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(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(substituted-benzylidene)-2-(pyridine-4-yl)thiazolidine-4-one as antitubercular agent: Their microwave assisted synthesis and molecular docking study

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Abstract: Present work describe the synthesis of a new series of (*Z*)-3-(4-(benzo[*d*]thiazol-2-ylthio) phenyl)-5-benzylidene-2-(pyridine-4-yl) thiazolidine-4-one **(4a-j)** from 3-(4-(benzo[*d*]thiazol-2-ylthio) phenyl)-2-(pyridine-4-yl) thiazolidine-4-one **(3)** via Knoevenagel condensation using conventional heating and microwave irradiation as environmentally begin approach. Microwave-stimulated synthetic route offers divers advantages such as reaction rate acceleration, less by-product, higher yield and reproducibility in the final product. The structures of all synthesized compounds were characterized on the basis of elemental analysis and spectral method (IR, ^{1}H, ^{13}C NMR & Mass). The bioactive assay showed that derivative **4f** displayed encouraging antitubercular activity in vitro against *Mycobacterium tuberculosis H37Rv* using MABA method in primary screening. Furthermore, docking study has been performed with Enoyl-[acyl-carrier-protein] reductase of *M. Tuberculosis* (PDB ID: 4COD) showed good binding interactions with docking score -7.972.

Keywords: Microwave, thiazolidine-4-one, antimycobacterial, molecular docking

Introduction

In the current scenario, the increasing rate of bacterial resistance to clinical antimicrobial agents is the major problem that facing the world today. In the case of *Mycobacterium Tuberculosis*, isoniazid (INH) and rifampicin (RIF) resistant *M. Tuberculosis*, was the most commonly observed type [1]. This requires the development of its alternatives and there is a real need to discover new drug entities with high efficiency towards pathogens and less toxicity,

which may be different from available resistant drugs. The synthesis of heterocyclic hybrids recognized in the field of medicinal chemistry due to their wide applicability. Microwave-assisted heating under controlled conditions has been shown to be an invaluable technology [2] for medicinal chemistry and drug discovery [3] applications since it often dramatically reduce reaction times, typically from days or hours to minutes or even seconds. The elegance of the reaction, high yield, short time span, simplified work-up procedure and eco-friendly conditions are the main advantages of the method and so that the Microwave assisted organic synthesis have revolutionized organic synthesis [4].

The literature studies revel that thiazolidine-4-one has been recognized to possess potent diverse activities with high reactivity [5-11]. The thiazolidine-4-dione ring has become a pharmacologically important class of heterocyclic compounds since the introduction of various glitazones into clinical use for the treatment of type II diabetes and diabetic complications. The chemical modification of this ring has constantly resulted in compounds with the broad spectrum of pharmacological activities. More over literature showed that many medicinal chemists have synthesized thiazolidine-4-one based newer scaffolds to evaluate better antitubercular potency [12-17]. In this accordance, we have directed our synthetic protocol emerging thiazolidine-4-one based potent antimycobacterial agents and were subjected to primary *in vitro* antimycobacterial activity. The synthesis of heterocyclic hybrids has been recognized in the field of medicinal chemistry because of their wide applicability. Under the framework of green chemistry, an expeditious procedure for the synthesis of pyridine analogous contributing thiazolidine-4-one and benzothiazole via Knoevenagel condensation to afford titled compounds using microwave irradiation to offer the new biologically active candidate with the improved potency that compared with standard drugs, is described in this study. The comparative study of non-conventional microwave induced synthetic approach with conventional heating approach has also been done. We have carried out *in silico* molecular docking study of targeted compounds with enoyl-[acyl-carrier-protein] reductase of *M. Tuberculosis* (PDB ID: 4COD) [18] to understand the binding interaction of targeted compounds.

Materials and Method

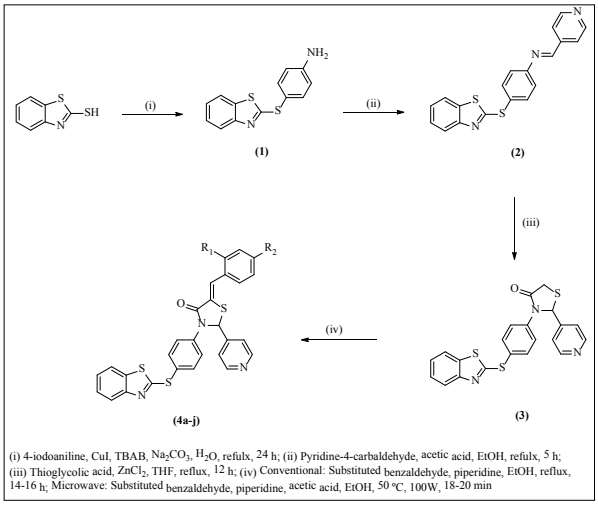
Laboratory Chemicals were supplied by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are uncorrected. The progress of reaction is monitored by thin-layer chromatography (TLC) plates (silica gel G). The IR spectra were obtained on Thermo scientific Nicolet iS10 FT-IR spectrometer (KBr pellets). The ^{1}H NMR & ^{13}C NMR spectra were collected on a Bruker Avance II 400 spectrometer using TMS as the internal standard in DMSO-d_6. Elemental analysis of the newly synthesized compounds was carried out on Carlo Erba 1108 analyzer. The mass spectra were recorded by Waters, Q-TOF micro mass (ESI-MS), SAIF, Chandigarh. The non-conventional reactions were conducted in a ‘‘QPro-M Modified Microwave Synthesis System’’ manufactured by Questron Technologies Corporation, Ontario L4Z 2E9 Canada. *In silico* molecular docking studies were carried out using Glide (grid-based ligand docking) program incorporated in the Schrödinger molecular modeling package by Maestro 11.0.

Experimental

Chemistry

4-(Benzo[d]thiazol-2-ylthio)aniline ***(1)*** was synthesized as described in the literature [19].

Synthetic route for compounds (4**a-j)**



Synthesis of (E)-N-(4-(benzo[d]thiazol-2-ylthio)phenyl)-1-(pyridin-4-yl)methanimine ***(2)***

To a solution of 4-(benzo[*d*]thiazol-2-ylthio) aniline **(1)** (1.0 mmol) in ethanol (3.5 mL), pyridine-4-carbalehyde (1.0 equal) and 2-3 drops of glacial acetic acid was added at room temperature and heated the reaction mixture at reflux temperature for about 5 hours. The course of the reaction was monitored by TLC (using ethylacetate: hexane, 5:5). After completion of the reaction, the resulting solution was cooled to room temperature and the precipitated solid was filtered under suction, washed with cold ether and recrystallized from hot ethanol to obtained pure **(2)**.

Yield 77 %; m.p. 147-149 ^{o}C; IR (KBr) ν cm^{-1}: 3008 (C-H), 1618 (C=N), 1263 (C=S); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.71 (s, 1H, N=CH), 8.75-8.01(m, 4H, Ar-H, pyridine), 7.88-7.16 (m, 8H, Ar-H).

Synthesis of 3-(4-(benzo[d]thiazol-2-ylthio) phenyl)-2-(pyridin-4-yl)thiazolidin-4-one ***(3)***

The Schiff base **(2)** (1.0 mmol) and thioglycolic acid (1.1 Equiv) were taken in a 25 mL round-bottomed flask containing 9.0 mL dry THF and (0.01 Equiv) $ZnCl_2$. The content of the flask was refluxed on a water bath for 12 hrs. After completion of reaction (TLC monitored using 2.5:7.5, EtOAc:Hexane), the reaction mass was allowed to cooled at room temperature and concentrated under reduce pressure, followed by trituration with 20% sodium bicarbonate solution to remove unreacted acid. The solution was filtered to collect solid. The obtained crude product was recrystallized using ethanol.

Yield 71 %; m.p. 179-181 ^{o}C; IR (KBr) ν cm^{-1}: 3057, 2964 (C-H), 1697 (C=O), 1595 (C=N), 1310 (C-S), 1177 (C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.56-7.78 (m, 4H, Ar-H, pyridine), 7.77-7.15 (m, 8H, Ar-H), 7.08 (s, 1H, N-CH-S), 4.39 (s, 2H, S-CH_2).

General procedure for synthesis of ***(4a-j)***

Conventional method

The thiazolidinedione **(3)** (1.0 mmol) and substituted benzaldehyde (1.0 Equiv) were dissolved in 8.5 mL EtOH. To this solution, piperidine (0.5 Equiv) were added at room temperature. The mixture was heated and stirred at 80 ºC for 14-16 h. The course of the reaction was monitored by TLC (using EtOAc: hexane, 5:5). After completion of reaction, a mixture was cooled to room temperature, diluted with ice-cold water and extracted with EtOAc (3 X 10 mL). The oragnic layer was washed with ice cold water, brine solution, separated, dried over Na_2SO_4, and concentrated under vacuum to an obtaion crude product. The resulting solid was recrystallized from ethanol to obtained pure **(4a-j)**.

Microwave method

To a suspension of thiazolidinone (3) (1.0 mmol) and substituted benzaldehyde (1.0 Equiv) in 8.5 mL EtOH, glacial acetic acid (0.05 Equiv) and piperidine (0.05 Equiv) were added. The reaction mixture was then introduced to the microwave oven and was irradiated for 18-20 min at 50 ºC (100 W) while monitoring the

course of the reaction by TLC (using EtOAc: hexane, 5:5). After completion of reaction, a mixture was cooled to room temperature and poured into the ice to obtain **(4a-j)** as solid. The resulting precipitated product was filtered off and was purified by recrystallization from ethanol.

Table-1 Comparison of conventional heating and non-conventional microwave technique

Compound No.	R_1	R_2	Conventional Method		Microwave irradiation	
			Yield %	Reaction time (hours)	Yield %	Reaction time (min)
1	-		83	24	-	
2	-		77	05	-	
3	-		71	12	-	
4a	-H	-H	63	14	85	18
4b	-H	-OH	66	14	82	18
4c	$-CH_3$	$-OCH_3$	59	16	80	20
4d	-H	$-NO_2$	58	16	75	20
4e	-H	-F	55	14	78	18
4f	-F	-H	63	14	80	18
4g	-H	-Cl	60	16	75	18
4h	-H	-Br	58	16	78	18
4i	pyridin-2-carbaldehyde		54	16	75	20
4j	pyridin-4-carbaldehyde		60	16	80	20

Physical and spectroscopic data of the final compounds

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-benzylidene-2-(pyridin-4-yl)thiazolidin-4-one ***(4a)***

m.p. 223-225 °C; IR (KBr) *v* cm^{-1}: 3042, 2850, 2733 (C-H, str.), 1993 (armoatic, combi, band), 1697 (C=O), 1600 (C=C), 1422 (vinyl C-H, bend), 705 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.45-6.79 (m, 17H, Ar-H), 6.25 (s, 1H, CH=C), 5.86 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 168.74 (C=N), 165.22 (C=O), 162.80, 159.63, 151.09, 147.97, 147.03, 146.65, 140.91, 137.52, 131.64, 130.04, 129.64, 128.57, 127.18, 119.80, 118.59 (aromatic ring); Anal. found (calc.) for $C_{28}H_{19}N_3OS_3$: C, 65.96 (65.99); H, 3.73 (3.76); N, 8.27 (8.24); ESI–MS: m/z Calculated 509.07, found $[M + H]^+$ 510.08.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(4-hydroxybenzylidene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4b)***

m.p. 257-259 °C; IR (KBr) *v* cm^{-1}: 3404 (O-H, str.), 3035, 2849, 2746 (C-H, str.), 2000 (armoatic, combi, band), 1698 (C=O), 1601 (C=C), 1423 (vinyl C-H, bend), 706 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 13.83 (b, 1H, OH, disappeared on D_2O exchange), 8.43-6.78 (m, 16H, Ar-H), 6.21 (s, 1H, CH=C), 5.91 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 169.14 (C=N), 166.21 (C=O), 163.46, 159.58, 150.93, 147.71, 147.04, 146.75, 139.95, 137.47, 131.16, 130.07, 129.15, 128.52, 127.09, 119.82, 118.57 (aromatic ring); ESI–MS: m/z Calculated 525.06, found $[M + H]^+$ 526.06.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(4-methoxybenzylidene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4c)***

m.p. 280-283 °C; IR (KBr) *v* cm^{-1}: 3040, 2852, 2736 (C-H, str.), 1995 (armoatic, combi, band), 1696 (C=O), 1603 (C=C), 1420 (vinyl C-H, bend), 700 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.51-6.58 (m, 16H, Ar-H), 6.23 (s, 1H, CH=C), 5.89 (s, 1H, N-CH-S), 3.76 (s, 1H, $-OCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 168.24 (C=N), 165.18 (C=O), 162.85, 159.59, 150.89, 147.47, 147.21, 146.62, 139.89, 137.52, 130.74, 130.04, 129.12, 128.45, 127.18, 119.78, 118.63 (aromatic ring) 58.52 (OCH_3); Anal. found (calc.) for $C_{29}H_{21}N_3O_2S_3$: C, 64.54 (64.57); H, 3.92 (3.89); N, 7.79 (7.82); ESI–MS: m/z Calculated 539.08, found $[M + H]^+$ 540.07.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(4-nitrobenzylidene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4d)***

m.p. 289-291 °C; IR (KBr) *v* cm^{-1}: 3039, 2850,

2731 (C-H, str.), 1997 (armoatic, combi, band), 1698 (C=O), 1598 (C=C), 1417 (vinyl C-H, bend), 710 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.45-6.91 (m, 16H, Ar-H), 6.21 (s, 1H, CH=C), 5.93 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 169.17 (C=N), 166.08 (C=O), 151.72 (C-NO_2), 162.75, 159.91, 147.32, 147.02, 146.79, 139.91, 137.67, 130.74, 131.23, 129.25, 128.45, 127.18, 119.88, 118.52 (aromatic ring); ESI–MS: m/z Calculated 554.05, found $[M + H]^+$ 555.06.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(4-fluorobenzylidene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4e)***

m.p. 249-251 °C; IR (KBr) *ν* cm^{-1}: 3042, 2850, 2742 (C-H, str.), 1995 (armoatic, combi, band), 1699 (C=O), 1600 (C=C), 1421 (vinyl C-H, bend), 710 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.47-6.81 (m, 16H, Ar-H), 6.20 (s, 1H, CH=C), 5.85 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 168.49 (C=N), 165.22 (C=O), 162.77, 160.09, 151.69, 148.24, 147.20, 146.62, 140.16, 137.56, 131.61, 130.04, 129.12, 128.45, 126.83, 120.37, 118.33 (aromatic ring); Anal. found (calc.) for $C_{28}H_{18}FN_3OS_3$: C, 63.77 (63.74); H, 3.42 (3.44); N, 7.99 (7.96); ESI–MS: m/z Calculated 527.06, found $[M + H]^+$ 528.07.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(2-fluorobenzylidene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4f)***

m.p. 265-267 °C; IR (KBr) *ν* cm^{-1}: 3038, 2852, 2740 (C-H, str.), 1992 (armoatic, combi, band), 1697 (C=O), 1601 (C=C), 1425 (vinyl C-H, bend), 708 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.49-6.92 (m, 16H, Ar-H), 6.23 (s, 1H, CH=C), 5.88 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 168.45 (C=N), 165.25 (C=O), 162.71, 160.11, 151.65, 148.28, 147.23, 146.59, 140.19, 138.06, 132.13, 130.31, 129.09, 128.51, 126.83, 119.76, 118.81 (aromatic ring); ESI–MS: m/z Calculated 527.06, found $[M + H]^+$ 528.07.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(4-chlorobenzylidene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4g)***

m.p. 247-250 °C; IR (KBr) ν cm^{-1}: 3040, 2850, 2739 (C-H, str.), 1996 (armoatic, combi, band), 1698 (C=O), 1600 (C=C), 1421 (vinyl C-H, bend), 708 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.48-6.68 (m, 16H, Ar-H), 6.20 (s, 1H, CH=C), 5.90 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 169.09 (C=N), 165.23 (C=O), 162.80, 159.61, 150.93, 147.42, 147.01, 146.72, 139.90, 137.51, 130.72, 130.04, 129.11, 128.83, 127.18, 119.78, 118.60 (aromatic ring); Anal. found (calc.) for $C_{28}H_{18}ClN_3OS_3$: C, 61.79 (61.81); H, 3.36 (3.33); N, 7.75 (7.72); ESI–MS: m/z Calculated 543.08, found $[M + H]^+$ 544.08.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(4-bromobenzylidene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4h)***

m.p. 289-291 °C; IR (KBr) ν cm^{-1}: 3042, 2850, 2735 (C-H, str.), 1997 (armoatic, combi, band), 1698 (C=O), 1600 (C=C), 1425 (vinyl C-H, bend), 710 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.52-6.78 (m, 16H, Ar-H), 6.20 (s, 1H, CH=C), 5.85 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 168.24 (C=N), 165.18 (C=O), 162.85, 159.59, 150.89, 147.47, 147.21, 146.62, 139.89, 137.52, 130.74, 130.04, 129.12, 128.45, 127.18, 119.78, 118.63 (aromatic ring); ESI–MS: m/z Calculated 586.98, found $[M + H]^+$ 588.01.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-2-(pyridin-4-yl)-5-(pyridin-4-ylmethylene)-thiazolidin-4-one ***(4i)***

m.p. 272-275°C; IR (KBr) ν cm^{-1}: 3045, 2852, 2734 (C-H, str.), 1995 (armoatic, combi, band), 1699 (C=O), 1605 (C=C), 1423 (vinyl C-H, bend), 708 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.57-7.12 (m, 16H, Ar-H), 6.24 (s, 1H, CH=C), 5.88 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 168.39 (C=N), 165.20 (C=O), 162.87, 159.91, 150.67,

145.23, 146.39, 147.84, 147.01, 146.62, 139.89, 137.52, 130.74, 130.04, 129.22, 128.45, 127.07 (aromatic ring); ESI–MS: m/z Calculated 510.06, found $[M + H]^+$ 511.06.

(Z)-3-(4-(benzo[d]thiazol-2-ylthio)phenyl)-5-(pyridin-2-ylmethylene)-2-(pyridin-4-yl) thiazolidin-4-one ***(4j)***

m.p. 246-249 °C; IR (KBr) ν cm^{-1}: 3043, 2851, 2733 (C-H, str.), 1994 (armoatic, combi, band), 1697 (C=O), 1602 (C=C), 1421 (vinyl C-H, bend), 708 (C-S, str.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.59-7.11 (m, 16H, Ar-H), 6.25 (s, 1H, CH=C), 5.89 (s, 1H, N-CH-S); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 168.37 (C=N), 165.23 (C=O), 162.81, 159.93, 150.72, 145.24, 146.45, 147.81, 147.03, 146.71, 139.86, 137.50, 130.71, 130.07, 129.25, 128.46, 127.09 (aromatic ring); Anal. found (calc.) for $C_{27}H_{18}N_4OS_3$: C, 63.49 (63.51); H, 3.52 (3.55); N, 10.99 (10.97); ESI–MS: m/z Calculated 510.06, found $[M + H]^+$ 511.07.

Biology

*In vitro antimycobacteri*al *activity against M. tuberculosis H_{37}Rv strain*

All compounds were evaluated for in vitro antimycobacterial activity against *Mycobacterium tuberculosis H_{37}Rv* in 7H9GC ± 0.05% broth medium by Microplate Alamar Blue Assay (MABA) method [20-21], where 7H9GC is Middlebrook 7H9 base with 0.2% glycerol + 0.1% casitone + 10% OADC enrichment. All the synthesized compounds were evaluated for their potency at concentration 50 µM in the initial screen. Compounds exhibiting <90% inhibition in the primary evaluation were not evaluated further, where as compounds exhibiting growth inhibition of ≥90% in the primary screen at 50 µM were planned to retest at the lower concentration. The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls and compared the results with the standard drugs, isoniazid and rifampicin. The results of this activity are described in Table 2.

Table- 2 Primary MABA MIC result (µM) of compounds **4a-j** against *M. tuberculosis H_{37}Rv*

Compound No.	% Inhibition	MIC µM
3	74	>100
4a	69	>100
4b	71	>100
4c	13	>100
4d	95	>100
4e	98	<50
4f	100	<50
4g	99	<50
4h	10	>100
4i	100	<50
4j	99	<50
Isoniazid	99	0.25
Rifampicin	99	40

In-silico studies

Molecular Docking

The *in vitro* activity result was supported worthwhile incorporating it with *in silico* studies. To validate the obtained antimycobacterial activity data and to provide understandable evidence to predict binding mode and approximate binding energy of a compound to a target in the terms of ligand-protein interaction, all synthesized compounds were docked against an enoyl-[acyl-carrier-protein] reductase protein of *M. tuberculosis* (PDB ID: 4COD) [18] as a biological target for docking study of newly synthesized compounds. *In silico* molecular docking studies were carried out using Glide (grid-based ligand docking) program incorporated in the Schrödinger molecular modeling package by Maestro 11.0. The crystal structure of the protein was

retrieved from PDB (www.pdb.org). The structure of 4COD contains 269 amino acids, co-crystal ligand *N*-((3R,5S)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin- 3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide and NAD. The protein crystal structure was further optimized and minimized using protein preparation wizard using default settings to rectifying PDB structure for docking process. The 3D input structures of the all targeted ligands were generated using the Marvin Suite program and were saved as SDF files. By using Lig Prep program incorporated in Maestro 11.0, other structural errors were removed and energy minimization was applied. The molecular docking evaluation was done with the help of ligand docking in glide (Maestro 11.0). The docking score, XP GScore, glide evdw (Van der Waals energy), glide ecoul (Coulomb energy), glide energy (Modified Coulomb-van der Waals interaction energy) and glide model (Model energy)

Table: 3 Docking scores of the compounds (**3** and **4a-j)** with enoyl-[acyl-carrier-protein] reductase of *M. Tuberculosis* (PDB ID: 4COD)

Comp. No.	docking score	XP GScore	glide evdw	glide ecoul	glide energy	glide emodel
3	-6.124	-6.124	-48.757	-3.75	-52.506	-69.193
4a	-5.165	-5.165	-48.939	0.011	-48.928	-64.464
4b	-6.286	-6.304	-44.649	-3.215	-47.863	-66.66
4c	-5.019	-5.019	-35.85	-0.073	-35.923	-67.484
4d	-5.604	-7.237	-43.686	-3.507	-47.193	-63.432
4e	-5.114	-5.673	-48.623	-1.888	-50.511	-68.596
4f	-7.972	-7.972	-51.572	-2.979	-54.551	-73.717
4g	-5.792	-5.792	-51.853	0.028	-51.825	-62.68
4h	-5.363	-5.363	-47.565	-3.151	-50.715	-61.506
4i	-5.303	-5.303	-49.035	0.572	-48.463	-63.216
4j	-5.068	-5.343	-45.734	-3.956	-49.691	-62.043
Isoniazid	-7.097	-7.097	-59.846	-5.832	-60.679	-75.767
Rifampicin	-6.002	-6.002	-37.77	-13.109	-50.878	-57.506

Result & Discussion

Chemistry

The simple and efficient synthesis of (*Z*)-3-(4-(benzo[*d*]thiazol-2-ylthio) phenyl)-5-benzylidene-2-(pyridine-4-yl) thiazolidine-4-one **(4a-j)** by the Knoevenagel condensation of aromatic aldehydes with 3-(4-(benzo[*d*]thiazol-2-ylthio) phenyl)-2-(pyridine-4-yl) thiazolidine-4-one **(3)** via conventional and microwave induced synthetic approach has been described (Scheme 1). The structures of compounds were established on the basis of their elemental analysis and spectral data. ^{1}H NMR spectrum of the final compound showed singlet at δ_{ppm} 6.23 for CH=C and singlet at δ_{ppm} 5.89 for N- CH-S and disappearance of 4.39 (s, 2H, S-CH_2) which showed in ^{1}H NMR spectrum of compound 3 confirming the formation of final compounds. ^{13}C NMR spectra of final compounds showed δ_{ppm} at 167.72 for C=O and 159.91 to 118.52 for corresponding aromatic carbons, confirming the formation of a final compound.

Biology

In vitro antitubercular activity

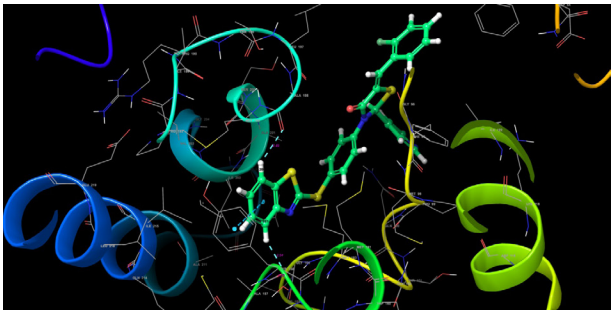
From the preliminary examination of the antimycobacterial activity results from Table 2, compound **4f, 4g, 4i and 4j** showed better activity (50 µM) against *M. tuberculosis*. Due to the better activity against tested microorganisms and mycobacteria, these compounds have been selected for further development and studies to acquire more information about structure activity relationships are in progress in our laboratories.

Docking studies

The results were described in the terms of docking score, XP GScore, glide evdw, glide ecoul, glide energy and glide emodel. A general trend was observed between the docking scores of the ligands and their corresponding MIC

values where the active compounds with high docking score, while compounds with higher MIC value were shown lower docking score. The Glide docking score of all the compounds were in the range from -7.972 to -5.019, where compound **4f** showed very good binding energy in the active pocket of receptor with -7.972 docking score, showed most potent as well with *in-vitro* antibacterial potency against *M. Tuberculosis H37Rv* with MIC value 50 µM that compared to standard drug Rifampicin (docking score -6.002, MIC 40 µM). Docking of the ligands to their receptors showed a root-mean-square deviation (RMSD) value less than 2 Å with binding energy -57.42 kcal/mol. The binding interaction of this compound showed that, compound **4f** binds with the amnio acid residue through π–π stacking with Tyr-158 along with aromatic hydrogen bonding with Met-199 and Ala-157. Figure 1 shows the fit of **4f** into the active site of the receptor.

Figure 1: 3D presentation of hydrogen bond interactions of a compound **4f** into the active site of oxidoreductase protein of *M. tuberculosis* (PDB ID: 4COD)



Conclusion

A series of newer analogs of pyridine were synthesized by incorporating thiazolidine-4-one and benzo[*d*]thiazole by Knoevenagel condensation using conventional as well as microwave irradiation, which attempt considerable advantages such as milder reaction conditions, reaction rate acceleration, less time consuming and higher chemical yields compared to those of conventional heating method. The final derivatives were assessed for their antituberculosis activity. Modification of substituents on benzene ring with various electron releasing and electron withdrawing substituents affect the activity. The *in vitro* antitubercular studies indicates that the analogs with aryl ring containing fluoro group and pyridine emerged as promising antitubercular in its primary evaluation. The compound **4f** showed their potency against *M. tuberculosis H37Rv* strain along with Glide XP docking score -7.972. This results giving the best choice for the preparation of new derivatives in order to improve antitubercular activity in future with more improved potency.

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