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DESIGN AND SYNTHESIS OF IMIDAZOLE BASED QUINOLINE DERIVATIVES AS ANTIMICROBIAL AND ANTITUBERCULAR AGENTS

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ABSTRACT

A synthesis of quinoline based imidazole derivatives 5a-l which have been synthesized by reaction of substituted derivatives 3a-f and substituted imidazole derivatives 4a-b in dimethyl form amide in presence of potassium bicarbonate. All the compounds were confirmed by ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, elemental analysis. All synthesized imidazole based quinoline derivatives were tested for antimicrobial activity in opposition to gram positive bacteria, gram negative bacteria and fungi. It was also evaluated for antitubercular activity.

KEYWORDS

Imidazole, 2-phenoxy quinoline, Antimicrobial activity and Antitubercular activity.

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INTRODUCTON

Tuberculosis is mainly common diseases which reside a main reason to death worldwide[1,2]. TB is cause by the *Mycobacterium tuberculosis* pathogen[3]. Worldwide one million TB patients die each and every year[4]. The development of novel drugs for TB leads to challenges for medicinal chemists. There is a requirement of more effective antitubercular agent[5]. Bacterial and fungal infection was also increase past some time. As per above information, we conclude that there is a critical requirement for a novel drug with quick action on human and different mechanism than existing drugs.

Simple heterocyclic moiety often shows amazing biological properties, constitute the most vital module of compounds of pharmaceutical

applications. Imidazole has occupied a unique position in heterocyclic chemistry. It is widely found in drugs as well as natural products. Imidazole and Imidazole based moiety have been continuously consider past few year because of their wide spectrum biological activity like anti-inflammatory, antimicrobial, antinociceptive, anticancer, antifungal and analgesic[6-9]. In recent year more interest has been devoted to synthesis quinoline based compounds for their various therapeutic and pharmacological properties[10-17]. In addition to various biological properties of quinoline based compound, additionally attached to imidazole moiety play a very important role in pharmacology. From the above fact our plan to develop a new variety of heterocycles which has contains quinoline as well as imidazole moiety.

In continuance of our research work to synthesized to heterocyclic compounds with more biological active and more effective than the existence drugs. Herein we reported new design, synthesis and biological activity of quinoline based imidazole derivatives. The synthesized compounds were confirmed by different spectroscopic methods.

MATERIAL AND METHODS

Chemistry

The chemicals were used without any extra purification. All reactions were supervised by using thin layer chromatography (TLC). TLC made by aluminum plates which has coated with silica gel 60 F254, of 0.25 mm thickness (Merck). Melting points of compounds were taken by using ThermoCal10 apparatus. (Analab Scientific Pvt. Ltd, India) and which are uncorrected. Shimadzu LCMS 2010 spectrometer were used for the mass spectra (Shimadzu, Tokyo, Japan) ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker Advance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd, Switzerland) The IR spectra were recorded using a FTIR MB 3000 spectrometer (ABB Bomem Inc., Canada/Agaram Industries, Chennai).

Synthesis of 2-(4-un (substituted) phenoxy)-6-un (substituted)-3-((2-un (substituted)-1H-imidazol-1-yl) methyl) quinoline (5a-l)

2-(4-(un) substituted phenoxy)-3-(chloromethyl)-6-(un)substituted quinoline 3a-f (1mmol), substituted imidazole 4a-b (1mmol) and K_2CO_3 (2mmol) in DMF (5mL) were transferred into a 50mL round bottom flask which attached to a condenser. The reaction mixture was heated 85^{o}C for 1.5-2 hr. The progress of the reaction was monitored by thin layer chromatography. Then reaction mixture was cooled at room temperature and the poured into ice water with continuous stirring followed by neutralization ph at 7. The separated material of 2-(4-un (substituted) phenoxy)-6-un (substituted)-3-((2-un (substituted)-1H-imidazol-1-yl) methyl) quinoline 5a-l was filtered and wash with water. The final product was recrystallized by chloroform: methanol (1:1).

3-((1H-imidazol-1-yl) methyl)-2-phenoxyquinoline (5a)

Cream solid; m.p. 234; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.23 (s, 2H, CH_2), 6.94 (d,1H of imidazole ring), 7.01 (d, 1H of Imidazole ring), 7.24-7.34 (aromatic 11H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 45.4 (N-CH_2), 120.2, 124.2, 126.3, 126.5, 127.4, 127.8, 129.2, 129.7, 131.4, 132.4, 134.3, 135.3, 135.8, 135.9, 144.2, 153.4; LC-MS: 301(M^+); anal. calcd (%) for $C_{19}H_{15}N_3O$: Calculated (found): C, 75.73(75.62); H, 5.02(5.24); N, 13.94(13.70).

3-((1H-imidazol-1-yl) methyl)-6-methyl-2-phenoxyquinoline (5b)

Cream solid; m.p. 232; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.43 (s, 3H, CH_3), 5.24 (s, 2H, CH_2), 6.92 (d,1H of imidazole ring), 7.1 (d, 1H of Imidazole ring), 7.21-7.76 (aromatic 10H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 21.34 (CH_3), 45.3 (N-CH_2), 120.0, 124.5, 126.2, 126.3, 127.3, 127.4, 129.5, 129.6, 131.4, 132.2, 134.5, 135.3, 135.7, 135.9, 144.2, 153.4; LC-MS: 315[M]$^+$; anal. calcd (%) for $C_{20}H_{17}N_3O$: Calculated (found): C, 76.17(76.34); H, 5.43(5.16); N, 13.32(13.56).

3-((1H-imidazol-1-yl) methyl)-6-methoxy-2-phenoxyquinoline (5c)

Cream solid; m.p. 236; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.82 (s, 3H, OCH_3), 5.31 (s, 2H, CH_2), 6.91 (d,1H of imidazole ring), 7.1 (d, 1H of Imidazole ring), 7.30-7.81 (aromatic 10H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 45.2 (N-CH_2), 55.1 (OCH_3), 108.6, 118.4, 119.4, 121.6, 122.7, 125.8, 126.1, 127.5, 129.7, 130.4, 136.9, 137.4, 145.6, 145.7, 156.4, 156.6; LC-MS: 331[M]$^+$; anal. calcd (%) for $C_{20}H_{17}N_3O_2$: C, 65.15; H, 4.10; N, 12.66; Found: Calculated (found): C, 72.49(72.12); H, 5.17(5.36); N, 12.68(12.36).

4-((3-((1H-imidazol-1-yl) methyl) quinolin-2-yl) oxy) benzonitrile (5d)

Cream solid; m.p. 237; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.33 (s, 2H, CH_2), 6.90 (d,1H of imidazole ring), 7.2 (d, 1H of Imidazole ring), 7.34-7.76 (aromatic 10H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 45.4 (N-CH_2), 105.4, 108.6, 118.6, 119.6, 122.4, 125.6, 126.3, 127.6, 129.6, 130.4, 136.6, 137.8, 145.5, 145.6, 156.5, 156.6; LC-MS: 326[M]$^+$; anal. calcd (%) for $C_{20}H_{14}N_4O$: Calculated (found): C, 73.61(73.52); H, 4.32(4.54); N, 17.17(17.36).

((3-((1H-imidazol-1-yl) methyl)-6-methylquinolin-2-yl) oxy) benzonitrile (5e)

Cream solid; m.p. 239; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.92 (d,1H of imidazole ring), 7.1 (d, 1H of Imidazole ring), 7.36-7.79 (aromatic 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 21.4(Ar-CH_3), 45.2 (N-CH_2), 105.2, 108.7, 118.5, 119.5, 121.4, 122.6, 125.7, 126.2, 127.4, 129.8, 130.5, 136.8, 137.6, 145.4, 145.7, 156.4, 156.8; LC-MS: 340[M]$^+$; anal. calcd (%) for $C_{21}H_{16}N_4O$: Calculated (found): C, 74.10(82.42); H, 4.74(4.94); N, 16.46(16.24).

4-((3-((1H-imidazol-1-yl) methyl)-6-methoxyquinolin-2-yl) oxy) benzonitrile (5f)

Cream solid; m.p. 237; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.80 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 6.92 (d,1H of imidazole ring), 7.1 (d, 1H of Imidazole ring), 7.35-7.74 (aromatic 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 45.1 (N-CH_2), 55.3 (Ar-OCH_3), 105.1, 108.8, 118.3, 119.6, 121.3, 122.4, 125.6, 126.0, 127.5, 127.9, 130.4, 133.6, 137.4, 145.3, 145.5, 156.3, 156.6 ; LC-MS: 356[M]$^+$; anal. calcd (%) for $C_{21}H_{16}N_4O_2$: Calculated (found): C, 70.77 (70.58); H, 4.53(4.21); N, 15.72(15.43)

3-((2-methyl-1H-imidazol-1-yl) methyl)-2-phenoxyquinoline (5g)

Cream solid; m.p. 233; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 6.92 (d,1H of imidazole ring), 7.03 (d, 1H of Imidazole ring), 7.21-7.71 (aromatic 10H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 13.0 (CH_3), 45.2 (N-CH_2), 120.0, 124.4, 126.1, 126.2, 127.3, 127.7, 129.4, 129.5, 131.1, 132.2, 134.1, 135.1, 135.6, 135.8, 144.1, 153.1; LC-MS: 315[M]$^+$; anal. calcd (%) for $C_{20}H_{17}N_3O$: Calculated (found): C, 76.17(76.38); H, 5.43(5.21); N, 13.32(13.11).

6-methyl-3-((2-methyl-1H-imidazol-1-yl) methyl)-2-phenoxyquinoline (5h)

Cream solid; m.p. 234; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.41 (s, 3H, CH_3 of imidazole ring), 2.44 (s, 3H, CH_3 of quinoline), 5.26 (s, 2H, CH_2), 6.94 (d,1H of imidazole ring), 7.03 (d, 1H of Imidazole ring), 7.22-7.77 (aromatic 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 13.0 (CH_3 of imidazole ring), 21.3 (CH_3 of quinoline ring), 45.3 (N-CH_2), 120.0, 124.5, 126.1, 126.3, 127.2, 127.6, 129.3, 129.5, 131.1, 132.0, 134.4, 135.0, 135.7, 135.9, 144.0, 153.2; LC-MS: 329[M]$^+$; anal. calcd (%) for $C_{21}H_{19}N_3O$: Calculated (found): C, 76.57(76.26); H, 5.81(5.46); N, 12.76(12.42)

6-methoxy-3-((2-methyl-1H-imidazol-1-yl) methyl)-2-phenoxyquinoline (5i)

Cream solid; m.p. 236; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 32.42 (s, 3H, CH_3 of imidazole ring), 3.80 (s, 3H, CH_3 of quinoline), 5.24 (s, 2H, CH_2), 6.92 (d,1H of imidazole ring), 7.02 (d, 1H of Imidazole ring), 7.20-7.72 (aromatic 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 13.0 (CH_3 of imidazole ring), 45.3 (N-CH_2), 55.4 (OCH_3), 120.1, 124.5, 126.0, 126.2, 127.2, 127.4, 129.4, 129.5, 131.2, 132.1, 134.4, 135.1, 135.6, 135.8, 144.1, 153.3; LC-MS: 345[M]$^+$; anal. calcd (%) for $C_{21}H_{19}N_3O_2$: Calculated (found): C, 73.03(73.14); H, 5.54(5.11); N, 12.17(12.49).

4-((3-((2-methyl-1H-imidazol-1-yl) methyl) quinolin-2-yl) oxy) benzonitrile (5j)

Cream solid; m.p. 234; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.43 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.96 (d,1H of imidazole ring), 7.2 (d, 1H of Imidazole ring), 7.39-7.73 (aromatic 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 13.10 (CH_3), 45.1 (N-CH_2), 105.3, 108.6, 118.6, 119.8, 121.0, 122.6, 125.9, 126.0, 127.4, 127.9, 130.4, 133.8, 137.1, 145.1, 145.3, 156.5, 157.5 ; LC-MS: 340[M]$^+$; anal. calcd (%) for $C_{21}H_{16}N_4O$: Calculated (found): C, 74.10(74.43); H, 4.74(4.52); N, 16.46(16.63).

4-((6-methyl-3-((2-methyl-1H-imidazol-1-yl) methyl) quinolin-2-yl) oxy) benzonitrile (5k)

Cream solid; m.p. 232; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3 of imidazole ring), 2.43 (s, 3H, CH_3 of quinoline ring), 5.30 (s, 2H, CH_2), 6.96 (d,1H of imidazole ring), 7.0 (d, 1H of Imidazole ring), 7.38-7.75 (aromatic 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 13.6 (CH_3 of imidazole ring), 21.3 (CH_3 of quinoline ring), 45.1 (N-CH_2), 105.3, 108.8, 118.6, 119.7, 121.0, 122.6, 125.8, 126.0, 127.6, 127.8, 130.4, 133.6, 137.2, 145.2, 145.3, 156.5, 157.6; LC-MS: 354[M]$^+$; anal. calcd (%) for $C_{22}H_{18}N_4O$: Calculated (found): C, 74.56(74.22); H, 5.12(5.41); N, 15.81(15.64)

4-((6-methoxy-3-((2-methyl-1H-imidazol-1-yl) methyl) quinolin-2-yl)oxy) benzonitrile (5l)

Cream solid; m.p. 235; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3 of imidazole ring), 3.81 (s, 3H, OCH_3 of quinoline ring), 5.31 (s, 2H, CH_2), 6.93 (d,1H of imidazole ring), 7.1 (d, 1H of Imidazole ring), 7.37-7.77 (aromatic 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 13.1 (CH_3), 55.5 (Ar-OCH_3), 45.2 (N-CH_2), 105.2, 108.6, 118.5, 119.6, 121.1, 122.5, 125.7, 126.0, 127.6, 127.8, 130.5, 133.7, 137.3, 145.2, 145.3, 156.4, 156.7; LC-MS: 370[M]$^+$; anal. calcd (%) for $C_{22}H_{18}N_4O_2$: Calculated (found): C, 71.34(71.56); H, 4.90(4.56); N, 15.13(15.26).

Biological Assay

***In vitro* antimicrobial activity**

All the synthesized compounds 5a-l were evaluated for antibacterial and antifungal activity. In which antibacterial activity against three gram positive bacteria (*Bacillus subtilis* MTCC 441, *clostridium tetani* MTCC 449, *streptococcus pneumonia* MTCC 1936) and three gram negative bacteria (*Escherichia coli* MTCC 227, *Salmonella typhi* MTCC 98, *Vibrio cholera* MTCC 3906) by using Ampicillin, Chloramphenicol, Ciprofloxacin as a standard drug. Antifungal activity against two fungal species (*Candida albicans* MTCC 227 and *Trichophyton rubrum*) where Nystatin and Griseofulvin use as standard drugs. The minimum inhibitory concentration (MIC) of all compounds 5a-l was determined by the broth micro dilution method according to National Committee for Clinical Laboratory Standards (NCCLS)[18]. The obtained results are presented in Table No.2.

***In vitro* antitubercular activity**

All the newly synthesized compounds were evaluated for antitubercular activity against *M. tuberculosis H$_{37}$RV* strain by using Lowenstein-Jensen medium (conventional method) as describe by Rattan[19]. The obtained results are presented in Table No.3 in the form of % inhibition. Isoniazid and Rifampicin used as the standard drugs.

RESULTS AND DISCUSSION

Chemistry

The targeted quinoline based imidazole derivatives 5a-l were synthesized as summarized in Scheme No.1. The starting material 2-(4-(un) substituted phenoxy)-3-(chloromethyl)-6-(un) substituted quinoline 3a-f were prepared by reduction followed by chlorination of 2-(4-(un)substitutedphenoxy)-6-(un)substitutedquinoline-3-carbaldehyde[20].

The final product 2-(4-un (substituted) phenoxy)-6-un (substituted)-3-((2-un (substituted)-1H-imidazol-1-yl) methyl) quinoline were synthesized using chloro-amine coupling reaction between 3a-f and 4a-b. DMF used as a solvent and potassium carbonate as a catalyst. The structure is confirm by the various spectroscopy techniques. In ^{1}H NMR spectroscopy of 5j compound: singlet at δ 3.10ppm showed methyl proton of imidazole ring. The signal at δ 2.0ppm is conformation of methylene which attached to quinoline ring. There is no NH proton, so we can confirm that chloro-amine coupling is done. The doublet at δ 6.95 and 7.05ppm is for two

proton of imidazole ring. Another nine aromatic protons are resonating at δ 7.39-7.73ppm.

BIOLOGICAL RESULTS

Antimicrobial activity

Gram +ve bacteria

The data of the MIC in against different bacteria are shown in Table No.2. Many of these compounds are show good activity. In which compound 5d [MIC=62.5] display stupendous activity, Compounds 5e and 5j [MIC=100] show tremendous activity, Compounds 5a and 5f [MIC=125] exhibit good activity in opposition to *B. subtilis* as compared to ampicillin [MIC=250]. Compounds 5b and 5e [MIC=125] demonstrate outstanding activity, Compounds 5a, 5d and 5g [MIC=200] demonstrate exquisite activity against *C.tetani* compare to ampicillin [MIC=250].

Gram -ve bacteria

In against *E.coli* compounds 5a, 5d, 5g and 5j [MIC=100] more active than other compared to ampicillin [MIC=100]. In opposition *S.typhi* compounds 5d demonstrate excellent activity. Compound 5d [MIC=62.5] demonstrate lofty activity in opponent to *S.typhi*. In opponent to *V. cholera* compound 5a show good activity.

Antifungal activity

The compounds 5a, 5d, 5i and 5j [MIC=500] demonstrate comparable activity to Griseofulvin [MIC=500] in opposition to fungal pathogen *C. albicans*. In opponent to T. rubrum 5g [MIC=500] show equivalent activity compared to Griseofulvin and Nystatin.

Antituberculosis activity

The result of anti TB activity is shown below in table XX. The compounds 5d, 5j, and 5k demonstrate exquisite results.

Table No.1: % Yield of quinoline based oxadiazole derivatives (5a-l)

S.No	Compound	R_1	R_2	R_3	M. P.	% Yield
1	5a	-H	-H	-H	234	89
2	5b	$-CH_3$	-H	-H	232	81
3	5c	$-OCH_3$	-H	-H	236	82
4	5d	-H	-CN	-H	237	77
5	5e	$-CH_3$	-CN	-H	239	79
6	5f	$-OCH_3$	-CN	-H	237	83
7	5g	-H	-H	$-CH_3$	233	88
8	5h	$-CH_3$	-H	$-CH_3$	234	78
9	5i	$-OCH_3$	-H	$-CH_3$	236	89
10	5j	-H	-CN	$-CH_3$	234	86
11	5k	$-CH_3$	-CN	$-CH_3$	232	88
12	5l	$-OCH_3$	-CN	$-CH_3$	235	82

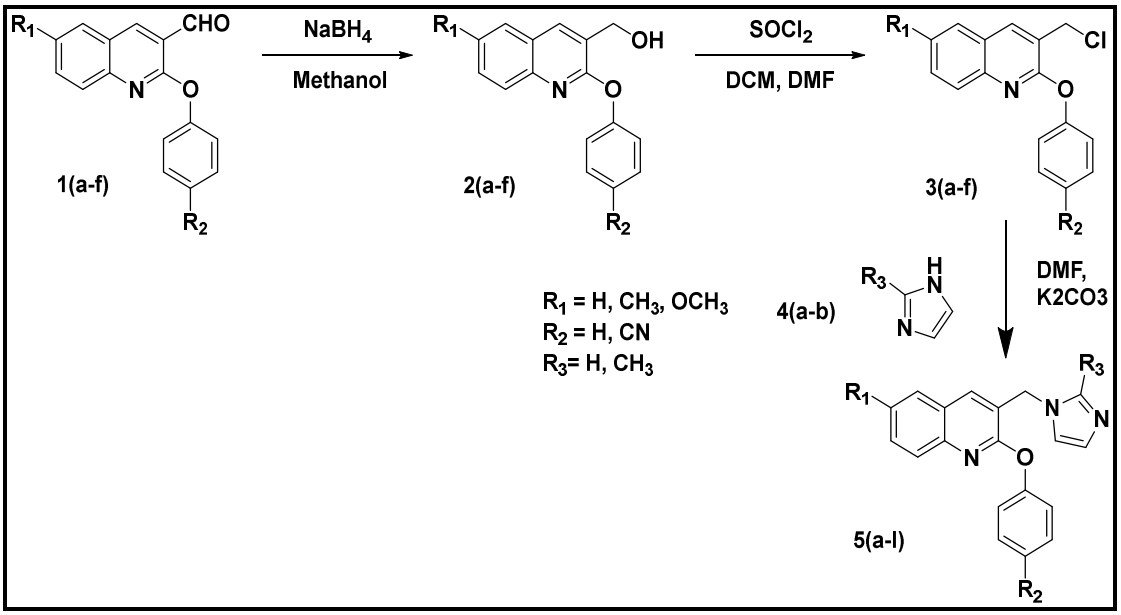
Table No.2: *In vitro* antimicrobial activity of synthesized compounds 5a-l

S.No	Compound	Gram +Ve bacteria			Gram -Ve bacteria			Fungi	
		B.S.	*C.T.*	*S.P.*	*E.C.*	*S.T.*	*V.C.*	*C.A.*	*T.R.*
1	5a	125	200	125	100	100	62.5	500	1000
2	5b	250	125	250	200	125	500	>1000	1000
3	5c	500	500	250	250	200	250	1000	>1000
4	5d	62.5	200	250	100	62.5	100	500	>1000
5	5e	100	125	200	250	125	125	1000	>1000
6	5f	125	500	250	250	125	250	>1000	1000
7	5g	250	200	200	100	100	125	1000	500
8	5h	250	250	125	200	250	250	1000	1000
9	5i	500	500	200	250	200	250	500	>1000
10	5j	100	500	250	100	100	100	500	1000
11	5k	500	250	250	250	500	250	1000	1000
12	5l	500	500	250	500	250	200	1000	1000
13	Am.	250	250	100	100	100	100	-	-
14	Ch.	50	50	50	50	50	50	-	-
15	Cip.	50	100	50	25	25	25	-	-
16	Ny.	-	-	-	-	-	-	100	500
17	Gr.	-	-	-	-	-	-	500	500

SP: *Streptococcus pneumoniae*, CT: *Clostridium tetani,* BS: *Bacillus subtilis*, ST: *Salmonella typhi*, VC: *Vibrio cholera*, EC: *Escherichia coli*, CA: *Candida albicans*, TR: Trichophytonrubrum, Ampi: Ampicillin; Cipr: Ciprofloxacin; Chlo: Chloramphenicol; Gri: Griseofulvin; Nyst: Nystatin. MTCC: Microbial Type Culture Collection Bolt value indicates compounds are more or equal potent than standard drug, - not tested, [MIC]: minimum inhibitory concentration

Table No.3: Antitubercular activity of 6a-l compounds

S.No	**METHOD**	**L.J.MEDIUM(CONVETIONAL METHOD)**		
	BECTERIA	**$H_{37}RV$**		
	CONCENTRATION	**250 µg/ml**		
	STANDARD DRUG	**ISONIAZIDE**		
	Compound	**% Inhibition**	**Compound**	**% Inhibition**
1	5a	87%	5h	68%
2	5b	30%	5i	87%
3	5c	82%	5j	96%
4	5d	98%	5k	90%
5	5e	98%	5l	62%
6	5f	65%	Isoniazid	99%
7	5g	83%	Rifampicin	98%



Scheme No.1: Synthesis of quinoline based oxadiazole derivatives (5a-l)

CONCLUSION

Some wonderful results have been obtained with fused imidazol based quinoline hybridized scaffold. Compound 5d appeared as the promising antimicrobial member within varies it shows better antitubercular activity. 5a, 5d, 5g and 5i compounds showed excellent antifungal activity against *Candida albicans*. Majority of the compounds showed excellent antibacterial activity against *Clostridium tetani* and *Bacillus subtilis*.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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