened against *M. tuberculosis* H37Rv to determine the minimum inhibitory concentration (MIC) with MABA assay in 96-well microplates. The resulting MICs (minimum inhibitory concentrations) of thiazolidinone compounds were compared with those of isoniazid and ciprofloxacin as reference compound as shown in **Table 2**.

TABLE 2: ANTI-TUBERCULAR ACTIVITY OF COMPOUNDS (4a-j) IN COMPARISON WITH ISONIAZID AND CIPROFLOXACIN

Compound	MIC (µg/ml)
4a	12.5
4b	6.25
4c	50
4d	25
4e	25
4f	50
4g	12.5
4h	50
4i	25
4j	1.6
Isoniazid	1.6
Ciprofloxacin	3.12

The results revealed that 4a, 4b, 4g, and 4j showed good activity ranging from 12.5 to 1.6 µg/ml. Candidates with electron withdrawing groups at phenyl ring on thiazolidinone moiety were found to have weak inhibitory activity while those with electron donating groups showed better antitubercular activity. The MIC values of isoniazid and ciprofloxacin were found to be 1.6 and 3.12 µg/mL respectively. The antitubercular activity of compound 4j was comparable to that of standard drug Isoniazid. Thus, by comparing the MIC values, it could be envisaged that the introduction of bulkier electron donating methoxy groups increases the activity. The increased hydrogen bonding due to an oxygen atom in the thiazolidinone ring and hydroxyl and methoxy groups could have contributed to better antitubercular activity.

Docking Study: To rationalize the antitubercular activity, docking study was performed for the designed molecules (4a-j) to investigate the possible interactions with Shikimate kinase from *Mycobacterium tuberculosis* (2IYQ). The interactions of the designed compounds with the amino acids in the active site of Shikimate kinase are listed in **Table 3** and the docking score of the compounds is presented in **Table 4.**

Fig. 2a, 3a, 4a show the docked reference compound Shikimate in the active site of the Shikimate kinase enzyme for validation of our docking protocol and confirmation of the biological data. **Fig. 2b, 3b, 4b** show Compound 4j docked in the enzyme's active site showing hydrogen bond, hydrophobic interaction, and Van der waal's interaction respectively. The oxygen atom of the thiazolidinone is oriented towards the polar region of the enzyme and interacts with LYS15, GLY80,

GLY81, ARG 117 with increased hydrogen bonding in comparison to the reference compound Shikimate. The methoxy groups in the phenyl attached to the thiazolidinone ring are inserted into the hydrophobic pocket and interact with ARG117, LEU119.

TABLE 3: INTERACTIONS OF DESIGNED MOLECULES AND SUBSTRATE, SHIKIMATE, IN THE ACTIVE SITE OF ENZYME SHIKIMATE KINASE

Compound	Hydrogen Bond	Charge Interaction	Hydrophobic Interaction	Van Der Waals Interaction
SHIKIMATE	GLY80, ARG58	LYS15, ARG117	LEU119, PRO11, GLY80, GLY81, ARG117	GLY81, LYS15, ARG58, ARG117, ARG136, PRO11, GLY80, LEU119
4a	ARG58, ARG117, ARG136	NIL	ARG117	PRO11, LYS15, ASP34, ARG58, GLY80, ARG117, LEU119, ARG136
4b	ARG117, LEU119	NIL	PRO11, LYS15, GLY80, ARG117, LEU119	PRO11, LYS15, ASP34, GLY80, GLY81, ARG117, LEU119, ARG136
4c	GLY80, GLY81, ARG117	NIL	ARG117, LEU119	PRO11, LYS15, ASP34, ARG58, GLY80, ARG117, LEU119, GLY81
4d	GLY80, GLY81, ARG117	NIL	ARG117, LEU119	PRO11, LYS15, ASP34, GLY80, ARG117, LEU119, GLY81
4e	ARG117	NIL	ARG117	PRO11, LYS15, ASP34, ARG58, GLY80, ARG117, LEU119, SER16, GLY81
4f	ARG117	NIL	ARG117, ASP34	PRO11, LYS15, ASP34, ARG58, GLY80, ARG117, LEU119, ARG136, GLY81
4g	LYS15, GLY80, ARG117	NIL	ARG117, LEU119	PRO11, LYS15, ASP34, GLY81, GLY80, ARG117
4h	ARG117	PHE49 (Aromatic Interaction)	ARG117, PRO11, LYS15, GLY80	PRO11, LYS15, ASP34, GLY81, GLY80, ARG117
4i	ARG58, ARG117, ARG136	NIL	ARG117, LEU119	PRO11, ASP34, ARG58, GLY81, GLY80, ARG117, LEU119, ARG136
4j	LYS15, GLY80, GLY81, ARG117	NIL	ARG117, LEU119	PRO11, LYS15, ARG58, GLY81, GLY80, ARG117, LEU119

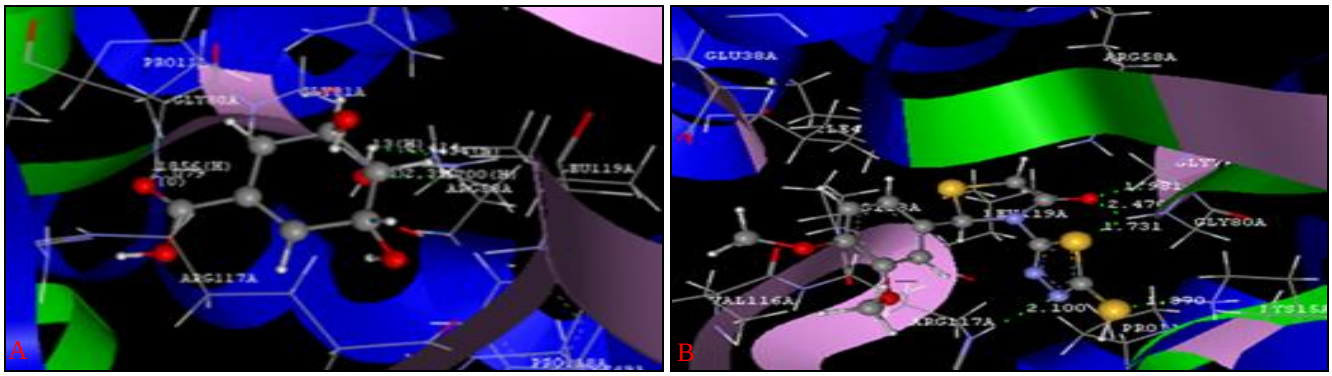


FIG. 2(A) AND 2(B): HYDROGEN BONDING INTERACTIONS OF SHIKIMATE WITH GLY80, ARG58 (2A) AND OF (4J) WITH LYS15, GLY80, GLY81, ARG117 IN THE ACTIVE SITE OF SK (PDB CODE: 2IYQ) RESPECTIVELY. (SHOWN IN GREEN DOTTED LINES)

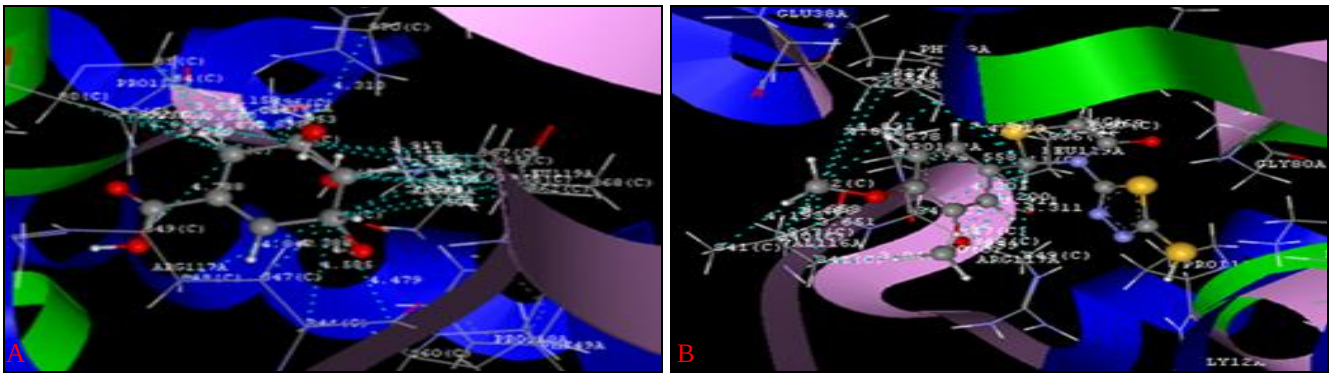


FIG. 3(A) AND 3(B): HYDROPHOBIC BONDING INTERACTIONS WITH LEU119, PRO11, GLY80, GLY81, ARG117 IN THE DOCKED MOLECULE OF SHIKIMATE (3A) AND ARG117, LEU119 IN THE DOCKED MOLECULE OF 4J (3B) IN THE ACTIVE SITE OF SK (PDB CODE: 2IYQ) RESPECTIVELY. (SHOWN IN CYAN BLUE DOTTED LINES)

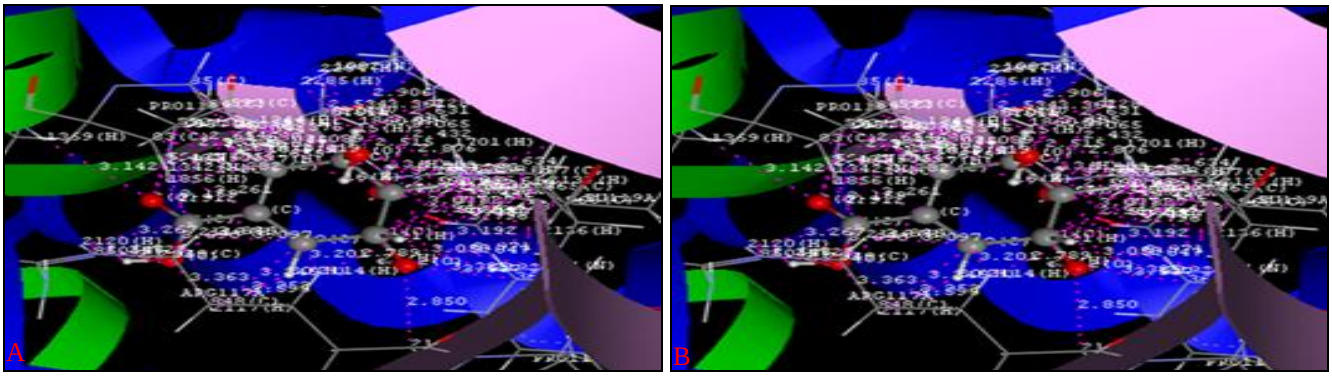


FIG. 4(A) AND 4(B): VANDER WAAL'S INTERACTIONS WITH GLY81, LYS15, ARG58, ARG117, ARG136, PRO11, GLY80, LEU119 IN THE DOCKED MOLECULE OF SHIKIMATE (4A) AND PRO11, LYS15, ARG58, GLY81, GLY80, ARG117, LEU119 IN THE DOCKED MOLECULE OF 4J (4B) IN THE ACTIVE SITE OF SK (PDB CODE: 2IYQ) RESPECTIVELY. (SHOWN IN PINK DOTTED LINES)

TABLE 4: DOCK SCORE OF DESIGNED MOLECULES

Compound	Dock Score
4a_3D_opt_P28	-63.5932
4b_3D_opt_P12	-58.8934
4c_3D_opt_P24	-47.9985
4d_3D_opt_P25	-48.1644
4e_3D_opt_P6	-48.3388
4f_3D_opt_P13	-44.6439
4g_3D_opt_P27	-48.4869
4h_3D_opt_P4	-54.1242
4i_3D_opt_P2	-45.8149
4j_3D_opt_P30	-60.9487
Shikimate_opt_P6	-54.2207

***In-silico* Drug-Likeness and Toxicity Predictions:** Currently, several approaches have been developed to assess drug-likeness of bioactive compounds based on topological descriptors, fingerprints of molecular structure or other properties such as molecular weight, water solubility, and cLogP.

admetSAR, a free online server was used to predict ADMET properties of 2-phenyl- 3-(5-sulfanyl-1, 3, 4-thiadiazol-2-yl)-1,3-thiazolidin-4-one derivatives. Bioactivity of the series was evaluated using an online server database, Molinspiration and calculated drug-likeness scores of all compounds were compared with the standard drug. ADMET properties, as derived from the admetSAR server, reveal that all molecules except 4h had better Human Intestinal Absorption (HIA) score than the control molecules, Isoniazid (INH) and Ciprofloxacin (CIP). Greater HIA denotes that the compound could be better absorbed from the intestinal tract upon oral administration. The penetration through the Blood-Brain Barrier (BBB) came out to be best for 4g but was not higher than the control molecule (0.9764 versus 0.9895, resp.).

When it comes to predicting the efflux by P-glycoprotein (P-gp), all molecules came out to be non-substrate and non-inhibitor of P-gp similar to our control molecule INH. AMES toxicity test is employed to know whether a compound is mutagenic or not. Though control INH comes out to be toxic, all the molecules displayed negative AMES toxicity test which means that the molecules are non-mutagenic. The carcinogenic profile also revealed that the ligands were non-carcinogenic similar to the control molecule. All molecules showed lower acute oral toxicity than the control INH. Important information obtained from the admetSAR server was the computed LD_{50} dose in a rat model. Comparing the LD_{50} doses, a compound with a lower dose is more lethal than the compound having higher LD_{50}. From our observation, we found that all molecules had higher LD_{50}, compared to the control INH. **Table 5** illustrates the various ADMET parameters obtained from the admetSAR tool.

Molecular properties of the synthesized compounds were calculated using Molinspiration software to satisfy Lipinski's rule of five, which is essential for rational drug design as shown in **Table 6.** In the current study, all the compounds exhibited drug-like characteristics based on Lipinski's rule of 5 that determines if the compound, has certain pharmacological or biological activity, to make it an orally active drug in humans. The molecular weights of all thiadiazolyl-thiazolidinone derivatives were found to be less than 500 Daltons, and thus these molecules are anticipated to be easily transported, diffused and absorbed as compared to large molecules. Several Number of hydrogen bond acceptors (O and N atoms) and

number of hydrogen bond donors (NH and OH) in the synthesized compounds (4a-j) were in accordance with the Lipinski's rule of five *i.e.* less than 10 and 5 respectively.

TABLE 5: VARIOUS ADMET PARAMETERS OF THE SYNTHESIZED MOLECULES OBTAINED FROM ADMETSAR TOOL

Compound Code	HIA	BBB	P-glycoprotein Substrate/ Inhibition	AMES toxicity	Carcinogeni -city	Acute Oral Toxicity	LD_{50} in rats
Isoniazid	0.9892	0.9895	NS/ NI	Toxic	NC	0.8032	2.0713
Ciprofloxacin	0.9786	0.7298	S/ NI	Toxic	NC	0.6186	2.5356
4a	0.9903	0.9012	NS/ NI	Nontoxic	NC	0.6029	2.3543
4b	1.0000	0.9681	NS/ NI	Nontoxic	NC	0.5593	2.3994
4c	0.9968	0.9375	NS/ NI	Toxic	NC	0.6008	2.3938
4d	0.9929	0.9752	NS/ NI	Nontoxic	NC	0.6367	2.5281
4e	0.9897	0.9751	NS/ NI	Nontoxic	NC	0.5895	2.5384
4f	0.9876	0.9749	NS/ NI	Nontoxic	NC	0.5880	2.5835
4g	0.9949	0.9764	NS/ NI	Nontoxic	NC	0.6207	2.4321
4h	0.9766	0.9717	NS/ NI	Nontoxic	NC	0.6173	2.5036
4i	0.9959	0.9454	NS/ NI	Toxic	NC	0.5979	2.3575
4j	0.9955	0.9012	NS/ NI	Nontoxic	NC	0.5611	2.4128

S-Substrate, NS-Non-substrate, NI-Non-inhibitor, NC- Non-carcinogenic

For all molecules, the calculated log P values were below 5 which is an indication for good water solubility. The topological polar surface area (TPSA) is calculated from number of oxygen and nitrogen atoms and by hydrogen atoms attached to them. Thus, the TPSA mimics the hydrogen bonding characteristic for a compound. TPSA is a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration correlating well with the admetSAR studies. Lipophilicity (log P value) and polar surface area (PSA) values are two important properties for the prediction of oral bioavailability of drug molecules. All molecules show TPSA values of less than 140Å indicating good intestinal absorption. Drug-likeness characterization indicated that all compounds obey Lipinski's rule of five and Veber's rule of less than 10 rotatable bonds. Thus these molecules are anticipated to be easily transported, diffused and absorbed and are likely to be orally bioavailable.

TABLE 6: MOLECULAR PROPERTIES OF THE SYNTHESIZED COMPOUNDS CALCULATED USING MOLINSPIRATION

Compound Code	Mol. Wt.	No. of Atom	H-Bond Acceptor n ON	TPSA	H-Bond Donor n OHNH	No. of rotating bond	Log P	N Violation
Isoniazid	137.14	10	4	68.01	3	1	-0.97	0
Ciprofloxacin	331.35	24	6	74.57	2	3	-0.7	0
4a	311.41	19	5	66.32	1	2	2.07	0
4b	325.44	20	5	55.33	0	3	2.61	0
4c	340.41	21	7	91.92	0	3	2.51	0
4d	329.86	19	4	46.09	0	2	3.23	0
4e	374.31	19	4	46.09	0	2	3.36	0
4f	313.40	19	4	46.09	0	2	2.67	0
4g	309.44	19	4	46.09	0	2	3.00	0
4h	311.82	19	4	45.04	0	2	2.52	0
4i	340.41	21	7	91.92	0	3	2.46	0
4j	355.47	22	6	64.56	0	4	2.20	0

The bioactivity scores of the synthesized compounds are compared with the standard drug based on GPCR ligand, ion channel modulator, nuclear receptor ligand, a kinase inhibitor, protease inhibitor, enzyme inhibitor in **Table 7**. A molecule having bioactivity score more than 0.00 is most likely to exhibit considerable biological activities, while values −0.50 to 0.00 are expected to be moderately active and if score is less than -0.50, it is presumed to be inactive.

The results reveal that the physiological actions of thiadiazolyl-thiazolidinone derivatives involve mechanism inhibiting some enzymes which

substantiates our design principle of inhibiting Shikimate kinase. The bioactivity score of compounds is suggestive of moderate interaction with the drug target. The most promising compound as per the bioactivity scores was identified to be molecule (4a). The compounds showed better bioactivity scores on comparison with standard Isoniazid but less bioactivity scores than standard Ciprofloxacin taken for the study.

TABLE 7: BIOACTIVITY SCORES OF THE SYNTHESIZED COMPOUNDS CALCULATED USING MOLINSPIRATION CHEMINFORMATICS SOFTWARE

Compound code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Isoniazid	-1.39	-1.45	-1.05	-2.33	-1.23	-0.66
Ciprofloxacin	0.12	-0.04	-0.07	-0.19	-0.20	0.28
4a	-0.27	-0.06	-1.22	-0.92	-0.78	-0.27
4b	-1.15	-1.03	-1.43	-1.55	-0.98	-0.36
4c	-1.19	-0.96	-1.45	-1.54	-1.00	-0.42
4d	-1.19	-0.99	-1.53	-1.69	-1.06	-0.38
4e	-1.32	-1.08	-1.56	-1.81	-1.16	-0.43
4f	-1.21	-1.11	-1.41	-1.59	-1.05	-0.41
4g	-1.25	-1.08	-1.55	-1.71	-1.08	-0.41
4h	-1.13	-0.93	-1.45	-1.48	-0.99	-0.26
4i	-1.19	-1.01	-1.38	-1.44	-1.00	-0.46
4j	-1.00	-0.96	-1.25	-1.38	-0.86	-0.34

CONCLUSION: In summary, using a systematic iteration of design, a series of 2-phenyl- 3-(5-sulfanyl-1, 3, 4-thiadiazol-2-yl)-1, 3-thiazolidin-4-one derivatives based on the molecular framework of thiadiazole and thiazolidinone were synthesized and evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv.

The biological data corroborate with the docking studies. The *in-vitro* antitubercular activity of compounds based on MIC values revealed that compounds 4a, 4b, 4g, and 4j showed good activity with MIC of 12.5 – 1.6 µg/ml. Compound 4j with MIC of 1.6 µg/ml was successfully identified with good docking scores and also drug-likeness values. This compound provides a potential new lead for further studies against tuberculosis. Studies for synergy with rifampicin are in progress.

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