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Synthesis and Biological Evaluation of Newer Nicotinic Acid Based 2,5- disubstituted 1,3,4-Oxadiazoles

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Abstract: A new series of 2-thiobenzyl nicotinic acid based 2,5-disubstituted oxadiazoles **4a-j** was synthesized from a parent compound 2-mercapto nicotinic acid by intermolecular cyclization of 2-thiobenzyl nicotinic acid hydrazide **3** with different substituted aromatic acids in an attempt to find new bioactive molecules. The synthesized compounds were characterized by IR, NMR, and mass spectra and evaluated for *in vitro* antimicrobial activity against certain bacterial and fungal strains using the broth microdilution method and antitubercular activity against *M. tuberculosis H₃₇Rv* were performed by L. J. agar method.

Keywords: 1,3,4-oxadiazole, nicotinic acid, antibacterial activity, antifungal activity, antitubercular activity.

1. Introduction

1,3,5-oxadiazoles have been the subject of extensive research because of their involvement in the regulation of different physiological processes. In particular, compounds bearing the 1,3,4-oxadiazole nucleus is known to have unique anti HIV [1] and antitubercular [2] activities. Differently substituted oxadiazoles have also been found to have other interesting activities such as anti-inflammatory [3], analgesic [4], anti-hepatitis B viral activities [5], antiviral [6], anticancer [7] and antimicrobial [8].

On the other hand, Pyridine bases are widely used in pharmaceuticals including nicotinamide and nicotinic acid. Pyridine-3-carboxylic acid is useful as fungicidal, agricultural, antimicrobial and industrial chemicals. Nicotinic acid and amide derivatives are the subject of many research studies due to their widespread potential pharmacological activities such as antimicrobial [9], anti-inflammatory [10], analgesic [11], antiviral [12], antimycobacterial [13] and anticancer [14].

As above mentioned findings, the goal of the present study was to bind hydrazide of

2-thiobenzyl nicotinic acid with different aromatic acids via oxadiazole moiety as linker and to study the antimicrobial activity of the synthesized compounds as shown in Figure I. Therefore, as a part of our ongoing research work on synthesis of biologically important hybrid pyridine-oxadiazole scaffolds [15-17], we report here the synthesis of 2-(2-(benzylthio) pyridin-3-yl)-5-(substituted)-1,3,4-oxadiazoles (**4a-j**) and their antimicrobial activity study.

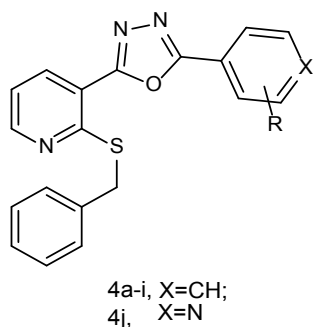


Figure. I. Structure of final nicotinic acid based oxadiazoles **4a-j**

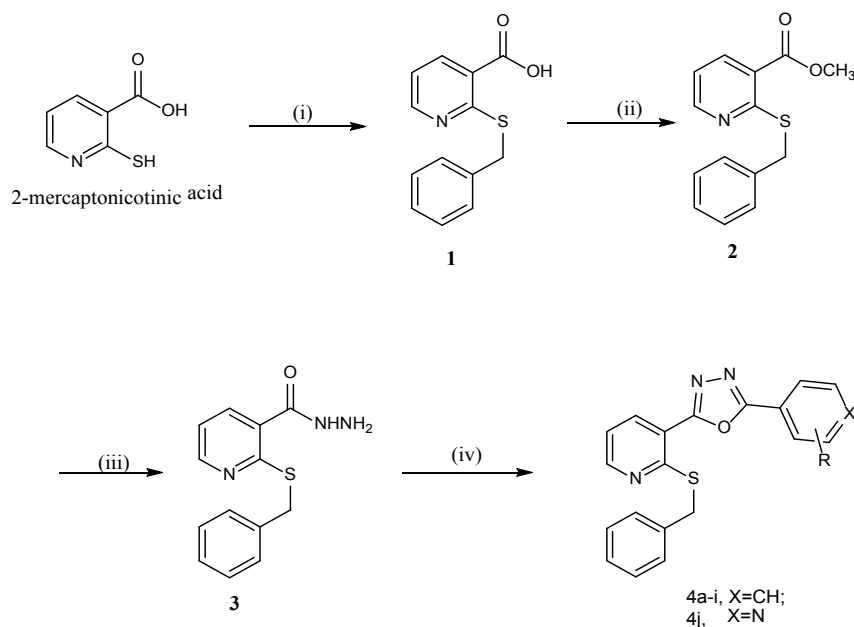
2. Results and Discussion

2.1. Chemistry

Parent compound, 2-benzylsulfanyl-nicotinic acid, was prepared according to literature procedure [18]. Final compounds 2-(2-(benzylthio) pyridin-3-yl)-5-(substituted)-1,3,4-oxadiazoles **4a-j** were synthesized by intermolecular cyclization under refluxed equimolar mixture of 2-benzylsulfanyl-nicotinic acid hydrazide **3** with acids in POCl_3 for as shown in scheme 1.

All the final compounds **4a-j** was reported for the first time and gave satisfactory analytical and spectroscopic data, which were in full accordance with their depicted structures. In particular, the FT-IR spectrum of the compound **3** exhibited broad stretching bands at around 3284 , 3318 cm^{-1} due to NH/NH_2 and strong stretching bands at 1636 cm^{-1} due to amide $\text{C}=\text{O}$ group. The ^1H NMR spectrum of **3** showed

Scheme-1. Synthetic protocol for final compounds **4a-j**



Scheme 1: (i) BnCl , KOH , isopropyl alcohol, reflux, 30 min. (ii) Methanol, conc. H_2SO_4 , refluxed 10h; (iii) $\text{N}_2\text{H}_4 \cdot 2\text{H}_2\text{O}$, methanol, refluxed 5h; (iv) POCl_3 , Ar-COOH , Reflux, 8-10 h

sharp singlet at δ 9.60 due to CONH and broad singlet at δ 4.19 due to NH₂ which vanished on D₂O exchange.

When different acids were cyclized with 2-benzylsulfanyl-nicotinic acid hydride **3** to the corresponding oxadiazoles **4a-j**, the absorption bands due to NH/NH₂ and amide carbonyl group disappeared in IR spectrum of **4a**, instead, new absorption bands due to C-O-C were observed at 1326, 1164 cm⁻¹, respectively. Furthermore, the ¹H NMR spectrum of compound **4a** showed no signal belonging to amine and amide which is strong evidence for formation of oxadiazole ring by intermolecular cyclization.

2.2. Antimicrobial activity

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan [19]. Antibacterial activity was screened against two gram positive (*Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442) and two gram negative (*Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC

2488) bacteria by using ampicillin as a standard antibacterial agent. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323, and griseofulvin was used as a standard antifungal agent.

2.2.1. Antibacterial activity and antifungal activity

The antimicrobial screening data are shown in Table 1. Results that showed MIC value less than that of standard drug were considered significant, results reveal that final compounds having **4a**, **4b**, **4h** and **4j**, showed significant bacterial inhibition against *S. aureus* while compounds **4b** and **4j** possessed pronounced activity against *P. aeruginosa* and *E. coli*, respectively. Compound **4h** substituted with fluoro atom at 4th position was found to be the most active compound at an MIC value of 62.5 μ g/ml against *S. aureus* as well as compound **4d** and **4j** also showed significant activity at MIC value of 62.5 μ g/ml against *E. coli*.

Table I. Minimum inhibitory concentrations of compounds **4a-j** (MICs, μ g/ml).

Compound	R	Gram positive bacteria		Gram negative bacteria		Fungal species		
		<i>S. aureus</i> MTCC-96	<i>S. pyogenus</i> MTCC-443	<i>E. coli</i> MTCC-442	<i>P. aeruginosa</i> MTCC-2488	<i>C. albicans</i> MTCC-227	<i>A. niger</i> MTCC-282	<i>A. clavatus</i> MTCC-323
4a	4-Cl-3-(NO ₂)	125	500	250	500	100	500	500
4b	4-NO ₂	100	100	200	62.5	1000	1000	1000
4c	4-CH ₃	250	500	500	1000	1000	1000	1000
4d	4-OCH ₃	500	1000	62.5	1000	500	1000	1000
4e	-CH ₂ C ₆ H ₅	1000	500	500	250	1000	500	200
4f	3-Br	250	250	250	250	250	1000	1000
4g	4-Cl	500	500	250	250	1000	500	500
4h	2-F	62.5	100	250	100	500	1000	1000
4i	C ₆ H ₅	1000	500	125	250	1000	1000	1000
4j	2-Cl	100	250	62.5	125	100	500	100
Ampicillin		250	100	100	100	-	-	-
Griseofulvin		-	-	-	-	500	100	100

Antifungal screening data is summarized in Table I. Results revealed that, the synthesized compounds showed variable degree of inhibition against the tested fungal species, none of the substituted oxadiazoles **4a-j** showed any significant antifungal activity except compounds **4a** and **4j** against *C. albicans*, *A. niger* and *A. clavatus*. Antifungal activity results revealed that, **4a** and **4j** was found to be most active compound at an MIC value of 100 µg/ml against *C. albicans* with comparison to griseofulvin.

2.2.2. Antitubercular activity

The investigation of antitubercular activity screening data is summarized in Table II. None of the synthesized compounds **4a-j** showed any significant antitubercular activity except compounds **4j**, which was found to exhibit comparable antitubercular activity (50 µg/ml), in comparison to rifampicin (40 µg/ml).

Table II. Minimum inhibitory concentrations (MICs, µg/ml) of **4a-j** against *M. tuberculosis* H₃₇Rv

Compound	MIC values (µg/ml) of <i>M. tuberculosis</i> H ₃₇ Rv	% Inhibition
4a	62.5	92%
4b	250	95%
4c	250	95%
4d	250	99%
4e	500	99%
4f	100	95%
4g	62.5	96%
4h	100	98%
4i	500	97%
4j	50	99%
Rifampicin	40	99%

3. Experimental

3.1. Materials, methods and instruments

All the reagents and solvents were purchased from commercial suppliers, dried and distilled before use. Melting points were determined in open capillaries on PMP-DM scientific melting point apparatus and are uncorrected. The IR spectra (in potassium bromide pellets) were recorded on a Thermo Scientific Nicolet iS10 FT-IR spectrometer and the wave numbers were given in cm⁻¹. The ¹H NMR spectra were recorded (CDCl₃/DMSO-*d*₆ mixture) on a Bruker Avance II 400 NMR spectrometer and ¹³C NMR spectra were recorded (CDCl₃/DMSO-*d*₆ mixture) on a Bruker Avance II 100 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) using TMS as an internal standard. The splitting pattern abbreviations are designed as s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra were recorded on micromass Q-T of micro (TOF MS ES⁺). Microanalysis of the compounds was done on a Heraeus Carlo Erba 1180 CHN analyzer. 2-Benzylsulfanyl-nicotinic acid was prepared according to literature procedure [18].

3.2 Synthesis of 2-benzylsulfanyl-nicotinic acid hydrazide (2) [17]

2-Benzylsulfanyl-nicotinic acid 1 (0.04 mol) and few drops of conc. H₂SO₄ as a catalyst in methanol (500 ml) was refluxed for 24 h in water bath. The reaction progress was monitored by TLC using a mixture of toluene: ethyl acetate (7:3) as the mobile phase. After the completion of the reaction, reaction mixture was poured into ice cold water and allowed to stand overnight in the freezer. Next day, the respective ester obtained was filtered, washed with 10% NaHCO₃ solution. Then wet solid ester was dissolved in methanol; to this solution was added hydrazine hydrate (0.085 mol) with constant stirring for 10 minutes. The resulting mixture was refluxed in water bath for 5 h. Conversion of reaction was periodically monitored by TLC using toluene: ethyl acetate: methanol (7:2:1) as the mobile phase and

allowed to stand overnight. The white crystals of respective hydrazide **2** formed were filtered, washed and after drying recrystallized from ethanol. Yield 65 %, m.p. 195-197 °C.

3.3 General procedure for synthesis of 2-(2-(benzylthio)pyridin-3-yl)-5-(substituted)-1,3,4-oxadiazoles. (4a-j)

A mixture of parent hydrazide **3** (1 mmol), respective acid (1 mmol) and phosphorus oxychloride (2.5 mmol) was refluxed at 100-110°C for 8-10 h. The excess solvent was distilled off under reduced pressure and the residue was quenched with ice cold water. The solid separated was filtered, washed with saturated NaHCO₃ solution and dried. The crude product was purified by recrystallization from ethanol to afford corresponding oxadiazole **4a-j**. (Scheme-1)

2-(2-(Benzylthio)pyridin-3-yl)-5-(4-chloro-3-nitrophenyl)-1,3,4-oxadiazole (4a).

Yield: 85%; m.p.: 170-172 °C; IR (KBr) cm⁻¹: 3073 (Aromatic C-H str.), 2849 (Aliphatic C-H str.), 1618 (C=N str.), 1584, 1384 (NO₂ str.), 1213, 1064 (C-O-C str.); ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 4.442 (s, 2H, SCH₂), 7.364–7.049 (m, 9H, Ar-H_{bn/py}), 8.017-7.994 (dd, 1H, 4-Hpy), 8.434-8.416 (dd, 1H, 6-Hpy), Anal. Calcd. For C₂₀H₁₃ClN₄O₃S (%): C-56.54, H-3.08, N-13.19; Found: C-56.45, H-3.03, N-13.03%; mass: m/z (M⁺) 424.

2-(2-(Benzylthio)pyridin-3-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (4b).

Yield: 75%; m.p.: 191-193 °C; IR (KBr) cm⁻¹: 3080 (Aromatic C-H str.), 2835 (Aliphatic C-H str.), 1622 (C=N str.), 1580, 1378 (NO₂ str.), 1220, 1060 (C-O-C str.); ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 4.491 (s, 2H, SCH₂), 7.371–7.032 (m, 10H, Ar-H_{bn/py}), 8.022-7.999 (dd, 1H, 4-Hpy), 8.454-8.436 (dd, 1H, 6-Hpy), Anal. Calcd. For C₂₀H₁₄N₄O₃S (%): C-61.53, H-3.61, N-14.35; Found: C-61.36, H-3.55, N-14.21%; mass: m/z (M⁺) 390.

2-(2-(Benzylthio)pyridin-3-yl)-5-(p-tolyl)-1,3,4-oxadiazole (4c).

Yield: 72%; m.p.: 185-187 °C; IR (KBr) cm⁻¹: 3060 (Aromatic C-H str.), 2855 (Aliphatic C-H str.), 1622 (C=N str.), 1220, 1056 (C-O-C str.); ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 2.256 (s, 3H, SCH₃), 4.398 (s, 2H, SCH₂), 7.384–6.869 (m, 10H, Ar-H_{bn/py}), 8.117-8.094 (dd, 1H, 4-Hpy), 8.352-8.517 (dd, 1H, 6-Hpy), Anal. Calcd. For C₂₁H₁₇N₃OS (%): C-70.17, H-4.77, N-11.69; Found: C-70.11, H-4.65, N-11.51%; mass: m/z (M⁺) 359.

2-(2-(Benzylthio)pyridin-3-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (4d).

Yield: 65%; m.p.: 200-202 °C; IR (KBr) cm⁻¹: 3065 (Aromatic C-H str.), 2875 (Aliphatic C-H str.), 1625 (C=N str.), 1215, 1066 (C-O-C str.); ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 3.856 (s, 3H, OCH₃), 4.380 (s, 2H, SCH₂), 7.478–6.875 (m, 10H, Ar-H_{bn/py}), 8.097-8.074 (dd, 1H, 4-Hpy), 8.369-8.525 (dd, 1H, 6-Hpy), Anal. Calcd. For C₁₂H₁₁N₃O₃S (%): C-67.18, H-4.56, N-11.19; Found: C-67.03, H-4.42, N-11.03%; mass: m/z (M⁺) 375.

2-Benzyl-5-(2-(benzylthio)pyridin-3-yl)-1,3,4-oxadiazole (4e).

Yield: 72%; m.p.: 182-184 °C; IR (KBr) cm⁻¹: 3077 (Aromatic C-H str.), 2872 (Aliphatic C-H str.), 1628 (C=N str.), 1226, 1042 (C-O-C str.); ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 3.725 (s, 2H, CH₂), 4.443 (s, 2H, SCH₂), 7.545–7.056 (m, 11H, Ar-H_{bn/py}), 8.067-8.044 (dd, 1H, 4-Hpy), 8.552-8.717 (dd, 1H, 6-Hpy), Anal. Calcd. For C₂₁H₁₇N₃OS (%): C-70.17, H-4.77, N-11.69; Found: C-70.02, H-4.56, N-11.45%; mass: m/z (M⁺) 359.

2-(2-(Benzylthio)pyridin-3-yl)-5-(3-bromophenyl)-1,3,4-oxadiazole (4f).

Yield: 65%; m.p.: 162-164 °C; IR (KBr) cm⁻¹: 3077 (Aromatic C-H str.), 2862 (Aliphatic C-H str.), 1632 (C=N str.), 1227, 1076 (C-O-C str.); ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 4.398 (s, 2H, SCH₂), 7.450–6.915 (m, 10H, Ar-H_{bn/}

py), 8.120-8.098 (dd, 1H, 4-Hpy), 8.325-8.500 (dd, 1H, 6-Hpy), Anal. Calcd. For $C_{20}H_{14}BrN_3OS$ (%): C-56.61, H-3.33, N-9.90; Found: C-56.55, H-3.23, N-9.84%; mass: m/z (M^+) 423.

2-(2-(Benzylthio)pyridin-3-yl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (4g).

Yield: 63%; m.p.: 178-180 °C; IR (KBr) cm^{-1} : 3055 (Aromatic C-H str.), 2875 (Aliphatic C-H str.), 1619 (C=N str.), 1235, 1082 (C-O-C str.); 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.409 (s, 2H, SCH_2), 7.652-6.988 (m, 10H, Ar- $H_{bn/py}$), 8.230-8.208 (dd, 1H, 4-Hpy), 8.429-8.604 (dd, 1H, 6-Hpy), Anal. Calcd. For $C_{20}H_{14}ClN_3OS$ (%): C-63.24, H-3.72, N-11.06; Found: C-63.12, H-3.61, N-11.01%; mass: m/z (M^+) 379.

2-(2-(benzylthio)pyridin-3-yl)-5-(2-fluorophenyl)-1,3,4-oxadiazole (4h).

Yield: 74%; m.p.: 194-196 °C; IR (KBr) cm^{-1} : 3065 (Aromatic C-H str.), 2859 (Aliphatic C-H str.), 1627 (C=N str.), 1236, 1063 (C-O-C str.), 1230 (C-F str.); 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.485 (s, 2H, SCH_2), 7.565-6.815 (m, 10H, Ar- $H_{bn/py}$), 8.235-8.113 (dd, 1H, 4-Hpy), 8.437-8.612 (dd, 1H, 6-Hpy), Anal. Calcd. For $C_{20}H_{14}FN_3OS$ (%): C-66.10, H-3.38, N-11.56; Found: C-66.01, H-3.53, N-11.45%; mass: m/z (M^+) 363.

2-(2-(Benzylthio)pyridin-3-yl)-5-phenyl-1,3,4-oxadiazole (4i).

Yield: 73%; m.p.: 205-207 °C; IR (KBr) cm^{-1} : 3064 (Aromatic C-H str.), 2863 (Aliphatic C-H str.), 1637 (C=N str.), 1219, 1031 (C-O-C str.); 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.459 (s, 2H, SCH_2), 7.404-7.011 (m, 11H, Ar- $H_{bn/py}$), 8.172-8.149 (dd, 1H, 4-Hpy), 8.657-8.822 (dd, 1H, 6-Hpy), Anal. Calcd. For $C_{20}H_{15}N_3OS$ (%): C-69.54, H-4.38, N-12.17; Found: 69.41, H-4.21, N-12.11%; mass: m/z (M^+) 345.

2-(2-(Benzylthio)pyridin-3-yl)-5-(2-chloropyridin-3-yl)-1,3,4-oxadiazole (4j).

Yield: 65%; m.p.: 210-212 °C; IR (KBr) cm^{-1} : 3046 (Aromatic C-H str.), 2854 (Aliphatic C-H

str.), 1637 (C=N str.), 1232, 1051 (C-O-C str.); 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.672 (s, 2H, SCH_2), 7.501-7.005 (m, 7H, Ar- $H_{bn/py}$), 8.082-8.049 (dd, 1H, 4-Hpy), 8.197-8.174 (dd, 1H, Hpy), 8.570-8.735 (dd, 1H, 6-Hpy), 8.654-8.819 (dd, 1H, Hpy) Anal. Calcd. For $C_{19}H_{13}ClN_4OS$ (%): C-59.92, H-3.44, N-14.71; Found: (%): C-59.85, H-3.31, N-14.65%; mass: m/z (M^+) 380.

3.5. In vitro evaluation of antimicrobial activity

The MICs of synthesized compounds were carried out by the broth micro dilution method [19]. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loop evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37°C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was sub cultured and incubated overnight at 37°C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic activity; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 $\mu g/ml$ concentration, as a stock solution. In primary screening 500, 250 and 125 $\mu g/ml$ concentrations of the synthesized drugs were taken. The active synthesized drugs

found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 µg/ml concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

3.6. In vitro evaluation of antitubercular activity

Drug susceptibility and determination of MIC of the test compounds against *M. tuberculosis H₃₇Rv* were performed by L. J. agar (MIC) method [19] where primary 1000, 500 and 250 µg/ml and secondary 200, 100, 62.5, 50, 25, 12.5, 6.25 and 3.25 µg/ml dilutions of each test compound were added liquid L. J. Medium and then media were sterilized by inspissations method. A culture of *M. tuberculosis H₃₇Rv* growing on Lowenstein-Jensen medium was harvested in 0.85% saline in bijoux bottles. All test compounds starting from a stock solution of 2000 µg/ml concentration of compounds were prepared in DMSO. These tubes were then incubated at 37°C for 24 h followed by streaking of *M. tuberculosis H₃₇Rv* (5 x 10⁴ bacilli per tube). These tubes were then incubated at 37°C. Growth of bacilli was seen after 12 days, 22 days and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis H₃₇Rv*. The concentration at which no development of colonies occurred or <20 colonies noted was taken as MIC concentration of test compound. The standard strain *M. tuberculosis H₃₇Rv* was tested with known drug rifampicin.

4. Conclusion

New 2,5-disubstituted 1,3,4-oxadiazole analogs were synthesized and have been investigated for their antimicrobial and antimycobacterial activities. From the results, it can be concluded

that Compound **4h** having 4-F substituent was found to be the most active compound at MIC value of 62.5 µg/ml against *S. aureus* as well as compound **4j** having two pyridine nucleus showed promising activity against gram positive bacteria, *S. aureus*, gram negative bacteria, *E.coli*, fungal species, *C. albicans*, and *M. tuberculosis H₃₇Rv* in coparition with standard drug. Compounds **4d** and **4j** also showed promising activity at MIC value of 62.5 µg/ml against gram negative bacteria, *E.coli*.

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