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ORIGINAL PAPER

Synthesis of 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol as potential antimycobacterial agents

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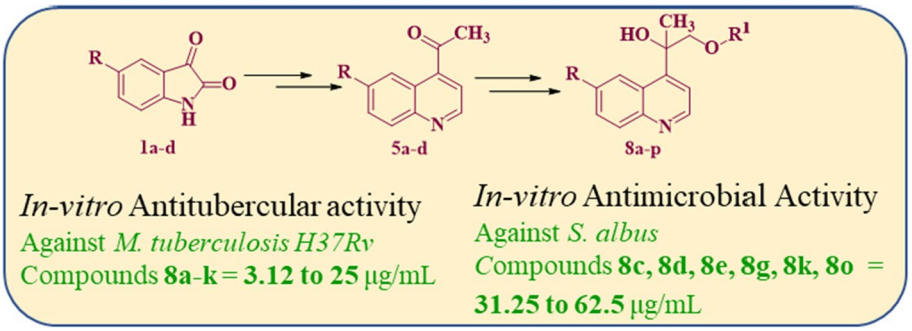
Abstract

Resistance to antibiotic drugs has directed global health security to a life-threatening situation due to mycobacterial infections. In search of a new potent antimycobacterial, a series of (±) 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) have been synthesized. The structures of the newly synthesized derivatives were characterized by spectrometric analysis. Derivatives **8a–p** were evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37Rv (ATCC 25177), antibacterial activity against *Proteus mirabilis* (NCIM2388), *Escherichia coli* (NCIM 2065), *Bacillus subtilis* (NCIM2063) *Staphylococcus albus* (NCIM 2178) and antifungal activity against *Candida albicans* (NCIM 3100), *Aspergillus niger* (ATCC 504). Thirteen 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–m)** derivatives reported moderate to good antitubercular activity against *M. tuberculosis* H37Rv with MIC 9.2–106.4 µM. Compounds **8a** and **8h** showed comparable activity with respect to the standard drug pyrazinamide. The active compounds screened for cytotoxicity activity against L929 mouse fibroblast cells showed no significant cytotoxic activity. Compounds **8c**, **8d**, **8e**, **8g**, **8k**, and **8o** displayed good activity against *S. albus*. Compounds **8c** and **8n** showed good activity against *P. mirabilis* and *E. coli*, respectively. The potential antimycobacterial activities imposed that the 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol derivatives could lead to compounds that could treat tuberculosis.

Graphical abstract



Keywords Quinoline · Antitubercular activity · Antimicrobial activity

Introduction

After COVID-19, tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis* (MTB) became grievous to global health security and is now the foremost cause of mortality from a single infectious agent. According to the World Health Organization (WHO) TB report 2021, 10

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million people developed TB in 2020 and 1.5 million died (Global tuberculosis report 2021). Over the years, the extensive development of drug resistance in the causative pathogen, MTB, has been an encumbrance of global commitments to end TB (Mabhula and Singh 2019; Sheikh et al. 2021). The current treatment regimens for TB disease rely on a combination of drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) and are associated with suboptimal efficacy, toxicity, and long duration and poor adherence which may ultimately lead to drug-resistant cases (Nguyen 2016; Sharma et al. 2021; Tiberi et al. 2018; Bald et al. 2017). Multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB therapy includes much more toxic and expensive drugs and is tainted by a diminished chance of success (Global tuberculosis report 2020; World Health Organization 2020). There is great demand for developing effective new anti-TB drugs with better efficacy, reduced duration of action, and improved patient compliance.

The quinoline pharmacophore (Fig. 1) fulfilled the medicinal need of society for the last five decades. The modification of quinoline by different functional groups has an immense impact on biological activity (Nayak et al. 2015; Rakesh et al. 2016; Cohen 2013). Many quinoline derivatives have been successfully marketed as antimycobacterial, antimalarial, and anticancer agents. The quinoline compounds are endowed with a wide variety of biological activities such as antituberculosis (Keri and Patil 2014; Gonçalves et al. 2010), antimicrobial (Marella et al. 2013; Hu et al. 2017a, b), anticancer (Bollu et al. 2017), antimalarial (Kalaria et al. 2018; Hu et al. 2017a, b), anti-inflammatory (Gupta and Mishra 2016) and antiviral (Guardia et al. 2018) activities. Quinolines-oxazole was reported for promising antitubercular activity (Lilienkampf et al 2009, 2012)**.**

The literature revealed that azolyl-ethanol pharmacophores are reported to be highly beneficial for antimicrobial potency, and have been extensively employed in the design of numerous new drug molecules. Notably, many azolyl ethanol derivatives as antimicrobial agents have been successfully marketed. (Sun et al. 2022; Ni et al. 2022) The azolyl alkoxy derivatives are reported for significant antimicrobial and antitubercular activity and are a part of many antimicrobial drugs. (Peng et al. 2016; Zhang et al. 2018) Implying facts, the intrinsic potent of quinoline which can be extended specifically using the effect of combining with alkoxy ethanol has compelled us to synthesize the 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) derivatives and screen for antimicrobial activity.

Results and discussion

Chemistry

The synthetic route for (±) 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) derivatives is presented in Scheme 1. 6-Substituted quinoline-2,4-dicarboxylic acids (**2a–d**) were synthesized via Pfitzinger reaction using pyruvic acid and 5-substituted isatin in the aqueous potassium hydroxide at 60 °C. (Shvekhgeimer 2004) The dicarboxylic acid (**2a–d**) on selective decarboxylation at 210 °C in nitrobenzene gave 6-substituted-4-quinoline carboxylic acid (**3a–d**). (Thakare et al. 2020) Acids (**3a–d**) were coupled with N,O-dimethylhydroxyamine hydrochloride (DMHA·HCl) using N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC·HCl) as a coupling reagent and N,N-dimethyl amino pyridine (DMAP) as a base in DCM gave 6-substituted-*N*-methoxy-*N*-methylquinoline-4-carboxamide (**4a–d**). (Thakare et al. 2020) Carboxamide (**4a–d**) on Grignard reaction with MeMgBr gave 1-(6-substituted quinolin-4-yl)ethenone (**5a–d**) (Thakare et al. 2021,

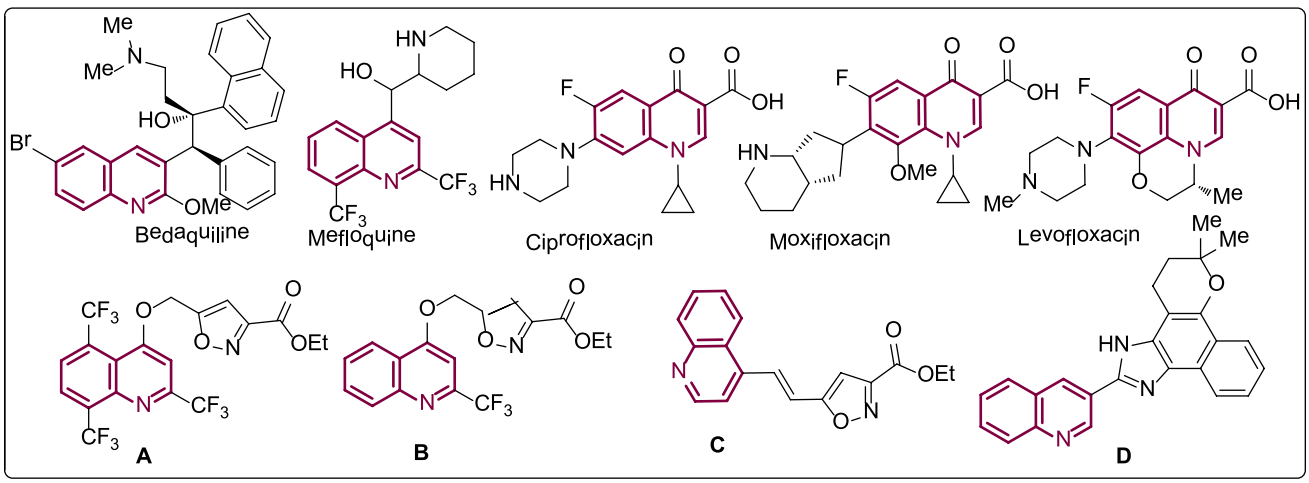
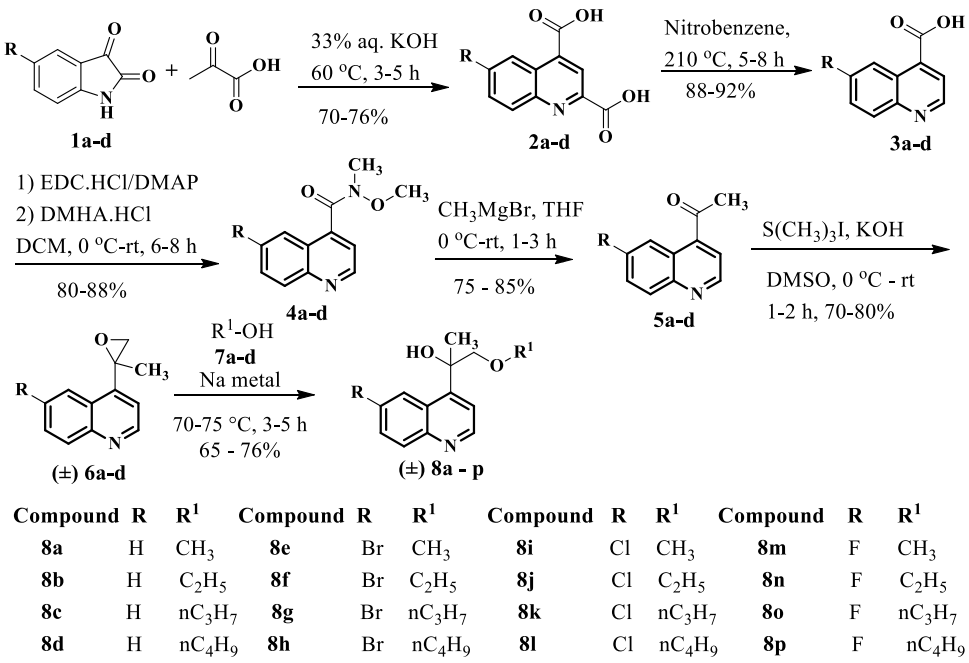


Fig. 1 Quinoline pharmacophore containing TB drugs and lead molecules A–D

Scheme 1 Synthesis of (±) 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**)



Compound	R	R^1	Compound	R	R^1	Compound	R	R^1	Compound	R	R^1
8a	H	CH_3	**8e**	Br	CH_3	**8i**	Cl	CH_3	**8m**	F	CH_3
8b	H	C_2H_5	**8f**	Br	C_2H_5	**8j**	Cl	C_2H_5	**8n**	F	C_2H_5
8c	H	nC_3H_7	**8g**	Br	nC_3H_7	**8k**	Cl	nC_3H_7	**8o**	F	nC_3H_7
8d	H	nC_4H_9	**8h**	Br	nC_4H_9	**8l**	Cl	nC_4H_9	**8p**	F	nC_4H_9

Table 1 Physical properties of compounds (±) **8a–p**

Compound	R	R1	Physical appearance	Yield(%)[a]	MP °C
8a	H	Methyl	White solid	68	84–88
8b	H	Ethyl	Off-white solid	70	82–84
8c	H	n-Propyl	Off-white solid	65	70–72
8d	H	n-Butyl	Off-white solid	70	68–72
8e	Br	Methyl	Off-white solid	74	168–172
8f	Br	Ethyl	Off-white solid	76	126–130
8g	Br	n-Propyl	Off-white solid	68	88–92
8h	Br	n-Butyl	Pale brown solid	65	68–72
8i	Cl	Methyl	Off-white solid	70	165–168
8j	Cl	Ethyl	Off-white solid	68	86–90
8k	Cl	n-Propyl	Off-white solid	73	62–66
8l	Cl	n-Butyl	Thick liquid	70	Liquid
8m	F	Methyl	Off-white solid	68	100–102
8n	F	Ethyl	Off-white solid	65	62–65
8o	F	n-Propyl	Brown solid	68	60–62
8p	F	n-Butyl	Off-white solid	70	56–57

[a]Isolated yield

2022). The epoxide ring of 6-substituted-4-(2-methyloxiran-2-yl)quinoline (**6a–d**) was achieved using sodium metal in respective solvent (**7a–d**) at 70–75 °C gave (±) 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**). The physical properties of compounds (**8a–p**) are presented in Table 1.

The structure of compounds (**8a–p**) was confirmed by spectral analysis. As a representative analysis, the ^{1}H NMR spectrum of 2-(6-chloroquinolin-4-yl)-1-ethoxypropan-2-ol, (**8j**) revealed a singlet in the aliphatic region at δ 1.73 for the methyl group attached at quaternary carbon, a broad singlet at δ 3.50 assigned to –OH proton. A triplet at δ 1.21 and a quartet at δ 3.60 integrated for three and two protons, respectively were assigned to the ethoxy group protons. Two doublets at δ 3.69 and 4.05, each integrated for one proton, correspond to diastereotopic geminal methylene protons of the (HO(CH3)C–CH2–O) group. The C-2 and C-3 protons of quinoline resonated as a doublet at δ 8.82 and δ 7.43, respectively. The C-5, C-7, and C-8 of quinoline appeared as a doublet, double doublet, and triplet at δ 8.75, 7.62, and 8.05, respectively. All the 1H-1H proton interactions were further confirmed by the COSY NMR spectrum. The ^{13}C NMR spectrum of compound **8j** showed five signals in the aliphatic region, The methyl group attached to quaternary carbon appeared at δ 26.6, the ethoxy group carbons appeared at δ 15.0 (CH3), 67.2 (CH2), the methylene carbon of C–CH2–O group showed a signal at δ 76.8 and a signal of quaternary carbon appeared at δ 74.8. The aromatic carbons resonated between δ 119.6 and 150.0. The structure of compound (**8j**) was further confirmed by molecular ion peaks (LC–MS) at $m/z = 266.08\ (M+H)+$, $268.08\ (M+2+H)+$. The structure of all synthesized compounds was confirmed similarly.

Biological activity

Antitubercular activity

All the synthesized (±) 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) derivatives, were evaluated for

antitubercular activity using microplate Alamar Blue assay (MABA) (Lourenço et al. 2007; Franzblau et al 1998). The antitubercular drugs isoniazid and pyrazinamide were used as the positive control. The antitubercular activity results in Minimum Inhibitory Concentration (MIC) in μM (μg/mL) have been presented in Table 2.

The antitubercular activity result analysis of 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) presented in Table 2 provided some lead compounds that exhibited good to excellent activity against *M. tuberculosis*, H37RV. The substituent effect on activity revealed that substitution of the halogen group at the 6-position of quinoline and alkoxy group of ether linkage affect the activity. Among the compounds, 1-alkoxy-2-(quinolin-4-yl)propan-2-ol (**8a-d**) compound **8a** (R = H, R1 = CH3) showed excellent activity with MIC 14.4 μM, which was more potent than the reference drug pyrazinamide. The -CH3 group which was substituted by the –C2H5 group in **8b** (R = H, R1 = C2H5), presented good activity with MIC 27.1 μM. The –CH3 group was substituted by the − *n*C3H7 group in compound **8c** (R = H, R1 = C3H7) the activity decreased by four-fold, and it showed MIC 102 μM. The –CH3 group was substituted by the − *n*C4H9 group in compound **8d** (R = H, R1 = C4H9) and showed good activity with MIC 24.1 μM which was comparable with respect to the reference drug pyrazinamide.

Among the compounds 2-(6-bromoquinolin-4-yl)-1-alkoxypropan-2-ol, (**8e–h**) compound **8e** (R = Br, R1 = CH3), good activity with MIC 21.2 μM which was comparable with respect to the drug pyrazinamide and two-fold less than the drug isoniazid. The substitution of –CH3 group by the –C2H5 or − *n*C3H7 group in compounds **8f** (R = Br, R1 = C2H5) and **8g** (R = Br, R1 = − *n*C3H7) the activity retained. Whereas, the -CH3 group was substituted by the − *n*C4H9 group in compound **8h** (R = Br, R1 = − *n*C4H9) the activity increased by two folds and it showed comparable activity with respect to the standard drug isoniazid. Among the 2-(6-chloroquinolin-4-yl)-1-alkoxypropan-2-ol (**8i–l**) derivatives, compound **8i** (R = Cl, R1 = CH3) displayed good activity with MIC 24.9 μM. The –CH3 group was substituted by the − *n*C3H7 group in compound **8k** (R = Cl, R1 = C3H7), and the activity was retained. Whereas the methyl group of ether was substituted by the –C2H5 group in **8j** (R = Cl, R1 = C2H5) or − *n*C4H9 group in **8l** (R = Cl, R1 = − *n*C4H9), the activity decreased by two-fold. The compounds **8j** and **8l** showed good activity with MIC 47.2 and 42.7 μM, respectively. From the 2-(6-chloroquinolin-4-yl)-1-alkoxypropan-2-ol (**8m–p**) derivatives, compound **8m** (R = F, R1 = CH3) showed moderate activity with MIC 106.4 μM. The -CH3 group of 2-(6-chloroquinolin-4-yl)-1-methoxypropan-2-ol was substituted by the –C2H5 group in the compound **8n** (R = F, R1 = C2H5) the activity decreased by four-fold. The –CH3 group of ether was substituted by − *n*C3H7 and − *n*C4H9 in the compounds **8o** (R = F, R1 = − *n*C3H7) and **8p** (R = F, R1 = − *n*C4H9), respectively the activity decreased by two-fold.

It is noteworthy that, amongst the sixteen derivatives, ten derivatives exhibited moderate to good antitubercular activity with 9.2–106.4 μM. The structure–activity relationship revealed that the unsubstituted quinoline and methyl, ethyl, and *n*-butyl group at the ether linkage showed good antitubercular activity; whereas the *n*-propyl group at the ether linkage showed moderate activity. The quinoline was substituted by the 6-bromo quinoline and the methyl, ethyl, *n*-propyl, and *n*-butyl group at the ether linkage showed good antitubercular activity. It was noticed that the activity increased for the *n*-propyl and *n*-butyl groups. The quinoline was substituted by the 6-chloro quinoline and the methyl, ethyl, and *n*-butyl group at the ether linkage antitubercular activity decreased; whereas for the *n*-propyl group at the ether linkage, antitubercular activity increased. The quinoline was substituted by the 6-fluoro quinoline the activity was decreased for all alkoxy substituents. 1-Methoxy-2-(quinolin-4-yl)propan-2-ol (**8a**) and 2-(6-bromoquinolin-4-yl)-1-butoxypropan-2-ol (**8h**) showed comparable activity with that of the standard drug.

Table 2 Antitubercular activity in MIC in μM (μg/mL) of compounds **8a–p**

Compound	R	R1	*M. tuberculosis*, H37 RV
8a	H	Methyl	14.4 (3.12)
8b	H	Ethyl	27.1 (6.25)
8c	H	*n*-Propyl	102 (25)
8d	H	*n*-Butyl	24.1 (6.25)
8e	Br	Methyl	21.2 (6.25)
8f	Br	Ethyl	20.2 (6.25)
8g	Br	*n*-Propyl	19.3 (6.25)
8h	Br	*n*-Butyl	9.2 (3.12)
8i	Cl	Methyl	24.9 (6.25)
8j	Cl	Ethyl	47.2 (12.5)
8k	Cl	*n*-Propyl	22.4 (6.25)
8l	Cl	*n*-Butyl	42.7 (12.5)
8m	F	Methyl	106.4 (25)
8n	F	Ethyl	401.6 (100)
8o	F	*n*-Propyl	190.1 (50)
8p	F	*n*-Butyl	180.5 (50)
Pyrazinamide			25.34 (3.12)
Isoniazid			11.67 (1.6)

Antimicrobial activity

Synthesized 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) derivatives were screened for their antibacterial activity against *P. mirabilis*, *E. coli*, *B. subtilis*, *S. albus*

using well diffusion method (NCCLS 2002; Joshi et al. 2015). Standard drug streptomycin and DMSO were used as the positive and negative control, respectively. Antifungal activity was performed against *C. albicans* and *A. niger* using the well diffusion method (NCCLS 2002; Joshi et al. 2015). The antifungal drugs fluconazole and ravuconazole were used as references. All the test solutions were prepared in DMSO at 500 µg/mL concentrations and the wells were filled with 80 µL (40 µg) of the samples, the result of antimicrobial activity in the zone of inhibition (mm) has been presented in Tables S1 and S2.

The antimicrobial activity result analysis of compounds **8a–p** showed that most of the compounds exhibited good to moderate antibacterial and antifungal activity. All the synthesized compounds were further evaluated for Minimum Inhibitory Concentration (MIC), ranging from 250 to 3.90 µg/mL. The antimicrobial screening results of MIC in µg/mL have been presented in Table 3.

The antibacterial activity analysis revealed that among the compounds 1-alkoxy-2-(quinolin-4-yl)propan-2-ol (**8a–d**) compounds **8a** (R = H, R1 = CH3) and **8b** (R = H, R1 = C2H5) showed moderate activity against *S. albus* and *C. albicans* and were found less active against *P. mirabilis*, *E. coli*, *B. subtilis* and *A. niger*. Compound **8c** (R = H, R1 = −*n*C3H7) showed good activity against *P. mirabilis* and *S. albus* and moderate activity against *E. coli* and *A. niger*. Compound **8d** (R = H, R1 = −*n*C4H9) showed good activity against *S. albus* and moderate activity against *B. subtilis*.

Amongst the compounds 2-(6-bromoquinolin-4-yl)-1-alkoxypropan-2-ol (**8e–h**), compounds **8e** (R = Br, R1 = CH3) and **8g** (R = Br, R1 = *n*C3H7) showed good activity against *S. albus*. Compound **8h** (R = Br, R1 = *n*C4H9) showed moderated activity against *P. mirabilis*, *B. subtilis* and *C. albicans*. From the compounds, 2-(6-choloroquinolin-4-yl)-1-alkoxypropan-2-ol (**8i-l**), compounds **8j** (R = Cl, R1 = CH3) and **8l** (R = Cl, R1 = *n*C3H7) showed moderate activity against *C. albicans* and *E. coli*, respectively. Compound **8k** (R = Cl, R1 = *n*C3H7) showed good activity against *S. albus*. Among the compounds, 2-(6-fluoroquinolin-4-yl)-1-alkoxypropan-2-ol (**8m–p**) compound **8n** (R = F, R1 = C2H5) showed good activity against *E. coli* and moderate activity against *A. niger*. Compounds **8o** (R = F, R1 = *n*C3H7) and **8p** (R = F, R1 = *n*C4H9) showed good activity against *S. albus* and *C. albicans*, respectively. It is noteworthy that, among the 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol, (**8a–p**) derivatives, six compounds showed good activity against *S. albus* with MIC 31.25–62.5 µg/mL.

Cytotoxicity

Cytotoxicity activity of 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) derivatives were performed on L929, a normal fibroblast cell line from the subcutaneous connective tissue of mouse at 12.5 and 25 µ/mL concentrations. Compounds **8a**, **8b**, **8c**, **8d**, **8e**, and **8f** showed no or

Table 3 Antimicrobial activity in MIC (µg/mL) of compounds (**8a–p**)

Comp	R	R1	*P. mirabilis*	*E. coli*	*B. subtilis*	*S. albus*	*C. albicans*	*A. niger*
8a	H	Methyl	> 250	> 250	> 250	**125**	**125**	> 250
8b	H	Ethyl	> 250	> 250	250	**250**	**125**	250
8c	H	n-Propyl	**62.5**	**125**	> 250	**62.5**	250	**125**
8d	H	n-Butyl	> 250	> 250	**125**	**62.5**	250	> 250
8e	Br	Methyl	> 250	> 250	> 250	**62.5**	> 250	> 250
8f	Br	Ethyl	> 250	> 250	> 250	> 250	> 250	> 250
8g	Br	n-Propyl	–	250	250	**62.5**	250	250
8h	Br	n-Butyl	**125**	250	**125**	> 250	**125**	> 250
8i	Cl	Methyl	250	> 250	> 250	250	250	> 250
8j	Cl	Ethyl	–	250	> 250	**125**	250	> 250
8k	Cl	n-Propyl	250	> 250	> 250	**31.2**	**125**	> 250
8l	Cl	n-Butyl	> 250	**125**	**250**	> 250	> 250	250
8m	F	Methyl	–	> 250	> 250	250	250	250
8n	F	Ethyl	> 250	**31.25**	> 250	250	> 250	**125**
8o	F	n-Propyl	–	250	250	**62.5**	> 250	> 250
8p	F	n-Butyl	–	**125**	> 250	250	**62.5**	> 250
Streptomycin		7.81	7.81	7.81	7.81	NA	NA	
Fluconazole		NA	NA	NA	NA	7.81	7.81	
Ravuconazole		NA	NA	NA	NA	7.81	31.25	

NA = Not applicable; – = inactive

less cytotoxicity. Whereas, compounds **8g** and **8h** showed less than 50% cell viability indicating cytotoxicity (Fig. 2).

Experimental

The solvents and chemicals used were laboratory-grade and were purified as per the literature methods. The reaction progress has been monitored by the Thin Layer Chromatography (TLC). TLC was performed on the Merck 60 F-254 silica gel plates using ethyl acetate:hexane (2:8 and 3:7) as eluent. Melting points were determined in capillary tubes in a silicon oil bath using a Veego melting point apparatus and were uncorrected. 1H (500 MHz) NMR and 13C (125 MHz) NMR spectra of all compounds were recorded on the Bruker at either 500 MHz (1HNMR) and 125 MHz (13C NMR), spectrometer instruments. The Bruker Compass Data Analysis 4.2 was used to record HRMS spectra. Thermo Fisher Scientific India Pvt. Ltd supplied silica Gel (200–400 mesh) for column chromatography.

General procedure for (±) 6-substituted-4-(2-methyloxiran-2-yl)quinoline (6a-d)

To the stirred solution of potassium hydroxide and trimethyl sulfonium iodide in dimethyl sulphoxide, 1-(6-substituted quinolin-4-yl)ethenone (**5a–d**) was added at 0–5 °C and the reaction mass was stirred at room temperature for 1–2 h. After the complete conversion of the reactant, the reaction mixture was quenched in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and distilled on a rotary evaporator. Purification of the product was accomplished by column chromatography using ethyl acetate:hexane (2:8) as eluent gave 6-substituted-4-(2-methyloxiran-2-yl)quinoline (**6a–d**).

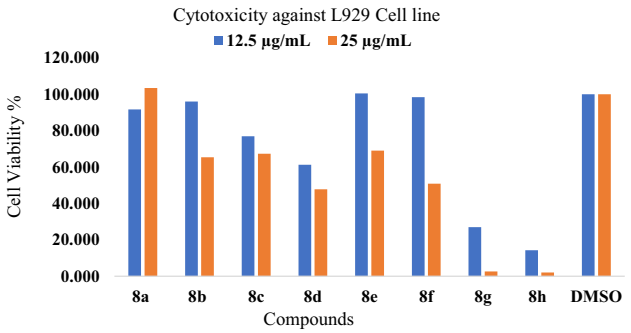


Fig. 2 Cell viability (%) against mouse embryonic fibroblast cells (L929)

rac-4-(2-Methyloxiran-2-yl)quinoline (6a)

Yield: 80%; Mp.: 68 °C; 1H NMR (500 MHz, CDCl3) δ 1.80 (s, 3H, C-CH3), 2.94 (d, *J* = 5.2 Hz, 1H, C–CH2–O), 3.18 (d, *J* = 5.2 Hz, 1H, C–CH2–O), 7.47 (d, *J* = 4.4 Hz, 1H, C-3 H), 7.63–7.57 (m, 1H, C-6 H), 7.73 (d, *J* = 1.2 Hz, 1H, C-7 H), 8.14 (dd, *J* = 18.0, 8.4 Hz, 2H, C-5, C-8 H), 8.90 (d, *J* = 4.4 Hz, 1H, C-1 H); 13C NMR (125 MHz, CDCl3) δ 23.8 (C–CH3), 54.4 (C–CH2–O), 57.1 (O–C–CH2), 118.6 (C-3), 124.1 (C-5), 125.6 (C-9), 126.8 (C-6), 129.3 (C-8), 130.3 (C-7), 146.8 (C-4), 148.2 (C-10), 150.4 (C-2).

rac-6-Bromo-4-(2-methyloxiran-2-yl)quinoline (6b)

Yield: 75%; Mp.: 70 °C; 1H NMR (500 MHz, CDCl3) δ 1.80 (s, 3H, C–CH3), 2.96 (d, *J* = 5.1 Hz, 1H, C–CH2–O), 3.21 (d, *J* = 5.2 Hz, 1H, C–CH2–O), 7.52 (d, *J* = 4.4 Hz, 1H, C-3 H), 7.70 (dd, *J* = 9.0, 2.2 Hz, 1H, C-7 H), 8.08–8.13 (m, 2H, C-8 H, C-5 H), 8.87 (d, *J* = 4.4 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 23.7 (C–CH3), 54.4 (C–CH2–O), 56.9 (O–C–CH2), 119.5(C-3), 122.1(C-6), 123.1(C-5), 126.4 (C-9), 130.4 (C-8), 132.8 (C-7), 146.2 (C-4), 146.6 (C-10), 150.6 (C-2).

rac-6-Chloro-4-(2-methyloxiran-2-yl)quinoline (6c)

Yield: 76%; Mp.: 74 °C; 1H NMR (500 MHz, CDCl3) δ 1.79 (s, 3H, C–CH3), 2.94 (d, *J* = 5.1 Hz, 1H, C–CH2–O), 3.19 (d, *J* = 5.2 Hz, 1H, C–CH2–O), 7.49 (d, *J* = 4.4 Hz, 1H, C-3 H), 7.67 (dd, *J* = 9.0, 2.2 Hz, 1H, C-7 H), 8.07–8.13 (m, 2H, C-5 H, C-8 H), 8.89 (d, *J* = 4.4 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 23.7 (C–CH3), 54.4 (C–CH2–O), 56.0 (O–C–CH2), 119.5 (C-3), 123.0 (C-5), 126.3 (C-9), 130.3 (C-8), 132.0 (C-7), 132.8 (C-6), 146.1 (C-4), 146.6 (C-10), 150.6 (C-2).

rac-6-Fluoro-4-(2-methyloxiran-2-yl)quinoline (6d)

Yield: 70%; Mp. 65 °C; 1H NMR (500 MHz, CDCl3) 1.78 (s, 3H, C–CH3), 2.94 (d, *J* = 5.2 Hz, 1H, C–CH2–O), 3.18 (d, *J* = 5.2 Hz, 1H, C–CH2–O),7.45–7.55 (m, 2H, C-7 H, C-3 H), 7.72 (dd, *J* = 9.7, 2.8 Hz, 1H, C-5 H), 8.15 (dd, *J* = 9.3, 5.6 Hz, 1H, C-8 H), 8.87 (d, *J* = 4.4 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 23.5 (C–CH3), 54.3 (C–CH2–O), 57.0 (O–C–CH2), 107.6 and 107.8 (C-5, *J* = 25.2 Hz), 119.3 and 119.5 (C-7, *J* = 25.2 Hz), 119.7 (C-3), 126.4 (C-10), 132.9 (C-8), 145.4 (C-4), 146.4 (C-9), 149.6 (C-2), 159.4 and 161.5 (C-6, *J* = 264.6 Hz).

General procedure for compound (±) 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (8a-p)

To the alcoholic solvent (**7a**–**d**) (10 mL), sodium metal (3.0 mmol) was added slowly under a nitrogen atmosphere and continued the reaction by stirring for 5 min. To this sodium alkoxide solution, 6-substituted-4-(2-methyloxiran-2-yl)quinoline (**6a**–**d**) was added and the reaction mixture was heated to 70–75 °C for 6 h. Reaction progress was monitored by the TLC. After the complete consumption of starting material, the solvent was distilled on a rotary evaporator. The residue was diluted with water and extracted with ethyl acetate (3 × 30 mL), the organic layer was washed with brine and dried over sodium sulfate and distilled under a vacuum. The crude product was purified by column chromatography furnished 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a**–**p**).

rac-1-Methoxy-2-(quinolin-4-yl)propan-2-ol (8a)

1H NMR (500 MHz, CDCl3) δ 1.77 (s, 3H, C–CH3), 3.42 (s, 3H, O–CH3), 3.49 (s, 1H, OH), 3.72 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 4.06 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 7.47 (d, *J* = 4.6 Hz, 1H, C-3 H), 7.52–7.55 (m, 1H, C-6 H), 7.66–7.70 (m, 1H C-7 H), 8.13 (dd, *J* = 8.5, 1.0 Hz, 1H, C-8 H), 8.63 (dd, *J* = 8.7, 0.7 Hz, 1H, C-5 H), 8.84 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 26.4 (C–CH3), 59.5 (O–CH3), 74.8 (HO–C–), 79.2 (C–CH2–O), 118.5 (C-3), 125.9 (C-5), 126.3 (C-9), 126.4 (C-6), 128.6 (C-8), 130.7 (C-7), 149.4 (C-4), 149.9 (C-10), 149.9 (C-2); HRMS (*m/z*): calculated for C13H16NO2: 218.1181(M + H) + , found 218.1186.

rac-1-Ethoxy-2-(quinolin-4-yl)propan-2-ol (8b)

1H NMR (500 MHz, CDCl3) δ 1.18 (t, *J* = 7.0 Hz, 3H, H3C–CH2), 1.76 (s, 3H, C–CH3), 3.57 (q, *J* = 7.0 Hz, 2H O–CH2–CH3), 3.66 (s, 1H, OH), 3.74 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 4.07 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 7.47 (d, *J* = 4.7 Hz, 1H, C-3 H), 7.52–7.54 (m, 1H, C-6 H), 7.65–7.69 (m, 1H, C-7 H), 8.13 (dd, *J* = 8.5, 1.0 Hz, 1H, C-8 H), 8.65 (dd, *J* = 8.7, 0.7 Hz, 1H, C-5 H), 8.82 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 15.0 (H3C–CH2–O), 26.5 (C–CH3), 67.2 (O–CH2), 74.7 (HO–C–), 77.0 (C–CH2–O), 118.5 (C-3), 125.8 (C-5), 126.3 (C-9), 126.5 (C-6), 128.6 (C-8), 130.6 (C-7), 149.3 (C-4), 149.9 (C-10), 150.1 (C-2); HRMS (*m/z*): calculated for C14H18NO2: 232.1338(M + H) + , found 232.1337.

rac-1-Propoxy-2-(quinolin-4-yl)propan-2-ol (8c)

1H NMR (500 MHz, CDCl3) δ 0.87 (t, *J* = 7.4 Hz, 3H, H3C–CH2), 1.54–1.58 (m, 2H, H3C–CH2–CH2–O), 1.77 (s, 3H, C–CH3), 3.51–3.43 (m, 2H, O–CH2–CH2), 3.58 (s, 1H, OH), 3.75 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 4.06 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 7.47 (d, *J* = 4.7 Hz, 1H, C-3 H), 7.53 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H, C-6 H), 7.71–7.65 (m, 1H, C-7 H), 8.13 (dd, *J* = 8.4, 1.0 Hz, 1H, C-8 H), 8.68–8.63 (m, 1H, C-5 H), 8.83 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 10.5 (H3C–CH2–CH2–O), 22.7 (H3C–CH2–CH2–O), 26.5 (C–CH3), 73.4 (O–CH2), 74.9 (HO–C–), 77.1(CH2–CH2–O), 118.5 (C-3), 125.8 (C-5), 126.4 (C-9), 126.5 (C-6), 128.6 (C-8), 130.6 (C-7), 149.3 (C-4), 149.9 (C-10), 150.0 (C-2); HRMS (*m/z*): calculated for C15H20NO2: 246.1494(M + H) + , found: 246.1498.

rac-1-Butoxy-2-(quinolin-4-yl)propan-2-ol (8d)

1H NMR (500 MHz, CDCl3) δ 0.87 (t, *J* = 7.4 Hz, 3H, H3C–CH2), 1.35 – 1.26 (m, 2H, H3C–CH2–CH2), 1.56 – 1.49 (m, 2H, H2C–CH2–CH2–O),1.76 (s, 3H, C–CH3), 3.48 – 3.52 (m, 2H CH2–CH2–O), 3.57 (s, 1H, OH), 3.74 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 4.06 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 7.47 (d, *J* = 4.7 Hz, 1H C-3 H), 7.53 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H, C-6 H), 7.67 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, C-7 H), 8.13 (dd, *J* = 8.4, 1.0 Hz, 1H, C-8 H), 8.65 (dd, *J* = 8.7, 0.7 Hz, 1H, C-5 H), 8.83 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 13.8 (H3C–CH2–CH2–CH2–O), 19.3 (H3C–CH2–CH2–CH2–O), 26.5 (C–CH3), 31.5 (H3C–CH2–CH2–CH2–O), 71.6 (O–CH2), 74.8 (HO–C–), 77.2 (H3C–CH2–CH2–CH2–O), 118.5 (C-3), 125.8 (C-5), 126.3 (C-9), 126.5 (C-6), 128.6 (C-8), 130.6 (C-7), 149.3 (C-3), 149.9 (C-10), 150.1 (C-2), HRMS (*m/z*): calculated for C16H22NO2: 260.1651 (M + H) + , found 260.1651.

rac-2-(6-Bromoquinolin-4-yl)-1-methoxypropan-2-ol (8e)

1H NMR (500 MHz, CDCl3) δ 1.68 (s, 3H, C–CH3), 3.33 (s, 3H, O–CH3), 3.68 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 3.78 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 5.26 (s, 1H, OH), 7.42 (t, *J* = 4.4 Hz, 1H, C-3 H), 7.71–7.63 (m, 1H, C-7 H), 7.89 (d, *J* = 8.8 Hz, 1H, C-8 H), 8.77 (d, *J* = 4.4 Hz, 1H, C-2 H), 9.09 (d, *J* = 2.4 Hz, 1H, C-5 H); 13C NMR (125 MHz, CDCl3) δ 31.4 (C–CH3), 64.2 (O–CH3), 79.5 (HO–C–CH2), 84.8 (C–CH2–O), 124.2 (C-6), 124.5 (C-3), 132.7 (C-10), 134.4 (C-5), 134.6 (C-8), 136.6 (C-7), 152.6 (C-4), 154.9 (C-9), 155.1 (C-2); HRMS (*m/z*): calculated for C13H15BrNO2: 296.0286(M + H) + , 296.291.

rac-2-(6-Bromoquinolin-4-yl)-1-ethoxypropan-2-ol (8f)

1H NMR (500 MHz, CDCl3) δ 1.21 (t, *J* = 7.0 Hz, 3H, H3C–CH2–O), 1.73 (s, 3H, C–CH3), 3.45 (s, 1H, OH), 3.63–3.57 (q, *J* = 7.0 Hz, 2H, O–CH2–CH3), 3.69 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 4.05 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 7.43 (d, *J* = 4.7 Hz, 1H, C-3 H), 7.75 (dd, *J* = 9.0, 2.2 Hz, 1H, C-7 H), 7.99 (d, *J* = 9.0 Hz, 1H, C-8 H), 8.84 (d, *J* = 3.8 Hz, 1H, C-2 H), 8.93 (d, *J* = 2.1 Hz, 1H, C-5 H); 13C NMR (125 MHz, CDCl3) δ 15.0 (H3C–CH2–O), 26.7 (C–CH3), 67.2 (H3C–CH2–O), 74.8 (HO–C–CH2), 76.8 (C–CH2–O), 119.1 (C-3), 120.1 (C-6), 127.6 (C-10), 129.0 (C-5), 132.1 (C-8), 132.2 (C-7), 148.0 (C-4), 149.2 (C-9), 150.2 (C-2); HRMS (*m/z*): calculated for C14H17BrNO2: 310.0443(M + H) +, 310.0450.

rac-2-(6-Bromoquinolin-4-yl)-1-propoxypropan-2-ol (8 g)

1H NMR (500 MHz, CDCl3) δ 0.89 (t, *J* = 7.4 Hz, 3H, H3C–CH2–CH2–O), 1.56–1.61 (m, 2H, H3C–CH2–CH2–O), 1.73 (s, 3H, C–CH3), 3.50 (t, *J* = 6.6 Hz, 2H, H3C–CH2–CH2–O), 3.69 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 4.04 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 7.42 (d, *J* = 4.6 Hz, 1H, C-3 H), 7.74 (dd, *J* = 9.0, 1.9 Hz, 1H, C-7 H), 7.98 (d, *J* = 9.0 Hz, 1H, C-8 H), 8.83 (t, *J* = 4.6 Hz, 1H, C-2 H), 8.94 (d, *J* = 1.9 Hz, 1H, C-5 H); 13C NMR (125 MHz, CDCl3) δ 10.5 (H3C–CH2–CH2–O), 22.7 (H3C–CH2–CH2–O), 26.6 (C–CH3), 73.5 (H3C–CH2–CH2–O), 74.9 (HO–C–CH2), 77.0 (C–CH2–O), 119.1 (C-3), 120.1 (C-6), 127.6 (C-10), 129.1 (C-5), 132.1 (C-8), 132.2(C-7), 148.0 (C-4), 149.3 (C-9), 150.1 (C-2); HRMS (*m/z*): calculated for C15H19BrNO2: 324.0599(M + H) +, found: 324.0606.

rac-2-(6-Bromoquinolin-4-yl)-1-butoxypropan-2-ol (8 h)

1H NMR (500 MHz, CDCl3) δ 0.89 (t, *J* = 7.3 Hz, 3H, H3C–CH2–CH2–CH2–O), 1.34–1.30 (m, 2H, H3C–CH2–CH2–CH2–O), 1.57–1.53 (m, 2H, H3C–CH2–CH2–CH2–O), 1.73 (s, 3H, C–CH3), 3.48 (s, 1H, HO–), 3.54 (t, *J* = 6.5 Hz, 2H, O–CH2–CH2–CH2–CH3), 3.69 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 4.03 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 7.42 (d, *J* = 4.7 Hz, 1H, C-3 H), 7.74 (dd, *J* = 9.0, 2.0 Hz, 1H, C-7 H), 7.98 (d, *J* = 9.0 Hz, 1H, C-8 H), 8.83 (dd, *J* = 7.8, 4.7 Hz, 1H, C-2 H), 8.94 (d, *J* = 2.0 Hz, 1H, C-5 H); 13C NMR (125 MHz, CDCl3) δ 13.8 (H3C–CH2–CH2–CH2–O), 19.3 (H3C–CH2–CH2–CH2–O), 26.6, 31.5 (H3C–CH2–CH2–CH2–O), 71.6 (O–CH2–CH2–CH2–CH3), 74.9 (HO–C–CH2), 76.8 (C–CH2–O), 119.1 (C-3), 120.1(C-6), 127.6 (C-10), 129.1 (C-5), 132.1(C-8), 132.2(C-7), 148.0(C-4), 149.3 (C-9), 150.1(C-2); HRMS (*m/z*): calculated for C16H21BrNO2: 338.0756(M + H) +, found: 338.0764.

rac-2-(6-Chloroquinolin-4-yl)-1-methoxypropan-2-ol (8i)

1H NMR (500 MHz, CDCl3) δ 1.75 (s, 3H, C–CH3), 3.00 (s, 1H, HO–), 3.40 (s, 3H, O–CH3), 3.75 (d, *J* = 6.8 Hz, 1H, C–CH2–O), 3.88 (d, *J* = 6.9 Hz, 1H, C–CH2–O), 7.49 (d, *J* = 4.4 Hz, 1H, C-3 H), 7.59 – 7.63 (m, 1H, C-7 H), 8.03 (d, *J* = 9.0 Hz, 1H, C-8 H), 8.82 (d, *J* = 2.3 Hz, 1H, C-5 H), 8.94 (d, *J* = 4.7 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 31.3 (C–CH3), 64.2 (O–CH3), 79.5 (HO–C–CH2), 84.7 (C–CH2–O), 124.4 (C-3), 131.0 (C-5), 131.2 (C-10), 132.1 (C-8), 134.1 (C-6), 135.9 (C-7), 152.6 (C-4), 152.4 (C-9), 154.9 (C-2); HRMS (*m/z*): calculated for C13H15ClNO2: 252.0791(M + H) +, found: 252.0792.

rac-2-(6-Chloroquinolin-4-yl)-1-ethoxypropan-2-ol (8j)

1H NMR (500 MHz, CDCl3) δ 1.21 (t, *J* = 7.0 Hz, 3H, H3C–CH2–O), 1.73 (s, 3H, C–CH3), 3.45 (s, 1H, HO–), 3.60 (q, *J* = 7.0 Hz, 2H, O–CH2–CH3), 3.69 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 4.05 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 7.43 (d, *J* = 4.7 Hz, 1H, C-3 H), 7.62 (dd, *J* = 9.0, 2.3 Hz, 1H, C-7 H), 8.05 (d, *J* = 9.0 Hz, 1H, C-8 H), 8.75 (d, *J* = 2.3 Hz, 1H, C-5 H), 8.82 (d, *J* = 4.7 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 15.0 (H3C–CH2–O), 26.6 (C–CH3), 67.2 (O–CH2–CH3), 74.8 (HO–C–CH2), 76.8 (C–CH2–O), 119.2 (C-3), 125.8 (C-5), 127.1 (C-10), 129.6 (C-8), 131.7 (C-6), 132.0 (C-7), 147.8 (C-4), 149.3 (C-9), 150.0 (C-2); HRMS (*m/z*): calculated for C14H17ClNO2: 266.0948(M + H) +, found: 266.0955.

rac-2-(6-Chloroquinolin-4-yl)-1-propoxypropan-2-ol (8 k)

1H NMR (500 MHz, CDCl3) δ 0.89 (t, *J* = 7.0 Hz, 3H, H3C–CH2–CH2–O), 1.57–1.61 (m, 2H H3C-CH2-CH2-O), 1.73 (s, 3H, C–CH3), 3.49 (t, *J* = 6.6 Hz, 2H, O–CH2–CH2–CH3), 3.60 (s, 1H, HO–), 3.69 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 4.04 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 7.42 (d, *J* = 4.7 Hz, 1H, C-3 H), 7.61 (dd, *J* = 9.0, 2.3 Hz, 1H, C-7 H), 8.05 (d, *J* = 9.0 Hz, 1H, C-8 H), 8.77 (d, *J* = 2.3 Hz, 1H, C-5 H), 8.79 (t, *J* = 4.7 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 10.5 (H3C–CH2–CH2–O), 22.7 (H3C–CH2–CH2–O), 26.6 (C–CH3), 73.5 (O–CH2–CH2–CH3), 74.9 (HO–C–CH2), 77.0 (C–CH2–O), 119.2 (C-3), 125.8 (C-5), 127.1 (C-10), 129.6 (C-8), 131.7 (C-2), 132.0 (C-7), 147.8(C-4), 149.4 (C-9), 149.9 (C-2); HRMS (*m/z*): calculated for C15H19ClNO2: 280.1104(M + H) +, found: 280.1107.

rac-1-Butoxy-2-(6-chloroquinolin-4-yl)propan-2-ol (8 l)

1H NMR (500 MHz, CDCl3) δ 0.89 (t, *J* = 7.0 Hz, 3H, H3C–CH2–CH2–CH2–O), 1.30–1.35 (m, 2H, H3C–CH2–CH2–CH2–O) 1.54–1.56 (m,

2H, H3C–CH2–CH2–CH2–CH2–O), 1.73 (s, 3H, C–CH3), 3.50 (s, 1H, HO–), 3.54 (t, *J* = 6.5 Hz, 2H O–CH2–CH2–CH2–CH3), 3.69 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 4.04 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 7.42 (d, *J* = 4.7 Hz, 1H, C-3 H), 7.62 (dd, *J* = 9.0, 2.3 Hz, 1H, C-7 H), 8.06 (d, *J* = 9.0 Hz, 1H, C-8 H), 8.76 (d, *J* = 2.3 Hz, 1H, C-2 H), 8.81 (d, *J* = 4.7 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 13.9 (H3C–CH2–CH2–CH2–O), 19.3 (H3C–CH2–CH2–CH2–O), 26.6 (C–CH3), 31.5 (H3C–CH2–CH2–CH2–O), 71.6 (O–CH2–CH2–CH2–CH3), 74.9 (HO–C–CH2), 77.0 (C–CH2–O), 119.2 (C-3), 125.8 (C-5), 127.1 (C-10), 129.6 (C-8), 131.7 (C-2), 132.0 (C-7), 147.8 (C-9), 149.4 (C-9), 150.0 (C-2); HRMS (*m/z*): calculated for C16H21ClNO2: 294.1261(M + H) + , found: 294.1266.

rac-2-(6-Fluoroquinolin-4-yl)-1-methoxypropan-2-ol (8 m)

1H NMR (500 MHz, CDCl3) δ 1.72 (s, 3H, C–CH3), 3.43 (s, 3H, O–CH3), 3.66 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 4.02 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 7.41 (d, *J* = 4.6 Hz, 1H, C-3 H), 7.45 (ddd, *J* = 9.3, 7.7, 2.8 Hz, 1H, C-7 H), 8.10 (dd, *J* = 9.2, 6.0 Hz, 1H, C-8 H), 8.39 (dd, *J* = 11.7, 2.8 Hz, 1H, C-5 H), 8.76 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 26.2 (C–CH3), 59.4 (O–CH3), 74.9 (HO–C–CH2), 79.0 (C–CH2–O), 110.4 and 110.6 (C-5, *J* = 23.94 Hz), 118.8 and 119.0 (C-7, *J* = 21.42 Hz), 119.0 (C-3), 127.0 and 127.1 (C-10, *J* = 10.08 Hz), 132.7 and 132.8 (C-8, *J* = 8.82 Hz), 146.5 (C-2), 149.0 and 149.1 (C-4, *J* = 2.52 Hz), 149.3 and 149.4 (C-9, *J* = 5.04 Hz), 158.6 and 160.6 (C-6, *J* = 246.96 Hz); HRMS (*m/z*): calculated for C13H15FNO2: 236.1087(M + H) + , found: 236.1092.

rac-1-Ethoxy-2-(6-fluoroquinolin-4-yl)propan-2-ol (8n)

1H NMR (500 MHz, CDCl3) δ 1.20 (t, *J* = 7.0 Hz, 3H, CH3–CH2–O), 1.73 (s, 3H, C–CH3), 3.51 (s, 1H, HO–), 3.60 (q, *J* = 7.0 Hz, 2H, O–CH2–CH3), 3.69 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 4.06 (d, *J* = 9.4 Hz, 1H, C–CH2–O), 7.42 (d, *J* = 4.6 Hz, 1H, C-3 H), 7.46 (ddd, *J* = 9.3, 7.7, 2.8 Hz, 1H, C-7 H), 8.11 (dd, *J* = 9.2, 6.0 Hz, 1H, C-8 H), 8.39 (dd, *J* = 11.7, 2.8 Hz, 1H, C-5 H), 8.79 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 15.0 (CH3–CH2–O), 26.4 (C–CH3), 67.2 (O–CH2–CH3), 74.8 (HO–C–CH2), 76.7 (C–CH2–O), 110.5 and 110.7 (C-5, *J* = 23.94 Hz), 118.8 and 119.0 (C-7, *J* = 23.94 Hz), 119.0 (C-3), 127.1 and 127.2 (C-10, *J* = 10.08 Hz), 132.7 and 132.8 (C-8, *J* = 10.08 Hz), 146.6 (C-2), 149.1 and 149.1 (C-4, *J* = 2.52 Hz), 149.4 and 149.5 (C-9, *J* = 5.04 Hz), 158.6 and 160.6 (C-6, *J* = 246.96 Hz); HRMS (*m/z*): calculated for C14H17FNO2: 250.1243(M + H) + , found: 250.1247.

rac-2-(6-Fluoroquinolin-4-yl)-1-propoxypropan-2-ol (8o)

1H NMR (500 MHz, CDCl3) δ 0.89 (t, *J* = 7.4 Hz, 3H, CH3–CH2–CH2–O), 1.64 – 1.55 (m, 2H, CH3–CH2–CH2–O), 1.73 (s, 3H, C–CH3), 3.45 (s, 1H, HO), 3.51 (t, *J* = 7.4 Hz, 2H, O–CH2–CH2–CH3), 3.69 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 4.05 (d, *J* = 9.3 Hz, 1H, C–CH2–O), 7.42 (d, *J* = 4.5 Hz, 1H, C-3 H), 7.46 (ddd, *J* = 9.3, 7.7, 2.8 Hz, 1H, C-7 H), 8.12 (dd, *J* = 9.2, 6.0 Hz, 1H, C-8 H), 8.40 (dd, *J* = 11.7, 2.8 Hz, 1H, C-5 H), 8.80 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 10.5 (CH3–CH2–CH2–O), 22.7 (CH3–CH2–CH2–O), 26.3 (C–CH3), 73.5 (O–CH2–CH2–CH3), 74.9 (HO–C–CH2), 76.9 (C–CH2–O), 110.5 and 110.7 (C-5, *J* = 23.94 Hz), 118.8 and 119.0 (C-7, *J* = 22.68 Hz), 119.1 (C-3), 127.2 and 127.1 (C-10, *J* = 10.08 Hz), 132.7 and 132.8 (C-8, *J* = 10.08 Hz), 146.6 (C-2), 149.1 and 149.1 (C-4, *J* = 3.78 Hz), 149.4 and 149.5 (C-9, *J* = 5.04 Hz), 158.6 and 160.59 (C-6, *J* = 246.96 Hz); HRMS (*m/z*): calculated for C15H19FNO2: 264.1400(M + H) + , found: 264.1411.

rac-1-Butoxy-2-(6-fluoroquinolin-4-yl)propan-2-ol (8p)

1H NMR (500 MHz, CDCl3) δ 0.89 (t, *J* = 7.4 Hz, 3H, CH3–CH2–CH2–CH2–O), 1.35 – 1.30 (m, 2H, CH3–CH2–CH2–CH2–O), 1.59 – 1.51 (m, 2H, CH3–CH2–CH2–CH2–O), 1.73 (s, 3H, C–CH3), 3.50 (s, 1H, HO–), 3.53 (t, *J* = 6.5 Hz, 2H, O–CH2–CH2–CH2–CH3), 3.70 (t, *J* = 9.0 Hz, 1H, C–CH2–O), 4.04 (d, *J* = 9.0 Hz, 1H, C–CH2–O), 7.41 (d, *J* = 4.6 Hz, 1H, C-3 H), 7.46 (ddd, *J* = 9.3, 7.7, 2.8 Hz, 1H, C-7 H), 8.11 (dd, *J* = 9.2, 6.0 Hz, 1H, C-8 H), 8.40 (dd, *J* = 11.7, 2.8 Hz, 1H, C-5 H), 8.79 (d, *J* = 4.6 Hz, 1H, C-2 H); 13C NMR (125 MHz, CDCl3) δ 13.8 (CH3–CH2–CH2–CH2–O), 19.3(CH3–CH2–CH2–CH2–O), 26.3 (C–CH3), 31.5 (CH3–CH2–CH2–CH2–O), 71.6 (O–CH2–CH2–CH2–CH3), 74.9 (HO–C–CH2), 76.9 (C–CH2–O), 110.5 and 110.7 (C-5, *J* = 25.2 Hz), 118.8 and 119.0 (C-7, *J* = 52.2 Hz), 127.1 and 127.2 (C-10, *J* = 10.08 Hz), 132.7 and 132.8 (C-8, *J* = 8.82 Hz), 146.5 (C-2), 149.1 and 149.1 (C-4, *J* = 2.52 Hz), 149.5 and 149.5 (C-9, *J* = 5.02 Hz), 158.6 and 160.6 (C-6, *J* = 246.96 Hz); HRMS (*m/z*): calculated for C16H21FNO2: 278.1556(M + H) + , found: 278.1561.

Biology

Antitubercular assay

The antitubercular activity against *M. tuberculosis* H37 RV (ATCC No-27294) strain was carried out using microplate Almar Blue assay (MABA) (Lourenço et al. 2007; Franzblau et al 1998). This methodology is non-toxic, use a thermally stable reagent, and shows a good correlation with the

proportional and BACTEC radiometric methods. Briefly, the addition of 200 µL of sterile de-ionized water to all outer perimeter wells of the sterile 96 wells plate to avoid the evaporation of medium in the test wells during incubation. The plates of 96 wells received 100 µL of the Middlebrook 7H9 broth and sequential dilution of compounds was made directly on the plate. Finally, drugs of 100 to 0.2 µg/mL concentrations were tested. The plates were incubated at 37 ºC for 5 days. 10% between 80 and 25 µL of freshly prepared 1:1 mixture of Almar Blue reagent was added to the plate and incubated for 24 h. The development of blue color in the well was interpreted as no bacterial growth, and the pink color was scored as growth. Further, the MIC was defined as the lowest drug concentration which prevented the color change from blue to pink.

Antibacterial activity

The in vitro antibacterial screening was carried out by the well diffusion method (NCCLS 2002; Joshi et al. 2015) against the standard strains of Gram-negative bacteria *coli* (NCIM 2574), *Proteus mirabilis* (NCIM 2388) and Gram-positive bacteria *Bacillus subtilis* (NCIM 2063) and *Staphylococcus albus* (NCIM 2178). All the strains were procured from the National Collection of Industrial Microorganisms (NCIM) NCL, Pune, India. All bacterial cultures were maintained at 4 ºC over nutrient agar slants throughout the experiment, the cultures were incubated overnight at 37 ºC in nutrient broth. Five hundred microliters of 24-48 h old fresh bacterial culture were spread over the nutrient agar plates. A sterile cotton swab was used for inoculation of the cultures in order to get uniform microbial growth. With the help of well borer, 5 mm diameter wells were punched on the agar plates. The synthesized compounds were dissolved in DMSO. The wells were filled with 80 µL solution of respective synthesized compounds in DMSO. As a vehicle control, DMSO was added to one agar plate. The plates were incubated for a period of 24–48 h at 37 ºC. After the incubation period, the antimicrobial activity was evaluated by measuring the zone of inhibition in mm using a measuring scale and the average was calculated. Each experiment was carried out in 5 replicates. The MIC was evaluated at 250, 125, 62.5, 31.25, 15.62, 7.81 and 3.90 µg/mL concentrations. The lowest concentration that showed no growth was considered the MIC.

Antifungal activity

The in vitro antifungal activity was carried out by the well diffusion method (NCCLS 2002; Joshi et al. 2015) against *C. albicans* (NCIM 3100) and *A. niger* (NCIM 504). The fungal strains were obtained from NCIM, NCL, Pune, India. The pure cultures were maintained by routine sub-culturing after every one-month interval on Potato Dextrose Agar slants (Hi-Media lab. Pvt. Ltd, Mumbai, India). Mueller Hinton agar plates were prepared by pouring 20 mL in each sterile petri—plate for fungal assay and allowed to solidify. During the assay, standard fungal cultures were grown on Potato-Dextrose broth. Five hundred microliters of 48–72 h old fresh fungal spore suspension were spread on the agar plates using a sterile cotton swab to get uniform growth. With the help of a well borer, 5 mm diameter wells were punched on the agar plates. The wells were filled with 80 µL of the samples. A standard plate with Fluconazole and Ravuconazole was used as a positive control. The plates were incubated for a period of 48–72 h at 30 °C. After the incubation period, the plates were observed for the clear zone of inhibition and it is measured in mm using a measuring scale and the mean was calculated. The experiments were carried out in five replicates. The micro-dilution susceptibility test in Sabouraud Liquid Medium (Oxoid) was used for the determination of minimum inhibition concentration (MIC). The stock solutions of the test compounds and reference drug were prepared in the DMSO at the concentration of 500 µg/mL. The MIC was evaluated at 250, 125, 62.5, 31.25, 15.62, 7.81, and 3.90 µg/mL concentrations. The tubes were inoculated with the test organisms, grown in the Potato-Dextrose broth. The tubes were kept for incubation for 48–72 h at 30 °C. The lowest concentration that showed no growth was considered the MIC.

Conclusions

In conclusion, a series of 2-(6-substituted quinolin-4-yl)-1-alkoxypropan-2-ol (**8a–p**) derivatives have been synthesized and screened for antitubercular and antimicrobial activities. Among the sixteen derivatives, thirteen derivatives (**8a**–**m**) showed moderate to good antitubercular activity *M. tuberculosis*, H37RV strain with MIC 3.12–25 µg/mL. Compounds 1-methoxy-2-(quinolin-4-yl)propan-2-ol (**8a**) and 2-(6-bromoquinolin-4-yl)-1-butoxypropan-2-ol (**8 h**) showed comparable and two-fold less antitubercular activity in comparison with the standard drug Pyrazinamide and Isoniazid, respectively. Compounds **8c** and **8n** showed good activity against *P. mirabilis*, and *E. coli*., respectively. Six compounds **8c**, **8d**, **8e**, **8g**, **8k** and **8o** exhibited good activity against *S. albus* with MIC 31.25–62.5 µg/mL. Therefore, the results warrant the need for a synthesis of quinolinepropanol libraries with a modification to ascertain the trend described in this work.

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Author contributions Synthesis and purification of compounds: AS, PPT, YN, AC, ALNS. The idea of research scheme, analysis and manuscript writing: YN, PCM.

Declarations

Conflict of interest These compounds are claimed as exemplifications in a patent application (Mhaske et al. 2021) All authors declare that they have no conflict of interest.

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