European Journal of Medicinal Chemistry 45 (2010) 957–966

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

New 1,3-oxazolo[4,5-*c*]quinoline derivatives: Synthesis and evaluation of antibacterial and antituberculosis properties

Sumesh Eswaran [a], Airody Vasudeva Adhikari [b,*], R. Ajay Kumar [c]

[a] *Anthem Biosciences Pvt. Ltd., 49 Bommasandra Industrial Area, Bommasandra, Bangalore 560099, Karnataka, India*
[b] *Department of Chemistry, National Institute of Technology Karnataka, Surathkal, Srinivasnagar, Mangalore 575025, Karnataka, India*
[c] *Department of Molecular Microbiology, Rajiv Gandhi Centre for Biotechnology Trivandrum 695014, Kerala, India*

ARTICLE INFO

Article history:
Received 15 September 2009
Received in revised form
15 November 2009
Accepted 20 November 2009
Available online 26 November 2009

Keywords:
1,3-oxazolo[4,5-*c*]quinoline
Antibacterial activity
Antituberculosis activity
X-ray crystallography

ABSTRACT

A new class of fused oxazoloquinoline derivatives was synthesized starting from 2-bromo-1-phenylethanones **1a-b** through multi-step reactions. The newly synthesized compounds were evaluated for their *in vitro* antibacterial against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (recultured) and antituberculosis activity against *Mycobacterium tuberculosis H37Rv* (ATCC 27294). Preliminary results indicated that most of the compounds demonstrated very good antibacterial and antituberculosis activities which are comparable with the first line drugs. Compounds **6a**, **6c**, **6g**, **6j**, **6k** and **6n** emerged as the lead antitubercular agents with **MIC**, **1 μg/mL** and **99%** bacterial inhibition while eight compounds, viz., **5a**, **15k**, **6a**, **6c**, **6g**, **6j**, **6k** and **6n** were found to be more potent than **INH** (MIC: 1.5 μg/mL) with MIC 1 μg/mL.

1. Introduction

Tuberculosis (TB) is a worldwide pandemic caused by different species of *mycobacteria*. The latest statistics reveals that around two million people throughout the world die annually from tuberculosis and there are around eight millions new cases each year, out of which developing countries show major share [1]. Among HIV-infected people with weakened immune system, TB is a leading killer epidemic. Every year about two millions people living with HIV/AIDS die from TB [2]. Furthermore, in recent times the appearance of multidrug-resistant TB (MDR-TB), a form of TB that does not respond to the standard treatments using first-line drugs is a serious threat to TB control and treatment. It's a shocking revelation that MDR-TB is present in almost all countries as per the recent survey, made by the World Health Organization (WHO) and its partners. A recent estimation by WHO has revealed that within next 20 years approximately 30 million people will be infected with the *bacillus* [3]. Keeping in view of the above statistics, WHO declared TB as a global health emergency and aimed at saving 14 million lives between 2006 and 2015 [4]. All the above facts reveal that there is an urgent need for development of new drugs with divergent and unique structure and with a mechanism of action possibly different from that of existing drugs.

Quinoline moiety is of great importance to chemists as well as biologists as it is one of the key building elements for many naturally occurring compounds. Among the numerous heterocyclic moieties of biological and pharmacological interest, the quinoline ring is endowed with various activities, such as antituberculosis [5], anti-malarial [6], anti-inflammatory [7], anticancer [8], antibiotic [9], antihypertensive [10], tyrokinase PDGF-RTK inhibiting agents [11], and anti HIV [12,13]. In addition to the medicinal importance, multi-substituted quinolines are valuable synthons used for the preparation of nano- and mesostructures with enhanced electronic and photonic properties [14–16].

It has been well-established that presence of aryl ring at 2nd position of quinoline moiety gives a very good antibacterial property to the target molecule and plays a significant role in development of new antibacterials [17,18]. These derivatives were found to be useful biological synthons and at present they are attracting much attention in the development of new drugs [19–21]. In addition, they are ideally suited for further modifications to obtain more efficacious antibacterial and antituberculosis agents.

On the other hand, it has been well established that oxazole derivatives possess a wide spectrum of chemotherapeutic activities including antituberculosis [22], antibacterial [23], anti-inflammatory (PDE4 inhibitor) [24], anticancer [25], antidepressant [26], and anticonvulsant properties [27]. On the basis of these observations and as a part of our general program in the continued research for new antibacterials [28] and antitubercular agents, we have designed

* Corresponding author, Tel.: +91 0 824 2474000x3203; fax: +91 0 824 2474033.
E-mail addresses: avchem@nitk.ac.in, avadhikari123@yahoo.co.in (A.V. Adhikari).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.11.036

some new fused oxazoloquinoline derivatives, wherein active 1,3-oxazole is fused at its 4,5-positions to c-position of quinoline ring, hoping that the newly designed molecules would exhibit enhanced biological activity. Though several reports are there to support the medicinal activity for condensed quinolines with various five and six membered heterocycles [29–33], but there are very few reports on the synthesis and evaluation of biological properties of fused oxazoloquinolines. In the present work, all the new structures have been designed on the basis of combinatorial synthesis, which is the current trend being practiced in most of the drug discoveries. In this communication, we report the synthesis of hitherto unknown title compounds **5a-n** and **6a-n**, starting from 2-bromo-1-phenyl-ethanones **1a-b** and evaluation of their *in vitro* antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* and antitubercular activity against *M. tuberculosis H37Rv* (ATCC 27294).

2. Results and discussion

2.1. Chemistry

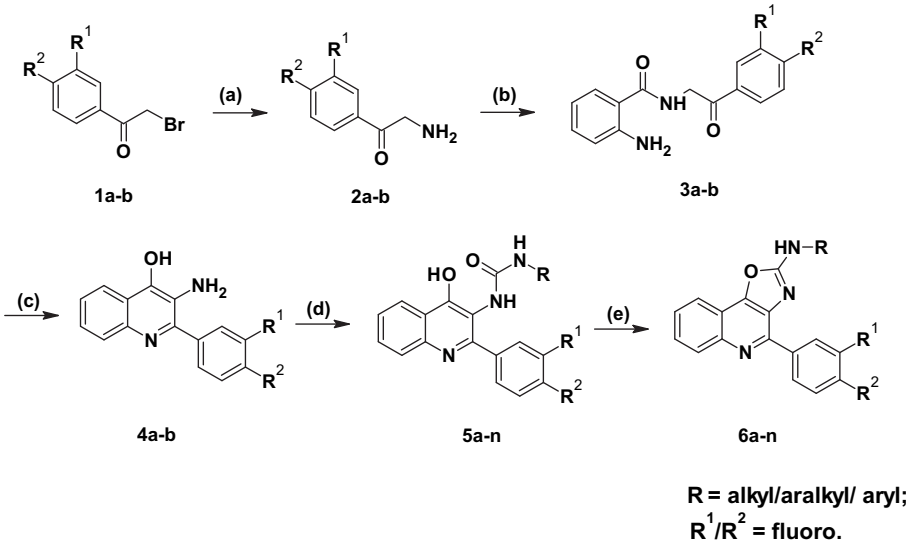
The reaction sequences employed for synthesis of title compounds are shown in Scheme 1. The starting materials viz., 2-bromo-1-phenylethanones **1a-b** were conveniently converted to **2a-b**, by reacting them with sodium azide in dimethyl formamide (DMF) at 0 °C and subsequent reduction of the intermediates to the corresponding amines using palladium in charcoal under hydrogen atmosphere. The aminoacetophenones **2a-b**, on heating at 80 °C with isatoic anhydride in basic medium gave 2-amino-N-[2-(3 or 4 fluorophenyl)-2-oxoethyl]benzamides **3a-b** in good yield. The compounds **3a-b** were readily cyclized to 2-aryl aminoquinolines, **4a-b** via, diazepinone intermediate in the presence polyphosphoric acid (PPA) at 150 °C. Further, the key intermediates, i.e., the urea derivatives, **5a-n** were obtained in excellent yield by refluxing the corresponding 2-aryl aminoquinolines, **4a-b** with different isocyanates in toluene. Finally, the target compounds, viz. 4-(3 and 4 fluorophenyl)-N-(substituted phenyl)[1,3]oxazolo[4,5-c]quinolin-2-amines (**6a-n**) were synthesized in good yield from their precursors **5a-n** by refluxing them with $POCl_3$ at 100 °C. The structures of all the newly synthesized compounds were confirmed by FTIR, ^1H and ^{13}C NMR and LC mass spectral studies and elemental analysis.

The formation of 2-aminoacetophenones, **2a-b** from 2-bromo-1-phenylethanones, **1a-b** was evidenced by its IR, ^1H NMR and mass spectra. Its IR spectrum showed strong bands at 3422 and 1678 cm^{-1} indicating the presence of $-NH_2$ and >C=O groups respectively, while its ^1H NMR spectrum showed one broad doublet at δ 4.62 due to benzylic $-CH_2-$ protons and the presence of a broad singlet at δ 8.48 (which disappeared on D_2O exchange) clearly confirmed the replacement of –Br by $-NH_2$ group. In fact, the total proton count for compounds 2a-b perfectly matched with their proposed structures. The LCMS spectrum of **2a** showed a molecular ion peak at m/z 154(100%), which matches with its molecular formula C_8H_8FNO.

The formation of anthranilamide, **3a-b** from 2-amino-acetophenones, **2a-b** was confirmed by its FTIR and ^1H NMR spectra. The FTIR spectrum of **3a** showed strong bands at 3426 and 3332 cm^{-1} indicating the presence of amino and amidic –NH groups; also the appearance of absorption bands at 1686 and 1652 cm^{-1} of ketonic and amidic >C=O group, respectively, clearly indicated the formation of **3a**. In its ^1H NMR spectrum the appearance of a broad singlet at δ 6.44 confirmed the presence of newly introduced $-NH_2$ group and also the presence of four aromatic peaks as multiplet at δ 7.12, 7.38 and 8.11 corresponding to four protons from the newly introduced phenyl ring confirmed the structure **3a**.

The cyclization of anthranilamide **3a-b** to the corresponding 3-amino-2-(3/4-fluorophenyl)quinolin-4-ol (**4a-b**) was evidenced by its ^1H NMR spectrum; the disappearance of one broad doublet of benzylic ($-CH_2$) protons from δ 4.67 and one broad singlet of $-NH_2$ from δ 6.44 clearly showed the smooth cyclization, also the appearance of a broad singlet at δ 11.44 of –OH proton (which disappeared on D_2O exchange) indicated the aromatization of quinoline ring. Further, the total proton count for compounds **4a-b** perfectly matched with their structures, which further established the cyclization. In its FTIR spectrum, compound **4a** exhibited a broad band at 3519 cm^{-1} due to OH stretching. The LCMS of it showed a molecular ion peak at m/z 255.2 (M + 1), which matches with its molecular formula $C_{15}H_{11}FN_2O$.

The structures of compounds **5a-n** were elucidated by their FTIR, NMR and LCMS analyses. The FTIR spectrum of **5a** revealed the presence of both –OH and –NH groups due to the appearance of absorbance bands at 3508 and 3324 cm^{-1} respectively, while that of >C=O was observed at 1653 cm^{-1}. The ^1H NMR spectrum of **5a** showed one singlet at δ 3.82 for three protons which correspond to



Scheme 1. Synthesis of substituted 1,3-oxazolo [4, 5-c]quinolin-2-amine. (a) i. NaN_3, DMF, 0 °C-RT, 8 h ii. Pd/C, MeOH, RT, 12 h, Yield: 58% (b) isatoic anhydride, Na_2CO_3, 80 °C, 15 min, pH ≈ 7 (c) PPA, 150 °C, 1.5 h. (d) Substituted isocyanate, toluene, 110 °C, 30 min (e) $POCl_3$, 80 °C, 2 h.

newly introduced –OCH_3, also the appearance of a sharp singlet at δ 8.07 that corresponds to –NH proton. Further, the LCMS showed its molecular ion peak at 404.2 (98%), which is in accordance with its molecular formula $C_{23}H_{18}FN_3O_3$.

The formation of the title compounds, **6a-n** from the corresponding urea derivatives, **5a-n** was evidenced by IR, ^{1}H & ^{13}C NMR and mass spectral data. The IR spectrum of **6a** showed a broad band at 3345 cm^{-1} due to –NH stretching, also the disappearance of –OH stretching band from 3508 cm^{-1} indicated the smooth cyclization leading to condensed oxazole ring. Its ^{1}H NMR spectrum indicated the presence of one singlet at δ 10.41 of –NH proton and the disappearance of a broad singlet from δ 11.86 of –OH clearly confirmed the cyclization. Further, the ^{13}C NMR of **6a** showed signals at δ: 56.31, 112.2, 114.5, 116.2, 116.5, 117.8, 118.14, 119.9, 121.0, 121.3, 125.4, 125.9, 126.9, 127.2, 128.7, 130.0, 131.13, 131.2, 134.9, 144.4, 150.6, 150.9, 160.1, 160.9 and 164.1 due to carbon atoms of quinoline and other two aromatic rings. The structure of **6a** was confirmed by LCMS. It showed the molecular ion peak at m/z 386.2 (98%), which conforms to its molecular formula $C_{23}H_{16}FN_3O_2$. Finally, the molecular structure of the compound **6j** was determined by single crystal X-ray diffraction studies. The ORTEP view of the molecular structure shows the spatial atomic positions of compound **6j**, as given in Fig. 1. The characterization data of newly synthesized compounds are summarized in Tables 1 and 2.

2.2. Pharmacology

2.2.1. Antibacterial studies

The newly synthesized compounds **5a-n, 6a-n** were screened for their *in vitro* antibacterial activity against *E. coli* (ATTC-25922), *S. aureus* (ATTC-25923), *P. aeruginosa* (ATCC-27853) and *K. pneumoniae* (recultured) bacterial strains by serial plate dilution method [34,35] using ciprofloxacin as standard. The MICs and zone of inhibition were determined for **5a-n** and **6a-n** and their results are summarized along with that of ciprofloxacin in Tables 3 and 4.

The investigation of antibacterial screening data revealed that all the tested compounds **5a-n** and **6a-n** showed moderate to very good inhibitory activity. The compounds **5a**, **5c-e**, **5g**, **5j**, **5k**, **5n**, **6a-d**, **6g**, **6j-l** and **6n** showed comparatively very good activity against all the bacterial strains with MIC 6.25 μg/mL. The good activity is attributed to the presence of pharmacologically active moieties like 4-tolyl, 4-fluoro phenyl, 3-cyano phenyl and 2-methoxy phenyl attached to –NH group of the title compounds.

2.2.2. Antituberculosis studies

The encouraging results from the antibacterial studies impelled us to go for the preliminary screening of the title compounds for their *in vitro* antituberculosis activity. The compounds were evaluated against *Mycobacterium tuberculosis H37Rv* using broth micro dilution method as per Martin et al with slight modification, with Resazurin as indicator [36,37] and the observed MICs are presented in Table 5. Isoniazid (**INH**) and Rifampicin (**RIF**) were used as standard drugs.

The antituberculosis screening data revealed that all the tested compounds **5a-n** and **6a-n** showed moderate to very good inhibitory activity. The compounds **5a**, **5k**, **6a**, **6c**, **6g**, **6j**, **6k** and **6n** showed very good antituberculosis activity. The good activity is attributed to the presence of substituted aryl group at position-2 of quinoline ring. Occurrence of pharmacologically active moieties like 2-methoxy phenyl, 3-chloro phenyl and 4-fluoro phenyl at –NH group of the title compounds enhances the activity. The structure–activity relationship (**SAR**) study reveals that with the introduction of 1,3-oxazole ring has tremendously increased the activity of the title molecules. It has been observed that the urea derivatives **5c**, **5g**, **5j** and **5n** which were inactive against **MTB**, on cyclization to 1,3-oxazoloquinolines i.e., **6c**, **6g**, **6j** and **6n** showed enhanced activity. It is interesting to note that eight compounds, viz., **5a**, **15k**, **6a**, **6c**, **6g**, **6j**, **6k** and **6n** were found to be more potent than **INH** (MIC: 1.5 μg/mL) with MIC 1 μg/mL whereas eleven compounds, viz., **5c**, **5d**, **5g**, **5j**, **5l**, **5n**, **6b**, **6d**, **6f**, **6i** and **6l** showed moderate activity at MIC 10 μg/mL.

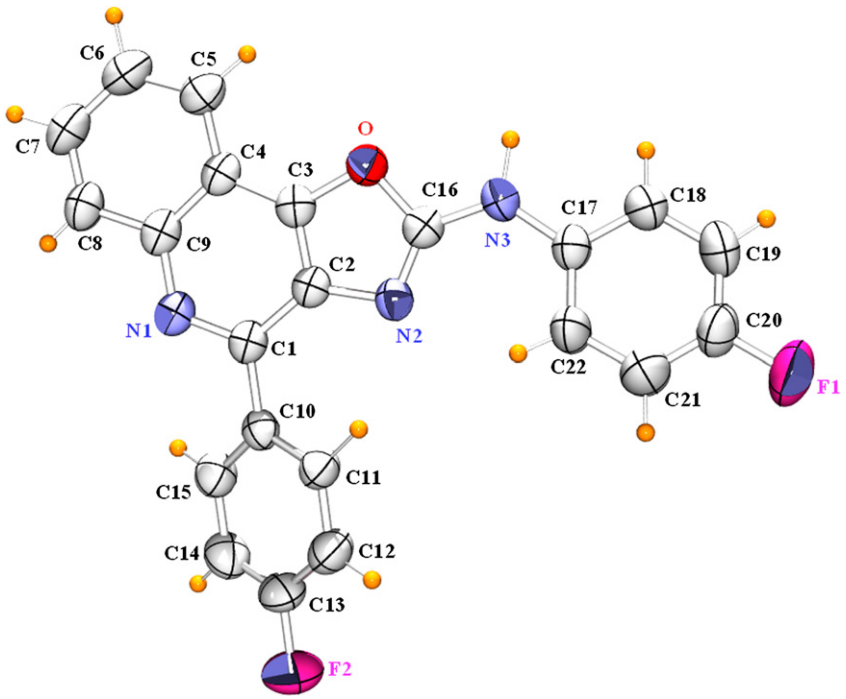
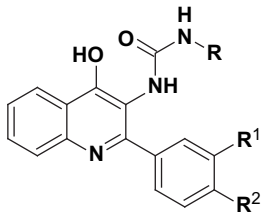


Fig. 1. ORTEP diagram showing the X-ray crystal structure of **6j**.

Table 1
Characterization data of compounds 5a-n.

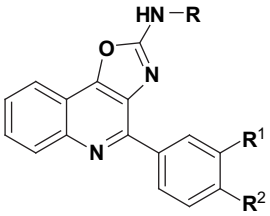


Compd	R	R^1	R^2	Molecular formula/ Mol. Weight	M.P (°C)	Yield %	Analysis % found Found (Calc.)		
							C	H	N
5a	2-methoxy phenyl	F	H	$C_{23}H_{18}FN_3O_3$/403	245	98	68.48 (68.44)	4.50 (4.55)	10.42 (10.46)
5b	4-(methylthio) phenyl	F	H	$C_{23}H_{18}FN_3O_2S$/419	247	95	65.86 (65.88)	4.33 (4.38)	10.02 (10.07)
5c	Benzyl	F	H	$C_{23}H_{18}FN_3O_2$/387	249	87	71.31 (71.36)	4.68 (4.71)	10.85 (10.89)
5d	Phenyl	F	H	$C_{22}H_{16}FN_3O_2$/373	254	95	70.77 (70.80)	4.32 (4.35)	11.25 (11.29)
5e	3-cyano phenyl	F	H	$C_{23}H_{15}FN_4O_2$/398	232	92	69.34 (69.39)	3.80 (3.86)	14.06 (14.08)
5f	Pentyl	F	H	$C_{21}H_{22}FN_3O_2$/367	259	85	68.65 (68.69)	6.04 (6.09)	11.44 (11.48)
5g	4-fluoro phenyl	F	H	$C_{22}H_{15}F_2N_3O_2$/391	265	95	67.52 (67.55)	3.86 (3.88)	10.74 (10.77)
5h	Phenylethyl	F	H	$C_{24}H_{20}FN_3O_2$/401	250	81	71.81 (71.85)	5.02 (5.07)	10.47 (10.44)
5i	3,5 dimethyl phenyl	H	F	$C_{24}H_{20}FN_3O_2$/401	275	96	71.81 (71.78)	5.02 (5.07)	10.47 (10.50)
5j	4-fluoro phenyl	H	F	$C_{22}H_{15}F_2N_3O_2$/391	290	92	67.52 (67.55)	3.86 (3.82)	10.74 (10.79)
5k	2-methoxy phenyl	H	F	$C_{23}H_{18}FN_3O_3$/403	255	95	68.48 (68.50)	4.50 (4.55)	10.42 (10.44)
5l	Benzyl	H	F	$C_{23}H_{18}FN_3O_2$/387	256	82	71.31 (71.33)	4.68 (4.64)	10.85 (10.88)
5m	Pentyl	H	F	$C_{21}H_{22}FN_3O_2$/367	261	80	68.65 (68.69)	6.04 (6.02)	11.44 (11.47)
5n	3-chloro phenyl	H	F	$C_{22}H_{15}ClFN_3O_2$/407	264	94	64.79 (64.82)	3.71 (3.76)	10.30 (10.33)

2.3. X-ray crystallographic analysis of 6j

The X-ray crystallographic analysis of **6j** was determined on a colorless plate crystal, with approximate dimensions 0.30 mm × 0.25 mm × 0.15 mm, grown from the slow evaporation of a dilute ethanol solution at room temperature. The crystal structure solution was solved by full matrix least-squares method using **SHELXL97**. All the atoms were located in different Fourier maps and refined isotropically, using a riding model and all the projections were generated using **ORTEP**. The details of the crystal data and refinement are shown in Table 6. Also the single crystal images for compound **6j** are given in Fig. 2.

Table 2
Characterization data of compounds 6a-n.



Compd	R	R^1	R^2	Molecular formula/ Mol. Weight	M.P (°C)	Yield %	Analysis % found Found (Calc.)		
							C	H	N
6a	2-methoxy phenyl	F	H	$C_{23}H_{16}FN_3O_2$/385	223	92	71.68 (71.66)	4.18 (4.22)	10.90 (10.94)
6b	4-(methylthio) phenyl	F	H	$C_{23}H_{16}FN_3OS$/401	233	96	68.81 (68.82)	4.02 (4.00)	10.47 (10.49)
6c	Benzyl	F	H	$C_{23}H_{16}FN_3O$/369	198	81[a]	74.78 (74.77)	4.37 (4.39)	11.38 (11.40)
6d	Phenyl	F	H	$C_{22}H_{14}FN_3O$/355	249	91	74.36 (74.39)	3.97 (3.99)	11.82 (11.88)
6e	3-cyano phenyl	F	H	$C_{23}H_{13}FN_4O$/380	274	98	72.6 (72.65)	3.44 (3.46)	14.73 (14.77)
6f	Pentyl	F	H	$C_{21}H_{20}FN_3O$/349	162	82[a]	72.19 (72.22)	5.77 (5.79)	12.03 (12.04)
6g	4-fluoro phenyl	F	H	$C_{22}H_{13}F_2N_3O$/373	257	89	70.77 (70.79)	3.51 (3.55)	11.25 (11.28)
6h	Phenylethyl	F	H	$C_{24}H_{18}FN_3O$/383	223	79[a]	75.18 (75.20)	4.73 (4.77)	10.96 (10.99)
6i	3,5 dimethyl phenyl	H	F	$C_{24}H_{18}FN_3O$/383	285	97	75.18 (75.21)	4.73 (4.75)	10.96 (10.95)
6j	4-fluoro phenyl	H	F	$C_{22}H_{13}F_2N_3O$/373	280	97	70.77 (70.80)	3.51 (3.52)	11.25 (11.22)
6k	2-methoxy phenyl	H	F	$C_{23}H_{16}FN_3O_2$/385	220	92	71.68 (71.70)	4.18 (4.20)	10.90 (10.90)
6l	Benzyl	H	F	$C_{23}H_{16}FN_3O$/369	168	77[a]	74.78 (74.80)	4.37 (4.39)	11.38 (11.36)
6m	Pentyl	H	F	$C_{21}H_{20}FN_3O$/349	182	81[a]	72.19 (72.22)	5.77 (5.79)	12.03 (12.00)
6n	3-chloro phenyl	H	F	$C_{22}H_{13}ClFN_3O$/389	293	92	67.79 (67.82)	3.36 (3.39)	10.78 (10.81)

[a] Yield obtained after column purification.

Table 3
Antibacterial activity of quinoline-urea derivative 5a-n.

Compound	MIC in μg/mL and zone of inhibition in mm			
	S. aureus (ATCC 25923)	*E. coli* (ATCC 25922)	*P. aeruginosa* (ATCC 27853)	*K.pneumoniae* (recultured)
5a	6.25 (19)	6.25 (22)	6.25 (18)	6.25 (19)
5b	50 (<10)	6.25 (22)	50 (<10)	50 (<10)
5c	6.25 (18)	6.25 (21)	6.25 (20)	6.25 (18)
5d	6.25 (17)	6.25 (20)	6.25 (18)	6.25 (20)
5e	6.25 (19)	6.25 (23)	6.25 (19)	6.25 (18)
5f	12.5 (12)	6.25 (22)	12.5 (11)	12.5 (12)
5g	6.25 (20)	6.25 (21)	6.25 (19)	6.25 (16)
5h	50 (<10)	50 (<10)	50 (<10)	50 (<10)
5i	50 (<10)	50 (<10)	50 (<10)	50 (<10)
5j	6.25 (18)	6.25 (24)	6.25 (17)	6.25 (16)
5k	6.25 (17)	6.25 (21)	6.25 (16)	6.25 (19)
5l	6.25 (16)	50 (<10)	50 (<10)	50 (<10)
5m	50 (<10)	6.25 (20)	50 (<10)	50 (<10)
5n	6.25 (18)	6.25 (22)	6.25 (20)	6.25 (20)
Ciprofloxacin (Standard)	6.25 (24)	6.25 (29)	6.25 (25)	6.25 (22)

The MIC values where evaluated at concentration range, 6.25–50 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm.

3. Experimental section

3.1. General

All reagents were purchased from Aldrich. Solvents used were extra dried. Final purifications were carried out using Quad biotage Flash purifier (A Dyax Corp. Company). TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and molybidinic acid. Melting points were determined using Buchi B-540 and are uncorrected. Elemental analyses were carried out on an automatic Flash EA 1112 Series, CHNSO Analyzer (Thermo). X-Ray diffraction studies where carried on an Xcalibur E Oxford Diffraction system (Varian, California, USA). All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz, 75.12 MHz), Bruker BioSpin Corp., Germany. Molecular weights of unknown compounds were checked by LCMS 6200 series Agilent Technology. Chemical shifts are reported in ppm (δ) with reference to internal standard TMS. The signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; brs, broad singlet, brt, broad triplet.

Table 4
Antibacterial activity of fused quinoline–oxazole derivative 6a-n.

Compound	MIC in μg/mL and zone of inhibition in mm			
	S. aureus (ATCC 25923)	*E. coli* (ATCC 25922)	*P. aeruginosa* (ATCC 27853)	*K.pneumoniae* (recultured)
6a	6.25 (21)	6.25 (24)	6.25 (21)	6.25 (21)
6b	6.25 (20)	6.25 (23)	6.25 (20)	6.25 (22)
6c	6.25 (22)	6.25 (23)	6.25 (19)	6.25 (18)
6d	6.25 (20)	6.25 (26)	6.25 (22)	6.25 (20)
6e	12.5 (11)	12.5 (16)	12.5 (14)	12.5 (12)
6f	12.5 (11)	6.25 (24)	12.5 (14)	12.5 (12)
6g	6.25 (22)	6.25 (25)	6.25 (25)	6.25 (19)
6h	50 (<10)	50 (<10)	50 (<10)	50 (<10)
6i	12.5 (11)	6.25 (24)	12.5 (14)	12.5 (12)
6j	6.25 (20)	6.25 (28)	6.25 (22)	6.25 (20)
6k	6.25 (22)	6.25 (27)	6.25 (19)	6.25 (23)
6l	6.25 (21)	6.25 (24)	6.25 (24)	6.25 (19)
6m	50 (<10)	50 (<10)	50 (<10)	50 (<10)
6n	6.25 (22)	6.25 (26)	6.25 (24)	6.25 (21)
Ciprofloxacin (Standard)	6.25 (26)	6.25 (28)	6.25 (31)	6.25 (25)

The MIC values where evaluated at concentration range, 6.25–50 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm.

Table 5
In vitro Antituberculosis evaluation of the synthesized compounds 5a-n, 6a-n.

Compd	MIC (μg/mL)	% Inhibition
5a	1	99
5b	>100[a]	0
5c	10	95
5d	10	95
5e	>100[a]	0
5f	>100[a]	0
5g	10	95
5h	>100[a]	0
5i	>100[a]	0
5j	10	95
5k	1	99
5l	10	95
5m	>100[a]	0
5n	10	95
6a	1	99
6b	10	95
6c	1	99
6d	10	95
6e	>100[a]	0
6f	10	95
6g	1	99
6h	>100[a]	0
6i	10	95
6j	1	99
6k	1	99
6l	10	95
6m	>100[a]	0
6n	1	99
Isoniazid (INH)	1.5	95
Rifampicin (RIF)	0.5	99

[a] MIC > 100 μg/mL indicates that the strain is resistant to tested substance.

Table 6
Crystal data and measurement detail for compound **6j**.

Crystal data	
Empirical formula	$C_{22}H_{13}F_2N_3O$
Formula weight	373.35
Crystal system	Monoclinic
Crystal dimension	0.30 mm × 0.25 mm × 0.15 mm
Space group	p21c
a (Å)	13.8773(4)
b (Å)	7.04841(16)
c (Å)	19.7470(6)
Volume (Å^3)	1843.63(9)
Angle α, β, γ	90, 107.34(3), 90
Z	8
Crystal density, g/cm^3	1.197
F_{000}	680
μ (mm^{-1})	0.08
Absorption coefficient	0.089
Cut-off used in R-factor calculations	$Fo^2 > 2\sigma(Fo^2)$
R (Fo)	0.0652
R_w (Fo^2)	0.1796
Temperature (T)	293(2)
Radiation wavelength	0.71073
Radiation type	MoKα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}	−17
h_{max}	17
k_{min}	−8
k_{max}	8
l_{min}	−24
l_{max}	24
Reflns (Fo)	4871
Structure refinement	SHELXL-97

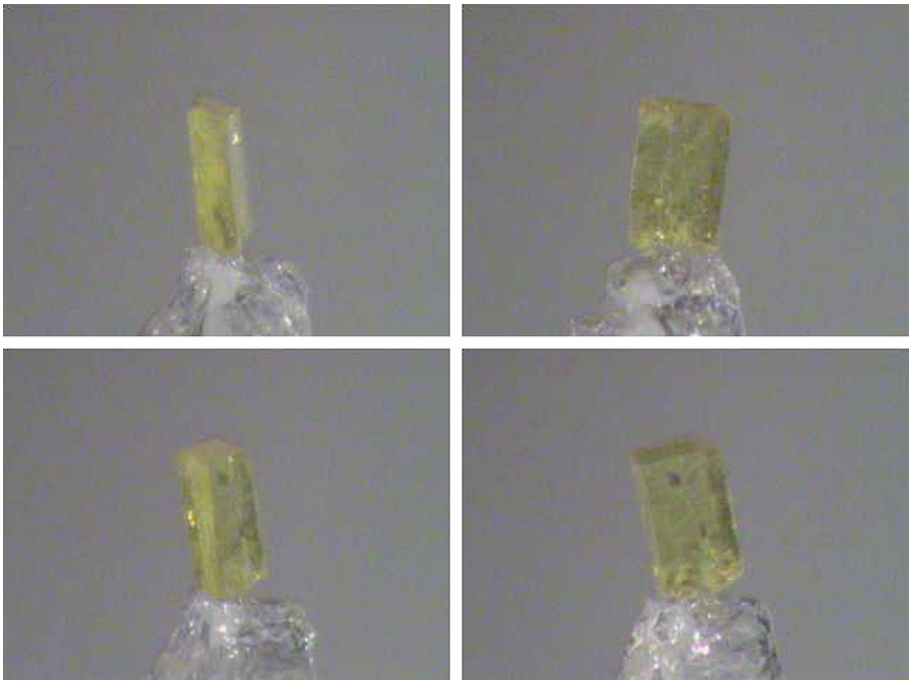


Fig. 2. Single crystal images of compound **6j**.

3.2. General procedure for the synthesis of 2-amino-1-(substituted fluorophenyl)ethanone 2a-b

To a solution of substituted 2-bromo-1-phenylethanone **1a-b** (43.3 mmol) in 100 mL of DMF at 0 °C, solid NaN_3 (52 mmol) was added portion wise while stirring and stirring was continued at room temperature for 6 h. The completion of the reaction was monitored by TLC. The reaction mixture was then poured into cold water (200 mL) and the compound was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was dried over sodium sulphate and concentrated to get the crude product as yellow oil. The crude product was taken as such for the next step without further purification. The crude oil thus obtained was dissolved in methanol (100 mL) and it was mixed with palladium in charcoal (10 mol%) while stirring; the stirring was continued under H_2 atmosphere (2 kg/cm^2) for 4 h. The reaction was monitored by TLC for completion. The reaction mixture was filtered and concentrated to get crude product as colorless oil. This crude oil was made HCl salt with 50 mL of 6 N HCl in 1,4 dioxane to get product as an off white solid.

*3.2.1. 2-Amino-1-(3-fluorophenyl)ethanone **(2a)***

Compound **2a** was obtained as off white solid. Yield 77%. IR (KBr, cm^{-1}) υ: 3422 (>NH), 1678 (>C=O), 1164 (>C–F). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 4.62 (brd, –CH_2, 2H), 7.36 (m, –CH, 1H), 7.64 (m, –CH, 1H), 7.88 (m, –CH, 2H), 8.48 (brs, –NH_2, 2H, disappeared on D_2O exchange).

*3.2.2. 2-Amino-1-(4-fluorophenyl)ethanone **(2b)***

Compound **2b** was obtained as off white solid. Yield 81%. IR (KBr, cm^{-1}) υ: 3438 (>NH), 1688 (>C=O), 1162 (>C–F). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 4.56 (brt, –CH_2, 2H), 7.39 (m, –CH, 2H), 8.09 (m, –CH, 1H), 8.53 (brs, –NH_2, 2H, disappeared on D_2O exchange).

*3.3. General procedure for the synthesis of 2-amino-N-[2-(substituted fluorophenyl)-2-oxoethyl]benzamide **3a-b***

A mixture of substituted 2-aminoacetophenone hydrochloride **2a-b** (33 mmol), isatoic anhydride (36 mmol) and sodium carbonate (20 mmol) dissolved in water (100 mL) was stirred for 5 min, the reaction mixture was gradually heated to 85 °C over 30 min. At 30 °C the mixture began to foam. On reaching 85 °C it was stirred for a further 10 min. After this, the solid phase was filtered off and washed with a solution of sodium carbonate and water to neutral pH. The solid was dried in vacuo and taken as such for the next step without any further purification.

*3.3.1. 2-Amino-N-[2-(3-fluorophenyl)-2-oxoethyl]benzamide **(3a)***

Compound **3a** was obtained as off white solid. Yield 85%. IR (KBr, cm^{-1}) υ: 3426,3334 (>NH), 1686, 1652 (>C=O), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ; 4.67 (d, –CH_2, 2H, J = 5.7), 6.44 (brs, –NH_2, 2H, disappeared on D_2O exchange), 6.52 (m, –CH, 1H), 7.12 (t, –CH, 1H), 7.38 (m, –CH, 1H), 7.64 (m, –CH, 1H), 7.86 (m, –CH, 2H), 8.11 (m, –CH, 2H), 8.54 (brt, –NH, 1H, disappeared on D_2O exchange).

*3.3.2. 2-Amino-N-[2-(4-fluorophenyl)-2-oxoethyl]benzamide **(3b)***

Compound **3b** was obtained as off white solid. Yield 85%. IR (KBr, cm^{-1}) υ: 3426,3334 (>NH), 1684, 1652 (>C=O), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ; 4.68 (d, –CH_2, 2H, J = 5.7), 6.4 (brs, –NH_2, 2H, disappeared on D_2O exchange), 6.52 (m, –CH, 1H), 6.70 (d, –CH, 1H, J = 8.1) 7.14 (t, –CH, 1H), 7.38 (m, –CH, 2H), 7.55 (d, –CH, 2H, J = 8.4), 8.11 (m, –CH, 2H), 8.57 (brt, –NH, 1H, disappeared on D_2O exchange).

*3.4. General procedure for the synthesis of 3-amino-2-(substituted fluorophenyl)quinolin-4-ol **4a-b***

Freshly prepared PPA (50 g) was added to 2-amino-N-[2-(substituted fluorophenyl)-2-oxoethyl]benzamides **3a-b** (18 mmol) and the reaction mixture was heated to 150–160 °C. The heating was continued for further 2 h at this temperature. Reaction completion was monitored by TLC. The reaction mixture was then poured onto solid sodium carbonate (60 g), and after foaming stopped, water (600 mL) was added. After 30 min of stirring the solid product obtained was filtered off and washed with plenty of water and dried.

*3.4.1. 3-Amino-2-(3-fluorophenyl)quinolin-4-ol **(4a)***

Compound **4a** was obtained as green solid. Yield 93%. IR (KBr, cm^{-1}) υ: 3519 (O–H), 3449 (>NH), 1164 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 3.38 (brs, $–NH_2$, 2H), 7.19 (m, –CH, 1H), 7.35(m, –CH, 1H), 7.64–7.50 (m, –CH, 5H), 8.11 (d, –CH, 1H, J = 8.1), 11.44 (brs, –OH, 1H).

*3.4.2. 3-Amino-2-(4-fluorophenyl)quinolin-4-ol **(4b)***

Compound **4b** was obtained as pale yellow solid. Yield 88%. IR (KBr, cm^{-1}) υ: 3519 (O–H), 3449 (>NH), 1169 (>C–F). ^1H NMR (400 MHz, DMSO-d_6) δ; 4.26 (brs, $–NH_2$, 2H, disappeared on D_2O exchange), 7.22 (t, –CH, 1H, J = 8.1), 7.44 (m, –CH, 2H), 7.52 (t, –CH, 1H, J = 5.4), 7.57 (d, –CH, 1H, J = 8.4), 7.79–7.75 (m, –CH, 2H), 8.12 (d, –CH, 1H, J = 8.1), 11.45 (brs, –OH, 1H, disappeared on D_2O exchange).

*3.5. General procedure for the synthesis of quinoline urea **5a-n***

To a suspension of 3-amino-2-(substituted fluorophenyl)-quinolin-4-ol **4a-b** (2 mmol) in dry toluene (4 mL) equimolar quantity of substituted isocyanate (2 mmol) was added slowly and the reaction mixture was heated at 110 °C for 2 h. The completion of the reaction was monitored by TLC. The solid obtained on cooling was filtered and washed with n-hexane (50 mL).

*3.5.1. 1-[2-(3-Fluorophenyl)-4-hydroxyquinolin-3-yl]-3-(2-methoxyphenyl)urea **(5a)***

Compound **5a** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3508 (O–H), 3344 (>NH), 1653 (>C=O), 1169 (>C–F), 1112 (>C–O). ^1H NMR (300 MHz, DMSO-d_6) δ; 3.82 (s, $–OCH_3$, 3H), 6.89–6.77 (m, –CH, 2H), 6.97(d, –CH, 1H, J = 9), 7.37–7.32 (m, –CH, 3H), 7.70–7.48 (m, –CH, 4H), 7.94 (d, –CH, 1H, J = 7.8), 8.07 (s, –NH, 1H), 8.16 (d, –CH, 1H, J = 8.1), 8.22 (brs, –NH, 1H), 11.86 (brs, –OH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 404 (M + 1)

*3.5.2. 1-[2-(3-Fluorophenyl)-4-hydroxyquinolin-3-yl]-3-[4-(methylthio)phenyl]urea **(5b)***

Compound **5b** was obtained as brown solid. IR (KBr, cm^{-1}) υ: 3494 (O–H), 3340 (>NH), 1645(>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 2.40 (s, $–SCH_3$, 3H), 7.28–7.13 (m, –CH, 2H), 7.42–7.31(m, –CH, 5H), 7.69–7.49 (m, –CH, 3H), 7.70 (s, –CH, 2H), 8.13 (d, –CH, 1H, J = 8.1), 8.75 (brs, –CH, 1H), 11.88 (brs, –OH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 420 (M + 1)

*3.5.3. 1-Benzyl-3-[2-(3-fluorophenyl)-4-hydroxyquinolin-3-yl] urea **(5c)***

Compound **5c** was obtained as pale yellow solid. IR (KBr, cm^{-1}) υ: 3504 (O–H), 3326 (>NH), 1650 (>C=O), 1169 (>C–F). LC–MS (ESI) m/z 388 (M + 1)

*3.5.4. 1-[2-(3-Fluorophenyl)-4-hydroxyquinolin-3-yl]-3-phenylurea **(5d)***

Compound **5d** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3512 (O–H), 3339 (>NH), 1648 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 6.89 (t, –CH, 1H, J = 7.8), 7.20 (m, –CH, 2H), 7.38–7.31 (m, –CH, 5H), 7.62–7.50 (m, –CH, 3H), 7.62 (s, –CH, 2H), 8.17 (d, –CH, 1H, J = 7.5), 8.74(brs, NH, 1H), 11.87 (brs, NH, 1H, disappeared on D_2O exchange).

*3.5.5. 1-(3-Cyanophenyl)-3-[2-(3-fluorophenyl)-4-hydroxyquinolin-3-yl]urea **(5e)***

Compound **5e** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3498 (O–H), 3332 (>NH), 2224 (–CN), 1648 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 7.45–7.32 (m, –CH, 4H), 7.62–7.49 (m, –CH, 5H), 7.71–7.70 (m, –CH, 2H), 7.82 (s, –CH, 1H), 8.16 (d, –CH, 1H, J = 8.1), 9.05 (brs, –NH, 1H, disappeared on D_2O exchange), 11.91 (brs, NH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 399 (M + 1)

*3.5.6. 1-[2-(3-Fluorophenyl)-4-hydroxyquinolin-3-yl]-3-pentylurea **(5f)***

Compound **5f** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3496 (O–H), 3324 (>NH), 1623 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 0.83 (t, $–CH_3$, 3H, J = 6.6), 1.23–1.15 (m, $–(CH_2)_3$, 6H), 2.89 (m, $–CH_2$, 2H), 6.1 (brt, NH, 1H), 6.95 (s, NH, 1H), 7.33 (m, –CH, 2H), 7.55–7.47(m, –CH, 3H), 7.67 (brs, –CH, 2H), 8.14 (d, –CH, 1H, J = 6.9), 11.86 (brs, NH, 1H, disappeared on D_2O exchange).

*3.5.7. 1-(4-Fluorophenyl)-3-[2-(3-fluorophenyl)-4-hydroxyquinolin-3-yl]urea **(5g)***

Compound **5g** was obtained as pale brown solid. IR (KBr, cm^{-1}) υ: 3510 (O–H), 3334 (>NH), 1642 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 7.08–7.00 (m, –CH, 2H), 7.37–7.30 (m, –CH, 5H), 7.58–7.45 (m, –CH, 4H), 7.70 (s, –CH, 1H), 8.16 (d, –CH, 1H, J = 8.4), 8.76 (brs, –NH, 1H), 11.88 (brs, NH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 392 (M + 1)

*3.5.8. 1-[2-(3-Fluorophenyl)-4-hydroxyquinolin-3-yl]-3-(2-phenylethyl)urea **(5h)***

Compound **5h** was obtained as pale brown solid. IR (KBr, cm^{-1}) υ: 3512 (O–H), 3298 (>NH), 1628 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 2.57 (t, $–CH_2$, 2H, J = 7.2), 3.14 (q, $–CH_2$, 2H, J = 6.9), 6.20 (t, NH, 1H, J = 6), 7.06 (s, NH, 1H), 7.28–7.11 (m, –CH, 5H), 7.39–7.31(m, –CH, 2H), 7.67–7.45 (m, –CH, 3H), 7.68 (s, –CH, 2H), 8.15 (d, –CH, 1H, J = 8.1), 11.76 (brs, NH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 402 (M + 1)

*3.5.9. 1-(3,5-Dimethylphenyl)-3-[2-(4-fluorophenyl)-4-hydroxyquinolin-3-yl]urea **(5i)***

Compound **5i** was obtained as pale yellow solid. IR (KBr, cm^{-1}) υ: 3510 (O–H), 3340 (>NH), 1644 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 2.17 (s, $–(CH_3)_2$, 6H), 6.53 (s, –CH, 1H), 7.06 (s, –CH, 2H), 7.32 (s, –NH, 1H), 7.41–7.33(m, –CH, 3H), 7.74–7.65 (m, –CH, 4H), 8.16 (d, –CH, 1H, J = 8.1), 8.54 (brs, –NH, 1H, disappeared on D_2O exchange), 11.82 (brs, NH, 1H, disappeared on D_2O exchange).

*3.5.10. 1-(4-Fluorophenyl)-3-[2-(4-fluorophenyl)-4-hydroxyquinolin-3-yl]urea **(5j)***

Compound **5j** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3502 (O–H), 3338 (>NH), 1648 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 7.14–7.00 (m, –CH, 2H), 7.46–7.28 (m, –CH, 6H), 7.74–7.65 (m, –CH, 4H), 8.16 (d, –CH, 1H, J = 8.1), 8.73 (brs, –NH, 1H, disappeared on D_2O exchange), 11.84 (brs, NH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 392 (M + 1)

*3.5.11. 1-[2-(4-Fluorophenyl)-4-hydroxyquinolin-3-yl]-3-(2-methoxyphenyl)urea **(5k)***

Compound **5k** was obtained as white solid. IR (KBr, cm^{-1}) υ: 3516 (O–H), 3334 (>NH), 1644 (>C=O), 1169 (>C–F). ^1H NMR (300 MHz, DMSO-d_6) δ; 3.82 (s, $–OCH_3$, 3H), 6.89–6.79 (m, –CH, 2H), 6.97(m, –CH, 1H), 7.41–7.33 (m, –CH, 3H), 7.73–7.68 (s, –CH, 4H), 7.96 (m, –CH, 1H), 8.04 (s, –CH, 1H), 8.15 (d, –CH, 1H, J = 8.1), 8.23 (brs, –NH, 1H), 11.83 (brs, NH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 404 (M + 1)

*3.5.12. 1-Benzyl-3-[2-(4-fluorophenyl)-4-hydroxyquinolin-3-yl]urea **(5l)***

Compound **5k** was obtained as yellow solid. IR (KBr, cm^{-1}) υ: 3504 (O–H), 3326 (>NH), 1650 (>C=O), 1169 (>C–F). LC–MS (ESI) m/z 388 (M + 1)

*3.5.13. 1-[2-(4-Fluorophenyl)-4-hydroxyquinolin-3-yl]-3-pentylurea **(5m)***

Compound **5m** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3494 (O–H), 3322 (>NH), 1622 (>C=O), 1169 (>C–F).^{1}H NMR (300 MHz, DMSO-d_6) δ; 0.85 (t, $-CH_3$, 3H, J = 6.6), 1.29–1.14 (m, $-(CH_2)_3$, 6H), 2.87 (m, $-CH_2$, 2H), 6.1 (t, NH, 1H,J = 5.4), 6.92 (s, NH, 1H), 7.36–7.30 (m, –CH, 3H), 7.70–7.62 (m, –CH, 4H), 8.14 (d, –CH, 1H, J = 7.8), 11.70 (brs, NH, 1H, disappeared on D_2O exchange).

*3.5.14. 1-(3-Chlorophenyl)-3-[2-(4-fluorophenyl)-4-hydroxyquinolin-3-yl]urea **(5n)***

Compound **5n** was obtained as yellow solid. 3512 (O–H), 3342 (>NH), 1622 (>C=O), 1169 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ; 6.95–6.91 (m, CH, 1H), 7.31–7.14 (m, –CH, 2H), 7.41–7.34 (m, –CH, 4H), 7.58 (s, –CH, 1H), 7.73–7.68 (m, –CH, 4H), 8.16 (d, –CH, 1H, J = 8.1), 8.89 (brs, –NH, 1H, disappeared on D_2O exchange), 11.86 (brs, NH, 1H, disappeared on D_2O exchange).

*3.6. General procedure for the synthesis of oxazoloquinoline **6a-n***

A mixture of substituted urea derivatives of quinoline **5a-n** (2 mmol) and freshly distilled $POCl_3$ (4 mL) was heated at 80 °C for 2 h. The reaction was monitored by TLC. After completion of the reaction, excess of $POCl_3$ was distilled off. The residue thus obtained was basified by saturated $NaHCO_3$ solution. After this, the solid phase was filtered and dried. Some of the final compounds were purified by biotage column chromatography using pet ether/ethyl acetate as the eluent.

*3.6.1. 4-(3-Fluorophenyl)-N-(2-methoxyphenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6a)***

Compound **6a** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 3.89 (s, $-OCH_3$, 3H), 7.19–7.08 (m, –CH, 3H), 7.41 (m, –CH, 1H), 7.80–7.68 (m, –CH, 3H), 8.09 (d, –CH, 1H, J = 6.6), 8.17 (d, –CH, 1H, J = 7.5), 8.27 (d, –CH, 1H, J = 7.5), 8.59–8.50 (m, –CH, 2H), 10.41 (s, NH, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 56.31, 112.2, 114.5, 116.2, 116.5, 117.8, 118.14, 119.9, 121.0, 121.3, 125.4, 125.9, 126.9, 127.2, 128.7, 130.0, 131.13, 131.2, 134.9, 144.4, 150.6, 150.9, 160.1, 160.9, 164.1. LC–MS (ESI) m/z 386 (M + 1)

*3.6.2. 4-(3-Fluorophenyl)-N-[4-(methylthio)phenyl][1,3]oxazolo[4,5-c]quinolin-2-amine **(6b)***

Compound **6b** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 2.50 (s, $-SCH_3$, 3H), 7.48–7.35 (m, –CH, 3H), 7.84–7.67 (m, –CH, 5H), 8.09 (d, –CH, 1H, J = 6.6), 8.26 (d, –CH, 1H, J = 7.5), 8.46 (d, –CH, 1H, J = 7.5), 8.48 (d, –CH, 1H, J = 8.1), 11.35 (s, NH, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 16.1, 114.5, 115.9, 116.2, 117.7, 118.0, 119.8, 125.8, 127.6, 128.0, 128.5, 129.8, 131.2, 132.0, 134.7, 136.0, 141.7, 144.4, 150.4, 158.8, 160.9, 164.2. LC–MS (ESI) m/z 402 (M + 1)

*3.6.3. N-benzyl-4-(3-fluorophenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6c)***

Compound **6c** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 4.67 (d, $-CH_2$, 2H, J = 5.7), 7.48–7.28 (m, –CH, 4H), 7.58–7.50 (m, –CH, 2H), 7.68–7.60 (m, –CH, 3H), 7.99 (d, –CH, 1H, J = 7.5), 8.11 (d, –CH, 1H, J = 7.5), 8.59 (m, –CH, 1H), 8.65 (d, –CH, 1H, J = 8.1), 9.12 (t, NH, 1H, J = 6). LC–MS (ESI) m/z 370 (M + 1)

*3.6.4. 4-(3-Fluorophenyl)-N-phenyl[1,3]oxazolo[4,5-c]quinolin-2-amine **(6d)***

Compound **6d** was obtained as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 7.36–7.08 (m, –CH, 1H), 7.47–7.37 (m, –CH, 3H), 7.77–7.65 (m, –CH, 3H), 8.06 (m, –CH, 2H), 8.30 (dd, –CH, 2H), 8.60 (m, –CH, 1H), 8.30 (d, –CH, 1H, J = 7.8), 11.23 (brs, NH, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 114.5, 116.0, 116.3, 118.3, 119.9, 123.4, 125.8, 127.5, 128.6, 129.6, 129.9, 131.1, 131.2, 134.7, 136.8, 138.4, 141.7, 144.5, 150.5, 159.0, 160.9, 164.2. LC–MS (ESI) m/z 356 (M + 1).

*3.6.5. 3-{[4-(3-Fluorophenyl)[1,3]oxazolo[4,5-c]quinolin-2-yl]amino}benzonitrile **(6e)***

Compound **6e** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 7.45–7.39 (m, –CH, 1H), 7.58 (d, –CH, 1H, J = 6.6), 7.81–7.63 (m, –CH, 4H), 8.11–8.01 (dd, –CH, 2H), 8.23 (d, –CH, 1H, J = 8.4), 8.35 (s, –CH, 1H), 8.58 (dd, –CH, 1H), 8.63 (d, –CH, 1H, J = 7.5), 11.72 (s, NH, 1H, disappeared on D_2O exchange). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 112.3, 114.6, 115.8 (CN), 116.1, 117.5, 117.8, 119.1, 119.7, 120.5, 122.6, 125.4, 126.5, 128.2, 128.4, 129.6, 130.9, 133.9, 139.4, 142.4, 144.8, 149.8, 158.0, 160.9, 164.2. LC–MS (ESI) m/z 381 (M + 1)

*3.6.6. 4-(3-Fluorophenyl)-N-pentyl[1,3]oxazolo[4,5-c]quinolin-2-amine **(6f)***

Compound **6f** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 0.91 (t, $-CH_3$, 3H, J = 6.6), 1.40–1.35 (m, $-(CH_2)_2$, 4H), 1.70–1.65 (m, $-CH_2$, 2H), 3.45 (m, $-N(CH_2)$, 2H), 7.33 (brt, NH, 1H), 7.66–7.59 (m, –CH, 3H), 7.97 (d, –CH, 1H, J = 7.5), 8.10 (d, –CH, 1H, J = 7.5), 8.66–8.54 (m, –CH, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.9, 22.3, 28.8, 29.3, 43.4, 115.2, 115.8, 116.15, 116.2, 118.8, 124.7, 124.8, 126.6, 127.3, 129.9, 130.0, 134.8, 139.9, 140.0, 143.9, 146.4, 149.6, 161.4, 161.8, 164.6. LC–MS (ESI) m/z 350 (M + 1)

*3.6.7. 4-(3-Fluorophenyl)-N-(4-fluorophenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6g)***

Compound **6g** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 7.41–7.27 (m, –CH, 2H), 7.44–7.41 (m, –CH, 1H), 7.86–7.65 (m, –CH, 6H), 8.09–8.06 (m, –CH, 1H), 8.22 (d, –CH, 1H, J = 7.5), 8.53 (d, –CH, 1H, J = 10.2), 8.64 (d, –CH, 1H, J = 7.8), 11.32 (s, NH, 1H, disappeared on D_2O exchange). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 114.8, 115.4, 115.7, 116.1, 116.4, 117.4, 119.6, 119.8, 119.9, 125.3, 128.2, 129.0, 129.3, 131.1, 134.4, 135.1, 143.1, 145.1, 149.4, 156.6, 158.6, 161.1, 164.3. LC–MS (ESI) m/z 374 (M + 1)

*3.6.8. 4-(3-Fluorophenyl)-N-(2-phenylethyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6h)***

Compound **6h** was obtained as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 3.00 (t, $-CH_2$, 2H, J = 7.2), 3.69 (q, $-CH_2$, 2H, J = 6.9), 7.32–7.19 (m, –CH, 5H), 7.46–7.40 (m, –CH, 1H), 7.8–7.64 (m, –CH, 3H), 8.06 (d, –CH, 1H, J = 8.1), 8.30 (d, –CH, 1H, J = 8.4), 8.55 (m, –CH, 2H), 8.93 (brt, NH, 1H). LC–MS (ESI) m/z 384 (M + 1)

*3.6.9. N-(3,5-dimethylphenyl)-4-(4-fluorophenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6i)***

Compound **6i** was obtained as off white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 2.31 (s, $-(CH_3)_2$, 6H), 6.74 (s, –CH, 1H), 7.44 (s, –CH, 2H), 7.56–7.50 (m, –CH, 2H), 7.87–7.76 (m, –CH, 2H), 8.09 (d, –CH, 1H, J = 8.4), 8.29 (d, –CH, 1H, J = 8.4), 8.77–8.72(m, –CH, 2H), 11.24 (s, NH, 1H, disappeared on D_2O exchange). LC–MS (ESI) m/z 384 (M + 1)

*3.6.10. N,4-Bis (4-fluorophenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6j)***

Compound **6j** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 7.33–7.27 (m, –CH, 2H), 7.54–7.48 (m, –CH, 2H), 7.86–7.74 (m, –CH, 4H), 8.10 (d, –CH, 1H, J = 7.8), 8.24 (d, –CH, 1H, J = 7.8), 8.78–8.75 (m, –CH, 2H), 11.37 (s, NH, 1H, disappeared on D_2O exchange). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 112.6, 116.1, 116.6, 117.8, 119.9, 127.0, 128.5, 129.0, 129.5, 131.9, 133.2, 137.0, 147.1, 149.6, 152.9, 160.5, 161.5, 163.6, LC–MS (ESI) m/z 374 (M + 1)

*3.6.11. 4-(4-Fluorophenyl)-N-(2-methoxyphenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6k)***

Compound **6k** was obtained as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 3.88 (s, –OCH_3, 3H), 7.11–7.05 (m, –CH, 3H), 7.18 (m, –CH, 2H), 7.49 (m, –CH, 2H), 7.83–7.72 (m, –CH, 2H), 8.09 (d, –CH, 1H, J = 7.8), 8.17 (d, –CH, 1H, J = 8.1), 8.27 (d, –CH, 1H, J = 8.4), 8.78–8.733 (m, –CH, 2H), 10.37 (s, NH, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 56.3, 112.1, 114.4, 116.0, 116.3, 119.9, 121.1, 125.2, 126.9, 130.8, 132.3, 132.4, 134.7, 141.2, 145.1, 150.5, 150.8, 160.0, 162.4, 165.7. LC–MS (ESI) m/z 386 (M + 1)

*3.6.12. N-benzyl-4-(4-fluorophenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6l)***

Compound **6l** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 4.67 (d, –CH_2, 2H, J = 6), 7.28 (m, –CH, 1H), 7.49–7.35 (m, –CH, 6H), 7.69–7.60 (m, –CH, 2H), 7.97 (d, –CH, 1H, J = 7.5), 8.10 (d, –CH, 1H, J = 7.5), 8.85 (m, –CH, 2H), 9.12 (t, NH, 1H, J = 6). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 47.5, 115.0, 115.1, 115.4, 118.8, 126.3, 127.3, 127.7, 128.0, 128.8, 129.9, 131.1, 133.6, 134.2, 137.3, 144.0, 147.0, 149.6, 161.2, 162.0, 165.3. LC–MS (ESI) m/z 370 (M + 1)

*3.6.13. 4-(4-Fluorophenyl)-N-pentyl[1,3]oxazolo[4,5-c]quinolin-2-amine **(6m)***

Compound **6m** was obtained as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 0.91 (t, –CH_3, 3H, J = 6.9), 1.37–1.34 (m, –$(CH_2)_2$, 4H), 1.69–1.64 (m, –CH_2, 2H), 3.47–3.35 (m, –N(CH_2), 2H), 7.42–7.36 (m, –CH, 2H), 7.66–7.58 (m, –CH, 2H), 7.94 (d, –CH, 1H, J = 7.5), 8.10 (d, –CH, 1H, J = 7.5), 8.49 (t, NH, 1H, J = 5.4), 8.86–8.81 (m, –CH, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.1, 22.4, 28.9, 29.6, 44.2, 115.2, 115.8, 116.4, 116.6, 118.8, 124.7, 124.6, 126.7, 127.3, 130.7, 131.0, 134.2, 139.7, 140.0, 143.9, 146.4, 149.6, 161.4, 161.5, 163.2. LC–MS (ESI) m/z 350 (M + 1)

*3.6.14. N-(3-chlorophenyl)-4-(4-fluorophenyl)[1,3]oxazolo[4,5-c]quinolin-2-amine **(6n)***

Compound **6n** was obtained as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ; 7.18–7.14 (m, –CH, 2H), 7.53–7.43 (m, –CH, 2H), 7.83–7.71 (m, –CH, 3H), 7.97 (s, –CH, 1H), 8.09 (d, –CH, 1H, J = 8.4), 8.26 (d, –CH, 1H, J = 8.4), 8.76–8.71 (m, –CH, 2H), 11.58 (s, NH, 1H, disappeared on D_2O exchange). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 114.2, 116.3, 116.3, 116.7, 117.7, 120.1, 123.0, 126.0, 128.8, 129.5, 130.7, 131.2, 132.6, 133.9, 134.3, 139.7, 140.5, 145.0, 151.1, 158.6, 162.6, 165.9. LC–MS (ESI) m/z 390 (M + 1)

3.7. Antibacterial testing by serial plate dilution method

Serial dilutions of the drug in Muller Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. A number of antimicrobial discs are placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. Using an agar punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone in mm. Activity of each compound was compared with ciprofloxacin as standard [38,39].

3.8. Antituberculosis activity broth micro dilution assay method

M. tuberculosis H37Rv was grown in Middlebrook 7H9 broth (Difco BBL, Sparks, MD, USA) supplemented with 10% OADC (Becton Dickinson, Sparks, MD, USA). The culture was diluted to McFarland 1 standard with the same medium. From this, 50 μl of this culture were added to 150 μl of fresh medium in 96 well microtite plates. Stock solutions (2 mg/mL) of the test compounds were prepared in Dimethyl Formamide (DMF). The compounds were tested at 1, 10 and 100 μg/mL concentrations. Control wells had the same volumes of DMF without any compound. Isoniazid (1.5 μg/mL) and Rifampicin (0.5 μg/mL) served as positive control. After incubation at 37 °C for 7 days, 15 μl of 0.01% Resazurin (Sigma, St. Louis. MO.USA) in sterile water was added to the first growth control wells and incubated for 24 hours. Once the first set of growth controls turned pink, the dye solution was added to the second set of growth controls and the test wells, and incubated for 24 hours at 37°C. Resazurin, a redox dye, is blue in the oxidized state and turns pink when reduced by the growth of viable cells. The control wells showed change of colour from blue to pink after 24 h at 37 °C. The compounds which prevented the change of colour of the dye were considered to be inhibitory to *M. tuberculosis*.

4. Conclusion

The present research study reports the successful synthesis, antibacterial and antituberculosis studies of a new class of fused 1,3-oxazolo[4,5-c]quinolines carrying biologically active groups. Their screening results revealed that all the compounds showed moderate to very good activity against pathogenic strains. Study of structure–activity relationship showed that the presence of aryl group at position-2 and the existence of fused oxazole in quinoline core are responsible for increased antibacterial and antituberculosis activity of the newly synthesized condensed heterocycles. It can be concluded that a combination of quinoline and oxazole has caused an enhanced antimicrobial effect and hence they are ideally suited for further modifications to obtain more efficacious antibacterial and antituberculosis compounds.

Acknowledgment

Authors are thankful to Dr. Ganesh Sambhasivam, CEO, Anthem biosciences, Bangalore, India, for his invaluable support and allocation of resources for this work. They are thankful to Dr. Suchetha Shetty, Department of Biochemistry, Justice K.S. Hegde Medical Academy, Deralakatte, India, for carrying out antibacterial screening. They are also grateful to Dr. Guru Row, Solid State and Structural Chemistry Unit (SSCU), Indian Institute Of Science, Bangalore, India, for carrying out single crystal X-ray diffraction studies.

References

[1] WHO Global Tuberculosis Control Report, 2008.
[2] R. Jain, B. Vaitilingam, A. Nayyar, P.B. Palde, Bioorg. Med. Chem. Lett. 13 (2003) 1051–1054.
[3] WHO Weekly epidemiological record No. 15. 78 (2003)121–128.
[4] M. Zignol, M.S. Hosseini, A. Wright, C.L. Weezenbeek, P. Nunn, C.J. Watt, C.G. Williams, C. Dye, J. Infect. Dis. 194 (2006) 479–485.
[5] A. Lilienkampf, J. Mao, B. Wan, Y. Wang, S.G. Franzblau, A.P. Kozikowski, J. Med. Chem. 52 (2009) 2109–2118.
[6] P. Nasveld, S. Kitchener, Trans. R. Soc. Trop. Med. Hyg. 99 (2005) 2–5.
[7] P.A. Leatham, H.A. Bird, V. Wright, D. Seymour, A. Gordon, Eur. J. Rheumatol. Inflamm. 6 (1983) 209–211.
[8] W.A. Denny, W.R. Wilson, D.C. Ware, G.J. Atwell, J.B. Milbank, R.J. Stevenson, U.S Patent 7064117 (2006).
[9] A. Mahamoud, J. Chevalier, A. Davin-Regli, J. Barbe, Jean-Marie Pages, Curr. Drug Targ. 7 (2006) 843–847.

[10] N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran, J.T. Leonard, Biol. Pharm. Bull. 27 (2004) 1683–1687.
[11] M.P. Maguire, K.R. Sheets, K. McVety, A.P. Spada, A. Zilberstein, J. Med. Chem. 37 (1994) 2129–2137.
[12] W.D. Wilson, M. Zhao, S.E. Patterson, R.L. Wydra, L. Janda, L. Strekowski, Med. Chem. Res. 2 (1992) 102–110.
[13] L. Strekowski, J.L. Mokrosz, V.A. Honkan, A. Czarny, M.T. Cegla, S.E. Patterson, R.L. Wydra, R.F. Schinazi, J. Med. Chem. 34 (1991) 1739–1746.
[14] A.K. Aggarwal, S.A. Jenekhe, Macromolecules 24 (1991) 6806–6808.
[15] X. Zhang, A.S. Shetty, S.A. Jenekhe, Macromolecules 32 (1999) 7422–7429.
[16] S.A. Jenekhe, L. Lu, M.M. Alam, Macromolecules 34 (2001) 7315–7324.
[17] M.E. Jason, W.C. Robert, C. Mark, G.C. Gary, H.H. Peter, A.J. Brian, A. MacLeod, M. Rose, M.L. Georgina, M. Elena, M. Fraser, R. Michael, R. Inmaculada, G.N.R. Michael, S. Bindi, L.T. Kwei, W. Brian, Bioorg. Med. Chem. Lett. 50 (2006) 5748–5751.
[18] J. Nilsson, E.Ø. Nielsen, T. Liljefors, M. Nielsen, O. Sterner, Bioorg. Med. Chem. Lett. 18 (2008) 5713–5716.
[19] M. Simeon, N. John, L. Georgia, K. Eleni, G. Vasiliki, T. Dimitrios, N. Pavlos, Int. J. of Antimicrob. Agents 29 (2007) 738–748.
[20] N. Kaila, K. Janz, S. DeBernardo, P.W. Bedard, R.T. Camphausen, S. Tam, D.H.H. Tsao, J.C. Keith Jr., C.N. Nutter, A. Shilling, R.Y. Sciame, Q. Wang, J. Med. Chem. 50 (2007) 21–39.
[21] K.E. Andersen, B.F. Lundt, A.S. Jørgensen, C. Braestrup, Eur J Med Chem. 31 (1996) 417–425.
[22] H. Sasaki, Y. Haraguchi, M. Itotani, H. Kuroda, H. Hashizume, T. Tomishige, M. Kawasaki, M. Matsumoto, M. Komatsu, H. Tsubouchi, J. Med. Chem. 49 (2006) 7854–7860.
[23] K. Mohamed, N.K. Venugopala, R. Mohana, R.G. Krishna, Lett. Drug Des. Discov. 6 (2009) 21–28.
[24] R. Kuang, Ho-Jane Shue, D.J. Blythin, Neng-Yang Shih, D. Gu, X. Chen, J. Schwerdt, L. Lin, P.C. Ting, X. Zhu, R. Aslanian, J.J. Piwinski, L. Xiao, D. Prelusky, P. Wu, J. Zhang, X. Zhang, C.S. Celly, M. Minnicozzi, M. Billah, Bioorg. Med. Chem. Lett. 17 (2007) 5150–5154.
[25] C. Jeong-woo, L. Sang-chul, M. Cheol-young, H. Sun-gwan, B. Sung-jin, K. Eun-ae, WO Patent 075888 A1 (2006).
[26] D.A. Evrard, D. Zhou, G.P. Stack, A.M. Venkatesan, A.A. Failli, S.C. Croce, US Patent 7153849 B2 (2006).
[27] A. Drabczyńska, C.E. Müller, B. Schumacher, S. Hinz, J.K. Wojciechowska, B. Michalak, E. Pękala, K.K. Kononowicz, Bioorg. Med. Chem. 12 (2004) 4895–4908.
[28] S. Eswaran, A.V. Adhikari, N.S. Shetty, Eur. J. Med. Chem. 44 (2009) 4637–4647.
[29] V. Colotta, F. Capelli, O. Lenzi, D. Catarzi, F. Varano, D. Poli, F. Vincenzi, K. Varani, P.A. Borea, D.D. Ben, R. Volpini, G. Cristalli, G. Filacchioni, Bioorg. Med. Chem. 17 (2009) 401–410.
[30] J.F. Gerster, K.J. Lindstrom, R.L. Miller, M.A. Tomai, W. Birmachu, S.N. Bomersine, S.J. Gibson, L.M. Imbertson, J.R. Jacobson, R.T. Knafla, P.V. Maye, N. Nikolaides, F.Y. Oneyemi, G.J. Parkhurst, S.E. Pecore, M.J. Reiter, L.S. Scribner, T.L. Testerman, N.J. Thompson, T.L. Wagner, C.E. Weeks, J.D. Andre, D. Lagain, Y. Bastard, M. Lupu, J. Med. Chem. 48 (2005) 3481–3491.
[31] M. Dinakaran, P. Senthilkumar, P. Yogeeswari, A. China, V. Nagaraja, D. Sriram, Bioorg. Med. Chem. 16 (2008) 3408–3418.
[32] A. Marco, Loza-Mejía, S. Olvera-Vázquez, K. Maldonado-Hernández, T.G. Salgado, I. González-Sánchez, F. Rodríguez-Hernández, J.D. Solano, R. Rodríguez-Sotres, A.L. Rocha, Bioorg. Med. Chem. 17 (2009) 3266–3277.
[33] T. Izumi, J. Sakaguchi, M. Takeshita, H. Tawara, Ken-ichi Kato, H. Dose, T. Tsujino, Y. Watanabe, H. Kato, Bioorg. Med. Chem. 11 (2003) 2541–2550.
[34] A.L. Barry, Procedure for testing antimicrobial agents in agar media. in: V.L. Corian (Ed.), Antibiotics in Laboratory Medicine. Williams and Wilkins, Baltimore, MD, 1980, pp. 1–23.
[35] D. James, Mac. Lowry, J.M. Jaqua, T.S. Sally, Appl. Microbiol. 20 (1970) 46–53.
[36] A. Martin, M. Camacho, F. Portaels, J.C. Palomino, Resazurin microtiter assay plate testing of *Mycobacterium tuberculosis* susceptibilities to second-line drugs: rapid, simple, and inexpensive method. Antimicrob. Agents Chemother. 47 (2003) 3616–3619.
[37] A.Y. Coban, C.C. Cekic, K. Bilgin, M. Uzun, A. Akgunes, E. Cetinkaya, B. Durupinar, Rapid susceptibility test for *Mycobacterium tuberculosis* to isoniazid and rifampin with resazurin method in screw-cap tubes. J Chemother. 18 (2006) 140–143.
[38] C.H. Fenlon, M.H. Cynamon, Comparative in vitro activities of ciprofloxacin and other 4-quinolones against Mycobacterium tuberculosis and Mycobacterium intracellulare. Antimicrob. Agents Chemother 29 (1986) 386–388.
[39] R. Davis, A. Markham, J.A. Balfour, Ciprofloxacin, An updated review of its pharmacology, therapeutic efficacy and tolerability. Drugs 51 (1996) 1019–1074.