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RESEARCH ARTICLE

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Design, synthesis and biological evaluation of novel quinoline-based carboxylic hydrazides as anti-tubercular agents

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In this study, seventeen novel quinoline-based carboxylic hydrazides were designed as potential anti-tubercular agents using molecular hybridization approach and evaluated *in-silico* for drug-likeness behavior. The compounds were synthesized, purified, and characterized using spectral techniques (like FTIR, ^{1}H NMR, and Mass). The *in-vitro* anti-tubercular activity (against *M*ycobacterium tuberculosis H37Ra) and cytotoxicity against human lung fibroblast cells were studied. Among the tested hydrazides, four compounds (**6h**, **6j**, **6l,** and **6m**) exhibited significant anti-tubercular activity with MIC values below 20 μg/mL. The two most potent compounds of the series, **6j** and **6m** exhibited MIC values 7.70 and 7.13 μg/mL, respectively, against *M*. tuberculosis with selectivity index >26. Structure–activity relationship studies were performed for the tested compounds in order to explore the effect of substitution pattern on the anti-tubercular activity of the synthesized compounds.

KEYWORDS
cytotoxicity, drug likeness, fibroblast, *M*ycobacterium tuberculosis, quinoline

Tuberculosis (TB) is a pulmonary infectious disease with pandemic proportions. TB is caused by different members of *Mycobacterium tuberculosis* complex, but predominantly by *Mycobacterium tuberculosis* (Mtb). According to the WHO global tuberculosis report of 2015, over 9.6 million people fell ill and more than 1.5 million people died due to TB-related complications in 2014.[1]

Combination of multiple drugs (Drug Combo), is currently used for the treatment of TB. Drug Combo speeds up the TB treatment as well as it reduces the chance of emerging drugs resistance. In the treatment regimen, first-line therapy includes the oral combination the four key drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) to which the *M. tuberculosis* isolate is likely to be susceptible.[2] Further, drugs like fluoroquinolones (levofloxacin generally preferred choice) and injectable drugs (generally used in the order: capreomycin, kanamycin, then amikacin) are preferentially given along with the first-line drugs. Second-line drugs are used in the order: thioamides, cycloserine, then aminosalicylic acid. Furthermore, some reserve drugs like clofazimine, amoxicillin, and clavulanate etc. are less frequent in use either due to their less effectiveness or lack of reliable clinical data. Overall drug combination depends upon several factors like efficacy, safety, cost, patient's resistance profile, previous use of the drug etc.[3] Although, drug combo is highly effective, but due to the lack of adherence to the therapy, increasing incidence of bacillary resistance including Multidrug-resistant TB (MDR-TB) and Extensively drug-resistant TB (XDR-TB) are frequently faced.[4] In MDR-TB, bacteria become resistant to at least isoniazid and rifampicin, while in XDR-TB in addition to these two drugs, bacteria gain resistant to one of the fluoroquinolones as well as one of the injectable drugs like kanamycin, amikacin, or capreomycin. The treatment and current management of patients with MDR/XDR-TB is extremely complex for medical, social, and public health systems.[5,6]

Recently, emerging cases of totally drug-resistant (TDR) as well as co-infection of TB with HIV have lead to an increasing occurrence of treatment failure.[7,8] As a result, there is compiling need for the search of novel drugs active against both sensitive and drug-resistant strains of Mtb, which can also act as a companion drug for existing treatment regimen of TB.

Quinoline-based natural and synthetic compounds have privileged position in the medicinal chemistry due to their diverse biological activities and this moiety is frequently used in novel drug design.[9–11] Among the diverse activities of quinoline, its antimicrobial activity is noteworthy. Quinoline acts as core pharmacophore in the several clinically approved drugs like mefloquine.[12] It is interesting to note that, latest FDA fast track approved anti-TB drug bedaquiline (**A**, Figure 1), also known as TMC207, also possesses quinoline moiety.[13] Bedaquiline possesses novel mechanism of action, it acts mainly by the inhibition of new target ATP synthase and exhibited potent activity against drug-sensitive as well as drug-resistant strains of *M. tuberculosis* with MIC 0.06 and 0.03 μg/mL, respectively.[14,15]

Inspired by the discovery of Isoniazid (INH), a critical frontline drug in TB treatment, many isonicotinic hydrazones were investigated as potential antimycobacterial agents.[16,17] One of such hydrazones "verazide" (**B**, Figure 1) exhibited high anti-Mtb activity during the *in vitro* studies (MIC 0.06 μg/mL). Further, verazide exhibited high efficacy against TB-induced lesions in the animal models.[18]

By considering the above mentioned facts as well as our continuous interest to develop novel carboxylic hydrazide as anti-tubercular agents, in the present study, we used molecular hybridization approach to design novel pharmacophoric model **C** (Figure 1)**,** consisting of carboxylic hydrazide subunit liked with quinoline moiety. Based upon the designed model **C**, a series of compounds **6a–q** (Table 2) were designed and *in-silico* evaluated for drug-likeness properties (Table 1). Further, designed compounds were synthesized, characterized, and evaluated for anti-Mtb activity as well as cytotoxicity. Structure–activity relationship (SAR) of the reported novel compounds (**6a–q**) based upon the main scaffold **C** was investigated, in order to find new improved hits in terms of anti-tubercular potency and pharmacokinetic properties.

1 | EXPERIMENTAL

1.1 | *In-silico* prediction of drug-likeness properties

Physicochemical and pharmacokinetic parameters of the designed compounds were *in-silico* predicted using different tools like FAF-*Drugs,*[19] Qikprop module of Schrödinger[20] and admetSAR.[21] The different parameters predicted were as follows: molecular weight, total solvent accessible surface area, octanol/water partition coefficient, aqueous solubility, number of rotatable bonds, number of hydrogen bond acceptor, number of hydrogen bond donor, acute oral toxicity, brain/blood partition coefficient, percentage human oral absorption and mutagenicity.

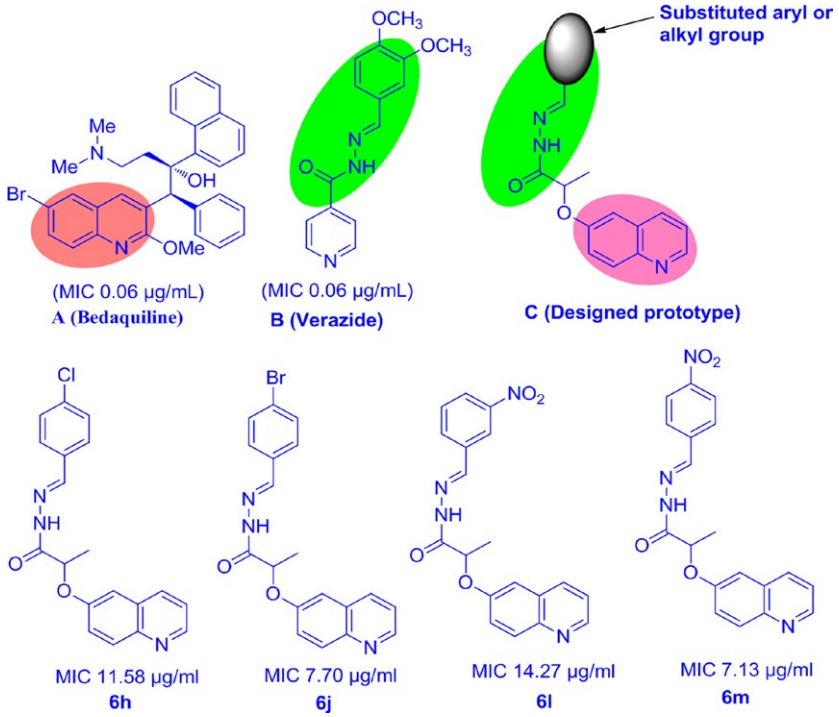


FIGURE 1 Designing of novel anti-Mtb agents and structures of some significantly active compounds

TABLE 1 *In-silico* predicted physicochemical and pharmacokinetic parameters of the designed compounds

Compound code	R	M wt[a]	SASA[b]	Log P[c]	Log S[d]	Rot[e]	HBA[f]	HBD[g]	Acu Tox[h]	Log BB[i]	% Oral abs[j]
6a	Ph	319.13	641.79	3.54	−4.01	5	1	5	Class III	−0.68	88.08
6b	Ph-2Me	333.15	667.75	3.90	−4.30	5	1	5	Class III	−0.69	92.46
6c	Ph-3MeO	349.14	680.90	3.51	−4.08	6	1	6	Class III	−0.76	84.87
6d	Ph-4MeO	349.14	681.64	3.51	−4.08	6	1	6	Class III	−0.76	94.26
6e	Ph-2F	337.12	650.82	3.64	−4.18	5	1	5	Class III	−0.59	91.82
6f	Ph-4F	337.12	653.41	3.64	−4.18	5	1	5	Class III	−0.57	86.14
6g	Ph-2Cl	353.09	663.54	4.17	−4.62	5	1	5	Class III	−0.54	79.06
6h	Ph-4Cl	353.09	668.44	4.17	−4.62	5	1	5	Class III	−0.52	82.37
6i	Ph-3Br	397.04	673.39	4.23	−4.82	5	1	5	Class III	−0.51	96.78
6j	Ph-4Br	397.04	673.48	4.23	−4.87	5	1	5	Class III	−0.51	93.08
6k	Ph-2NO_2	364.12	680.76	3.37	−4.10	6	1	8	Class III	−1.74	81.09
6l	Ph-3NO_2	364.12	682.49	3.37	−4.10	6	1	8	Class III	−1.82	68.68
6m	Ph-4NO_2	364.12	682.63	3.37	−4.10	6	1	8	Class III	−1.82	62.72
6n	Ph-4CN	344.13	682.52	3.26	−3.98	5	1	6	Class III	−1.56	77.64
6o	Ph-3,4DiCl	387.05	688.80	4.80	−5.23	5	1	5	Class III	−0.39	90.41
6p	Ph-3,4,5TMeO	409.16	750.77	3.45	−4.25	8	1	8	Class III	−0.91	87.48
6q	Isopropyl	285.15	609.68	3.53	−4.02	6	1	5	Class III	−0.77	78.58

[a]Molecular weight (130 to 725); [b]Solvent accessible surface area (300 to 1000); [c]Log partition coefficient between n-octanol and water (−2 to 6.5); [d]Log aqueous solubility (−6.5 to 0.5); [e]No. of rotatable bonds (0 to 15); [f]No. of hydrogen bond acceptors (2 to 20); [g]No. of hydrogen bond donors (0 to 6); [h]Acute oral toxicity (LD_{50} for class III ranges 0.5–5 g/Kg); [I]Log brain/blood partition coefficient (−3 to 1.2); [j]Percentage human oral absorption (>75% is high, <20% is low).

1.2 | Chemistry

1.2.1 | Methods and materials

All reagents and solvents purchased from Sigma-Aldrich (Bangalore, India) or SD fine companies were used as received without further purification. The progress of reaction was monitored by thin layer chromatography (TLC) using ethyl acetate and hexane (in suitable proportion) as mobile phase and silica as stationary phase. Melting points were uncorrected and determined in open capillary tubes on a Precision Buchi B530 (Flawil, Switzerland) melting point apparatus containing silicon oil. The IR spectra of the synthesized compounds were recorded using FTIR spectrophotometer (Shimadzu IR Prestige 21; Shimadzu, Mumbai, India). ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-400 spectrometer (Bruker India Scientific Pvt. Ltd., Mumbai, India) using TMS as an internal standard (chemical shifts δ in ppm, *J* values in Hz). Elemental analysis was performed on Vario EL III M/s Elementar C, H, N, and S analyzer. ESI-MS were recorded on MICROMASS Quattro-II LCMS system (Waters Corporation, Milford, CT, USA).

1.2.2 | General chemistry

All the synthesized compounds were primarily characterized by the non-spectral methods like TLC and melting points; further characterization was done by the spectral techniques like FTIR, ^{1}H NMR, and Mass. Five representative compounds of the series (**6c, 6e, 6i, 6k,** and **6q**) were also characterized by the ^{13}C NMR and elemental analysis. FTIR spectrum of the tested compounds exhibited the expected absorption bands, for example, all compounds possessed hydrogen at carboxylic hydrazide bond (=N–N**H**–C=O), a corresponding stretching peak (broad, moderate intensity) appeared in IR spectrum at 3175–3210 cm^{-1}. Another discrete and characteristic peak (sharp, strong intensity), appeared at the region 1680–1703 cm^{-1} corresponding to the stretching of carbonyl group (–NH–**C=O**). The ^{1}H NMR spectrum of the compounds showed, characteristic doublet around δ ~ 1.8 corresponding to the methyl group (attached at the carbon connecting carbonyl and oxygen), while single proton at the adjacent carbon appeared as quartet δ ~ 5. Further, proton at the 5th position of quinoline showed characteristic peak (δ 7.15–7.20). Hydrazide proton shifted to most down field and appeared as singlet (δ 9.30–10.04), further, single proton attached at the imine carbon also appeared at strong down field region (δ 8.80–8.90). The peak pattern and counting of NMR signals corresponding to the other protons of compounds were observed in compliance with the proposed structure. ^{13}C NMR data of the five representative compounds were also found in compliance with the proposed structure. The calculated and observed elemental values

TABLE 2 Anti-Mtb and toxicity evaluation of the synthesized compounds

Compound code	R	MIC Mtb after 7 days (μM)	Toxicity MRC5 (μM)	MIC in μg/mL	Selectivity ratio
6a	Ph	162.30	>512	51.79	>3.15
6b	Ph-2Me	234.60	>512	78.15	>2.18
6c	Ph-3MeO	258.40	>512	90.21	>1.98
6d	Ph-4MeO	110.30	>512	38.51	>4.64
6e	Ph-2F	251.40	>512	84.75	>2.03
6f	Ph-4F	180.20	>512	60.74	>2.84
6g	Ph-2Cl	>5120	>512	>180.78	Not tested
6h	**Ph-4Cl**	**32.80**	**>512**	**11.58**	**>15.60**
6i	Ph-3Br	141.30	>512	56.10	>3.62
6j	**Ph-4Br**	**19.40**	**>512**	**7.70**	**>26.39**
6k	Ph-2NO_2	105.20	>512	38.30	>4.86
6l	**Ph-3NO_2**	**39.20**	**>512**	**14.27**	**>13.06**
6m	**Ph-4NO_2**	**19.60**	**>512**	**7.13**	**>26.12**
6n	Ph-4CN	87.90	>512	30.24	>5.82
6o	Ph-3,4DiCl	407.60	>512	157.76	>1.25
6p	Ph-3,4,5TMeO	422.70	>512	172.95	>1.21
6q	Isopropyl	291.20	>512	83.03	>1.75
	Rifampicin	0.18		0.14	

Compounds exhibited significant anti-Mtb activity (MIC ≤ 20 μg/ mL) respective rows are represented by bold font.

of C H N were found within the acceptable range. Mass spectrum (ESI-MS) of the synthesized compounds exhibited the corresponding M + 1 peak.

1.3 | Biological evaluation

1.3.1 | Evaluation of anti-tubercular activity

The Minimal Inhibitory Concentration (MIC) against mycobacteria of all the synthesized compounds was evaluated by serial dilution method. The *in vitro* assay was based on a method in which a luminescent *M. tuberculosis* H37Ra strain Lehmann &Neumann (ATCC® 25177™) transformed with pSMT1 luciferase reporter plasmid is used. The tested compounds were solubilized in DMSO (Sigma-Aldrich, St. Louis, MO, USA) at stock concentration of 10 mM. Serial dilutions of each compound were made in liquid 7H9 medium [Middlebrook 7H9 broth based (BD Difco, Franklin Lakes, NJ, USA)] with 10% oleic acid, albumin, dextrose, catalase (OADC) enrichment. Volumes of 20 μL of the serial dilutions were added in triplicate to 96 well, flat-bottomed micro well plates. The bacterial suspension was made by thawing and dissolving a frozen Mycobacteria pellet in 7H9-10% OADC. The dissolved pellet was passed through a 5.0 μM filter (Millipore, Billerica, MA, USA) to eliminate clumps and left for 1 h to recover at 37 °C, 5% CO_2. Next, the bacterial suspension was diluted in 7H9-10% OADC to obtain 50 000 Relative Light Units (RLU)/mL and a volume of 180 μL of bacteria was added to each well. A bacterial replication was analyzed by luminometry after 6 days of incubation. The bacterial suspension from each well was collected and transferred to a black 96-well plate to evade cross luminescence between wells. The luminescent signal was evoked by addition of the substrate for the bacterial luciferase, 1% n-decanal in ethanol to each well by the Discover multi-plate reader from Promega and the light emission in each well was measured.[22]

1.3.2 | Cytotoxicity evaluation

Cytotoxic effects on the MRC-5, human lung fibroblast cell (ATCC® CCL-171™) were determined for the derivatives by a neutral red uptake assay. The neutral red uptake assay relies on the ability of viable cells to bind and incorporate the neutral red dye (toluylene red). The acute toxic concentration (IC_{50}) of a compound is defined as the concentration at which the uptake of the neutral red dye by the cells is reduced by 50%. The MRC-5 cells were grown in Dulbecco's modified Eagle's medium (DMEM) with 10% Fetal calf serum (FCS) until a semi-confluent layer of cells was obtained. The cells were trypsinized, washed and 40 000 cells were seeded per well of a 96-well plate and left for recovery at 37 °C, 5% CO_2. The following days, the compounds were

solubilized in DMSO to stock concentrations of 10 μM. A serial dilution of each compound was made in DMEM with 10% FCS. The MRC-5 cells were washed and exposed to the derivatives by adding the serial dilutions of the compounds to the wells. The plates were left for incubation at 37 °C, 5% CO_2 for 24 h. After exposure, the cells were washed with 200 μL of PBS, and 200 μL of neutral red working solution (Sigma) was added to each well. Subsequently, the plates were incubated for 3 h at 37 °C, 5% CO_2. The wells were washed with 200 μL of PBS and 200 μL of ethanol/acetic acid (50%) mixture. The plates were left on the shaker until the color became homogeneous purple and the optical density was measured at 530 nm (NR max) and 620 nM (reference wavelength) with the Paradigm detection platform.[23]

2 | RESULTS AND DISCUSSION

2.1 | *In-silico* prediction of drug-likeness properties

The values of *in-silico* predicted physicochemical and pharmacokinetic parameters of the designed compounds are shown in Table 1, while their range such parameters followed by 95% of known drugs are also shown on the footnotes of Table 1.[24,25] The results of the predicted drug-likeness parameters revealed that, value of descriptors like mol. wt, HBA, HBD and log P followed Lipinski rule of five and their values lied within the prescribed range. Compound **6o** may have less aqueous solubility, due to its low value of predicted log S, but still it lied within the range (−6.5 to 0.5). Furthermore, descriptors like SASA, Rot, logBB were also found within the range. Predicted acute oral toxicity values of all the compounds lie in "class III" which revealed that, compounds possessed fairly high lethal dose and can be considered suitable for the druggable point of view. All designed compounds exhibited good predicted values of percentage human oral absorption (except compounds **6l** and **6m**) and none of the compound possessed mutagenicity (predicted in qualitative terms). So overall, based upon the values of predicted drug-likeness parameters, all compounds possessed the drug-likeness behavior.

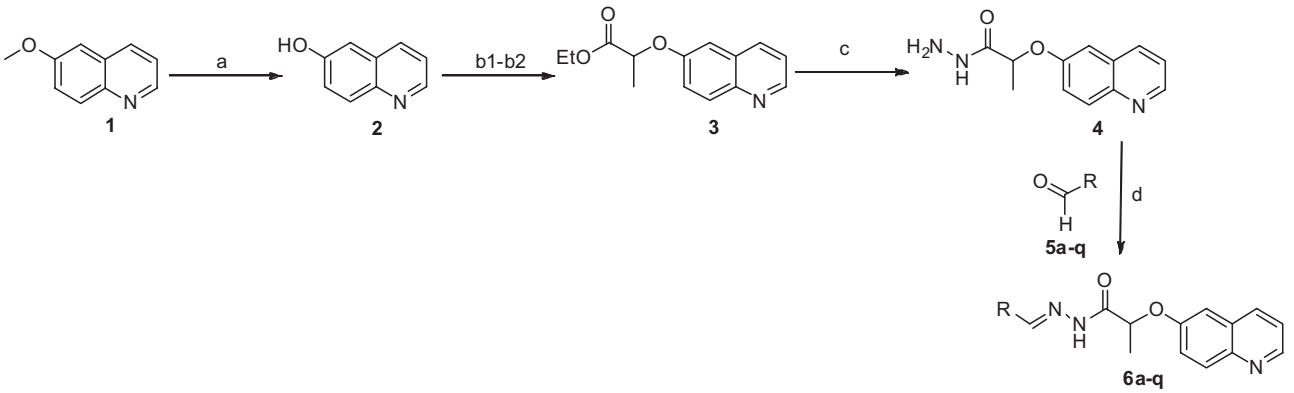
2.2 | Chemistry

The synthetic route and optimized reaction conditions used for the designed compounds **6a–q**, are illustrated in Scheme 1. Synthesis of target compounds involved sequence of reactions, first step involved demethylation reaction of 6-methoxyquinoline (**1**) using Aluminum trichloride in dry DCM, which afforded intermediate 6-hydroxyquinoline (**2**). Reaction of intermediate **2** with ethyl 2-bromopropanoate was first tried under b1 conditions, but condition b1 not provided the complete conversion of **2** into **3** as per TLC, while under condition b2, complete conversion took place (as per TLC) and afforded the intermediate **3**. In further step, intermediate **3** was treated with hydrazine hydrate which involved the replacement of ethoxy group with hydrazine and afforded the intermediate **4**. In final step of Scheme 1, to obtain the desired schiff base compounds (**6a–q**), intermediate **4** was condensed with specific aldehydes containing selected R groups (**5a–q**) to afford the titled compounds in good to excellent yield.

2.3 | Biological evaluation

2.3.1 | Evaluation of anti-tubercular activity

All purified compounds were evaluated for their inhibitory potency against H37Ra strain of *M. Tuberculosis* using



SCHEME 1 Reagents and conditions: (a) $AlCl_3$, dry DCM, 24 h, rt (b1) ethyl 2-bromopropanoate, K_2CO_3, CH_3CN, reflux, 12 h (b2) ethyl 2-bromopropanoate, K_2CO_3, DMF, 100 °C, 10 h (c) NH_2–NH_2.H_2O, catalytic glacial AcOH, EtOH, reflux 8 h (d) EtOH, catalytic AcOH, reflux 2–3 h

luminometry method. The minimum inhibitory concentration (MIC) values (in terms of μg/mL and μM) of tested compounds and standard drug rifampicin are shown in Table 2. Among the tested compounds, four compounds (**6h**, **6j**, **6l,** and **6m**) displayed significant anti-Mtb activity with MIC <20 μg/mL (highlighted by bold font in Table 2). In further study, we investigated the effect of different substitution pattern of phenyl ring on anti-tubercular potency of compounds. Prototype compound **6a** containing un-substituted phenyl ring exhibited weak anti-Mtb activity. Further, substitution of phenyl ring with electron-donating groups like methyl and methoxy at *ortho* and *meta* position respectively, further decreased their anti-tubercular potency. Whereas, substitution by methoxy group at the *para* position (**6d**) slightly enhanced the potency (38.51 μg/mL). Further, substitution with strong electron withdrawing fluoro group at *ortho* and *para* position (compound **6e** and **6f**) also resulted decrease in anti-tubercular potency (84.75 and 60.74 μg/mL respectively). Interestingly, chloro substitution at *ortho* position of phenyl ring (**6g**) markedly decreased the potency (>180.78 μg/mL), while at the *para* position (**6h**), potency against Mtb was significantly increased (11.58 μg/mL). Substitution with bromo at *meta* position (**6i**) not significantly changed the anti-tubercular potency, while *para* substituted compound **6j** exhibited seven times more potency (7.70 μg/mL) as compared to the unsubstituted one. Among the nitro substituted compounds (**6k, 6l** and **6m),** compound **6k** exhibited moderate while compounds **6l** and **6m** showed significant anti-tubercular potency. Over all anti-Mtb potency of compounds **6k, 6l** and **6m** changed in the order *ortho* < *meta* < *para* (MIC 38.33, 14.27 and 7.13 μg/mL), respectively. Further, 4-cyano substituted compound **6n** exhibited moderate potency while di-chorlo and trimethoxy substituted compounds (**6o** and **6p**) exhibited very weak anti-Mtb potency. Compounds constitute isopropyl group instead of phenyl (**6q**), also exhibited weak anti-Mtb activity. So, overall SAR study of the tested compounds revealed that, their anti-tubercular potency changed significantly with the position and nature of the substituent on phenyl ring. Compounds substituted with electron withdrawing group of moderate to large size at the *para* position of phenyl ring (especially **6j** and **6m**) exhibited significant inhibitory potency against Mtb with good safety index.

In the recent studies, several carbohydrazide of heterocyclic moieties containing *N′*-benzylidene at terminal part, are reported as potent inhibitor of pantothenate synthetase enzyme of *M. tuberculosis.*[26,27] Moreover, our reported compounds also exhibit the similar pharmacophoric features, so probably they may share the similar mechanism of action, but further studies are required to know the exact mechanism of action.

2.3.2 | Cytotoxicity evaluation

All the synthesized compounds were evaluated for their cytotoxic effect on the MRC-5, human lung fibroblast cell at concentration of 512 μM. Interestingly, none of the compound showed toxicity at the tested concentration.

3 | CONCLUSION

In summary, we designed and synthesized seventeen (**6a–q**) novel quinoline-based carboxylic hydrazides with anti-Mtb properties based on molecular hybridization as well as *in-silico* evaluated for drug likeness. Based upon the predicted *in-silico* physicochemical and pharmacokinetic parameters, all the compounds possessed drug-likeness behavior. Subsequently, compounds (**6a–q**) were tested to evaluate their cytotoxicity and whole cell activity against Mtb. Four compounds (**6h**, **6j**, **6l**, and **6m)** exhibited significant anti-Mtb activity (MIC <20 μg/mL), in which two most potent compounds (**6j** and **6m)** exhibited MIC values 7.70 and 7.13 μg/mL, respectively against Mtb. None of the compound exhibited cytotoxicity against lung fibroblast cells at tested concentration (512 μM). SAR study of the tested compounds revealed that, electron withdrawing group of moderate to large size especially at *para* position of phenyl ring (like **6h**, **6j,** and **6m**) significantly increased the potency against *M. tuberculosis* while retaining a good safety index. The tested compounds exhibited moderate potency against Mtb as compared to the reference drug rifampicin. We consider this study as a helpful starting point for further lead optimization efforts aiming to find more potent anti-tubercular agents with an improved physicochemical profile.

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CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Data S1. Supplementary material.