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Original article

Design, synthesis and docking studies of quinoline-oxazolidinone hybrid molecules and their antitubercular properties

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ABSTRACT

New series of quinoline-oxazolidinone hybrid molecules were synthesized based on the preliminary docking studies. All the newly synthesized compounds were characterized by spectral analyses. The newly synthesized compounds were screened for their antimycobacterial properties based on the promising preliminary antibacterial screening results. Amongst tested compounds, compounds **8a**, **8j** and **13a** were active at 0.65 μg/mL against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. The mode of action of these active compounds was carried out by docking of receptor enoyl-ACP reductase with newly synthesized candidate ligands **8a**, **8j** and **13a**. These compounds exhibited well established bonds with one or more amino acids in the receptor active pocket. From the docking studies, compound **8j** was considered to be the best inhibitor.

1. Introduction

Microbial infections are a growing problem in contemporary medicine, yet only a few antimicrobial agents are used in clinical practice. *Mycobacterium tuberculosis* (MTB) is a pathogenic bacterial species in the genus *Mycobacterium* and the causative agent of most cases of tuberculosis [1]. Tuberculosis (TB), a lung infection and is one of the contagious and deadly diseases which have added to the woes of the mankind. The main reason for the widespread of this disease is the population growth, emergence of multi-drug resistant TB strains, financial burden in the developing countries and unsuccessful attempt to synthesize a new drug with novel mechanism of action.

Isoniazid has been widely used as a frontline anti-tubercular drug for the treatment of tuberculosis for the past 40 years. The primary molecular target of the Isoniazid (INH) is the NADH-dependent enoyl-ACP reductase encoded by the *Mycobacterium* gene inhA [2]. InhA catalyzes the reduction of long-chain trans-2-enoyl-ACP in the type II fatty acid biosynthesis pathway of *M. tuberculosis*. Inhibition of InhA disrupts the biosynthesis of the mycolic acids that are central constituents of the mycobacterial cell wall [3]. Therefore, inhibitors targeting InhA directly without a requirement for activation would be promising candidates for the development of agents against the ever increasing threat from drug-resistant *M. tuberculosis* strains. Several series of direct InhA inhibitors, including pyrazole derivatives, indole-5-amides [4] and alkyl diphenyl ethers [5] have been identified recently that show both *in vivo* and *in vitro* activity.

Among important heterocyclic compounds, quinoline-based heterocycles are well known to exhibit excellent antimicrobial activities, particularly anti-TB properties [6–10]. Moreover, quinoline and its derivatives have been shown to possess antimalarial [11–13], antibiotic [14,15], anticancer [16] anti-inflammatory [17], antihypertensive [18], tyrokinase PDGF-RTK inhibition [19] and anti-HIV properties [20,21].

Further, different oxazolidinone derivatives were shown to possess a wide range of antimicrobial properties [22]. Interestingly, the oxazolidinones when linked with active heterocyclic pharmacophores play an important role against Gram-positive infections [23]. However, these oxazolidinones were inactive against Gram-negative bacteria and hence require multi-dosing regimen, as a result they produce serious side effects [24]. Linezolid, a new

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oxazolidinone has been extensively studied for the treatment of multidrug-resistant tuberculosis [25]. Besides, it is well reported in the literature that quinolone-oxazolidinone hybrid molecules bearing different cyclic amines as spacer groups displayed very good antimicrobial properties when two pharmacophoric groups are incorporated together [26,27].

We recently investigated and reported the discovery of various quinoline derivatives having potent antimycobacterial properties [28–30]. Based on the preliminary docking studies, we have designed the synthesis of quinoline-oxazolidinone hybrid molecules. In the first series, **8a**–**l**, the docking studies revealed that the substituents carrying fluoro, methoxy and trifluoromethyl substituted phenyl rings displayed a better *in silico* conformation. The results from the second series of compounds were promising with respect to few pharmacologically important amines viz, simple alkylamines, different substituted piperazines, morpholine etc. Bearing in mind the most active structures of the set of compounds screened, we have synthesized two different series of compounds containing various substituted acid chlorides and amines. In this communication we report the synthesis and characterization of hitherto unknown quinoline derivatives carrying oxazolidinone ring as an active pharmacophore (**8a**–**l**, **13a**–**n**). Further, it comprises the investigation of *in vitro* antibacterial activity against five strains, viz. *Staphylococcus aureus* (ATCC-25923), *Pseudomonas aeruginosa* (ATCC-27853), *Escherichia coli* (ATCC-25922), clinical isolates of *Klebsiella pneumoniae* and *Streptococcus pyogenes* and antimycobacterial properties against *M. tuberculosis* $H_{37}Rv$, *Mycobacterium smegmatis* (ATCC 19420) and *Mycobacterium fortuitum* (ATCC 19542). The present contribution also describes our efforts to understand the influence of two pharmacophoric groups attached together on the antibacterial and anti-tubercular activity and to obtain active compounds with enhanced activity.

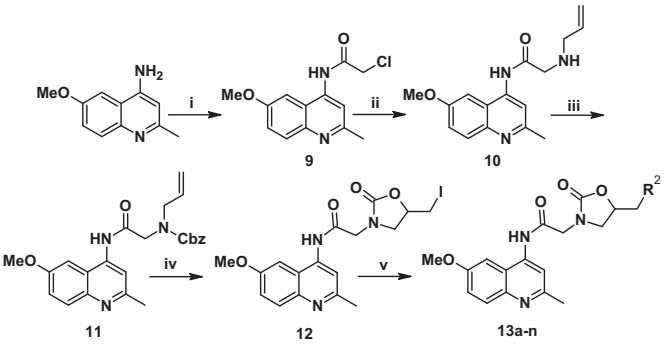
2. Results and discussion

2.1. Chemistry

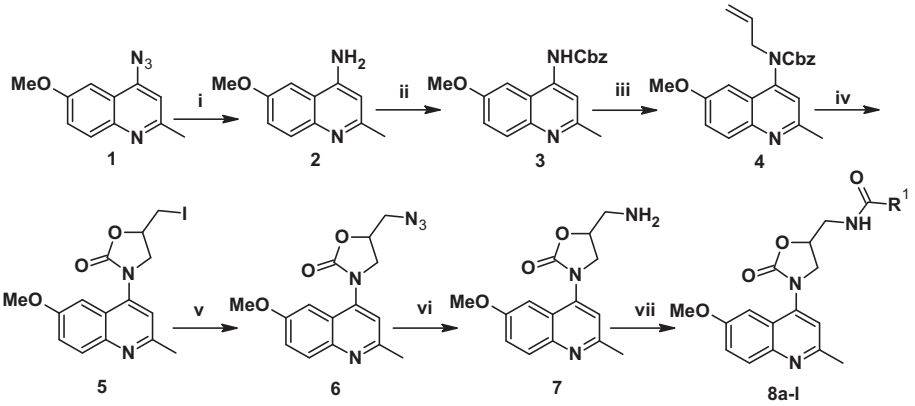
The title compounds were synthesized through a multistep synthetic route as shown in Scheme 1 and 2. The intermediate 4-azido-6-methoxy-2-methylquinoline (**1**) was synthesized according to the synthetic method reported in our earlier work [31].

As mentioned in Scheme 1, 4-azido-6-methoxy-2-methylquinoline (**1**) was reduced to amine intermediate **2** using hydrogen under pressure with Pd/C as a catalyst. The product, 4-aminoquinoline derivative **2** was protected with benzyl chloroformate using sodium hydride as a base to get the intermediate 6-methoxy-2-methyl-quinolin-4-yl-carbamic acid benzyl ester (**3**), which was further alkylated using allyl bromide to obtain the intermediate **4**. It was then subjected to cyclization to form 5-(iodomethyl)-3-(6-methoxy-2-methylquinolin-4-yl)-1,3-oxazolidin-2-one (**5**) using iodine in acetonitrile medium. The intermediate **5** was converted to its amine scaffold **7** through an azide intermediate **6**. Finally, the title compounds, **8a**–**l** were obtained by treating the intermediate **7** with different aliphatic and aromatic acid chlorides. As depicted in Scheme 2, the amine intermediate **2** was treated with chloroacetyl chloride to obtain the acetylated intermediate **9**. Further the compound **9** was reacted with allylamine to get the intermediate **10** and it was further protected with benzyl chloroformate to get the compound **11**. The key intermediate 2-[5-(iodomethyl)-2-oxo-1,3-oxazolidin-3-yl]-*N*-(6-methoxy-2-methylquinolin-4-yl)acetamide (**12**) was obtained by cyclization of compound **11** using iodine in acetonitrile medium. Finally the title compounds **13a**–**n** were obtained in good yields by treating the compound **12** with different alkylamines, piperidine, pyrrolidine, morpholine, different substituted piperazines etc. The crude product (**8a**–**l** and **13a**–**n**) was purified on a Biotage parallel column purifier using EtOAc/Pet ether (4:1) to MeOH/DCM (2–4%) as eluant.

The newly synthesized compounds were characterized by FTIR, ^1H NMR, ^{13}C NMR, LCMS and elemental analysis data. The spectral data of newly synthesized intermediates and title compounds are given in experimental section. The results of *in vitro* preliminary antibacterial and anti-tubercular activities of compounds **8a**–**l** and



Scheme 2. (i) Chloroacetyl chloride, DCM, Et_3N, 10–20 °C, 2 h (ii) Allylamine, acetonitrile, K_2CO_3, 60 °C, 2 h (iii) Benzyl chloroformate, sodium bicarbonate, acetone/water, 0–10 °C, 2 h (iv) I_2, acetonitrile, 25–28 °C, 16 h. (v) Different substituted amines, acetonitrile, K_2CO_3, 80 °C, 4 h.



Scheme 1. (i) Pd/C, H_2, MeOH, 2 h (ii) Sodium hydride, DMF, benzyl chloroformate, 0–10 °C, 2 h (iii) Sodium hydride, DMF, allyl bromide, 0–25 °C, 1 h (iv) I_2, acetonitrile, 20 h. (v) Sodium azide, DMF, 25 °C, 2 h (vi) Pd/C, H_2, MeOH, 2 h (vii) Different acid chlorides and benzoyl chlorides, DCM, Et_3N, 0 °C, 1 h.

13a–**n** are tabulated in Table 1. Their characterization data and second level anti-tubercular screening results are tabulated in Table 2.

2.2. Biological results

All the title compounds were screened for their *in vitro* antibacterial and anti-tubercular properties following standard methods.

2.2.1. Antibacterial activity

Antibacterial activity of title compounds were investigated against five different bacterial strains viz, *S. aureus*, *S. pyogenes*, *P. aeruginosa*, *K. pneumoniae* and *E. coli* using ciprofloxacin as reference, by serial dilution method.

Results of antibacterial screening of compounds **8a**–**l** and **13a**–**n** indicate that the compounds showed MIC values between 0.1 and 12.5 μg/mL concentrations. It has been observed that the compounds **8a**,**b**, **8d** and **8i**,**j** displayed substantial activity against *S. aureus*, *S. pyogenes* and *P. aeruginosa*. Amongst them, compound **8a** showed better activity at 0.2 μg/mL against *S. pyogenes* which is more potent than the reference compound. The compounds, **8a**, **8d**, and **8i** showed good activity at 0.1 μg/mL against *K. pneumoniae* *strain* whereas all other compounds showed meagre activity between 0.8 and 12.5 μg/mL. Only four compounds, **8a**, **8d**, **8i** and **8j** showed considerable activity against *E. coli* strain. Table 1 summarizes the antibacterial screening results (MIC μg/mL) of tested compounds along with that of standard. It has been noticed that the structures of active compounds consists of simple groups viz, acetyl, cyclopropyl, and fluoro groups. It is interesting to note that the activity decreased by two fold when 4-fluorobenzoyl ring (**8d**) was replaced by 2-fluorobenzoyl group (**8e**). The results further reveals that the title compounds, **8a**–**l** carrying 4-methoxybenzoyl (**8i**), 4-fluorobenzoyl (**8d**) and trifluoromethyl benzoyl (**8j**) substituents are active in this series. The promising activity of the compounds from the second series is mainly attributed to the presence of simple alkyl amines, morpholine and methyl, ethyl and acetyl substituted piperazine-1-yl groups.

Table 1
Preliminary *in vitro* antibacterial and antimycobacterial screening data of the title compounds **8a**–**l** and **13a**–**n**.

Cpd[a]	MIC in μg/mL								
	S.a[b]	*S.p*[c]	*P.a*[d]	*K.p*[e]	*E.c*[f]	MTB[g]	MS[h]	MF[i]	(%)[j]
8a	0.8	0.2	0.4	0.1	0.2	1	10	10	95
8b	0.8	0.4	0.4	1.6	0.8	1	10	10	90
8c	1.6	1.6	3.125	6.25	1.6	10	100	100	85
8d	0.8	0.4	0.4	0.1	0.2	1	10	10	90
8e	1.6	3.125	3.125	6.25	6.25	1	10	10	90
8f	3.125	3.125	>12.5	6.25	>12.5	100	100	100	0
8g	1.6	6.25	>12.5	1.6	3.125	100	100	100	0
8h	3.125	1.6	3.125	3.125	3.125	100	100	100	0
8i	0.8	0.4	0.2	0.1	0.2	10	10	10	85
8j	0.8	0.4	0.4	0.8	0.4	1	10	10	90
8k	0.8	1.6	3.125	0.8	1.6	1	100	100	85
8l	1.6	3.125	6.25	6.25	3.125	100	100	100	85
13a	0.8	0.8	0.2	0.4	0.2	1	10	10	95
13b	1.6	3.125	0.4	0.1	0.4	1	10	10	90
13c	0.8	0.4	1.6	0.1	0.4	1	10	10	90
13d	0.8	0.2	0.8	1.6	1.6	10	100	100	85
13e	0.8	0.8	1.6	1.6	1.6	10	100	100	80
13f	1.6	1.6	0.8	3.125	0.8	10	100	100	85
13g	1.6	0.8	0.8	1.6	1.6	100	100	100	0
13h	0.8	0.2	0.4	0.1	0.1	1	10	10	95
13i	1.6	3.125	1.6	>12.5	>12.5	10	100	100	90
13j	6.25	3.125	1.6	>12.5	>12.5	100	100	100	0
13k	3.125	6.25	3.125	>12.5	>12.5	100	100	100	0
13l	6.25	1.6	>12.5	6.25	6.25	100	100	100	0
13m	>12.5	6.25	>12.5	6.25	6.25	100	100	100	0
13n	>12.5	6.25	>12.5	6.25	>12.5	100	100	100	0
CIP[k]	1.0	0.4	0.4	0.05	0.025	–	–	–	–
INH[l]	–	–	–	–		0.7	50	12.5	>95
RIF[m]	–	–		–	–	0.5	1.5	1.5	>95

[a] Compound.
[b] *S. aureus* (ATCC-25923).
[c] *S. Pyogenes*.
[d] *P. aeruginosa* (ATCC-27853).
[e] *K. pneumoniae*.
[f] *E. coli* (ATCC-25922).
[g] *M. tuberculosis* $H_{37}Rv$ (ATCC 27294).
[h] *M. smegmatis* (MC2) ATCC 19420.
[i] *M. fortuitum* (ATCC 19542).
[j] Percentage of inhibition against *M. tuberculosis* $H_{37}Rv$.
[k] Ciprofloxacin.
[l] Isoniazid.
[m] Rifampicin.

2.2.2. Anti-tubercular activity

Based on the encouraging results from the antibacterial screening, title compounds were further tested for their both preliminary and second level *in vitro* antimycobacterial activity against *M. tuberculosis* $H_{37}Rv$, *M. smegmatis* (ATCC 19420) and *M. fortuitum* (ATCC 19542) using isoniazid (INH) and rifampicin (RIF) as standards. The results of preliminary and second level antimycobacterial screening of the tested compounds are tabulated in Tables 1 and 2 respectively.

From the results of preliminary antimycobacterial screening of compounds **8a**–**l** and **13a**–**n**, it has been observed that compounds **8a**–**e**, **8i**–**k**, **13a**–**f** and **13h**,**i** were active at concentrations between 1 and 10 μg/mL. Further, second level screening results revealed that compounds **8a**, **8j** and **13a** were active at 0.625 μg/mL against *M. tuberculosis* $H_{37}Rv$ strains. These compounds are more potent than the reference compound isoniazid MIC = 0.7 μg/mL against *M. tuberculosis* $H_{37}Rv$, 50 μg/mL against *M. smegmatis* and 12.5 μg/mL against *Mycobacterium fortuitum*. Also, the compounds **8a** and **13a** exhibited promising activity against *M. smegmatis* strain at 2.5 μg/mL concentration whereas compound **8j** displayed activity at 2.5 μg/mL against *M. fortuitum* strain.

2.3. Docking studies

Considering the well obtained *in vitro* results, it was thought worthy to screen for supportive coordination between *in silico* studies with *in vitro* results. Considering enoyl-ACP reductase as the target receptor, comparative and automated docking studies with newly synthesized candidate lead compounds was performed to determine the best *in silico* conformation. The Lamarckian genetic algorithm, inculcated in the docking program AutoDock 4.2, was employed for the purpose. Fig. 1 shows the native crystal structure of enoyl-ACP reductase obtained from Protein Data Bank (http://www.pdb.org/pdb/home/home.do) with the PDB ID2H7 M [32].

The docking of receptor enoyl-ACP reductase with newly synthesized lead candidate ligands exhibited well established bonds with one or more amino acids in the receptor active pocket. Docking studies were performed for lead compounds **8a**, **8j**, **13a** and the reference compound Isoniazid (**INH**). The active pocket was considered to be the site where 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide (Pyrrolidine carboxamide) was complexed with enoyl-ACP reductase in 2H7M. The active pocket consisted of 8 amino acid residues as Gly 96, Lys 165, Tyr 158, Met 103, Pro 156, Ala 157, Ile 215 and Met 199 as shown in Fig. 2. The synthesized ligand molecules having 2D structure were converted to energy minimized 3D structures and were further used for *in silico* protein–ligand docking. The images of docked ligands including the considered standard Isoniazid (INH) has been shown in Fig. 3. *In silico* studies revealed the three

Table 2
Characterization and second level *in vitro* antimycobacterial screening data of compounds **8a**–**l** and **13a**–**n**.

Characterization data						Second level screening results)		
						MIC (μg/mL		
Cpd[a]	R^1/R^2	Mol. For.	M. Wt.	clogP[b]	(%)[c]	MTB[d]	MS[e]	MF[f]
8a	Me	$C_{17}H_{19}N_3O_4$	329.35	1.20	80	0.625	2.5	10
8b	Cyclopropyl	$C_{19}H_{21}N_3O_4$	355.38	1.92	65	1.25	10	10
8c	Cyclobutyl	$C_{20}H_{23}N_3O_4$	369.41	2.33	59	2.5	–	–
8d	4-Fluorophenyl	$C_{22}H_{20}FN_3O_4$	409.41	3.25	62	1.25	10	10
8e	2-Fluorophenyl	$C_{22}H_{20}FN_3O_4$	409.41	3.25	60	1.25	5	10
8f	Ph	$C_{22}H_{21}N_3O_4$	391.41	3.09	78	–	–	–
8g	4-Ethylphenyl	$C_{24}H_{25}N_3O_4$	419.47	4.0	85	–	–	–
8h	4-Methylphenyl	$C_{23}H_{23}N_3O_4$	405.44	3.58	70	–	–	–
8i	4-Methoxyphenyl	$C_{23}H_{23}N_3O_5$	421.44	2.97	86	5	5	10
8j	4-Trifluoromethylphenyl	$C_{23}H_{20}F_3N_3O_4$	459.41	4.01	51	0.625	10	2.5
8k	4-Methoxy-2-methylphenyl	$C_{24}H_{25}N_3O_5$	435.47	3.45	66	1.25	–	–
8l	4-Chlorophenyl	$C_{22}H_{20}ClN_3O_4$	425.86	3.65	71	–	–	–
13a	Dimethylamino	$C_{19}H_{24}N_4O_4$	372.41	1.01	80	0.625	2.5	10
13b	Diethylamino	$C_{21}H_{28}N_4O_4$	400.47	1.69	65	1.25	10	10
13c	4-Methylpiperazinyl	$C_{22}H_{29}N_5O_4$	427.50	0.77	59	1.25	10	10
13d	4-Ethylpiperazinyl	$C_{23}H_{31}N_5O_4$	441.52	1.11	62	10	–	–
13e	4-Acetylpiperazinyl	$C_{23}H_{29}N_5O_5$	455.50	0.04	60	5	–	–
13f	4-Isopropylpiperazinyl	$C_{24}H_{33}N_5O_4$	455.54	1.42	75	5	–	–
13g	4-Tert.butylpiperazinyl	$C_{25}H_{35}N_5O_4$	469.57	1.64	71	–	–	–
13h	Morpholinyl	$C_{21}H_{26}N_4O_5$	414.45	0.61	78	1.25	10	10
13i	Cyclopropylamino	$C_{20}H_{24}N_4O_4$	384.42	0.93	85	10	–	–
13j	Pyrolidinyl	$C_{21}H_{26}N_4O_4$	398.45	1.33	70	–	–	–
13k	Piperidinyl	$C_{22}H_{28}N_4O_4$	412.48	1.74	86	–	–	–
13l	Methylcyclohexylamino	$C_{24}H_{32}N_4O_4$	440.53	2.56	71	–	–	–
13m	4-Methylpiperidinyl	$C_{23}H_{30}N_4O_4$	426.50	2.07	67	–	–	–
13n	Cyclopentylamino	$C_{22}H_{28}N_4O_4$	412.48	1.77	74	–	–	–
Std[g]	Isoniazid (INH)	–	–	–	–	0.7	50	12.5
	Rifampicin (RIF)	–	–	–	–	0.5	1.5	1.5

'–' The compounds with MIC value more than 100 μg/mL in the initial screening results were not taken for second level screening.
[a] Compound.
[b] Chemdraw 8.
[c] Isolated yield.
[d] *Mycobacterium tuberculosis* $H_{37}Rv$.
[e] *Mycobacterium smegmatis* (ATCC 19420).
[f] *Mycobacterium fortuitum* (ATCC 19542).
[g] Standard.

synthesized molecules showed good binding energy towards the target protein ranging from −4.93 kJ mol^{-1} to −10.08 kJ mol^{-1}. The binding energy, inhibition constant and total internal energy of all the four compounds including standard INH has been depicted in Table 3. Finally considering *in vitro* and *in silico* molecular docking results, among these newly synthesized molecules, **8j** showed the best result and was considered as the best inhibitor of enoyl-ACP reductase and can be effective anti-tubercular drug. The dock pose with least binding energy has the highest affinity and hence is the best dock conformation. Image showing the crevice of the portion of the target protein and **8j** ligand docked in best of its conformation are depicted in Fig. 4.

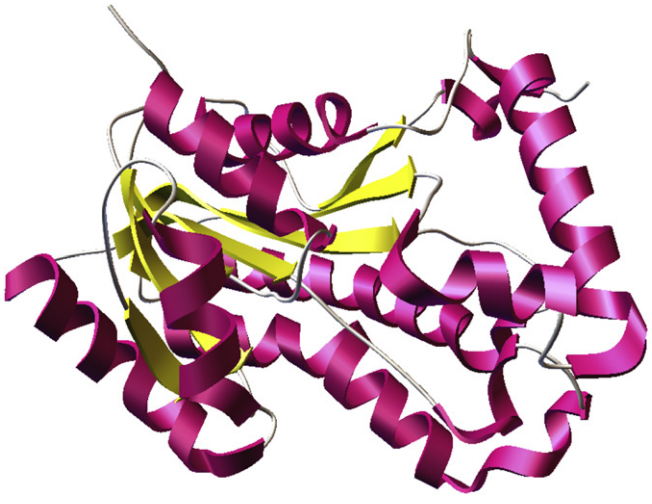


Fig. 1. Secondary structure of Asymmetric subunit chain A of enoyl-ACP reductase (PDB ID 2H7M).

3. Conclusion

Two new series of quinoline derivatives carrying oxazolidinone ring (**8a**–**l** and **13a**–**n**) were synthesized from 4-azido-6-methoxy-2-methylquinoline (**1**) and characterized by spectral and elemental analyses. These new chemical entities were evaluated for their *in vitro* antibacterial and antituberculosis activities against different pathogenic strains. Among the tested compounds from the first series **8a**–**l**, majority of the compounds displayed substantial antibacterial and antimycobacterial activities against most of the bacterial strains. Their enhanced activity is attributed to the presence of acetyl, cyclopropyl, amido, 4-fluorophenyl, 4-methoxyphenyl and 4-trifluoromethylphenyl groups in their structures. The compounds **8a** and **8j** were found to be active antimycobacterial agents. Results of antimicrobial screening of **13a**–**n** revealed that the compounds **13a**–**d** and **13h** displayed significant activity against most of the bacterial strains out of which compound **13a** showed enhanced antimycobacterial properties. The promising activities of these compounds are mainly due to the presence of alkylamines, methyl, ethyl and acetyl substituted

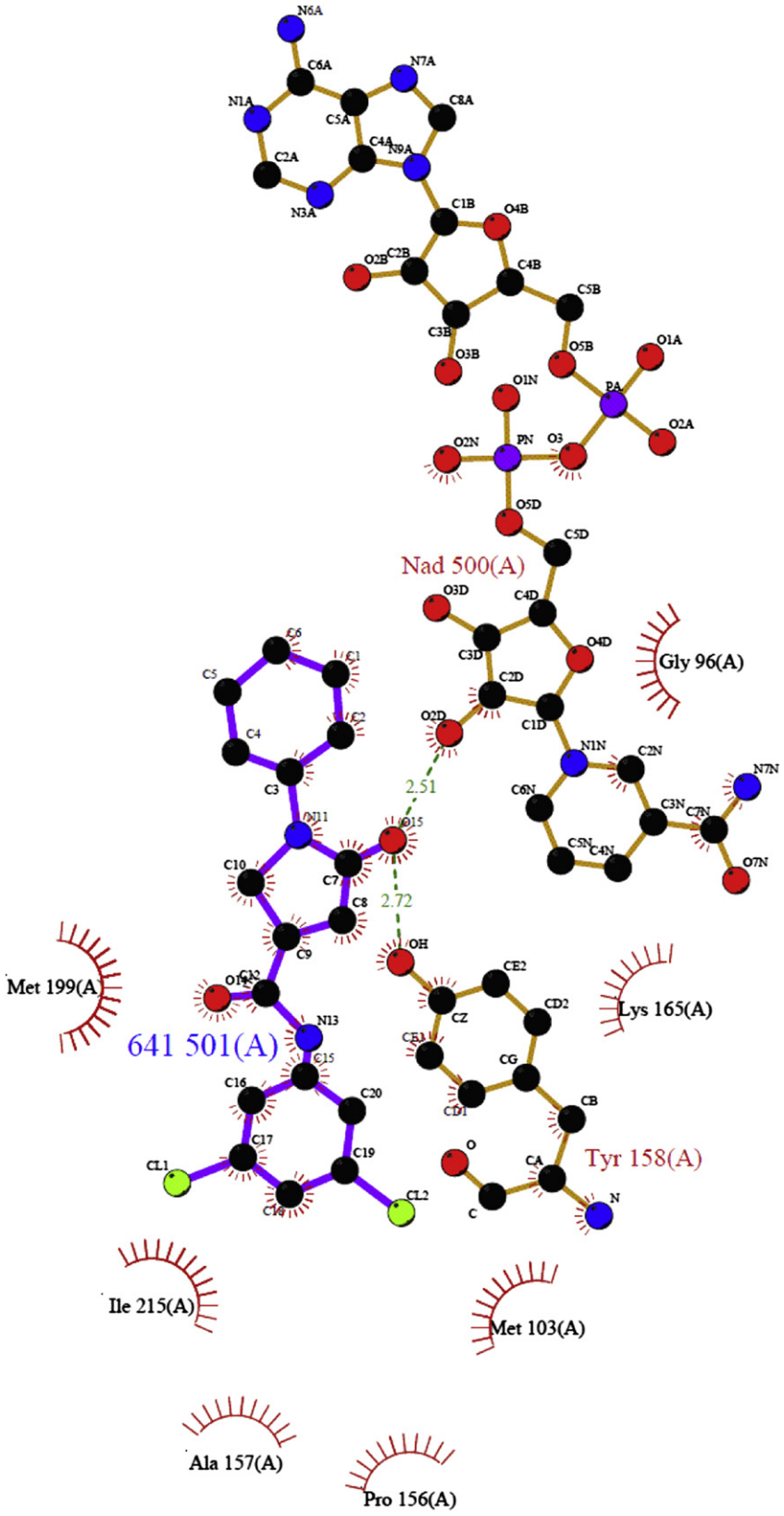


Fig. 2. PDB sum's ligplot results for 2H7M, showing all eight amino acid residues of active pocket.

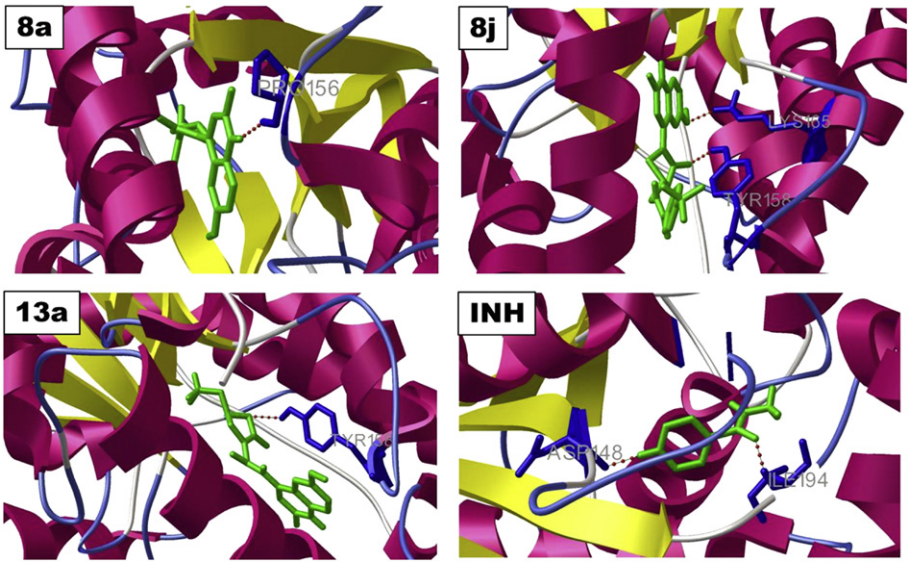


Fig. 3. Showing all ligands docked in best of its conformation. Image **8a** shows molecule **8a** bound to PRO156, image **8j** shows molecule **8j** bound to TYR158 and LYS165, image **13a** shows molecule **13a** bound to TYR158 and the image INH shows considered standard INH bound to ASP148 and ILE 194 (In all cases in the image, the ligands are represented in green colour, the particular H bound amino acid(s) with ligand in blue colour and all H bonds shown as equidistant red spheres aligned on green line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

piperazines are responsible for their improved activity. The compounds **8a**, **8j** and **13a** were found to be active antimycobacterials and potential candidates for further studies.

4. Experimental

4.1. General

Melting points were determined using Buchi B-540 by open capillary and are uncorrected. The FTIR spectra (in KBr pellets) were recorded on a Shimadzu FTIR 157 spectrophotometer. Final compound purifications were carried out using Quad Biotage Flash purifier (A Dyax Corp. Company). All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz), Bruker BioSpin Corp., Germany, using TMS (tetra methyl silane) as an internal standard. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. The mass spectra were recorded either on single Quadrupole mass or XCT Ion trap spectrometer operating at 70 eV. The mass spectra of a few were recorded on a 410 Prostar binary PDA detector (Varian Inc, USA). Elemental analysis was performed on Flash EA 1112 Thermo Electron Corporation CHNSO analyzer. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) on silica gel 40 F254 (Merck, Darmstadt, Germany, Merck), coated on aluminium plates, visualized by UV light and $KMnO_4$ solution. Starting materials were purchased from Aldrich Chemical Company or Spectrochem Chemical Company and used without further purification. All solvents were of analytical grade and freshly distilled prior to use.

Table 3
The binding energy (kJ mol^{-1}), inhibition constant and total internal energy (kJ mol^{-1}) of compounds, **8a**, **8j** and **13a** and **INH** (reference standard).

Compound	Binding Energy (kJ mol^{-1})	Inhibition Constant
8a	−9.74	72.39 ηm
8j	−10.08	40.7 ηm
13a	−8.73	398.13 ηm
INH	−4.93	244.97 μm

4.2. Procedure for the preparation of 6-methoxy-2-methylquinolin-4-amine (*2*)

To a clear solution of 4-azido-6-methoxy-2-methylquinoline (**1**) (15 g) in methanol (150 mL) was added Pd/C (10 mol %). The reaction mass was hydrogenated with H_2 pressure (3 kg/cm^2) for 2 h. The reaction completion was monitored by TLC. After the completion of the reaction, the catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford a pale yellowish gummy solid **2** (12.57 g, 95%); ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.71 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 6.80 (s, 2H, NH_2), 7.09 (s, 1H, ArH), 7.21 (d, 1H, $J = 3$ Hz, ArH), 7.36 (dd, 1H, $J = 9.3$ Hz, ArH), 7.89 (d, 1H, $J = 9.3$ Hz, ArH); LC/MS (ESI-MS) m/z 188.6 (M+1).

4.3. Procedure for the preparation of (6-methoxy-2-methylquinolin-4-yl)-carbamic acid benzyl ester (*3*)

A clear solution of 6-methoxy-2-methylquinolin-4-amine (**2**, 12.5 g, 66.41 mmol) in 60 mL of dry DMF was added dropwise to a suspension of sodium hydride (3.5 g, 73.05 mmol) in 15 mL of dry

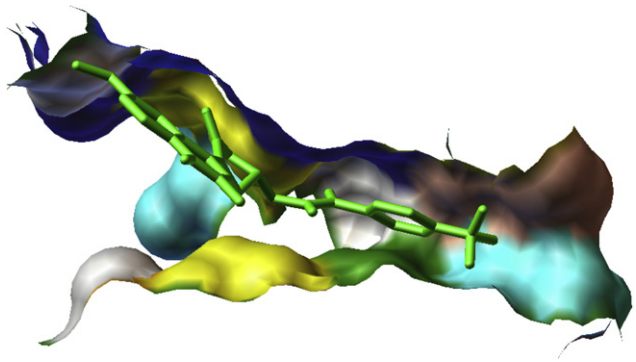


Fig. 4. Image showing the crevice of the portion of the target protein and **8j** ligand docked in best of its conformation. Ligand molecule being shown in ball and stick in green colour and the target protein molecule in molecular surface view coloured by molecule. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

DMF at 0 °C. After maintaining the reaction mass for 15 min at 0–10 °C, a clear solution of benzyl chloroformate (12.46 g, 73.05 mmol) in 25 mL of dry DMF was added dropwise. The reaction completion was monitored by TLC between 0 and 10 °C and the reaction was completed. The reaction mass was then quenched with saturated solution of ammonium chloride and extracted with ethyl acetate (150 mL × 2). The combined organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 80% ethyl acetate in petroleum ether as eluant to get an off white colour solid (12.84 g, 60%); m.p 154.9–155.1 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.70 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 5.30 (s, 2H, OCH_2), 6.92 (d, 1H, J = 2.7 Hz, ArH), 7.22 (s, 1H, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.45 (m, 5H, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH), 8.01 (s, 1H, NH); Anal. for $C_{19}H_{18}N_2O_3$; calcd; C 70.79, H 5.63, N 8.69; found; C 70.90, H 5.72, N 8.72; LC/MS (ESI-MS) m/z 323.13 (M+1).

4.4. Procedure for the preparation of allyl-(6-methoxy-2-methyl-quinolin-4-yl)-carbamic acid benzyl ester (**4**)

To a suspension of sodium hydride (2.85 g, 59.56 mmol) in dry DMF (15 mL) at 0 °C was added a solution of 6-methoxy-2-methyl-quinolin-4-yl-carbamic acid benzyl ester (**3**, 12.8 g, 39.70 mmol) in dry DMF (70 mL) drop wise. The reaction mass was maintained for 15 min between 10 and 15 °C. The reaction mass was re-cooled to 0 °C and to this a clear solution of allyl bromide (5.76 g, 47.64 mmol) in dry DMF (12 mL) was added dropwise. The reaction completion was monitored by TLC between 10 and 25 °C. After the completion of the reaction, the reaction mass was quenched with saturated solution of ammonium chloride and the product was extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 60% ethyl acetate in petroleum ether as eluant to get **4** as a pale yellow gummy solid (10.79 g, 75%); ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.71 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.05–4.12 (m, 1H, CH_2), 4.50–4.55 (m, 1H, CH_2), 5.09–5.15 (m, 2H, CH_2), 5.19 (s, 2H, OCH_2), 5.87–5.98 (m, 1H, CH), 6.83 (d, 1H, J = 2.7 Hz, ArH), 7.21(s, 1H, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.42–7.55 (m, 5H, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); Anal. for $C_{22}H_{22}N_2O_3$; calcd; C 72.91, H 6.12, N 7.73; found; C 72.76, H 6.30, N 7.61; LC/MS (ESI-MS) m/z 363.17 (M+1).

4.5. Procedure for the preparation of 5-iodomethyl-3-(6-methoxy-2-methyl-quinolin-4-yl)-oxazolidin-2-one (**5**)

A mixture of allyl-(6-methoxy-2-methyl-quinolin-4-yl)-carbamic acid benzyl ester (**4**, 10 g, 27.59 mmol), iodine (14 g, 55.18 mmol) in acetonitrile was stirred at 26–30 °C for 20 h. The reaction completion was monitored by TLC. When the reaction was completed, the solvent was removed, the crude residue was extracted with ethyl acetate (200 mL). The organic layer was washed with 10% sodium thiosulphate solution, followed by water and brine solution. It was then dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 60–80% ethyl acetate in petroleum ether as eluant to get **5** as a pale yellow gummy solid (6.59 g, 60%); m.p 130.4–131.1 °C; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.70 (s, 3H, CH_3), 3.51–3.55 (m, 2H, CH_2), 3.87–3.90 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 4.29 (m, 1H, CH), 4.79–4.87 (m, 1H, OCH), 7.07 (d, 1H, J = 2.7 Hz, ArH), 7.22 (s, 1H, ArH), 7.36(dd, 1H, J = 9.3 Hz, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR δ ppm ($CDCl_3$-75 MHz): δ 6.70, 24.98, 53.67, 55.85, 72.12, 100.91, 118.64, 122.68, 123.60, 130.85, 141.04, 145.57, 155.25, 156.51, 157.77; Anal. for $C_{15}H_{15}IN_2O_3$; calcd; C 45.24, H 3.80, N 7.04; found; C 45.18, H 3.89, N 7.24.

4.6. Procedure for the synthesis of 5-azidomethyl-3-(6-methoxy-2-methyl-quinolin-4-yl)-oxazolidin-2-one (**6**)

Sodium azide (1.49 g, 50.2 mmol) was added to a clear solution of 5-iodomethyl-3-(6-methoxy-2-methyl-quinolin-4-yl)-oxazolidin-2-one (**5**, 10 g, 25.1 mmol) in dry DMF (100 mL) at 25 °C. The reaction mass was stirred for 2 h. The reaction completion was monitored by TLC and after the completion of the reaction it was quenched with ice cold water. The off white coloured solid obtained was filtered, washed with water and vacuum dried to get **6** (7.0 g, 89%) as an off white solid; m.p 115.0–115.4 °C; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.70 (s, 3H, CH_3), 3.56–3.62 (m, 1H, CH_2), 3.84 (m, 1H, CH_2), 3.93 (s, 3H, OCH_3), 3.94–3.97 (m, 1H, CH) 4.16 (m, 1H, CH), 4.80–4.87 (m, 1H, OCH), 7.07 (d, 1H, J = 2.7 Hz, ArH), 7.22 (s, 1H, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); LC/MS (ESI-MS) m/z 314.12 (M+1).

4.7. Procedure for the synthesis of 5-aminomethyl-3-(6-methoxy-2-methyl-quinolin-4-yl)-oxazolidin-2-one (**7**)

A mixture of 5-azidomethyl-3-(6-methoxy-2-methyl-quinolin-4-yl)-oxazolidin-2-one (**6**, 5 g) in methanol (50 mL), Pd/C (0.5 g, 10% w/w) was hydrogenated at 3 kg/cm^2 H_2 pressure for 2 h. The catalyst was filtered and the filtrate was concentrated under reduced pressure to get **7** as a pale yellow gummy solid (Yield-75%); IR (KBr, cm^{-1}) ν_{max}: 3350, 2962, 2930, 1750; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.70 (s, 3H, CH_3), 3.56–3.62 (m, 1H, CH), 3.84 (m, 1H, CH), 3.91 (br, 2H, NH_2), 3.93 (s, 3H, OCH_3), 3.94–3.97 (m, 1H, CH) 4.16 (m, 1H, CH), 4.80–4.87 (m, 1H, OCH), 7.07 (d, 1H, J = 2.7 Hz, ArH), 7.22 (s, 1H, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); Anal. for $C_{15}H_{17}IN_3O_3$; calcd; C 62.71, H 5.96, N 14.63; found; C 62.82, H 5.77, N 14.58; LC/MS (ESI-MS) m/z 288.13(M+1).

4.8. General procedure for the synthesis of N-{[3-(6-methoxy-2-methylquinolin-4-yl)-2-oxo-1,3-oxazolidin-5-yl]methylamide series (**8a–l**)

A clear solution of 5-aminomethyl-3-(6-methoxy-2-methyl-quinolin-4-yl)-oxazolidin-2-one (**7**) (1 mmol) in dichloromethane (8 mL) was added triethylamine (2 mmol) at 0 °C. Different alkyl/substituted aryl acid chlorides (1.1 mmol) was added dropwise at 0 °C. The reaction mass was maintained at 0 °C for 30 min. Reaction completion was monitored by TLC. When the reaction was complete, it was diluted with dichloromethane and washed with 10% sodium bicarbonate solution. The organic layer was washed with water, brine solution and then dried over anhydrous sodium sulphate. Finally it was concentrated under reduced pressure. The crude product was purified by Biotage parallel column purifier using 40–80% ethyl acetate in petroleum ether as eluant. The spectral data for the final compounds, **8a–l** is given below.

4.8.1. N-{[3-(6-Methoxy-2-methylquinolin-4-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (**8a**)

Appearance: off white solid; m.p 162.9–163.1 °C; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750, 1670; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.06 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.77–3.80 (m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.93–3.99 (m, 1H, CH), 4.10–4.16 (m, 1H, CH), 4.94–4.99 (m, 1H, OCH), 6.41–6.45 (m, 1H, NH), 7.07 (d, 1H, J = 2.7 Hz, ArH), 7.22 (s, 1H, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 22.55, 24.98, 39.21, 53.67, 55.85, 72.12, 100.91, 118.64, 122.68, 123.60, 130.85, 141.04, 145.57, 155.25, 156.51, 157.77, 174.81; Anal. for $C_{17}H_{19}N_3O_4$; calcd; C 62.00, H 5.81, N

12.76; found; C 62.26, H 5.90, N 12. 62; LC/MS (ESI-MS) *m/z* 330.14 (M+1).

*4.8.2. N-{[3-(6-Methoxy-2-methylquinolin-4-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}cyclopropane carboxamide (**8b**)*

Appearance: off white solid; m.p 169.6–170.1 °C; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750, 1670; ^{1}H NMR ($CDCl_3$-300 MHz) δ 0.8–0.83 (m, 2H, CH_2), 0.98–1.02 (m, 2H, CH_2), 1.41–148 (m, 1H, CH), 2.70 (s, 3H, CH_3), 3.77–3.80 (m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.93–3.99 (m, 1H, CH), 4.10–4.16 (m, 1H, CH), 4.94–4.99 (m, 1H, OCH), 6.41–6.45 (m, 1H, NH), 7.07 (d, 1H, J = 2.7 Hz, ArH), 7.22 (s, 1H, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 7.76, 14.63, 24.89, 41.97, 50.38, 55.66, 73.54, 100.09, 118.25, 122.47, 123.49, 130.76, 141.28, 145.41, 155.73, 156.42, 157.72,,174.81; Anal. for $C_{19}H_{21}N_3O_4$; calcd; C 64.21, H 5.96, N 11.82; found; C 64.36, H 5.90, N 11.94; LC/MS (ESI-MS) *m/z* 356.2 (M+1).

*4.8.3. N-{[3-(6-Methoxy-2-methylquinolin-4-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}cyclobutane carboxamide (**8c**)*

Appearance: Brown gummy solid; m.p 187.6–188.9; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750, 1670; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.01–1.2(m, 2H, CH_2), 1.36–1.48 (m, 4H, CH_2), 1.98 (m, 1H, –CH), 2.70 (s, 3H, CH_3), 3.77–3.80 (m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.93–3.99 (m, 1H, CH), 4.10–4.16 (m, 1H, CH), 4.94–4.99 (m, 1H, OCH), 6.40–6.48 (m, 1H, NH), 7.07 (d, 1H, J = 2.7 Hz, ArH), 7.22 (s, 1H, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 17.76, 24.89, 25.11, 39.5, 41.97, 50.90, 55.66, 73.54, 100.09, 118.25, 122.47, 123.49, 130.76, 141.28, 145.41, 155.73, 156.42, 157.72, 174.81; Anal. for $C_{20}H_{23}N_3O_4$; calcd; C 65.03, H 6.28, N 11.37; found; C 64.88, H 6.42, N 11.74; LC/MS (ESI-MS) *m/z* 370.17(M+1).

*4.8.4. 4-Fluoro-N-[3-(6-methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-benzamide (**8d**)*

Appearance: Off white solid; m.p 171.6–172 °C; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750, 1670; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.63 (s, 3H, CH_3), 3.78(s, 3H, OCH_3), 3.84–4.21 (m, 4H, CH_2), 5.02–5.06 (m, 1H, OCH), 6.96 (d, 1H, J = 2.7 Hz, ArH), 7.0–7.12 (m, 2H, ArH), 7.31–7.37 (m, 3H, ArH), 7.79–7.84 (m, 2H, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.80, 42.47, 50.44, 55.36, 73.56, 100.84, 115.49, 115.78, 118.31, 122.32, 123.44, 129.46, 129.54, 129.66, 130.98, 141.02, 145.53, 155.80, 156.28, 157.70, 167.09; LC/MS (ESI-MS) *m/z* 410.15(M+1).

*4.8.5. 2-Fluoro-N-[3-(6-methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-benzamide (**8e**)*

Appearance: pale yellow viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.63 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.84–4.21 (m, 4H, CH_2), 5.02–5.06 (m, 1H, OCH), 6.41–6.48(m, 1H), 6.96 (d, 1H, J = 2.7 Hz, ArH), 7.0–7.12 (m, 2H, ArH), 7.31–7.37 (m, 2H, J = 9.3 Hz, ArH), 7.79–7.84 (m, 2H, ArH), 7.95 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.85, 42.32, 50.53, 55.54, 73.58, 100.75, 116.16, 118.41, 121.15, 122.54, 123.51, 124.17, 128.78, 130.83, 133.49, 141.14, 145.51, 155.78, 156.47, 157.16, 157.72, 163.66, 168.24; Anal. for $C_{22}H_{20}FN_3O_4$; calcd; C 64.54, H 4.92, N 10.26; found; C 64.67, H 5.02, N 10.40; LC/MS (ESI-MS) *m/z* 410.15(M+1).

*4.8.6. N-[3-(6-Methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-benzamide (**8f**)*

Appearance: yellow gummy solid; m.p 148.9–151.0; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.43 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.97–4.21 (m, 4H, CH_2), 5.05–5.10 (m, 1H, OCH), 6.83–6.87 (m, 1H), 6.99 (d, 1H, J = 2.7 Hz, ArH), 7.14 (s, 1H, ArH), 7.37 (dd, 1H, J = 9.3 Hz, ArH), 7.61–7.68 (m, 3H, ArH), 7.88–7.91 (m, 2H, ArH), 7.97 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.85, 42.32, 50.53, 55.54, 73.58, 100.75, 118.41, 122.54, 123.51, 127.09, 129.46, 130.45, 130.83, 131.30, 141.14, 142.83, 145.51, 155.78, 156.47, 157.72, 168.24; Anal. for $C_{22}H_{21}N_3O_4$; calcd; C 67.51, H 5.41, N 10.74; found; C 67.67, H 5.53, N 10.60; LC/MS (ESI-MS) *m/z* 392.16 (M+1).

*4.8.7. 4-Ethyl-N-[3-(6-methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-benzamide (**8g**)*

Appearance: pale yellow solid; m.p 88.2–89 °C ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.20 (t, 3H, J = 7.2 Hz, CH_3), 2.20 (q, 2H, J = 7.2 Hz, CH_2), 2.70 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.97–4.21 (m, 4H, CH_2), 5.05–5.10 (m, 1H, OCH), 6.83–6.87 (m, 1H), 6.99 (d, 1H, J = 2.7 Hz, ArH), 7.14 (s, 1H, ArH), 7.26 (d, 2H, J = 8.1 Hz), 7.37 (dd, 1H, J = 9.3 Hz, ArH), 7.73 (d, 2H, J = 7.8 Hz, ArH), 7.97 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 14.60, 24.85, 27.90, 42.32, 50.53, 55.54, 73.58, 100.75, 118.41, 122.54, 123.51, 127.09, 129.46, 130.45, 130.83, 141.14, 142.83, 145.51, 155.78, 156.47, 157.72, 168.24; Anal. for $C_{24}H_{25}N_3O_4$; calcd; C 68.72, H 6.01, N 10.02; found; C 68.56, H 6.20, N 10.24; LC/MS (ESI-MS) *m/z* 420.19 (M+1).

*4.8.8. N-[3-(6-Methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-4-methylbenzamide (**8h**)*

Appearance: brown solid; m.p 81.3–81.9 °C; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750, 1670; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.43 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.97–4.21 (m, 4H, CH_2), 5.05–5.10 (m, 1H, OCH), 6.83–6.87 (m, 1H), 6.99 (d, 1H, J = 2.7 Hz, ArH), 7.14 (s, 1H, ArH), 7.26 (d, 2H, J = 8.1 Hz), 7.37 (dd, 1H, J = 9.3 Hz, ArH), 7.73 (d, 2H, J = 7.8 Hz, ArH), 7.97 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 21.51, 24.85, 42.32, 50.53, 55.54, 73.58, 100.75, 118.41, 122.54, 123.51, 127.09, 129.46, 130.45, 130.83, 141.14, 142.83, 145.51, 155.78, 156.47, 157.72, 168.24; Anal. for $C_{23}H_{23}N_3O_4$; calcd; C 68.13, H 5.72, N 10.36; found; C 68.56, H 5.98, N 10.24; LC/MS (ESI-MS) *m/z* 406.17 (M+1).

*4.8.9. 4-Methoxy-N-[3-(6-methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-benzamide (**8i**)*

Appearance: off white solid; m.p 137.1–137.7 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.70 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.97–4.21 (m, 4H, CH_2), 5.05–5.10 (m, 1H, OCH), 6.83–6.87 (m, 1H), 6.99 (d, 1H, J = 2.7 Hz, ArH), 7.14 (s, 1H, ArH), 7.26 (d, 2H, J = 8.1 Hz), 7.37 (dd, 1H, J = 9.3 Hz, ArH), 7.80 (d, 2H, J = 7.8 Hz, ArH), 7.97 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.85, 42.32, 50.53, 55.50, 55.54, 73.58, 100.75, 118.41, 122.54, 123.51, 127.09, 129.46, 130.45, 130.83, 141.14, 142.83, 145.51, 155.78, 156.47, 157.72, 168.24; Anal. for $C_{23}H_{23}N_3O_5$; calcd; C 68.55, H 5.50, N 9.97; found; C 68.80, H 5.86, N 9.20; LC/MS (ESI-MS) *m/z* 422.17 (M+1).

*4.8.10. N-[3-(6-Methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-4-trifluoromethylbenzamide (**8j**)*

Appearance: brown colour viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.43 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.97–4.21 (m, 4H, CH_2), 5.05–5.10 (m, 1H, OCH), 6.83–6.87 (m, 1H), 6.99 (d, 1H, J = 2.7 Hz, ArH), 7.14 (s, 1H, ArH), 7.82 (d, 2H, J = 8.4 Hz), 7.37 (dd, 1H, J = 9.3 Hz, ArH), 7.96 (d, 2H, J = 8.1 Hz, ArH), 7.97 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.85, 42.32, 50.53, 55.54, 73.58, 100.75, 113.20, 118.41, 120.30, 122.54, 123.51, 127.09, 127.36, 129.46, 130.45, 133.32, 133.93, 134.60, 134.63, 135.33, 141.14, 142.83, 145.51, 155.78, 156.47, 157.72, 168.24; Anal. for $C_{23}H_{20}F_3N_3O_4$; calcd; C 60.13, H 4.39, N 9.15; found; C 60.22, H 4.30, N 9.20; LC/MS (ESI-MS) *m/z* 460.14 (M+1).

*4.8.11. 4-Methoxy-N-[3-(6-methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-2-methylbenzamide (**8k**)*

Appearance: yellow viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.20 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.97–4.21 (m, 4H, CH_2), 5.05–5.10 (m, 1H, OCH), 6.58–6.60

(m, 1H), 6.70 (s, 1H, ArH), 6.97 (d, 1H, $J = 9.0$ Hz, ArH), 6.99 (d, 1H, $J = 2.7$ Hz, ArH), 7.07 (s, 1H, $J = 9.0$ Hz, ArH), 7.14 (s, 1H, ArH), 7.37 (dd, 1H, $J = 9.3$ Hz, ArH), 7.97 (d, 1H, $J = 9.3$ Hz, ArH); 21.51, 24.85, 42.32, 50.53, 55.50, 55.54, 73.58, 100.75, 116.33, 117.23, 118.41, 122.54, 123.51, 128.94, 130.45, 130.83, 138.66, 141.14, 142.83, 145.51, 155.78, 156.47, 157.72, 168.24; Anal. for $C_{24}H_{25}N_3O_5$; calcd; C 66.19, H 5.79, N 9.65; found; C 66.15, H 5.92, N 9.59; LC/MS (ESI-MS) *m/z* 436.18 (M+1).

4.8.12. 4-Chloro-N-[3-(6-methoxy-2-methyl-quinolin-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-benzamide (**8l**)

Appearance: yellow viscous liquid; IR (KBr, cm^{-1}) ν_{max}: 2962, 2930, 1750, 1670; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.64 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.97–4.21 (m, 4H, CH_2), 5.05–5.10 (m, 1H, OCH), 6.83–6.87 (m, 1H), 6.99 (d, 1H, $J = 2.7$ Hz, ArH), 7.14 (s, 1H, ArH), 7.37 (dd, 1H, $J = 9.3$ Hz, ArH), 7.56 (d, 2H, $J = 8.1$ Hz), 7.79 (d, 2H, $J = 7.8$ Hz, ArH), 7.97 (d, 1H, $J = 9.3$ Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.85, 42.32, 50.53, 55.54, 73.58, 100.75, 118.41, 122.54, 123.51, 128.25, 129.46, 130.89, 133.69, 140.09, 141.14, 142.83, 145.51, 155.78, 156.47, 157.72, 168.24; Anal. for $C_{22}H_{20}ClN_3O_4$; calcd; C 62.05, H 4.73, N 9.87; found; C 62.27, H 4.62, N 9.77; LC/MS (ESI-MS) *m/z* 426.12 (M+1).

4.9. Procedure for the synthesis of 2-chloro-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**9**)

Triethylamine (2.5 mmol) was added to a cooled solution of 6-methoxy-2-methylquinolin-4-amine (**2**, 1 mmol) in dichloromethane (15 mL) at 0 °C. A clear solution of chloroacetyl chloride (1.2 mmol) in dichloromethane 5 mL was added dropwise to the above reaction mixture. The reaction mass maintained for 2 h at temperature between 10 and 20 °C. The reaction completion was monitored by TLC. After the completion of the reaction, it was diluted with dichloromethane, washed with water, followed by brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography using 60% ethyl acetate in pet ether as eluant to get a pale yellow solid. (Yield-68%); m.p 153.7–154 °C ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.72 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.37 (s, 2H, CH_2), 6.98 (d, 1H, $J = 2.7$ Hz, ArH), 7.38 (dd, 1H, $J = 9.3$ Hz, ArH), 7.97 (d, 1H, $J = 9.0$ Hz, ArH), 8.09 (s, 1H, ArH), 8.97 (brs, 1H, NH); LC/MS (ESI-MS) *m/z* 265.07 (M+1).

4.10. Procedure for the synthesis of 2-allylamino-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**10**)

To a suspension 2-chloro-*N*-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**9**, 1 mmol), in 10 mL acetonitrile, potassium carbonate (2 mmol) and allylamine (5 mmol) was added and stirred at 60 °C for 2 h. The reaction completion was monitored by TLC. After completion of the reaction, the contents were cooled and filtered. The filtrate was concentrated under reduced pressure. The residue obtained was diluted with n-hexane and filtered the solid to get **10** (Yield-70%) as white solid; m.p 163–163.8 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.56 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 4.02 (d, 2H, $J = 5.1$ Hz, CH_2), 4.39 (s, 2H, CH_2), 5.13–5.21 (m, 2H, CH_2), 5.82–5.93 (m, 1H, CH), 7.20 (d, 1H, $J = 2.7$ Hz, ArH), 7.38 (dd, 1H, $J = 9.3$ Hz, ArH), 7.97 (d, 1H, $J = 9.0$ Hz, ArH), 8.09 (s, 1H, ArH), 8.97 (m, 1H, NH); LC/MS (ESI-MS) *m/z* 286.15 (M+1).

4.11. Allyl-[(6-methoxy-2-methyl-quinolin-4-ylcarbamoyl)-methyl]-carbamic acid benzyl ester (**11**)

A suspension of 2-allylamino-*N*-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**10**, 1 mmol) in acetone/water (1:1, 20 mL) was added sodium bicarbonate (3.0 mmol) followed by the dropwise addition of benzyl chloroformate (1.2 mmol) at 0 °C. The reaction mass was maintained between 0 and 10 °C for 2 h. The reaction completion was monitored by TLC. When the reaction was complete, the reaction mass was concentrated under reduced pressure. The residue was extracted with dichloromethane, washed with 10% sodium bicarbonate solution, water and brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get **11** as off white solid (Yield-80%); m.p 156.7–157 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.57 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 4.02 (d, 2H, $J = 5.1$ Hz, CH_2), 4.39 (s, 2H, CH_2), 5.09–5.21 (m, 4H, CH_2), 5.82–5.93 (m, 1H, CH), 7.20 (d, 1H, $J = 2.7$ Hz, ArH), 7.35–7.39 (m, 4H, ArH), 7.52 (m, 2H, ArH), 7.82 (d, 1H, $J = 9.0$ Hz, ArH), 7.92 (d, 1H, $J = 10.2$ Hz, ArH), 10.06 (brs, 1H, NH); LC/MS (ESI-MS) *m/z* 420.19(M+1).

4.12. 2-(5-Iodomethyl-2-oxo-oxazolidin-3-yl)-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**12**)

To a solution of allyl-[(6-methoxy-2-methyl-quinolin-4-ylcarbamoyl)-methyl]-carbamic acid benzyl ester (**11**, 10 g, 23.83 mmol) in acetonitrile (100 mL) was added iodine (12.09 g, 47.66 mmol). The reaction mass stirred at 25–28 °C for 16 h. The reaction completion was monitored by TLC. Once the reaction was complete, the solvent was removed and the crude residue was diluted with ethyl acetate, washed the organic layer with 10% sodium thiosulphate solution, followed by water and brine solution. The organic layer was dried over anhydrous sodium sulphate and finally concentrated under reduced pressure. The crude product was purified by flash column chromatography using 60–80% ethyl acetate in petroleum ether as eluant to get **12** as a pale yellow gummy solid (Yield-56%). m.p 99.8–100.5; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.70 (s, 3H, CH_3), 3.39–3.44 (m, 2H, CH_2), 3.56–4.01 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 4.23 (d, 2H, $J = 9.0$ Hz, CH_2), 4.69–4.73 (m, 1H, CH), 7.24 (d, 1H, $J = 2.4$ Hz, ArH), 7.33 (dd, 1H, $J = 9.3$ Hz, ArH), 7.94 (d, 1H, $J = 9.3$ Hz, ArH), 8.08 (s, 1H, ArH), 8.90–9.40 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 6.14, 24.81, 49.76, 51.87, 56.03, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 456.2 (M+1).

4.13. General procedure for the synthesis of 2-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide derivatives (**13a–n**)

A mixture of 2-(5-iodomethyl-2-oxo-oxazolidin-3-yl)-*N*-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**12**, 0.2 g, 0.439 mmol), potassium carbonate (0.151 g, 1.09 mmol), different substituted amines (1.1 mmol) in 10 mL of acetonitrile was heated to 80 °C for 4 h. The reaction completion was monitored by TLC and when the reaction was completed, the reaction mass was filtered through a celite bed, filtrate was concentrated under reduced pressure. The crude residue was purified using biotage parallel column purifier using ethyl acetate in petroleum ether (4:1) to 4–6% methanol in dichloromethane as eluant. The spectral data for the final compounds, **13a–n** is given below.

4.13.1. 2-(5-Dimethylaminomethyl-2-oxo-oxazolidin-3-yl)-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13a**)

Appearance: white solid; m.p 111.2–111.9; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.39 (s, 6H, NCH_3), 2.67–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, $J = 2.4$ Hz, ArH), 7.33 (dd, 1H, $J = 9.3$ Hz, ArH), 7.94 (d, 1H, $J = 9.3$ Hz, ArH), 8.08 (s, 1H, ArH), 9.20–9.40 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.81, 45.28,

49.76, 51.87, 54.48, 56.03, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; Anal. for $C_{19}H_{24}N_4O_4$; calcd; C 61.28, H 6.50, N 15.04; found; C 61.52, H 6.66, N 15.28; LC/MS (ESI-MS) *m/z* 373.18 (M+1).

*4.13.2. 2-(5-Diethylaminomethyl-2-oxo-oxazolidin-3-yl)-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13b**)*

Appearance: off white solid; m.p 129.1–130 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.11 (t, 3H, J = 7.2 Hz, CH_3), 2.45 (q, 2H, J = 7.2 Hz, CH_2), 2.67–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 1H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.33 (dd, 1H, J = 9.3 Hz, ArH), 7.94 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.20–9.40 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 12.06, 24.81, 48.14, 49.76, 51.87, 54.48, 56.03, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; Anal. for $C_{21}H_{28}N_4O_4$; calcd; C 62.98, H 7.05, N 13.99; found; C 63.12, H 7.14, N 13.78; LC/MS (ESI-MS) *m/z* 401.21 (M+1).

*4.13.3. N-(6-Methoxy-2-methyl-quinolin-4-yl)-2-[5-((4-methyl-piperazin-1-yl)methyl)-2-oxo-oxazolidin-3-yl]-acetamide (**13c**)*

Appearance: pale yellow viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.33 (s, 3H, CH_3), 2.53–2.56 (m, 4H, NCH_2), 2.58–2.60 (m, 4H, NCH_2), 2.67–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.33 (dd, 1H, J = 9.3 Hz, ArH), 7.94 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.20–9.40 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.81, 42.90, 49.76, 51.60, 51.87, 53.74, 54.82, 56.03, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 428.20 (M+1).

*4.13.4. 2-[5-((4-Ethyl-piperazin-1-yl)methyl)-2-oxo-oxazolidin-3-yl]-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13d**)*

Appearance: brown viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.15 (t, 3H, J = 7.2 Hz, CH_3), 2.48 (q, 2H, J = 7.2 Hz, CH_2), 2.55–2.58 (m, 4H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.33 (dd, 1H, J = 9.3 Hz, ArH), 7.94 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.21–9.48 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 9.80, 24.81, 47.44, 49.76, 51.87, 52.08, 52.38, 54.82, 56.03, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; Anal. for $C_{23}H_{31}N_5O_4$; calcd; C 62.57, H 7.08, N 15.86; found; C 62.66, H 6.98, N 15.98; LC/MS (ESI-MS) *m/z* 442.24 (M+1).

*4.13.5. 2-[5-((4-Acetyl-piperazin-1-yl)methyl)-2-oxo-oxazolidin-3-yl]-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13e**)*

Appearance: brown gummy solid; m.p 148.7–149 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.20 (s, 1H, CH_3), 2.55–2.58 (m, 4H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.33 (dd, 1H, J = 9.3 Hz, ArH), 7.94 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.21–9.48 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 21.09, 24.81, 49.76, 51.87, 52.93, 52.38, 54.82, 56.03, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73, 170.01; LC/MS (ESI-MS) *m/z* 456.22 (M+1).

*4.13.6. 2-[5-((4-Isopropyl-piperazin-1-yl)methyl)-2-oxo-oxazolidin-3-yl]-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13f**)*

Appearance: brown gummy solid; 166.9–168.0; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.03(d, 6H, J = 6.6 Hz, CH_3), 2.55–2.58 (m, 4H, NCH_2), 2.66 (m, 1H, CH), 2.69–2.71 (m, 4H, NCH_2), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.33 (dd, 1H, J = 9.3 Hz, ArH), 7.94 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.12–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 18.30, 24.81, 49.76, 51.87, 52.08, 52.38, 54.70, 54.82, 56.60, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; Anal. for $C_{24}H_{33}N_5O_4$; calcd; C 63.28, H 7.30, N 15.37; found; C 63.40, H 7.44, N 15.30; LC/MS (ESI-MS) *m/z* 456.26 (M+1).

*4.13.7. 2-[5-((4-Tert-butyl-piperazin-1-yl)methyl)-2-oxo-oxazolidin-3-yl]-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13g**)*

Appearance: tan colour solid; m.p 172.7–173.4 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.11 (s, 9H, CH_3), 2.55–2.58 (m, 4H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.35 (dd, 1H, J = 9.3 Hz, ArH), 7.96 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.81, 27.09, 49.76, 51.87, 52.08, 52.38, 52.99, 54.82, 56.60, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 470.27 (M+1).

*4.13.8. N-(6-Methoxy-2-methyl-quinolin-4-yl)-2-(5-morpholin-4-ylmethyl-2-oxo-oxazolidin-3-yl)-acetamide (**13h**)*

Appearance: pale yellow solid; m.p 127.3–128 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.64 (m, 4H, CH_2), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.75 (m, 4H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.35 (dd, 1H, J = 9.3 Hz, ArH), 7.96 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.81, 51.87, 52.08, 54.45, 54.82, 56.60, 67.04, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 415.19 (M+1).

*4.13.9. 2-(5-Cyclopropylaminomethyl-2-oxo-oxazolidin-3-yl)-N-(6-methoxy-2-methyl-quinolin-4-yl) -acetamide (**13i**)*

Appearance: pale yellow viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 0.98 (m, 2H, CH_2), 1.01 (m, 2H, CH_2), 1.6 (m, 1H, CH), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 6.71(brs, 1H, NH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.35 (dd, 1H, J = 9.3 Hz, ArH), 7.96 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 7.20, 24.81, 26.7, 45.59, 51.87, 52.08, 56.60, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 385.18 (M+1).

*4.13.10. N-(6-Methoxy-2-methyl-quinolin-4-yl)-2-(2-oxo-5-pyrrolidin-1-ylmethyl-oxazolidin-3-yl)-acetamide (**13j**)*

Appearance: brown gummy solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.64–1.67 (m, 4H, CH_2), 2.57–2.63 (m, 4H, CH_2), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.35 (dd, 1H, J = 9.3 Hz, ArH), 7.96 (d, 1H, J = 9.3 Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 23.59, 24.81, 45.59, 51.87, 52.08, 54.54, 56.60, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 399.20 (M+1).

*4.13.11. N-(6-Methoxy-2-methyl-quinolin-4-yl)-2-(2-oxo-5-piperidin-1-ylmethyl-oxazolidin-3-yl)-acetamide (**13k**)*

Appearance: pale yellow solid; m.p 131.9–140.5 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.35–1.57 (m, 6H, CH_2), 2.43–2.49 (m, 4H, CH_2),

2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, $J = 2.4$ Hz, ArH), 7.35 (dd, 1H, $J = 9.3$ Hz, ArH), 7.96 (d, 1H, $J = 9.3$ Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.64, 24.81, 26.13, 45.59, 51.87, 52.08, 55.14, 56.60, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 413.21(M+1).

4.13.12. 2-{5-[(Cyclohexyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13l**)

Appearance: brown solid; m.p 152.8–153.1 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.27–1.37 (m, 6H, CH_2), 1.67 (m, 2H, CH_2), 1.83–2.03 (m, 2H, CH_2), 2.39 (s, 3H, NCH_3), 2.52(m, 1H, CH), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, $J = 2.4$ Hz, ArH), 7.35 (dd, 1H, $J = 9.3$ Hz, ArH), 7.96 (d, 1H, $J = 9.3$ Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.81, 25.95, 26.40, 29.07, 45.59, 51.87, 52.08, 56.60, 67.93, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 441.24(M+1).

4.13.13. N-(6-Methoxy-2-methyl-quinolin-4-yl)-2-[5-(4-methyl-piperidin-1-ylmethyl)-2-oxo-oxazolidin-3-yl]-acetamide (**13m**)

Appearance: off white solid; m.p 143.9–144.4 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 0.81 (d, 3H, $J = 3.3$ Hz, CH_3), 1.10–1.58 (m, 5H, CH_2), 2.04–2.13 (m, 2H, CH_2), 2.72–2.74 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 2.79–2.85 (m, 2H, CH_2), 3.64–3.90 (m, 1H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 7.24 (d, 1H, $J = 2.4$ Hz, ArH), 7.35 (dd, 1H, $J = 9.3$ Hz, ArH), 7.96 (d, 1H, $J = 9.3$ Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 21.82, 30.45, 33.98, 24.81, 45.59, 51.87, 52.08, 53.40, 56.60, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 427.23 (M+1).

4.13.14. 2-(5-Cyclopentylaminomethyl-2-oxo-oxazolidin-3-yl)-N-(6-methoxy-2-methyl-quinolin-4-yl)-acetamide (**13n**)

Appearance: brown viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.12–1.87 (m, 8H, CH_2), 2.60 (m, 1H, CH), 2.76 (s, 3H, CH_3), 3.64–3.90 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.08–4.26 (m, 2H, CH_2), 4.76–4.81 (m, 1H, OCH), 6.71(brs, 1H, NH), 7.24 (d, 1H, $J = 2.4$ Hz, ArH), 7.35 (dd, 1H, $J = 9.3$ Hz, ArH), 7.96 (d, 1H, $J = 9.3$ Hz, ArH), 8.08 (s, 1H, ArH), 9.23–9.38 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 23.50, 24.81, 32.73, 47.29, 51.87, 52.08, 56.60, 58.85, 72.72, 98.62, 111.71, 119.03, 122.50, 129.89, 139.97, 143.32, 156.50, 157.81, 158.64, 166.73; LC/MS (ESI-MS) *m/z* 413.21 (M+1).

4.14. Antibacterial study

The newly synthesized final compounds were evaluated for their *in vitro* antibacterial activity against ATCC-25922 *E. coli*, ATCC-25923 *S. aureus*, ATCC-27853 *P. aeruginosa*, clinical isolate of *K. pneumoniae* and *S. pyogenes* bacterial strains by serial plate dilution method. The compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and was diluted further (a twofold serial dilution) using Muller Hinton broth. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes and their pH was adjusted to 7.2–7.4 using phosphate buffer. A standardized suspension of the test bacterium (as per the Clinical and Laboratory Standards Institutes (CLSI) guidelines) was inoculated and incubated for 18–24 h at 37 °C [33]. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. Activity of each compound was compared with ciprofloxacin as standard [34,35]. MIC (μg/mL) were determined for **8a**–**l** and **13a**–**n** and the corresponding results are summarized in Table 1.

4.15. Anti-tuberculosis study

The compounds were screened for their *in vitro* anti-mycobacterial activity against *M. tuberculosis* H_{37}Rv ATCC 27294, and non-tubercular mycobacterial (NTM) species like *M. smegmatis* (MC2) ATCC 19420, and *M. fortuitum* ATCC 19542 by Resazurin Assay method [36] and their MIC values were determined. The standard drugs, viz. isoniazid (INH) and rifampicin (RIF) were used as a reference. The screening results of the title compounds **8a**–**l** and **13a**–**n** and the standard drugs are reported in Tables 1 and 2.

M. tuberculosis strains were 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 2 standard with the same medium. From this, 50 μL of this culture was added to 150 μL of fresh medium in 96 well microtitre 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. Further, the second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Control tubes had the same volumes of DMF without any substrate. Rifampicin (RIF) and isoniazid (INH) were used as the reference compounds. After incubation at 37 °C for 7 days, 20 μL of 0.01% Resazurin (Sigma, St. Louis. MO, USA) in water was added to each tube. Resazurin, a redox dye, is blue in the oxidized state and turns pink when reduced by the growth of viable cells. The control tubes showed a colour change from blue to pink after 1 h at 37 °C. Compounds which prevented the change of colour of the dye were considered to be inhibitory to *M. tuberculosis*. Inoculum size of 0.01 ml was taken and sub cultured on Middlebrook 7H10 plates (Difco BBL, Sparks, MD, USA). After incubation of 7 days, number of colonies were counted in control and test plates for calculation of strength (in %) of the compound in question which was effective in reducing significant population in initial inoculum.

4.16. Experimental protocol

4.16.1. In silico studies

The ligands were drawn in ChemDraw Ultra 6.0 (Chem Office package) assigned with proper 2D orientation and the structure of each compound was analyzed for connection error in bond order. OSIRIS, an ADMET based Java library layer that provides reusable cheminformatics functionality and is an entirely in-house developed drug discovery informatics system was used to predict the total drug score via *in silico*. Energy of the molecules was minimized using Dundee PRODRG2 server [37]. The energy minimized compounds were then read as input for AutoDock 4.2, in order to carry out the docking simulation. All the hetero atoms were removed from the 2H7M.pdb, to make complex less receptor free of any ligand before docking. The Graphical User Interface program "AutoDock Tools" was used to prepare, run, and analyze the docking simulations. Kollman united atom charges, solvation parameters and polar hydrogens were added to the receptor for the preparation of protein in docking simulation. Since ligands are not peptides, Gasteiger charge was assigned and then non-polar hydrogens were merged. AutoDock requires pre-calculated grid maps, one for each atom type, present in the ligand being docked and it stores the potential energy arising from the interaction with macromolecule. This grid must surround the region of interest (active site) in the macromolecule. In the present study, the binding site was selected based on the amino acid residues, which are involved in binding with Pyrrolidine carboxamide of enoyl-ACP reductase as obtained from PDB with ID 2H7M which would be

considered as the probable best accurate region as Pyrrolidine carboxamide behaves to be a novel class of potent enoyl-ACP reductase inhibitors and is solved by experimentally crystallographic data. Therefore, the grid was centred at the region including all the 8 amino acid residues (Gly 96, Lys 165, Tyr 158, Met 103, Pro 156, Ala 157, Ile 215 and Met 199) that surround active site as in Fig. 2. The grid box size was set at 70, 78, and 58 Å for *x*, *y* and *z* respectively, and the grid centre was set to 12.309, 32.635 and 59.923 for *x*, *y* and *z* respectively, which covered all the 8 amino acid residues in the considered active pocket. Auto Grid 4.0 Program, supplied with AutoDock 4.0 was used to produce grid maps. The spacing between grid points was 0.375 Å. The Lamarckian Genetic Algorithm (LGA) was chosen to search for the best conformers. During the docking process, a maximum of 10 conformers was considered for each compound. All the AutoDock docking runs were performed in Intel CentrinoCore2Duo CPU @ 2.20 GHz of IBM system origin, with 2 GB DDR RAM. AutoDock 4.0 was compiled and run under Windows XP operating system.

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