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Synthesis, antituberculosis studies and biological evaluation of new quinoline derivatives carrying 1,2,4-oxadiazole moiety

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ABSTRACT:

Tuberculosis is the infectious disease caused by *mycobacterium tuberculosis* (Mtb), responsible for the utmost number of deaths annually across the world. Herein, twenty-one new substituted 1,2,4-oxadiazol-3-ylmethyl-piperazin-1-yl-quinoline derivatives were designed and synthesized through multistep synthesis followed by *in vitro* evaluation of their antitubercular potential against Mtb WT H37Rv. The compound **QD-18** was found to be promising with MIC value of 0.5 µg/ml and **QD-19** to **QD-21** were also remarkable with MIC value of 0.25 µg/ml. Additionally, we have carried out experiments to confirm the metabolic stability, cytotoxicity and pharmacokinetics of these compounds along with kill kinetics of **QD-18**. These compounds were found to be orally bioavailable and highly effective. Altogether, these results indicate that **QD-18**, **QD-19**, **QD-20** and **QD-21** are promising lead compounds for the development of a novel chemical class of antitubercular drugs.

Keywords: Quinoline; Oxadiazole; Antitubercular activity; Cytotoxicity; Bioavailability.

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1. Introduction:

Tuberculosis (TB) continues to be a serious and potentially fatal infection with a worldwide distribution. The World Health Organization (WHO) reported TB is the ninth foremost cause of death worldwide and leading cause from a single infectious agent[1]. The high mortality rate of TB has even beaten the number of deaths caused by human immunodeficiency virus[1]. Worldwide, the mortality rate due to TB has dropped by 3% per year and new TB cases have decreased only about 2% per year[2]. Furthermore, according to an estimate one-third of the world's population is infected with a latent form of TB[3]. The appearance of multidrug-resistant TB (MDR–TB) has given a huge challenge throughout the world in the fight against TB[3]. All the above facts reveal that there is a serious need for the development of new drugs with divergent unique structure and with a mechanism of action possibly different from that of existing drugs.

Quinoline compounds are important privileged structures in medicinal chemistry due to wide medical benefits, such as anti-inflammatory[5], anticancer[6], antihypertensive[7], tyrokinase PDGF-RTK inhibiting agents[8], anti-HIV[9,10], anti-malarial[11,12] and anti-bacterial[13,14] activities. They are also known to exhibit excellent anti-TB[15] properties. For example, the USFDA approved Bedaquiline is a clinically important anti-TB drug for the treatment of MDR-TB[16]. On the other hand, it has been well recognized that 1,2,4-oxadiazole nucleus is an active pharmacophore and shows diverse biological potential[17]. It attracted researchers for development of new therapeutic agents and it also revealed the prominence of the nucleus. An idea to keep piperazine as a spacer between quinoline and 1,2,4-oxadiazole nucleus was supported from a literature survey. A variety of piperazine incorporated benzothiazinone-piperazine derivatives, nitrofuranyl methyl piperazines are anti-TB agents[18,19] and well-known antiparasitic drug piperaquine contain piperazine as a spacer is also used in combination with dihydroartemisinin to treat malaria[20].

We have designed new quinoline derivatives containing substituted 4-Piperazin-1-yl-quinoline carrying 1,2,4-oxadiazole moiety. In the present work, all the new structures have been designed on the basis of combinatorial synthesis along with keeping structural activity relationship studies in the mind which is the current trend being practiced in most of the drug discoveries. In a

continuing effort to develop new drug candidates for the treatment of TB, we herein describe the synthesis and biological activities of a series of quinoline derivatives carrying 1,2,4-oxadiazole moiety.

2. Results and Discussion

2.1. Chemical synthesis

Twenty-one new compounds containing a hybrid of substituted quinoline and 1,2,4-oxadiazole were synthesized according to the synthetic methodologies presented in the scheme (figure-1). The 3-Chloro-phenylamine was converted to 2-[(3-Chloro-phenylamino)-methylene]-malonic acid diethyl ester (**2**) by reacting with diethyl ethoxymethylenemalonate at 110 °C and subsequent cyclisation in dowtherm medium at 240 °C afforded 7-chloro-4-hydroxyquinoline (**3**). The chlorination of intermediate using $POCl_3$ at reflux temperature result in 4,7-Dichloro-quinoline (**4**) and condensation of 4,7-Dichloro-quinoline and piperazine in IPA at 95 °C result in 7-Chloro-4-piperazin-1-yl-quinoline (**5**) with excellent yield. The common intermediate, [4-(7-Chloro-quinolin-4-yl)-piperazin-1-yl]-acetonitrile (**6**) was synthesized by coupling of chloroacetonitrile with 7-Chloro-4-piperazin-1-yl-quinoline. Intermediates **7**(**a-c**) were prepared via suzuki coupling of respective boronic acids with intermediate **6** using $Pd_2(dba)_3$ catalyst and s-Phos. The intermediate **6** and **7**(**a-c**) were readily converted into corresponding hydroxy-acetamidine **8**(**a-d**) by treating with hydroxylamine in presence of suitable base. The quinoline amide derivatives **9**(**a-f**), **10**(**a-f**), **11**(**a-f**) and **12**(**d-f**) were obtained by acid amine coupling of **8**(**a-d**) with carboxylic acids in presence EDCI and HOBt with good yield. The target compounds, viz. quinoline derivatives carrying 1,2,4-oxadiazole moiety i.e., **QD-1** to **QD-21** were synthesized in good yield from their precursors by heating them with DBU at 90 °C. All the newly synthesized compounds were characterized by FTIR, ^{1}H and ^{13}C NMR and LC-MS studies.

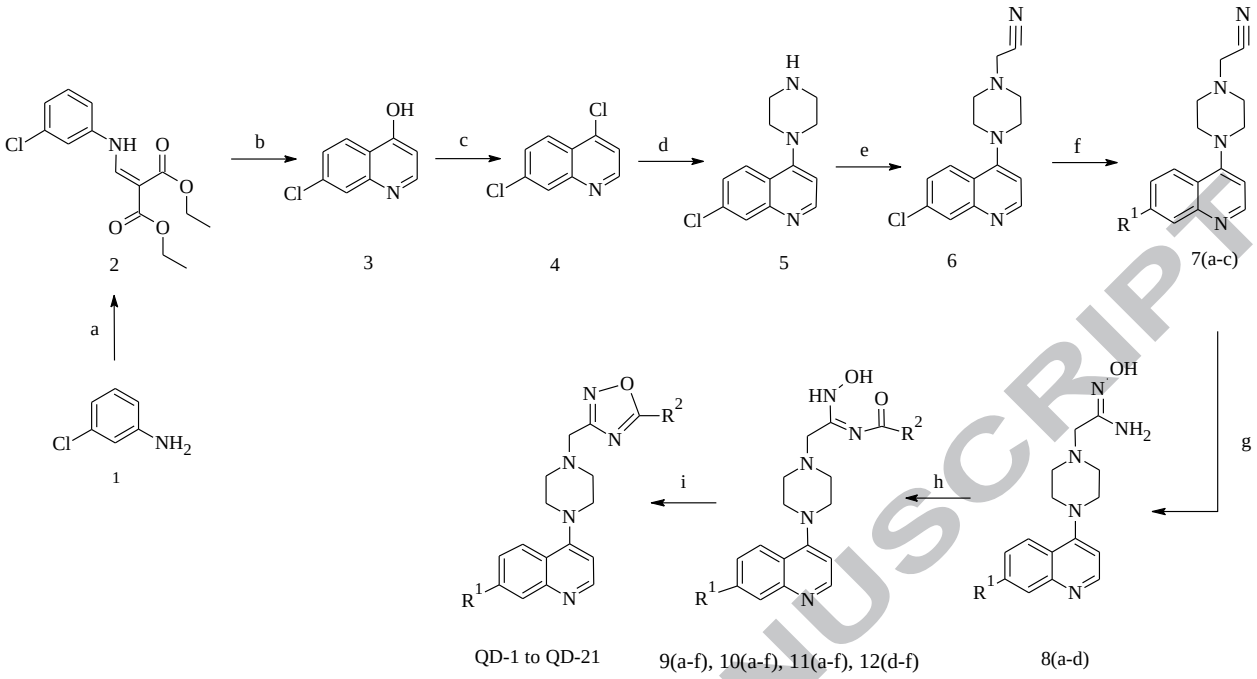


Figure 1. scheme for synthesis of quinoline derivatives carrying 1,2,4-oxadiazole.

Reagents and conditions: (a) 3-Chloro-phenylamine, diethyl ethoxymethylenemalonate, 110 °C; (b) dowtherm medium, 240 °C; (c) 7-chloro-4-hydroxyquinoline, $POCl_3$, reflux; (d) 4,7-Dichloro-quinoline, piperazine, IPA, 95 °C; (e) 7-Chloro-4-piperazin-1-yl-quinoline, chloroacetonitrile, Et_3N, ACN, DMF, RT; (f) [4-(7-Chloro-quinolin-4-yl)-piperazin-1-yl]-acetonitrile, aromatic boronic acids, $Pd_2(dba)_3$, s-Phos, K_3PO_4, 1,4-dioxane, water, 100 °C; (g) quinoline intermediate (6, 7a-c) hydroxylamine hydrochloride, $NaHCO_3$/ Et_3N, methanol, 70 °C; (h) hydroxy-acetamidine derivatives, aromatic/aliphatic acid, EDCI, HOBT, DIPEA, RT (i) amide derivatives, DBU, DMF, 90 °C.

2.2 Biology

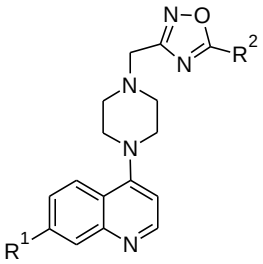
2.2.1. Antituberculosis studies

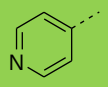
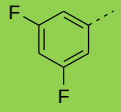
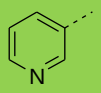
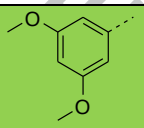
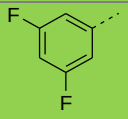
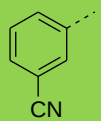
Antitubercular activity of compounds (**QD-1** to **QD-21**) was evaluated against Mtb WT H37Rv using broth micro dilution method[21]. A turbidometric assay was employed and the results were counted. Isoniazid (INH) and rifampicin (RIF) were used as standard drugs. The first dilution that shows growth inhibition is recorded as MIC (Minimum Inhibitory Concentration). The MIC (µg/ml) values of all compounds against Mtb strain H37Rv are tabulated in table-1.

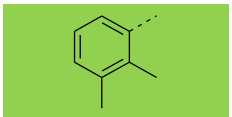
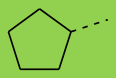
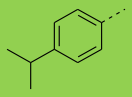
Antituberculosis screening data revealed that compound **QD-4**, **QD-5** and **QD-6** possess a promising inhibitory activity of MIC 2 µg/ml. The activity is attributed to the presence of

substituted 4-pyridine ring at position-7 of quinoline ring and occurrence of 2,3-dimethyl phenyl, cyclopentyl and 4-isopropyl phenyl at position-3 of 1,2,4-oxadiazole ring in the compounds **QD-4**, **QD-5** and **QD-6** respectively. Compound **QD-18** containing chloro group at position-7 of quinoline ring and 4-isopropyl phenyl at position-3 of 1,2,4-oxadiazole ring was found to be more potent with excellent inhibition of MIC 0.5 µg/ml. Replacing 4-pyridine ring with 3-pyridine at position-7 of quinoline has tremendously increased the activity of compounds QD-19, 20 and 21 to MIC 0.25 µg/ml. The compounds which have shown MIC <1 µg/ml were considered to be promising for further studies.

Table 1. Antitubercular activity of quinoline derivatives carrying 1,2,4-oxadiazole ring against Mtb strain H37Rv



S.No	$R^1 \rightarrow$ 		Cl	
	R^2 ↓	Compound ID (QD-XX) MIC_Mtb (µg/ml) Cytotoxicity IC_{50} (µM)		
1		QD-01 >128 -	QD-07 256 -	QD-13 32 -
2		QD-02 16 -	QD-08 64 -	QD-14 >128 -
3		QD-03 32 -	QD-09 >256 -	QD-15 64 -

4		QD-04	QD-10	QD-16	QD-19
		2	32	64	0.25
		-	-	-	>100
5		QD-05	QD-11	QD-17	QD-20
		2	128	32	0.25
		-	-	-	>50
6		QD-06	QD-12	QD-18	QD-21
		2	32	0.5	0.25
		-	-	>100	>100
7		INH[a]			
		0.015			
8		RIF[a]			
		0.03			

([a]Isoniazid (INH) and Rifampicin (RIF) were used as a control against Mtb strain H37Rv)

The lead compound **QD-18**, which recorded MIC value of 0.5 µg/mL against Mtb WT H37Rv was also tested on well characterised mono-resistant (SDR) strains of Mtb, viz. Rif-r, InH-r, SM-r, Mox-r, Kan-r and CS-r. During the assay rifampivin, isoniazid, moxifloxacin and linezolid were used as a control. The MIC (µg/ml) values are tabulated in table-2. This assay was read by colorimetric assay on day-7 using resazurin dye. **QD-18** showed encouraging MIC against mono-resistant strains of Mtb which are tabulated in table-2.

Table 2. Antitubercular Activity of QD-18 against mono-resistant (SDR) strains of Mtb

Compound ID[b]	MIC (µg/mL)					
	RMPr	INHr	SMr	KMr	MOXr[e]	CSr
QD-18	3.81	4.17	28.58	3.24	4.01	3.68
Rifampicin	>4	<0.02	0.05	<0.02	0.23	<0.02
Isoniazid	0.49	>8	1.00	0.49	0.49	3.78
Moxifloxacin	0.42	0.49	0.94	0.21	>16	0.46

Linezolid	1.68	2.33	14.08	1.91	3.65	10.34

([b]RMPr, rifampicin resistant; INHr, isoniazid resistant; SMr, streptomycin resistant; KMr, Kanamycin resistant; MOXr, moxifloxacin resistant; CSr, d-Cycloserine resistant)

Treatment of tuberculosis preferably requires a drug with a narrow spectrum such as isoniazid. All the four compounds (**QD-18**, **19**, **20** and **21**) were found to be inactive against Gram +ve and Gram -ve bacterial strains. It shows these compounds exhibit only specific activity towards *mycobacterium tuberculosis*. Vancomycin and ciprofloxacin were used as a control. The MIC (µg/ml) values against Gram +ve and Gram -ve bacteria are tabulated in table-3.

Table 3. Antimicrobial Activity of QD-18 against ESKAPE panel of bacterial stains

Compound ID	MIC (µg/mL)					
	Escherichia coli ATCC25922	Acinetobacter baumanii ATCC 19606	Staphylococcus aureus ATCC 33591	Enterococcus faecium ATCC 51559	Pseudomonas aeruginosa ATCC 15442	Klebsiella pneumoniae ATCC 700603
QD-18	>32	>32	>32	>32	>32	>32
QD-19	>32	>32	>32	>32	>32	>32
QD-20	256	512	512	64	512	256
QD-21	>32	>32	>32	>32	>32	>32
Vancomycin	>512	256	2	<1	512	512
ciprofloxacin	0.007	<1	<1	8	<1	<1

2.2.2. Cytotoxicity studies of QD-18, QD-19, QD-20 & QD-21

We evaluated the cytotoxicity of the **QD-18**, **QD-19**, **QD-20** and **QD-21** against the HepG2 cell line by MTT Cytotoxicity assay[22]. After 48 hours of plating, HepG2 cells were treated with test/ control items ranging concentration from 100-1.56 µM. The data obtained in the cytotoxicity studies of quinoline derivatives indicated a high selectivity of these compounds against Mtb. when treated for 24 h, the IC_{50} value of **QD-18**, **QD-19** and **QD-21** were found to be > 100 µM and **QD-20** was found to > 50 µM (IC_{50} values are tabulated in table-1). Astemizole was used as a control and IC_{50} value of astemizole was found to be 7.97 µM. These four compounds were selected for further experiments as these possessed the highest potency against Mtb and the lowest cytotoxicity. **QD-1** to **QD-17** compounds did not display promising antitubercular activity and consequently were excluded from the cytotoxicity studies.

2.2.3. Metabolic stability of QD-18, QD-19, QD-20 & QD-21 in Human liver microsomes

The major site of drug metabolism in the body is liver. Hence, measurement of the rate of clearance and identity of the metabolites of a drug is important. Metabolic stability of **QD-18** to **QD-21** was estimated in human liver microsomes with cofactor and without cofactor[23,24]. The comparative data of compound concentration at five time points (0, 15, 30, 60 and 120 min) were examined for all the four test compounds and for control samples those are dichofenac and imipramine. Retention of **QD-19**, **QD-20** and **QD-21** in percentage ranges between 18 to 23 % and **QD-18** has comparatively slite higher retention of 39.7 % at 120 min with cofactors. It is agreed from the comparative data tabulated in table-4 and figure-2 with cofactors also in table-5 and figure-3 without cofactors that these test compounds are metabolically stable enough to proceed further as a lead compounds.

Table 4. Metabolic stability of QD-18, QD-19, QD-20 and QD-21 in human liver microsomes with cofactors at different time intervals.

Comparative data: Metabolic stability in Human Liver microsomes - With Cofactors					
	% remaining compared to 0.0 min				
Test/ control compounds	**0.0 min**	**15 min**	**30 min**	**60 min**	**120 min**
QD-18	100.00	82.04	67.24	55.31	39.71
QD-19	100.00	65.06	47.32	31.71	18.08
QD-20	100.00	60.77	54.77	37.95	21.91
QD-21	100.00	74.11	56.82	40.08	22.98
Diclofenac	100.00	85.90	75.20	59.77	30.64
Imipramine	100.00	98.48	88.43	92.72	86.89

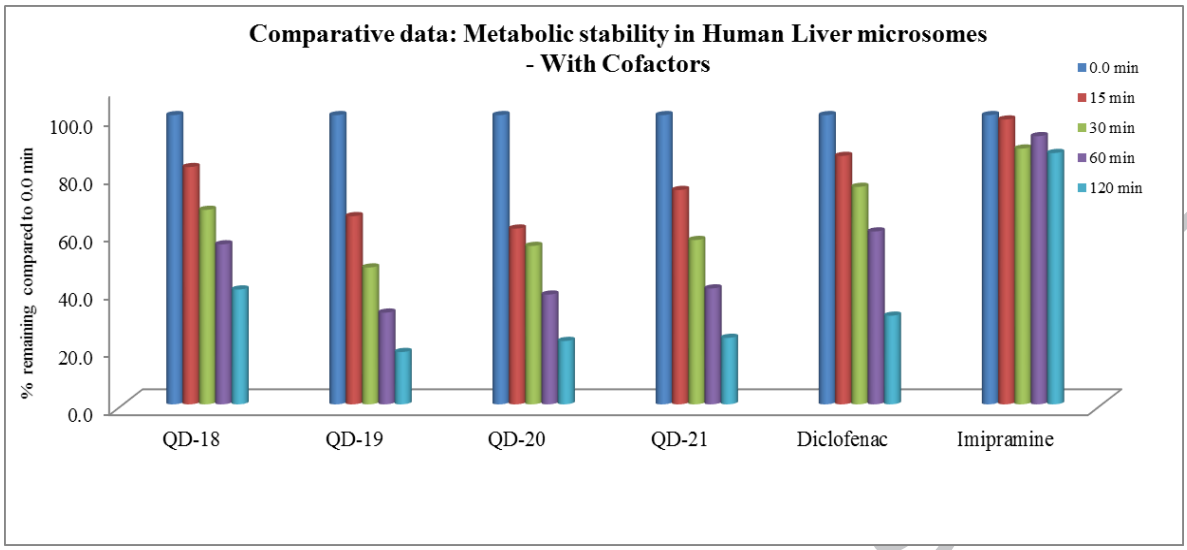


Figure 2. Graphical presentation of metabolic stability of QD-18, QD-19, QD-20 and QD-21 in human liver microsomes with cofactors at different time intervals.

Table 5. Metabolic stability of QD-18, QD-19, QD-20 and QD-21 in human liver microsomes without cofactors at different time intervals.

Comparative data: Metabolic stability in Human Liver microsomes - Without Cofactors		
% remaining compared to 0.0 min		
Test/ control compounds	**0.0 min**	**120 min**
QD-18	100.00	89.19
QD-19	100.00	77.99
QD-20	100.00	97.83
QD-21	100.00	76.54
Diclofenac	100.00	100.79
Imipramine	100.00	97.18

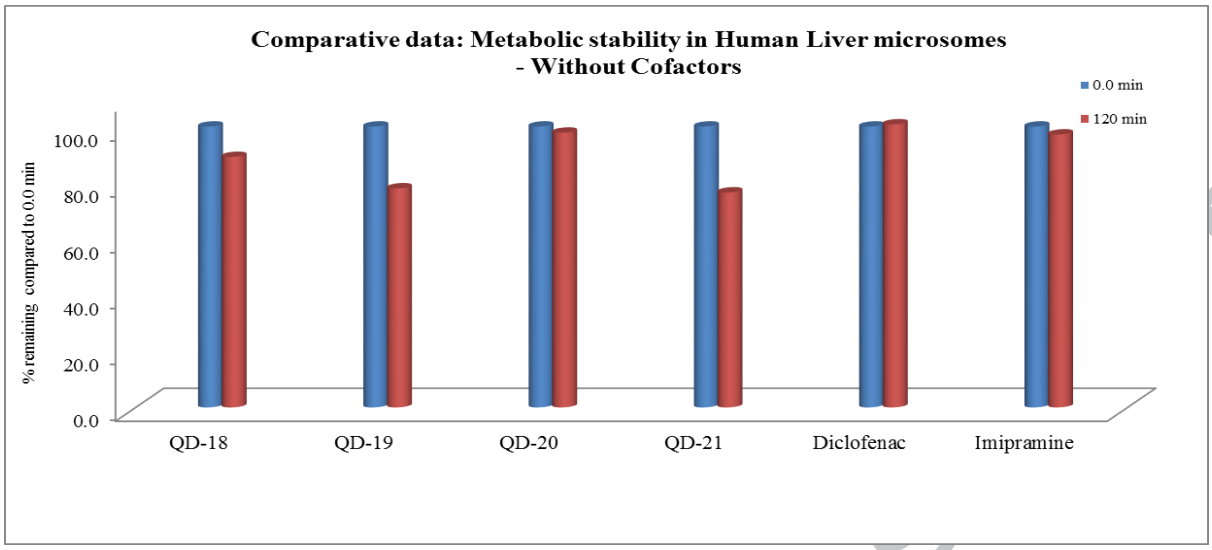


Figure 3. Graphical presentation of metabolic stability of QD-18, QD-19, QD-20 and QD-21 in human liver microsomes without cofactors at different time intervals.

2.2.4. Single Dose Oral Pharmacokinetics Study of QD-18, QD-19, QD-20 and QD-21 in Male BALB/c Mice

Bioavailability or oral absorption of the drug is one of the essential requirement for a compound intended to be developed into an orally administered drug, it is a basic requirement that must be met by a candidate compound[25,26]. Herein, adult healthy male BALB/c mice aged 8-10 weeks were used for experimentation after a minimum three days of acclimation. Fasted animals were administered with **QD-18**, **QD-19**, **QD-20** and **QD-21** respectively in recommended vehicle by oral route with a dose of 30 mg/kg body weight and at a dose volume of 10 ml/kg body weight. These compounds showed good $T_{1/2}$, C_{max} and AUC (h*ng/ml) which is tabulated in table-6. The data was analyzed and graphs were plotted as a plasma concentration V/S time (figure 4 and 5). Compound QD-20 has a high Cmax of 9599.59 ng/ml and AUC_{last} of 20015.13 h*ng/ml but comparatively short elimination time $T_{1/2}$ of 0.75 h. Compound QD-18 has a high elimination time $T_{1/2}$ of 1.63 h but comparatively short Cmax of 2503.25 ng/ml and AUC_{last} of 5268.26 h*ng/ml. Compound QD-19 and QD-21 possess moderately high Cmax of 6407.59, 7442.73 ng/ml, AUC_{last} of 8289.39, 11860.96 h*ng/ml and T1/2 of 0.94, 1.05 h respectively. It is evident from the pharmacokinetics studies, these compounds are encouraging molecules for the development of a novel chemical class of antitubercular drugs.

Table 6. Single Dose Oral Pharmacokinetics Studies of QD-18, QD-19, QD-20 and QD-21 in Male BALB/c Mice (30 mg/kg b.w.)

Single Dose Oral Pharmacokinetics Studies of QD-18, QD-19, QD-20 and QD-21				
	Mean PK Parameters			
Parameters	**QD-18**	**QD-19**	**QD-20**	**QD-21**
Route of administration	Oral	Oral	Oral	Oral
Dose (mg/kg b.w.)	30	30	30	30
C_{max} (ng/ml)	2503.25	6407.59	9599.59	7442.73
T_{max} (h)	1.00	0.50	0.50	0.50
AUC_{last} (h*ng/ml)	5268.26	8289.39	20015.13	11860.96
AUC_{inf} (h*ng/ml)	5330.73	8307.67	20157.60	11932.67
AUC_{extrap} (%)	1.17	0.22	0.71	0.60
$T_{1/2}$ (h)	1.63	0.94	0.75	1.05
MRT_{last} (h)	1.50	1.34	1.31	1.38

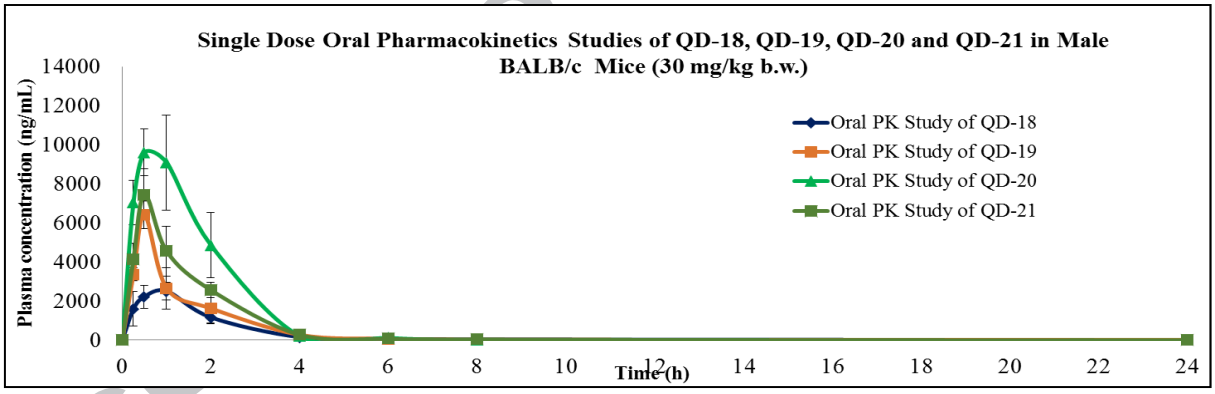


Figure 4. Plot of plasma concentration (ng/mL) v/s time curve

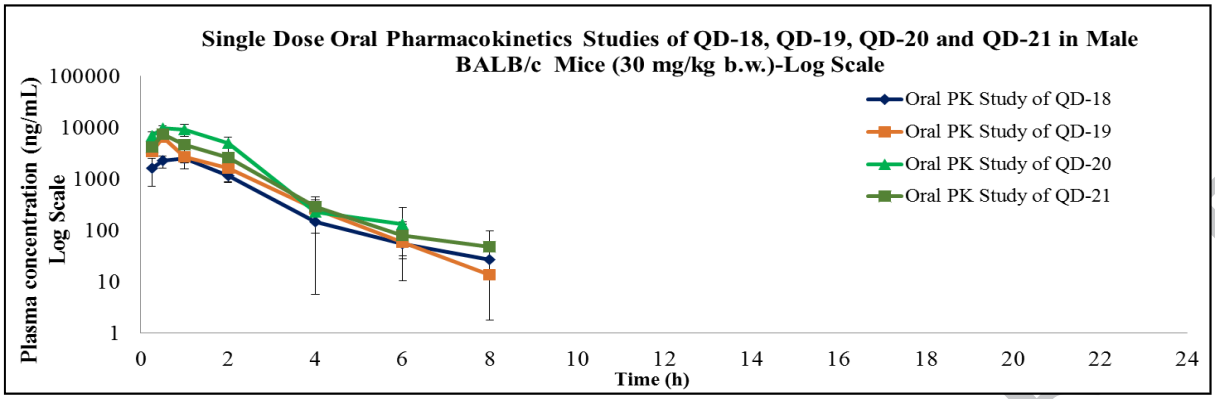


Figure 5. Plot of plasma concentration (ng/mL) v/s time in log scale

2.2.5. Kill kinetics of QD-18 on the WT strain of Mtb (Mycobacterium tuberculosis WT H37Rv)

The killing kinetics pattern of **QD-18** was evaluated[27,28] on different days (Day-0, 3, 7, 14, 21) post exposure to the compound. The assay was started at an inoculum of 3-8 X 10^7cfu/ml. Since the MIC of the compound was found to be low (0.5 µg/ml), a 2-fold 13-conc. DR (64 µg/mL -2-0.002 µg/mL) was set up for the compound exposure to Mtb culture. The survivors were enumerated by plating multiple dilutions (10^{-1} to 10^{-8} dil.s) of culture to get countable colony forming units (cfu) on different days: Day-0, Day-3, Day-7, Day-14, and Day-21. The QC drug used was Rifampicin (with similar procedure). The maximum effect (Emax) obtained on any of the enumeration days were tabulated in table-7. The compound **QD-18** demonstrated an Emax of 1.1 $\log_{10}$cfu/ml. As per the bactericidal definition (≥2 $\log_{10}$cfu/ml kill), it was found to be a bacteriostatic compound. The data was analyzed and time-kill curve of **QD-18** were plotted (figure-6 and 7).

Table-7. The maximum effect (Emax) of QD-18 obtained on Day-0, Day-3, Day-7, Day-14 and Day-21

Killing kinetics on Day-0, Day-3, Day-7, Day-14, Day-21 Emax achieved ($\log_{10}$ cfu/ mL)					
KK E max	Day-0	Day-3	Day-7	Day-14	Day-21
QD-18	0.0	0.2	1.1	0.9	0.9
RIF	0.0	4.2	6.2	6.2	6.3

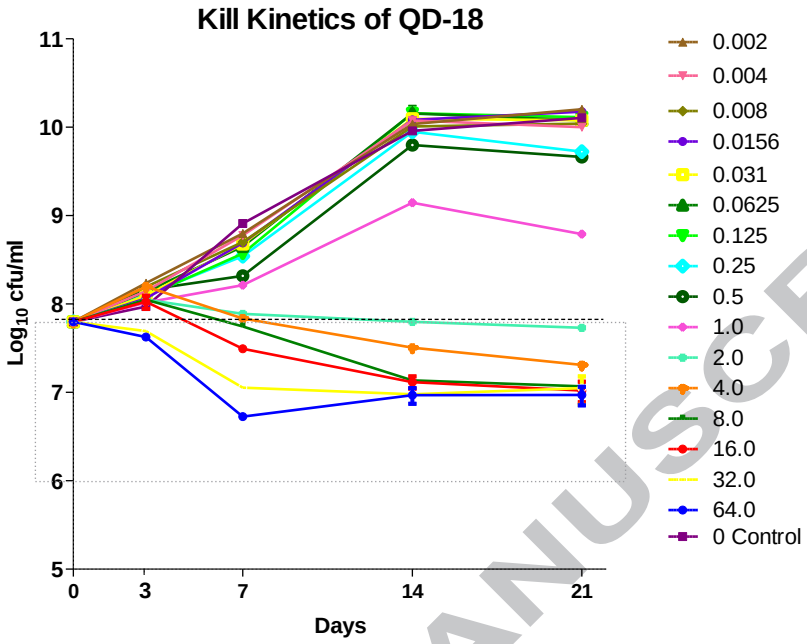
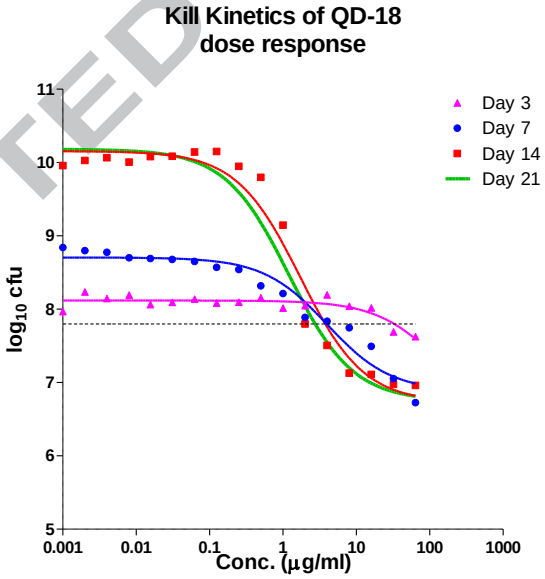


Figure 6. Time-kill curve of QD-18



	Day 0	Day 3	Day 7	Day 14	Day 21
R square	1.000	0.7491	0.9335	0.9777	0.9659

Figure 7. Dose-response curve of QD-18

3. Conclusion:

The present research study reports the successful synthesis, characterization of a new series of quinoline derivatives carrying 1,2,4-oxadiazole moiety. Compound **QD-18**, **QD-19**, **QD-20** and **QD-21** are a novel class of TB-specific compounds with excellent MIC values. The **QD-18** exibited MIC value of 0.5 µg/ml and **QD-19** to **QD-21** exhibited significant MIC value of 0.25 µg/ml against Mtb WT H37Rv. These compounds are metabolically stable, bioavailable and nontoxic with good $T_{1/2}$ and AUC (h*ng/ml) to take for further studies in an animal model of TB-infection. **QD-18** exhibited encouraging MIC against mono-resistant strains of Mtb. It is bacteriostatic in nature and the PK revealed it to be orally bioavailable with blood levels above MIC 2.5 µg/mL. Our efforts to perform PK study of **QD-20** and **QD-21** will be continued in forthcoming days. Nevertheless, being a novel class of compounds, these represent good candidate lead molecules.

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Highlights:

- Compound QD-18, QD-19, QD-20 and QD-21 are potent against Mtb WT H37Rv with encouraging MIC values.
- Four identified compounds are tuberculosis specific, orally bioavailable, non-cytotoxic and metabolically stable.
- Compound QD-20 and QD-21 exhibited an excellent pharmacokinetic profile.
- A series of quinoline hybrids synthesized are a new class of anti-tubercular molecules.

Graphical abstract

A new series of quinoline carrying 1,2,4-oxadiazole moiety have been synthesized and evaluated for their antituberculosis studies. Majority of them showed moderate to good antituberculosis activity.