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MICROWAVE IRRADIATED SYNTHESIS, BIOLOGICAL EVALUATION AND MOLECULAR DOCKING STUDIES OF 3-((SUBSTITUTED-BENZO[D]THIAZOL-2-YLAMINO)METHYL)-5-(PYRIDIN-4-YL)-1,3,4-OXADIAZOLE-2(3H)-THIONE

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Keywords:

Mannich base, Microwave, Antimicrobial, Antimycobacterial, Molecular docking, *In silico* ADME

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ABSTRACT: A series of new Mannich base derivatives were designed, synthesized by conventional and non-conventional microwave method, compared and evaluated for their antimicrobial and anti-mycobacterial activity. Structures of the newly synthesized compounds were assigned on the basis of elemental analysis, IR, 1H NMR, 13C NMR and mass spectral studies. The bioactive assay showed that Mannich base derivative 1c displayed encouraging anti-tubercular activity *in vitro* against Mycobacterium tuberculosis H37Ra using MABA method in primary screening. The antibacterial and antifungal efficacy of these derivatives using broth micro dilution method, showed potency for 1c against *Escherichia coli*, 1g against *Staphylococcus aureus*, *Candida albicans* and 1j against *Candida albicans* in comparison with reference drugs. Furthermore, docking study has been performed for three different PDBs (3JZF, 4NZ9 and 2WHF) of different strains that showed good binding interactions. Moreover, the synthesized compounds were also analyzed for ADME properties and showed potential to build up as good oral drug candidates.

INTRODUCTION: In the current scenario, the increasing rate of bacterial resistance to clinical antimicrobial agents is the major problem that facing world today. For example, fluoroquinolones and third and fourth-generation cephalosporins resistant *Escherichia coli* [1], Methicillin-resistant *Staphylococcus aureus* [2], same as in the case of *Mycobacterium tuberculosis*, isoniazid (INH) and rifampicin (RIF) resistant *M. tuberculosis* [3], was the most commonly observed type. Recently, the emergence of extensively drug-resistant (XDR) strains has been observed.

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M. tuberculosis XDR strains are multi-drug resistant (MDR) isolates resistant to a fluoroquinolone or a second-line injectable drug. This requires the development of its alternatives. On the other hand, many other antimicrobial drugs are toxic too. So, 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. This provides a great opportunity to synthetic chemists for the synthesis of new compounds possessing lower cytotoxicity and with better antimicrobial potency.

Evaluating potential drug candidate with the desired biological properties is time-consuming and expensive. Consequently, increasing interest is being directed toward technologies that allow more rapid synthesis and screening of chemical substances to identify compounds with functional qualities [4].

Microwave-assisted heating under controlled conditions has been shown to be an invaluable technology for medicinal chemistry and drug discovery applications since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds [5]. Many reaction parameters can be evaluated in a few hours to optimize the desired chemistry. 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 [6, 7].

The biological activity of the compounds depends on structure of molecule and it has been observed that heterocyclic compounds are more biological active as compared to others. Pyridine and its derivatives are the important chemical compounds with tremendous applications in medicinal field. On the other hand, 1,3,4-Oxadiazoles are thermally stable and neutral heteroaromatic molecules and associated with potent pharmacological activity due to the presence of toxophoric –N=C–O– linkage displaying broad spectrum of biological activity [8]. The literature studies revels that Mannich bases are recognized to possess potent diverse activities with high reactivity [9, 10]. Mannich base derivative plays an important role in medical field with distinct pharmacological importance [11], viz., anticancer [12], antihelmintic [13], antimicrobial [14], antioxidant [15], antihistaminic [16], antitumor [17], along with other traditional activities. The synthesis of heterocyclic hybrids has been recognized in the field of medicinal chemistry because of their wide applicability. The discovery of a drug has always depended on creative thinking, good science and serendipity [18]. The biologically orientated synthesis can generate compounds with multiple activities. So, it is thoughtful and worthwhile to design new biologically active scaffold contributing pyridine, 1,3,4-oxadiazole and benzimidazole *via* Mannich base synthesis to afford multiple biological activity in single structure.

From the current literature survey, many researchers have reported the synthesis of Mannich base reaction by conventional method as well as microwave induced method [19 - 22]. Under the framework of green chemistry, an expeditious procedure for the synthesis of pyridine analogous contributing 1,3,4-oxadiazole and benzothiazole via Mannich base reaction to afford titled compounds using microwave irradiation to offer new biologically active candidate with 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. All the newly synthesized scaffolds were subjected to *in vitro* anti-microbial and anti-mycobacterial activity. We have also carried out *in silico* molecular docking study of our targeted compounds with three different PDBs to understand binding interaction of targeted compounds. *In silico* ADME properties of all synthesized compounds have also been calculated to determine their drug-likeness properties and compared it with standard drug.

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. 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 and ^{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 micromass (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: 5-(Pyridine-4-yl)-1,3,4-oxadiazole-2(3H)-thione (A) was synthesized as described in literature [23].

General Procedure for Synthesis of (1a-j):

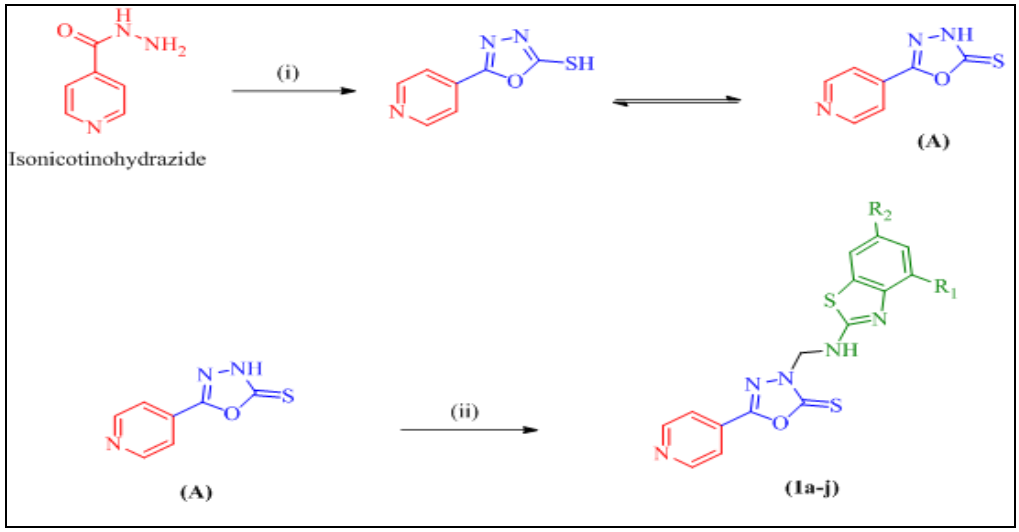
Conventional Method: The oxadiazole (A) (1.0 mmol) were dissolved in (5 mL) ethanol:DMF, 1:4.

To this solution, 37% formaldehyde (0.15mL) were added and allowed to stirre at 5-10 °C for about 10min. Then solution of substituted benzo[d] thiazole (1.0 equiv) in (5mL, ethanol: DMF, 1:4) were added drop wise to resulting reaction mixture at the same temperature with vigorous stirring. The mixture was stirred for 1 hour, followed by heating at 80 °C for 8-9 hours. The course of reaction was monitored by TLC (using DCM: Methanol, 9:1). After completion of reaction (monitored by TLC using DCM: Methanol, 9:1), reaction mass was kept overnight at room temperature. The resulting solid was collected by filtration, washed with cold petroleum ether (2 X 2.5mL), dried and recrystallized from ethanol to obtained pure 1a-j.

Microwave Method: The oxadiazole (A) (1.0 mmol) were dissolved in (5 mL) ethanol: DMF, 1:4. To this solution, 37% formaldehyde (0.15 mL) were added and allowed to stirre at 5-10 °C for about 10min. Then solution of substituted benzo[d] thiazole (1.0 equiv) in (5mL, ethanol: DMF, 1:4) were added drop wise to resulting reaction mixture at the same temperature with vigorous stirring. The mixture was stirred for 1 hour.

The reaction mixture was then introduced to microwave oven and was irradiated for 10-12 min at 75 °C (400 W) while monitoring the course of reaction by TLC (using DCM:Methanol, 9:1). Then after reaction mass was kept overnight at room temperature. The resulting solid was collected by filtration, washed with cold petroleum ether (2 X 2.5mL), dried and recrystallized from ethanol to obtained pure 1a-j.

Synthetic Route for Compounds 1a-j:



(i) Potassium-o-ethy dithicarbonate, IPA:MeOH, 80 °C, 4 hours
(ii) Conventional: 37%HCHO, substituted-2-amino-benzo[d]thiazole, DMF:EtOH, 80 °C, 8-9 hours
Microwave: 37%HCHO, substituted-2-amino-benzo[d]thiazole, DMF:EtOH, 400 W, 10-12 min

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)
A	-		90	05	-	
1a	-H	-H	63	08	85	10
1b	-H	$-CH_3$	66	08	82	10
1c	$-CH_3$	-H	59	08	80	10
1d	-H	$-NO_2$	58	09	75	12
1e	$-NO_2$	-H	55	09	78	12
1f	-H	-F	63	09	80	11
1g	-F	-H	60	08	75	10
1h	-H	-Br	58	08	78	10
1i	-H	-Cl	54	09	75	10
1j	-H	$-OCH_3$	60	08	80	10

3-((benzo[d] thiazol -2 -ylamino) methyl)-5-(pyridine-4-yl)-1,3,4-oxadiazole-2(3H) - thione (1a): m.p. 250-252 °C; IR (KBr) *ν* cm^{-1}: 3207 (N-H), 3089 (aromatic C-H), 2945 (methylene C-H, str.), 1620 (C=N), 1450 (methylene C-H, bend.), 1332 (C-N), 1295 (C=S), 1123 (cyclic ether, C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.79 (t, 1H, J=6.36 Hz, NH, disappeared on D_2O exchange), 8.60- 8.09 (m, 4H, CH, pyridine), 7.83-7.55 (m, 4H, CH, benzothiazole), 5.82 (d, 2H, J= 6.4 Hz, CH_2); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 176.82 (C=S), 170.11 (S-C=N), 156.79 (N=C-O), 150.54 (C-NO_2), 141.58 (C_1 and C_5, pyridine), 128.86 (C_2 and C_4, pyridine), 131.93 (C_3, pyridine), 123.85, 121.80, 118.94, 118.05, 117.91 (aromatic ring), 75.30 (CH_2); Anal. found (calc.) for $C_{15}H_{11}N_5OS_2$ (%): C, 52.77 (52.75); H, 3.25; (3.21); N, 20.51 (20.53); ESI–MS: m/z calculated 341.04, found $[M + H]^+$ 342.04.

3-(((6-methylbenzo[d]thiazol-2-yl)amino)methyl) -5-(pyridin-4-yl)-1,3,4-oxadiazole -2(3H) - thione (1b): m.p. 268-272 °C; IR (KBr) *ν* cm^{-1}: 3209 (N-H), 3090 (aromatic C-H), 2945 (methylene C-H, str.), 1621 (C=N), 1453 (methylene C-H, bend.), 1335 (C-N), 1298 (C=S), 1125 (cyclic ether, C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.78 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.67- 8.11 (m, 4H, CH, pyridine), 7.84- 7.54 (m, 3H, CH, benzothiazole), 5.83 (d, 2H, J = 6.4 Hz, CH_2), 2.34 (s, 3H, CH_3); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 176.12 (C=S), 169.92 (S-C=N), 156.75 (N=C-O), 141.55 (C_1 and C_5, pyridine), 129.14 (C_2 & C_4, pyridine), 131.87 (C_3, pyridine), 122.17, 120.78, 119.32, 118.94, 118.08 (aromatic ring), 74.98 (CH_2), 21.09 (CH_3); Anal. found (calc.) for $C_{16}H_{13}N_5OS_2$ (%): C, 54.07 (54.03); H, 3.69 (3.65); N, 19.70 (19.73); ESI–MS: m/z calculated 355.06, found $[M + H]^+$ 356.06.

3-(((4-methylbenzo[d]thiazol-2-yl)amino)methyl) -5-(pyridin-4-yl)-1,3,4-oxadiazole-2(3H) - thione (1c): m.p. 235-237 °C; IR (KBr) *ν* cm^{-1}: 3210 (N-H), 3093 (aromatic C-H), 2947 (methylene C-H, str.), 1624 (C=N), 1450 (methylene C-H, bend.), 1331 (C-N), 1295 (C=S), 1123 (cyclic ether, C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.82 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.65- 8.06 (m, 4H, CH, pyridine), 7.87- 7.51 (m, 3H, CH, benzothiazole), 5.80 (d, 2H, J = 6.4 Hz, CH_2), 1.98 (s, 3H, CH_3); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 177.42 (C=S), 168.98 (S-C=N), 156.93 (N=C-O), 142.05 (C_1 and C_5, pyridine), 129.28 (C_2 and C_4, pyridine), 132.08 (C_3, pyridine), 121.87, 120.48, 119.82, 118.94, 118.15 (aromatic ring), 75.12 (CH_2), 20.15 (CH_3); ESI–MS: m/z calculated 355.06, found $[M + H]^+$ 356.06.

3-(((6-nitrobenzo[d]thiazol-2-yl)amino) methyl) - 5 -(pyridin-4-yl) - 1, 3,4-oxadiazole-2(3H)-thione (1d): m.p. 288-290 °C; IR (KBr) *ν* cm^{-1}: 3215 (N-H), 3092 (aromatic C-H), 2948 (methylene C-H, str.), 1623 (C=N), 1451(methylene C-H, bend.), 1330 (C-N), 1297 (C=S), 1124 (cyclic ether, C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.81 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.64- 8.14 (m, 4H, CH, pyridine), 7.80- 7.59 (m, 3H, CH, benzothiazole), 5.81 (d, 2H, J = 6.4 Hz, CH_2); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 176.02 (C=S), 170.02 (S-C=N), 156.93 (N=C-O), 150.88 (C-NO_2), 141.58 (C_1 & C_5, pyridine), 129.17 (C_2 & C_4, pyridine), 131.67 (C_3, pyridine), 121.87, 119.58, 118.34, 117.91, 117.58, 116.75 (aromatic ring), 75.34 (CH_2); Anal. found (calc.) for $C_{15}H_{10}N_6O_3S_2$ (%): C, 46.60 (46.63); H, 2.64 (2.61); N, 21.72 (21.75); ESI–MS: m/z calculated 386.03, found $[M + H]^+$ 387.03.

3-(((4-nitrobenzo[d]thiazol-2-yl)amino) methyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole - 2(3H) - thione (1e): m.p. 285-287 °C; IR (KBr) *ν* cm^{-1}: 3210 (N-H), 3090 (aromatic C-H), 2945 (methylene C-H, str.), 1622 (C=N), 1449 (methylene C-H, bend.), 1335 (C-N), 1299 (C=S), 1127 (cyclic ether, C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.83 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.63- 8.18 (m, 4H, CH, pyridine), 7.79- 7.61 (m, 3H, CH, benzothiazole), 5.83 (d, 2H, J = 6.4 Hz, CH_2); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 176.34 (C=S), 171.09 (S-C=N), 157.03 (N=C-O), 151.02 (C-NO_2), 141.78 (C_1 & C_5, pyridine), 129.47 (C_2 and C_4, pyridine), 132.12 (C_3, pyridine), 123.65, 121.77, 119.84, 118.89, 118.08, 117.47 (aromatic ring), 75.29 (CH_2); ESI–MS: m/z calculated 386.03, found $[M + H]^+$ 387.03.

3-(((6-fluorobenzo[d]thiazol-2-yl)amino)methyl)-5 - (pyridin-4-yl)-1,3,4-oxadiazole - 2(3H)-thione (1f): m.p. 219-221 °C; IR (KBr) *ν* cm^{-1}: 3212 (N-H), 3088 (aromatic C-H), 2951 (methylene C-H, str.), 1620 (C=N), 1454 (methylene C-H, bend.), 1332 (C-N), 1297 (C=S), 1127 (cyclic ether, C-O);

^{1}H NMR (DMSO-d_6) δ (ppm): 9.81 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.65- 8.16 (m, 4H, CH, pyridine), 7.82- 7.60 (m, 3H, CH, benzothiazole), 5.82 (d, 2H, J = 6.4 Hz, CH_2); ^{13}C NMR (100MHz, DMSO-*d_6*) δ (ppm): 176.02 (C=S), 170.02 (S-C=N), 159.86 (C-F), 156.93 (N=C-O), 141.58 (C_1 & C_5, pyridine), 129.17 (C_2 and C_4, pyridine), 131.67 (C_3, pyridine), 121.93, 119.63, 118.74, 118.01, 117.89, 115.96 (aromatic ring), 75.11 (CH_2); ESI–MS: m/z calculated 359.03, found $[M + H]^+$ 360.03.

3-(((4-fluorobenzo[d]thiazol-2-yl)amino)methyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole - 2(3H) - thione (1g): m.p. 246-248 °C; IR (KBr) *ν* cm^{-1}: 3214 (N-H), 3089 (aromatic C-H), 2952 (methylene C-H, str.), 1623 (C=N), 1455 (methylene C-H, bend.), 1330 (C-N), 1298 (C=S), 1125 (cyclic ether, C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.83 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.67- 8.13 (m, 4H, CH, pyridine), 7.78- 7.57 (m, 3H, CH, benzothiazole), 5.80 (d, 2H, J = 6.4 Hz, CH_2); ^{13}C NMR (100MHz, DMSO-*d_6*) δ (ppm): 176.12 (C=S), 170.29 (S-C=N), 160.19 (C-F), 156.87 (N=C-O), 142.08 (C_1 and C_5, pyridine), 128.89 (C_2 & C_4, pyridine), 131.69 (C_3, pyridine), 121.90, 119.61, 118.75, 118.11, 117.93, 115.87 (aromatic ring), 75.19 (CH_2); ESI–MS: m/z calculated 359.03, found $[M + H]^+$ 360.03.

3-(((6-bromobenzo[d]thiazol-2-yl)amino)methyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole-2(3H) - thione (1h): m.p. 259-261 °C; IR (KBr) *ν* cm^{-1}: 3214 (N-H), 3091 (aromatic C-H), 2946 (methylene C-H, str.), 1621 (C=N), 1450 (methylene C-H, bend.), 1332 (C-N), 1295 (C=S), 1125 (cyclic ether, C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.81 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.65- 8.16 (m, 4H, CH, pyridine), 7.80- 7.62 (m, 3H, CH, benzothiazole), 5.81 (d, 2H, J = 6.4 Hz, CH_2); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 176.3 (C=S), 171.06 (S-C=N), 157.03 (N=C-O), 141.62 (C_1 & C_5, pyridine), 128.97 (C_2 and C_4, pyridine), 131.45 (C_3, pyridine), 122.27, 121.8, 119.64, 118.74, 117.9 (aromatic ring), 115.73 (C-Br), 75.22 (CH_2); ESI–MS: m/z calculated 481.95 , found $[M + H]^+$ 482.9.

3-(((6-chlorobenzo [d]thiazol-2-yl) amino) methyl) -5-(pyridin-4-yl)-1,3,4-oxadiazole-2(3H)-thione (1i): m.p. 259-261 °C; IR (KBr) *ν* cm^{-1}: 3215 (N-H), 3090 (aromatic C-H), 2945 (methylene C-H, str.), 1620 (C=N), 1453 (methylene C-H, bend.), 1330 (C-N), 1292 (C=S), 1123 (cyclic ether, C-O); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.82 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.67- 8.14 (m, 4H, CH, pyridine), 7.82- 7.60 (m, 3H, CH, benzothiazole), 5.82 (d, 2H, J = 6.4 Hz, CH_2); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 175.83 (C=S), 171.21 (S-C=N), 156.98 (N=C-O), 142.82 (C_1 and C_5, pyridine), 130.57 (C_2 and C_4, pyridine), 129.64 (C-Cl), 132.45 (C_3, pyridine), 121.97, 120.43, 119.56, 118.88, 117.68 (aromatic ring), 75.09 (CH_2); ESI–MS: m/z calculated 375.0, found $[M + H]^+$ 376.0.

3-(((6-methoxybenzo[d]thiazol - 2- yl) amino) methyl) -5-(pyridin-4-yl)-1,3,4-oxadiazole-2(3H)-thione (1j): m.p. 290-292 °C; IR (KBr) *ν* cm^{-1}: 3214 (-N-H), 3092 (aromatic C-H), 2946 (methylene C-H, str.), 1622 (C=N), 1453 (methylene C-H, bend.), 1330 (C-N), 1295 (C=S), 1125 (cyclic ether, C-O); ^{1}H NMR (DMSO-*d_6*) δ (ppm): 9.81 (t, 1H, J = 6.36 Hz, NH, disappeared on D_2O exchange), 8.68-8.12 (m, 4H, CH, pyridine), 7.80- 7.55 (m, 3H, CH, benzothiazole), 5.81 (d, 2H, J = 6.4 Hz, CH_2), 2.73 (s, 3H, -OCH_3); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 176.42 (C=S), 170.23 (S-C=N), 156.59 (N=C-O), 141.39 (C_1 and C_5, pyridine), 129.07 (C_2 and C_4, pyridine), 131.67 (C_3, pyridine), 122.59, 121.87, 119.58, 118.34, 118.04, 117.91 (aromatic ring), 75.23 (CH_2), 59.76 (-OCH_3); Anal. found (calc.) for $C_{16}H_{13}N_5O_2S_2$ (%): C, 51.76 (51.74); H, 3.54 (3.53); N, 18.84 (18.86); ESI–MS: m/z calculated 371.05, found $[M + H]^+$ 371.05.

Biology:

***In vitro* Antimicrobial Activity:** The minimum inhibitory concentration (MIC) of the synthesized compounds was determined by the broth micro dilution method [24, 25]. DMSO was used as diluents to achieve the desired drug concentration to test standard bacterial strains. The highest dilution showing at least 99 % inhibition was considered the MIC. The MICs of all the synthesized compounds were screened against four different strains *viz.* two gram-positive bacteria; *Staphylococcus aureus* (MTCC–96) and *Streptococcus pyogenes* (MTCC–443), two gram-negative bacteria; *Escherichia coli* (MTCC–442) and *Pseudomonas aeruginosa* (MTCC–441), and for fungi, *Candida albicans* (MTCC–227), *Aspergillus niger* (MTCC–282), and

Aspergillus clavatus (MTCC–1323) were used. The susceptibility of the organisms was determined by the above mentioned method and compared with standard drugs, chloramphenicol, ciprofloxacin and norfloxacine for antibacterial where as griseofulvin and nysatine as antifungal. The results of this activity are described in **Table 2**.

TABLE 2: ANTIMICROBIAL ACTIVITY (MICS, µM) OF A & 1A-J

Compound No.	Antibacterial activity Minimal Bactericidal Concentration				Antifungal activity Minimal Fungicidal Concentration		
	E. coli MTCC 442	*P. aeruginosa* MTCC 441	*S. aureus* MTCC 96	*S. pyogenus* MTCC 443	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
	Micromolar (µM)						
A	100	250	125	125	1000	>1000	>1000
1a	125	100	250	250	1000	>1000	>1000
1b	100	100	125	125	1000	>1000	>1000
1c	50	250	100	100	>1000	>1000	>1000
1d	250	250	125	100	500	500	200
1e	200	100	100	250	>1000	250	500
1f	250	250	62.5	500	>1000	500	1000
1g	62.5	62.5	50	100	250	>1000	>1000
1h	100	200	500	500	1000	1000	1000
1i	250	250	250	250	500	>1000	>1000
1j	200	250	500	500	250	>1000	>1000
Drug	Micromolar (µM)						
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	25	25	50	50			
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

***In vitro* Antimycobacterium Activity against *M. Tuberculosis H37Rv* 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 [26, 27]. Where 7H9GC is Middlebrook 7H9 base with 0.2% glycerol+0.1% casitone+10% OADC enrichment.

TABLE 3: PRIMARY MABA MIC RESULT (µM) OF COMPOUNDS 1A-J AGAINST *M. TUBERCULOSIS* $H_{37}RV$

Compound No.	% Inhibition	MIC µM
A	0	>100
1a	66	>50
1b	6	>100
1c	100	<50
1d	65	>50
1e	10	>100
1f	21	>100
1g	3	>100
1h	16	>100
1i	0	>100
1j	30	>100
Isoniazide	99	0.25
Rifampicin	99	40

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 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, isoniazide and rifampicin. The results of this activity are described in **Table 3**.

***In-silico* Studies:**

Molecular Docking: The *in vitro* activity result was supported worthwhile incorporating it with *in silico* studies. To validate the obtained antimicrobial and 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 three different proteins. On the basis of biological study against *M. tuberculosis* strain $H_{37}Rv$, *E. coli*, and *S. aureus* we have

selected an oxido-reductase protein of *M. tuberculosis* (PDB ID: 2WHF), long peptide chain biotin carboxylase of *E. coli* (PDB ID: 3JZF) and enoyl-acyl-carrier-protein reductase of *S. aureus* (PDB ID: 4NZ9) respectively 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 all these three proteins was retrieved from PDB (www.pdb.org). The structure of 2WHF contains 413 amino acids, co-crystal ligand 1-(3-methylphenyl)-1*H*-benzimidazol-5-amine and heme along with 1.58 Å depth resolution. The Crystal structure of 3JZF having X-ray diffraction resolution 2.13 Å contains two chains, co- crystallized ligand 2-[(2-chlorobenzyl) amino]-1-(cyclohexylmethyl)- 1*H*-benzimidazole - 5 -carboxamide along with 486 amino acids. The crystal structure of 4NZ9 having depth of resolution 2.3 Å contains ligand 1-(4-methoxy-3-methylbenzyl)-5,6,7,8-tetrahydro- 1*H*-naphtho[2,3-*d*]imidazole and 279 aminoacids. 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), glide emodel (Model energy) and hydrophobic interactions between the protein and the synthesized compounds were recorded.

TABLE 4: DOCKING SCORES OF THE COMPOUNDS (A AND 1A-J) WITH LONG PEPTIDE CHAIN BIOTIN CARBOXYLASE OF *E. COLI* (PDB ID: 3JZF)

Compound No.	docking score	XP GScore	glide evdw	glide ecoul	glide energy	glide emodel
PDB ID: 3JZF						
A	-6.913	-6.917	-21.998	-2.629	-24.626	-29.59
1a	-7.713	-7.713	-47.624	-4.518	-52.142	-70.412
1b	-7.713	-7.713	-47.624	-4.518	-52.142	-70.412
1c	-8.44	-8.44	-54.376	-5.364	-59.74	-87.837
1d	-7.324	-7.324	-51.786	-5.915	-57.701	-79.372
1e	-8.208	-8.209	-42.662	-4.508	-47.171	-69.652
1f	-7.82	-7.821	-52.721	-2.447	-55.168	-79.603
1g	-8.132	-8.133	-54.653	-4.574	-59.227	-85.85
1h	-8.406	-8.407	-45.364	-6.131	-51.494	-73.051
1i	-8.099	-8.1	-48.838	-4.899	-53.737	-76.081
1j	-6.61	-6.61	-51.689	-3.483	-55.172	-70.779
Chloramphenicol	-7.814	-7.814	-50.435	-5.804	-58.89	-82.37
Ciprofloxacin	-8.982	-8.982	-57.634	-6.764	-62.07	-88.621

TABLE 5: DOCKING SCORES OF THE COMPOUNDS (A AND 1A-J) WITH ENOYL-ACYL-CARRIER-PROTEIN REDUCTASE OF *S. AUREUS* (PDB ID: 4NZ9)

Compound No.	docking score	XP GScore	glide evdw	glide ecoul	glide energy	glide emodel
PDB ID: 4NZ9						
A	-5.023	-5.027	-19.528	-1.356	-20.884	-28.181
1a	-8.048	-8.048	-35.792	-5.216	-41.009	-65.694
1b	-7.622	-7.622	-45.982	1.039	-44.943	-65.643
1c	-8.194	-8.195	-49.192	-3.557	-52.748	-77.657
1d	-8.048	-8.048	-35.792	-5.216	-41.009	-65.694
1e	-7.245	-7.246	-49.341	-3.244	-52.586	-77.023
1f	-8.205	-8.206	-45.811	-2.737	-48.548	-66.645
1g	-9.054	-9.055	-48.458	-3.569	-52.027	-78.492
1h	-7.775	-7.776	-46.835	-1.77	-48.605	-72.037
1i	-7.968	-7.969	-43.809	-2.346	-46.155	-69.858
1j	-7.019	-7.019	-41.475	-3.192	-44.667	-69.586
Chloramphenicol	-7.814	-7.814	-50.435	-5.804	-58.89	-82.37
Ciprofloxacin	-8.982	-8.982	-57.634	-6.764	-62.07	-88.621

TABLE 6: DOCKING SCORES OF THE COMPOUNDS (A AND 1A-J) WITH OXIDOREDUCTASE protein OF *M. TUBERCULOSIS* (PDB ID: 2WHF)

Compound No.	docking score	XP GScore	glide evdw	glide ecoul	glide energy	glide emodel
PDB ID: 2WHF						
A	-3.241	-3.244	-20.733	1.313	-19.42	-24.491
1a	-5.234	-5.234	-42.207	-0.757	-42.963	-63.19
1b	-5.608	-5.609	-43.041	-0.376	-43.417	-64.332
1c	-7.094	-7.094	-43.536	-6.002	-49.539	-71.625
1d	-6.594	-6.594	-46.228	-2.25	-48.478	-74.516
1e	-6.03	-6.03	-46.573	-3.349	-49.922	-77.612
1f	-5.234	-5.234	-42.207	-0.757	-42.963	-63.19
1g	-6.081	-6.081	-42.521	-3.759	-46.28	-70.45
1h	-5.478	-5.478	-43.08	-7.161	-50.241	-75.054
1i	-5.702	-5.703	-47.876	0.368	-47.507	-71.394
1j	-5.783	-5.783	-47.433	-1.154	-48.587	-72.61
Isoniazide	-5.097	-5.097	-35.846	-5.832	-41.679	-50.767
Rifampicin	-6.002	-6.002	-37.77	-13.109	-50.878	-57.506

ADME prediction: A computational study to predict ADME properties of synthesized compounds 1a-j was performed using DruLito software in accordance to determine drug likeness properties. We have calculated physiochemical properties *i.e.*, molecular weight (MW), molar refractivity logarithm of partition coefficient (iLog Po/w), Alog P, number of hydrogen bond acceptors (HBA), number of hydrogen bond donors (HBD), topological polar surface area (TPSA), number of rotatable bonds (ROTB) to forecasting Lipinski's druglikeness. The results were displayed in **Table 7** and **Table 8**.

TABLE 7: PHARMACOKINETIC PARAMETERS IMPORTANT FOR GOOD ORAL BIOAVAILABILITY OF THE SYNTHESIZED COMPOUNDS 1A-J

Comp. No.	nRB	MR	TPSA	Log k_p (cm/s) Skin permeation	AlogP	Silicos IT logS_w	% ABS
A	1	44.92	86.8	-6.71	0.373	-3.12	79.05
1a	4	91.82	129.1	-5.75	1.521	-5.81	64.46
1b	4	96.79	129.1	-5.58	1.967	-6.19	64.46
1c	4	96.79	129.1	-5.58	1.967	-6.19	64.46
1d	5	100.65	174.92	-6.14	1.734	-5.16	48.65
1e	5	100.65	174.92	-6.14	1.734	-5.16	48.65
1f	4	91.78	129.1	-5.79	1.43	-6.08	64.46
1g	4	91.78	129.1	-5.79	1.43	-6.08	64.46
1h	4	99.52	129.1	-5.74	1.973	-6.6	64.46
1i	4	96.83	129.1	-5.51	1.889	-6.4	64.46
1j	5	98.32	138.33	-5.95	1.002	-5.92	61.27
Chloramphenicol	7	74.38	115.38	-7.46	0.981	-2.38	69.19
Ciprofloxacin	3	95.25	74.57	-9.09	-1.502	-3.50	83.27
Isoniazide	2	35.13	68.01	-7.63	-1.707	-1.64	84.53
Rifampicin	5	230.18	216.66	-8.1	-1.575	-4.59	34.25

TABLE 8: LIPINSKI'S RULE OF 5 FOR DRUG LIKENESS OF THE ALL SYNTHESIZED COMPOUNDS 1A-J

Comp No.	MW (<500)	HBA(<10)	HBD (<5)	ilog$P_{o/w}$ (<5)	Mlog$P_{o/w}$ (<5)	Lipinski violations
A	179.3	3	1	1.34	0.96	0
1a	341.41	4	1	2.85	1.59	0
1b	355.44	4	1	3.13	1.84	0
1c	355.44	4	1	3.14	1.84	0
1d	386.41	6	1	2.52	0.44	0
1e	386.41	6	1	2.41	0.44	0
1f	359.4	5	1	2.93	1.72	0
1g	359.4	5	1	2.9	1.72	0
1h	420.31	4	1	3.25	1.96	0
1i	375.86	4	1	3.17	1.84	0
1j	371.44	5	1	3.16	1.04	0

RESULT AND DISCUSSION:

Chemistry: 5 - (Pyridine-4-yl) - 1, 3, 4-oxadiazole-2(3H)-thione A were prepared from isoniazide on reaction with potassium-*o*-ethyl dithiocarbonate in methanol: IPA, 1:9 as described in the literature. The synthetic route of the 3-((substituted-benzo[d] thiazol-2-ylamino)methyl)-5-(pyridine-4-yl) - 1, 3, 4-oxadiazole-2(3*H*)-thione 1a-j is outlined in **Scheme 1**. 5-(Pyridine-4-yl)-1,3,4-oxadiazole-2 (3H)-thione on reaction with substituted benzo[d] thiazole and 37% formaldehyde in ethanol: DMF, 1:4 afforded titled compounds 1a-j *via* conventional and microwave induced synthetic approach. We have carried out the MW reaction under the Q-proM modified microwave reactor.

The structures of compounds were established on the basis of their elemental analysis and spectral data. The IR spectrum of compound A showed an absorption band at 3439 cm^{-1} for N-H str. of 1,3,4-oxadiazole. ^1H NMR spectrum of A revealed double doublet at δ_{ppm} 8.25 and 7.89 for aromatic CH proton of pyridine, and δ_{ppm} 13.04 for SH proton (thiol-thion tautomerism) respectively. Appearance of band at cm-1 3207 for N-H, 3009 for aromatic C-H, 2945 for methylene C-H, str. and 1620 for C=N confirmed the formation of final compound by IR spectrum. ^1H NMR spectrum of final compound showed triplet at δ_{ppm} 9.79 for NH which disappeared on D_2O exchange, and doublet at δ_{ppm} 5.82 for CH_2 proton. ^{13}C NMR spectra of final compounds showed δ_{ppm} at 75.35 for CH_2, 176.82 for C=S and 128.86 to 117.9 for corresponding aromatic carbons, confirming the formation of a final compound.

Biology:

***In vitro* Antimicrobial Activity:** The minimum inhibitory concentration (MIC) of all the synthesized compounds were screened against four different strains *viz*. two gram-positive bacteria *Staphylococcus aureus* (MTCC–96) and *Streptococcus pyogenes* (MTCC–443), two gram-negative bacteria *Escherichia coli* (MTCC–442) and *Pseudomonas aeruginosa* (MTCC–441), and fungi, *Candida albicans* (MTCC–227), *Aspergillus niger* (MTCC–282), and *Aspergillus clavatus* (MTCC– 1323), susceptibility of the organisms was determined by the broth dilution method and compared with standard drugs, chloramphenicol, ciprofloxacin and griseofulvin. The results of this activity are described in **Table 2**. Compounds 1c with a CH_3 group at 2-position displayed promising activity with MIC values 50 μM, comparable to that of the reference drugs, chloramphenicol and ciprofloxacin against *E. coli*. Compound 1g with a -F group at 2-position showed potency at 50 μM against *S. aureus* compared to standard drug. All the other compounds were poor to moderately active. Alternatively, new Mannich derivatives were tested as potential antifungal agents. Compounds 1g and 1j possessing -F and -OCH_3 substituent on benzo[d]thiazole motif displayed significant activity with MIC value 250 μM against *C. albicans*, this was better than that of the reference drug griseofulvin.

***In vitro* Anti-Tubercular Activity:** From preliminary examination of the antimycobacterial activity results **Table 3**, compound 1c containing methyl group at ortho position on aromatic ring, showed better activity (50μM) against *M. tuberculosis.* Due to the better activity against tested microorganisms and mycobacteria, compound 1c has been selected for further development and studies to acquire more information about structure activity relationships are in progress in our laboratories.

Docking studies: The Docking studies of all the compounds were carried out using Schrödinger software to find out interaction between ligand and target protein. All the synthesized compounds were docked against three different proteins corresponding to their biological evaluation. The docking results revealed that all the compounds were energetically favorable in terms of Glide dock score (**Table 4, 5** and **6**). 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 show lower docking score.

For PDB ID: 3JZF, the Glide docking score of all the compounds were in the range from -8.44 to -6.61, where compound 1c showed very good binding energy in the active pocket of receptor with -8.44 docking score, showed most potent as well

with *in-vitro* antibacterial potency against *E. coli* with MIC value 50 µM that compared to standard drug chloramphenicol (docking score -7.814, MIC 50 µM) and ciprofloxacin (docking score -8.982, MIC 25µM). Docking of the ligands to their receptors showed a root-mean-square deviation (RMSD) value less than 2 Å with binding energy -45.187 kcal/mol. The binding interaction of this compound showed that, compound 1c binds with the amnio acid residue through π catation & π–π stacking with Lys159 along with hydrogen bonding with Gly166, Agr167 and Gly166. **Fig. 2a** shows the fit of 1c into active site of the receptor. The 2D plot of protein-ligand interaction diagram of 1c was figured out in 2b.

For PDB ID: 4NZ9, docking of the ligands to their receptors showed a RMSD value less than 2 A˚ with binding energy -54.976 kcal/mol and docking score of all the compounds were in range from -9.054 to -5.023. The docking results indicated 1g shows very good binding energy in the active pocket of receptor with docking score -9.054. The compound 1g form the interactions with amino acid residues Tyr157 through π–π stacking and hydrogen bonding with Tyr157, Ala95 and Ala198. The flouro substituent at benzene ring of most active compound 1g were more favourable for hydrophobic interactions and fitted well into the hydrophobic pocket. On the basis of activity data and docking result, it was found that 1g had potential to inhibit enoyl-acyl-carrier-protein reductase of *S. aurus.* Figure 3a shows the fit of compound 1g into active site of the receptor and the 2D plots of ligand interaction map are shown in **Fig. 3b**.

For PDB ID: 2WHF, the Glide docking score of all the compounds were in the range from -7.094 to -3.241, where compound 1c showed very good binding energy in the active pocket of receptor with -7.094 docking score, showed most potent as well with *in-vitro* antimycobacterial potency against *M. tuberculosis* with MIC value 50µM. Docking of the ligands to their receptors showed a RMSD value less than 2 Å with binding energy -49.53 kcal/mol. The binding interaction of this compound showed that, compound 1c binds with the amino acid residue through hydrogen bonding with Thr239, Thr242 and Asn177. **Fig. 4a** shows the fit of 1c into active site of the receptor. The 2D plot of protein-ligand interaction diagram of 1c was figured out in 4b.

ADME Prediction: After synthesizing final compounds 1a-j, we have evaluated ADME calculation by using reference standard compound isoniazid and rifampicin for the assessment of drug likeness as well as pharmacokinetic properties. A computational study for prediction of ADME properties and to obtain new drug-like leads generated hits were subjected to Lipinski's Rule of Five for compounds 1a-j was evaluated using DruLiTo software. The absorption (% ABS) was calculated by % ABS=109 - (0.345 X TPSA) (Zhao *et al.*, 2002). The compound 1c and 1g displayed zero violation of Lipinski's rule of five showing good druge-likeness properties and likely to be developed as an orally active drug candidate as mentioned. Most of the compounds follow the criteria for orally active drug, and therefore, these compounds may have a good potential for eventual development as oral agents.

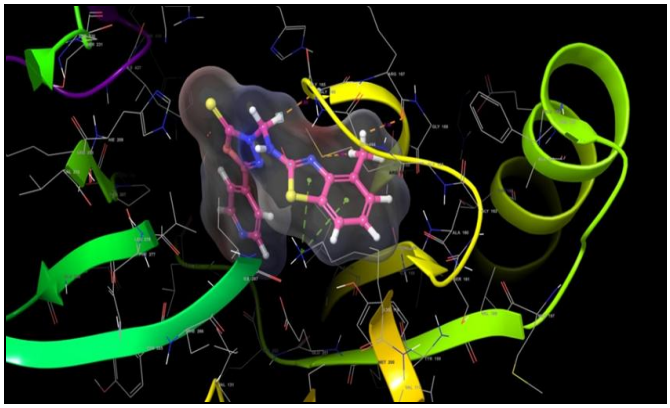


FIG. 2A: 3D PRESENTATION OF HYDROGEN BOND INTERACTIONS OF A COMPOUND 1C INTO THE ACTIVE SITE OF LONG PEPTIDE CHAIN BIOTIN CARBOXYLASE OF *E. COLI* (PDB ID: 3JZF)

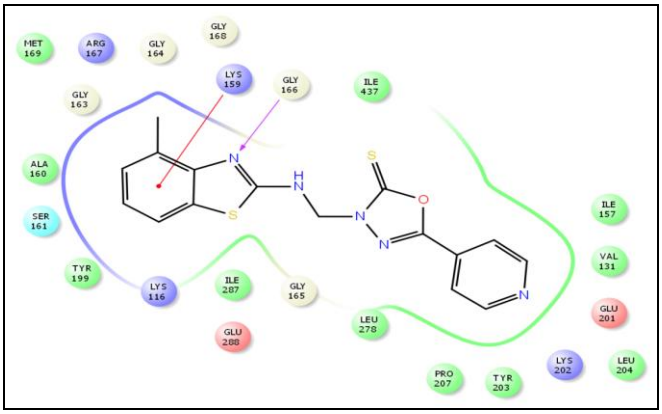


FIG. 2B: 2D PRESENTATION OF LIGAND 1C INTERACTING WITH AMINO ACID RESIDUES

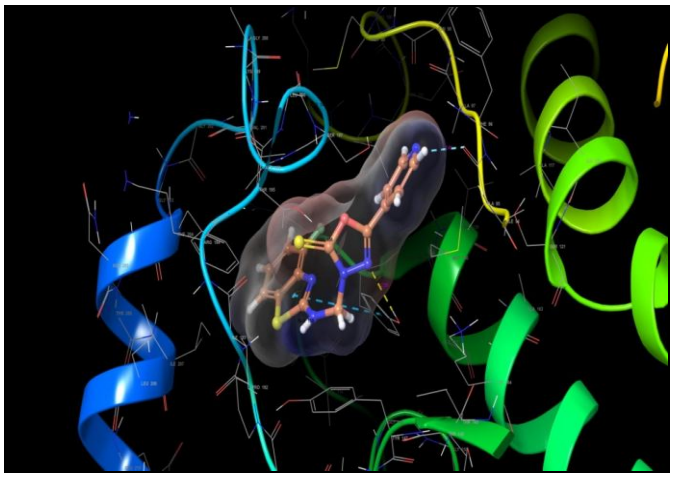


FIG. 3A: 3D PRESENTATION OF HYDROGEN BOND INTERACTIONS OF A COMPOUND 1G INTO THE ACTIVE SITE OF LONG ENOYL-ACYL-CARRIER-PROTEIN REDUCTASE OF *S. AUREUS* (PDB ID: 4NZ9)

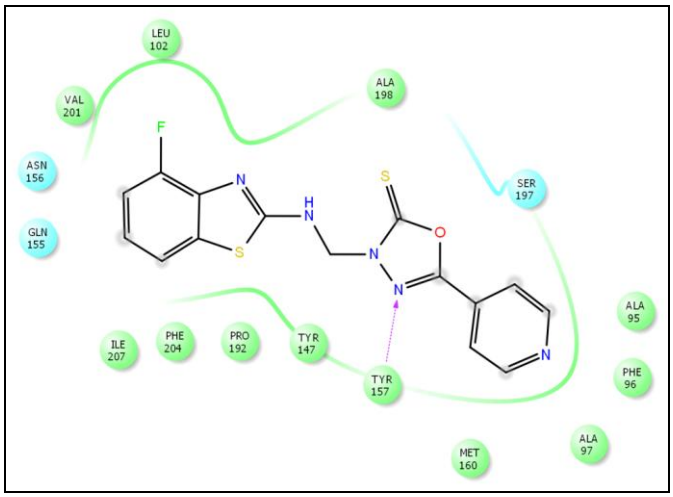


FIG. 3B: 2D PRESENTATION OF LIGAND 1G INTERACTING WITH AMINO ACID RESIDUES

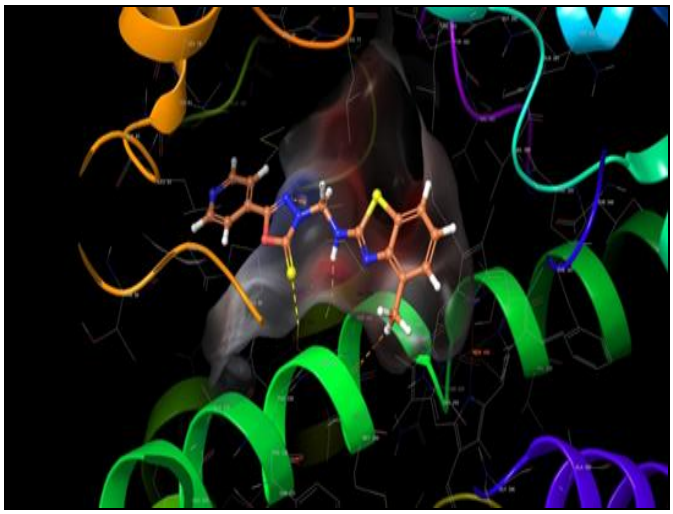


FIG. 4A: 3D PRESENTATION OF HYDROGEN BOND INTERACTIONS OF A COMPOUND 1C INTO THE ACTIVE SITE OF OXIDOREDUCTASE PROTEIN OF *M. TUBERCULOSIS* (PDB ID: 2WHF)

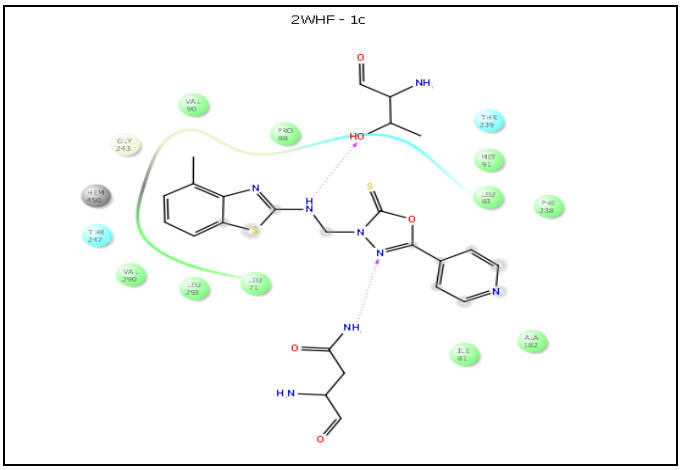


FIG. 4B: 2D PRESENTATION OF LIGAND 1C INTERACTING WITH AMINO ACID RESIDUES

CONCLUSION: A series of newer analogs of pyridine were synthesized by incorporating 1,3,4-oxadiazole and bezo[d]thiazole by Mannich base reaction 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 Mannich derivatives were assessed for their antimicrobial and antituberculosis activity. Modification of substituents on bezo[d]thiazole ring with various electron releasing and electron withdrawing substituents affect the activity.

The *in vitro* antibacterial studies indicates that the analogs with methyl group and flouro group containing bezo[d]thiazole emerged as promising antimicrobials while analogous bearing methoxy and flouro group showed better antifungal activity. It was also observed that the promising antimicrobials have proved to be better antitubercular also in its primary evaluation. The compound 1c showed their potency against *E. coli* as well as *M. tuberculosis* H37Rv strain along with Glide XP docking score -8.44 and -7.094 respectively.

The compound 1g proved potent against *S. aureus* with -9.054 docking score. The calculated ADME parameters validate for better pharmacokinetic properties giving the best choice for the preparation of new derivatives in order to improve antibacterial and anti-tubercular activity in future with more improved potency.

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