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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis of quinolinyl Schiff bases and azetidinones as enoyl ACP-reductase inhibitors

Shrinivas D. Joshi[1] · Uttam A. More[1,2] · Deepak Parkale[1] · Tejraj M. Aminabhavi[1] · Andanappa K. Gadad[3] · Mallikarjuna N. Nadagouda[1] · Rahul Jawarkar[4]

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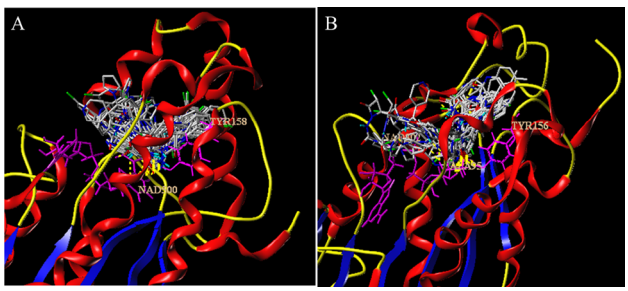
Abstract New series of quinoline derivatives were synthesized from 2-chloroquinoline-3-carbaldehydes. In the reaction sequence, substituted acetanilides were cyclized to give 2-chloroquinoline-3-carbaldehydes **2a–d**, which were transformed to **6a–d**, which were then cyclized to give azetidinones **9a–d**. The key scaffolds viz., 2-methoxy derivatives **3a–d**, obtained from **2a–d** were converted to target Schiff bases **4a–d**, **5a–d** and azetidinones **7a–d**, **8a–d** in good yields. Structures of these compounds were established by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The compounds **4a–d** to **9a–d** were evaluated for in vitro antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Vibrio cholera* and antitubercular activity against *Mycobacterium tuberculosis* H_{37}Rv. The Schiff bases and azetidinone derivatives exhibited good antibacterial and antitubercular activities. Bacterial enoyl ACP-reductase catalyzes the final step in each cycle of bacterial fatty acid biosynthesis and is an attractive target for the development of new antimicrobial agents. Molecular docking into active site of enoyl ACP-reductase was performed on 2H7M.PDB and 4JX8.PDB files to understand ligand–protein interactions. The compounds obtained from the present research can be used as scaffolds in fragment-based design of new potent drugs.

Graphical Abstract Molecular modeling, synthesis, spectral, antimicrobial studies of quinolinyl Schiff bases and azetidinones using crystal structure of *E. coli* and *M. tuberculosis* enoyl ACP-reductase (4JX8/2H7M PDB) and compared with in vitro antimicrobial activity.



Keywords Quinolines · Pyrroles · Schiff bases · Antibacterial activity · Antitubercular activity · Surflex-Dock

Introduction

Tuberculosis (TB), is a communicable disease, spreads through air and caused by the bacterium *Mycobacterium tuberculosis* (MTB), is regarded as a serious global problem. According to statistics, about one-third of the world's population is infected with TB affecting nearly 8 million

This paper is affectionately dedicated to my teacher Dr. V. H. Kulkarni for his service to Pharmacy Profession.

✉ Shrinivas D. Joshi
shrinivasdj@rediffmail.com

[1] Novel Drug Design and Discovery Laboratory, Department of Pharmaceutical Chemistry, S.E.T's College of Pharmacy, Sangolli Rayanna Nagar, Dharwad, Karnataka 580 002, India

[2] Centre for Research and Development, Prist University, Thanjavur, Tamil Nadu 613 403, India

[3] School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Champs-Fleurs, Mount-Hope, Trinidad and Tobago

[4] Department of Pharmaceutical Chemistry, Sahyadri College of Pharmacy, Methawade, Sangola, Maharashtra 413 307, India

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people worldwide with an annual mortality rate of 2 million (Snider, 1994; Dye *et al*., 1999). The emergence of multi-drug-resistant tuberculosis (MDR-TB) and extensive drug-resistant tuberculosis (XDR-TB) has become one of the biggest challenges in the treatment of TB, creating an urgent need to develop new drugs and strategies for efficient treatment. However, the bacterial resistance to multiple antibacterial agents or antibiotics is a serious problem to fight against infectious diseases, resulting in increased mortality, morbidity and healthcare costs. There is thus a need to develop novel chemical entities that are effective against the life-threatening infectious diseases caused by multidrug-resistant strains of the Gram-positive pathogens like *Staphylococcus*, *Bacillus* and *Streptococcus* and Gram-negative pathogens like *Escherichia*, *Vibrio* and *Pseudomonas* strains.

Despite many efforts to develop new structural prototypes, quinolines are one of the most versatile class of compounds against microbes. Quinoline is an important class of heterocyclic compounds found in many synthetic and naturally occurring medicinal plants with a wide range of pharmacological activities such as antibacterial (Kidwai *et al*., 2000), antifungal (Malendez Gomez *et al*., 2008), antiviral (Carta *et al*., 2011), anti-inflammatory (Chen *et al*., 2006), antimalarial (Modapa *et al*., 2009) and antiproliferative (Mol *et al*., 2008). Quinoline scaffold is versatile and capable of binding to multiple receptor targets and consequently, its structural modifications, might exhibit multiple activities. Quinoline derivatives have exhibited good anti-tuberculosis (anti-TB) activity and are the promising compounds in discovering new anti-TB agents (de Souza *et al*., 2009; Candea *et al*., 2009; Ferreira *et al*., 2010).

Recently, anti-TB activity of a series of quinolinylhydrazones has been reported (Fattorusso *et al*., 2008; Savini *et al*., 2002). Bedaquiline (also known as TMC 207 or R207910) is a quinoline anti-TB drug developed by Johnson & Johnson Pharmaceuticals Research and Development. This new potent chemical entity inhibits drug-sensitive and drug-resistant MTB in vitro and shows bactericidal activity in patients with drug-susceptible pulmonary tuberculosis and is currently undergoing phase II clinical trials (Rustomjee *et al*., 2008). In view of the worldwide spread of multidrug resistance of MTB, there is an urgent need to discover anti-TB agents with novel structures. Enoyl acyl carrier protein reductase (ENR) from MTB and *E. coli*, is one of the key enzymes involved in the bacterial fatty acid elongation cycle and has been validated as an effective antimicrobial target.

Bacterial fatty acid biosynthesis is catalyzed by a set of distinct, mono-functional enzymes communally known as the type II FAS (FASII). In mammalians, these enzymes differ significantly from the type I FAS (FASI), in which all of the enzymatic activities are encoded in one or two multifunctional polypeptides. This typical difference in the FAS molecular organization between most bacteria and mammals makes easy to design specific inhibitors of improved selectivity and lesser toxicity. The pyridine nucleotide cofactor hydride ion utilized by the *E. coli* and *M. tuberculosis* enoyl ACP-reductases (FabI and InhA, respectively) is the 4*S* hydrogen, whereas the mammalian type I synthase uses the 4*R* hydrogen (Quemard *et al*., 1995). MTB contains unique signature fatty acids, the mycolic acids, which are unusually long chain α-alkyl, *β*-hydroxy fatty acids of 60–90 carbons (Banerjee *et al*., 1994).

The 2-azetidinone ring system known as *β*-lactam since 1907 represents the common structural feature of a number of broad spectrum *β*-lactam antibiotics including penicillins, cephalosporins, monobactams, clavulanic acid, sulbactams and carbapenems, which are used as chemotherapeutic agents to treat microbial diseases and bacterial infections (Papp-Wallace *et al*., 2011). The 2-azetidinone derivatives have been reported to possess a wide range of biological activities like antifungal (Halve *et al*., 2007), anticancer (Veinberg and Vorona, 2004) and anti-TB (Dubey *et al*., 2011). The report from Massengo-Tiasse et al. gives clear picture of diversity in ENR, which was discovered to be the target of the INH, which is primary antituberculosis drug and that of synthetic triclosan, very widely used in every day products such as soap, toothpaste and plastics was also found to be well inhibitor of ENR. These findings argued that differences between mammalian FAS I ENRs and bacterial FAS II ENRs rendered the bacterial enzymes good antimicrobial target candidates (Massengo-Tiasse and Cronan, 2009).

On the basis of the observations discussed above and in search of novel antibacterial and antitubercular agents (Joshi *et al*., 2008; 2013a, b; 2014a, b; More *et al*., 2014, 2015), we report here new type of quinoline derivatives in which active pharmacophores, viz., hydrazones and azetidinones that are incorporated at the 3rd position of quinoline ring. Such newly designed molecules could exhibit improved biological activity. In our design concept of quinoline derivatives, we have introduced the isoniazid pharmacophore, a first line anti-TB drug and 4-pyrrol-1-yl benzoic acid hydrazide (Joshi *et al*., 2008), into the core structure of the starting material viz., quinoline-3-carbaldehyde. Epiroprim which contain pyrrole fragment and AEA16 (6-{(1*E*)-3-[3-(3-methyl-1-benzofuran-2-yl)azetidin-1-yl]-3-oxoprop-1-en-1-yl}-1,8-naphthyridin-2(1*H*)-one) which contain azetidine fragment has suggested us to introduce the pyrrole and azetidinone fragments into quinoline moiety, with the expectation to improve its activity, possibly by the incorporation of a multiple mode of action through a different target (Fig. 1). The two atoms

(N and O) are critical for the interactions with the bacterial cell receptor, therefore are responsible for antimicrobial activities. These interactions have usually precise geometric requirements, which may be described in terms of the distances between the atoms and their mutual orientation in the pharmacophore. Bedaquiline gives an idea to make change of various electron withdrawing and donating atoms substitution at 6th position of quinoline. That of INH was replaced with pyrrolyl benzohydrazide, here the pyridine moiety was replaced with benzene and pyrrole to get better insight.

Based on this concept, we propose the synthesis of substituted-2-chloroquinoline C(3)-functionalized derivatives. In some derivatives, chlorine atom is replaced by the methoxy atom at the C(2) position of quinoline moiety, with the aim to establish the importance of this substituent for biological activity. In the light of the above facts, and with a hope to obtain novel compounds with significant antimicrobial activity, we report here the synthesis of novel quinolinylhydrazone and azetidinone derivatives and evaluate their possible antibacterial, antitubercular and cytotoxic activities. Docking studies were performed to assess the binding mode of the active compounds into the enoyl ACP-reductase enzyme binding site using Surflex-Dock program of Sybyl-X 2.1.1 software (Tripos International, 2012).

Results and discussion

Chemistry

Synthetic strategies adopted to obtain the target compounds are depicted in Scheme 1. FTIR, ^{1}H NMR, ^{13}C NMR and mass spectral data are in agreement with the proposed structures of all the synthesized compounds.

Synthesis of scaffolds is depicted in Scheme 1. The 6-substituted-2-chloroquinoline-3-carbaldehydes **2a–d** were chosen as starting material to design several Schiff bases and azetidinones. Various 4-substituted acetanilides **1a–d** were treated with DMF-$POCl_3$ complex (Vilsmeier-Haack reagent) to obtain 6-substituted-2-chloroquinoline-3-carbaldehydes **2a–d**. The 6-substituted-2-chloroquinoline-3-carbaldehydes **2a–d** upon treatment with methanol in the presence of KOH furnished 6-substituted-2-methoxyquinoline-3-carbaldehydes **3a–d**.

FTIR spectrum of **3a** has a strong stretching band at 1689 cm^{-1} due to carbonyl group. In the ^{1}H NMR spectrum, the singlet at δ 4.21 which was accounted for methoxy group, while two singlets at δ 10.49 and δ 8.60 were accounted for CHO and C_4–H. A multiplet at δ 7.85–7.89 was assigned for two protons of C_5–H and C_8–H, while two triplets at δ 7.75 and δ 7.46 were assigned for two protons of C_6–H and C_7–H, respectively. The ^{13}C NMR spectrum of **3a** also supported the structure via CHO and OCH_3 resonances that appeared at δ 189.32 and δ 53.81, respectively. The signals at δ 161.22, δ 148.97, δ 139.98, δ 132.54, δ 129.73, δ 127.29, δ 125.02, δ 124.39 and δ 120.06 were due to carbons C_2, C_9, C_4, C_7, C_5, C_8, C_{10}, C_6 and C_3 of quinoline ring, respectively. The mass spectrum of **3a** showed a molecular ion peak at *m/z* 188.74 that confirms its molecular weight.

The Schiff bases **4a–d** were prepared by reacting 6-substituted-2-methoxyquinoline-3-carbaldehydes **3a–d** with isoniazid in the presence of glacial acetic acid showed carbonyl amide stretching around 1648–1671 cm^{-1} and N–H bands at 3183–3238 cm^{-1} region. The ^{1}H NMR and ^{13}C NMR data were also in agreement with the formation of Schiff bases. The ^{1}H NMR spectra of **4a–d** showed two

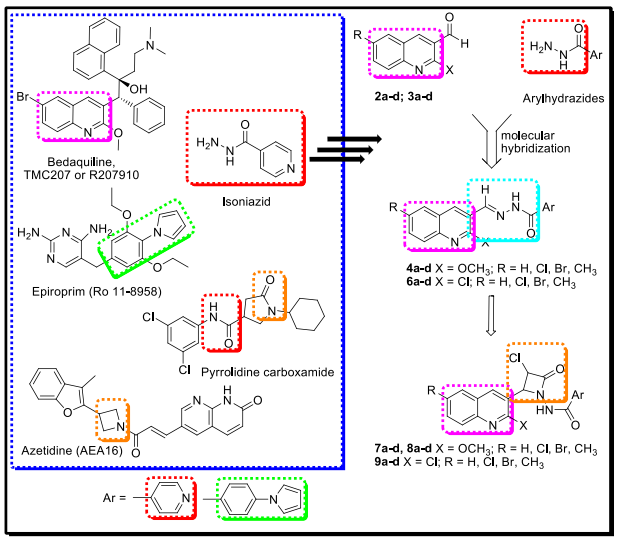
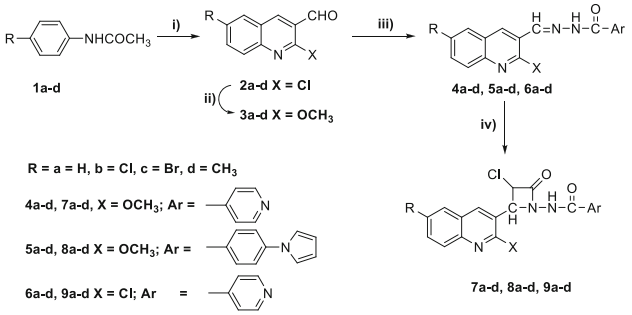


Fig. 1 Design concept of quinoline derivatives



Reagents and conditions: i) DMF/$POCl_3$; ii) MeOH/KOH, 100-110 ^{0}C; iii) Ar-CO-NH-NH_2, EtOH, reflux; iv) NEt_3, $ClCH_2COCl$, benzene.

Scheme 1 Synthesis of isonicotinic acid hydrazide/pyrrol-1-yl benzoic acid hydrazide derived quinolinylhydrazones and azetidinonylquinolines

singlets around δ 8.64–9.37 and at δ 12.09–12.46, which were attributed to N=CH and NH protons, respectively.

The compounds **5a–d** were prepared by the reaction of 6-substituted-2-methoxyquinoline-3-carbaldehydes **3a–d** with 4-(1*H*-pyrrol-1-yl)benzohydrazide in the presence of glacial acetic acid. Cyclization of **4a–d** with monochloroacetylchloride in the presence of triethylamine in dry benzene afforded *N*-(3-chloro-2-(2-methoxy-6-substitutedquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamides **7a–d**. Compounds **5a–d** upon treatment with monochloroacetylchloride in the presence of triethylamine in dry benzene gave **8a–d**. Further, reaction of **2a–d** with isoniazid in ethanol in the presence of glacial acetic acid gave Schiff bases **6a–d**, which upon further treatment with monochloroacetylchloride in the presence of triethylamine in dry benzene gave *N*-(3-chloro-2-(2-chloro-6-substitutedquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamides **9a–d**.

The cyclization of quinoline hydrazone **4d** to the corresponding 3-chloro-2-(2-methoxy-6-methylquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamide **7d** was evidenced by its ^{1}H NMR data, wherein the disappearance of a singlet at δ 8.65 corresponding to CH=N proton and the appearance of two doublets at δ 4.50 and δ 4.42 corresponding to protons of CH–Cl and CH–N of azetidinone ring, respectively, confirmed the cyclization. The formation of azetidinone was further supported by ^{13}C NMR data of **7d**. While CH=N carbon of compound **4d** in hydrazone structure was observed at δ 148.71 in its ^{13}C NMR spectrum, the same carbon atom (CH–N) was observed at δ 91.25 after cyclization to azetidinone ring due to sp^3 hybridization. Further evidence for the formation of azetidinone **7d** was obtained by recording the mass spectra. The mass spectrum of compound **7d** showed a molecular ion peak at *m/z* 396.83, which is in conformity with the molecular formula, $C_{20}H_{17}ClN_4O_3$. Mass spectra showed accurate molecular ion peaks at *m/z* 382.01, 416.25, 459.70, 446.89, 480.33, 524.78, 460.91, 386.00, 419.66, 463.12 and 400.25 for compounds **7a–c**, **8a–d** and **9a–d**, respectively.

Our synthetic strategy was to synthesize a highly biologically active heterocycle containing –CH=N– and azetidinone moieties. As the results, we have obtained a mixture of the diastereomers of quinoline derivatives in 3rd and 4th steps as per Scheme 1. Generally the compounds bearing the *trans* configuration were obtained in higher yields. So we have mentioned here only major products. Separation of the compounds was performed by column chromatography, upper spot obtained with high yield were isolated, analyzed and discussed in present work.

Antibacterial and antitubercular activities (in vitro)

Preliminary antimicrobial screening revealed that compounds **4a–d** to **9a–d** showed moderate to good inhibitory activity against all strains. Quinoline analogs are known to have antimicrobial activity and heterocyclic groups such as pyrrole attached to quinoline help to improve the antimicrobial activity of quinoline class of molecules (Karal *et al*., 2007). Also, quinolinylhydrazones and azetidinones have shown antibacterial and antitubercular activities. Therefore, in present work, quinolinylhydrazones and azetidinones have been synthesized and screened for antibacterial and antitubercular activities. The antibacterial activity of compounds **4a–d** to **9a–d** expressed in terms of minimum inhibitory concentration (MIC) is shown in Table 1 along with the activity of ciprofloxacin and norfloxacin for comparison. All the compounds showed enhanced activity against Gram-negative bacteria than Gram-positive bacteria with the antibacterial activity at MIC values of 0.4–50 μg/mL. All the compounds showed antibacterial activity with the MIC values between 0.4 and 3.125 μg/mL against *Vibrio cholera* and *E. coli.*

The antitubercular screening data revealed that all the compounds have shown good to moderate inhibitory activity against MTB. In vitro antitubercular activity of quinoline derivatives **4a–d** to **9a–d** are reported in Table 1 together with the isoniazid (INH) used as reference drug. Compounds **5c** and **5d** were quite potent inhibitors (MIC 1.6 μg/mL) compared to isoniazid (MIC 0.2 μg/mL), while **5b**, **7d** and **8a** showed good activity with inhibition of mycobacterium at 3.125 μg/mL. A good anti-TB activity may be attributed to the presence of pharmacologically active hetero-aryl groups viz., pyrrole, pyridine, azetidinone etc., attached to quinoline ring. It is encouraging to observe that compounds **5c** and **5d** showed very good antitubercular activity against MTB (MIC 1.6 μg/mL).

Compounds **7a–d**, **8a–d** and **9a–d**, which have the azetidinone ring, were observed less potent than the starting Schiff bases against MTB. The antibacterial and antitubercular activities increased when chlorine atom was at 2nd position of quinoline replaced by methoxy group, indicating the relevance of methoxy group for exhibiting biological activity.

Cytotoxicity analysis

None of them were found toxic when analyzed against the Vero-C1008 cell line. Hence the activities of the above synthesized compounds were not due to cytotoxicity of the compounds.

Table 1 Primary antibacterial and antituberculosis activities screen results of synthesized compounds **4a–d** to **9a–d**

Compound	MIC values (μg mL^{-1})				*M. tuberculosis* $H_{37}Rv$
	Gram-negative organisms[a]		Gram-positive organisms[b]		
	Vc	Ec	Sa	Bs	
4a	1.6	3.125	6.25	6.25	6.25
4b	0.8	1.6	12.5	25	12.5
4c	1.6	1.6	25	12.5	6.25
4d	0.8	1.6	25	25	6.25
5a	1.6	3.125	50	12.5	6.25
5b	0.8	0.8	25	6.25	3.125
5c	0.4	0.8	6.25	25	1.6
5d	0.8	1.6	12.5	25	1.6
6a	3.125	3.125	6.25	25	12.5
6b	1.6	1.6	12.5	50	12.5
6c	0.8	0.8	12.5	25	12.5
6d	1.6	1.6	12.5	25	25
7a	0.8	0.8	12.5	25	6.25
7b	0.4	0.8	12.5	25	6.25
7c	0.4	0.4	3.125	3.125	6.25
7d	0.4	0.8	12.5	25	3.125
8a	0.4	0.4	25	12.5	3.125
8b	0.4	0.4	25	12.5	6.25
8c	0.8	0.8	12.5	1.6	6.25
8d	0.4	0.4	12.5	12.5	6.25
9a	1.6	1.6	6.25	6.25	12.5
9b	0.8	0.8	6.25	6.25	12.5
9c	0.4	0.4	12.5	12.5	12.5
9d	0.8	0.8	12.5	12.5	12.5
CFX	1	2	2	2	–
NFX	1	12	2	2	–
INH					0.2

CFX ciprofloxacin, *NFX* norfloxacin, *INH* isoniazid

The screening organisms, [a] Gram-negative bacteria: *Escherichia coli* ATCC 10536 (Ec), *Vibrio cholera* (recultured) (Vc); [b] Gram-positive bacteria: *Staphylococcus aureus* ATCC 11632 (Sa), *Bacillus subtilis* ATCC 60511 (Bs)

Molecular docking studies

Molecular modeling of quinolines binding to ENR was performed to study whether this target was the ideal site to exhibit their mechanism of antibacterial and antimycobacterial activities. The molecular docking studies (Table 2) showed that all the compounds interact with the enoyl ACP-reductase enzyme. The Schiff bases of quinolines **5a–d** with a methoxy group at the 2nd position have shown better docking scores compared to Schiff bases **4a–d** against ENR from both organisms; however, the quinoline derivatives having 2-chloro substitution displayed less docking scores compared to 2-methoxy substitution. Quinolinyl Schiff bases have exhibited higher docking scores than the other compounds in the series against ENR from both organisms. Such superior activity of quinolinyl Schiff bases may be due to the presence of toxophoric –CH=N–NH–C(=O)– moiety.

ENR from *Mycobacterium tuberculosis*

The molecular docking studies of the examined compounds showed their binding to ENR active site with the position and orientation very close to that resulting from the crystal structure of pyrrolidine carboxamide complex with enoyl ACP-reductase. In pyrrolidine carboxamide, the oxo group at 5th position of pyrrolidine interact with Tyr158 and co-factor NAD^+ (Fig. 2A) and compounds **5b** and **8a**

Table 2 Surflex-Dock scores (kcal/mol) of quinoline derivatives

M. tuberculosis		*E. coli*	
Compound	*C* score	Compound	*C* score
5b	8.70	**AEA16**	9.02
5d	7.74	**5d**	8.08
STD	7.70	**5a**	8.06
5c	7.62	**8a**	7.88
4d	7.17	**5c**	7.79
8a	7.01	**4d**	7.50
7d	6.97	**5b**	7.22
5a	6.94	**4b**	7.18
6d	6.78	**4a**	7.05
4b	6.75	**4c**	7.01
4c	6.70	**6d**	6.97
6c	6.55	**6b**	6.83
6b	6.40	**6c**	6.81
8d	6.23	**6a**	6.74
6a	6.21	**7b**	6.56
4a	6.04	**7a**	6.40
7a	5.92	**7c**	6.20
7b	5.81	**7d**	5.86
8c	5.20	**9b**	5.72
9d	4.61	**9a**	5.61
8b	4.61	**8d**	5.53
9c	4.31	**8b**	5.49
9a	4.20	**8c**	5.43
7c	3.71	**9d**	4.56
9b	3.01	**9c**	4.27

STD: 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide; AEA16: (6-{(1*E*)-3-[3-(3-methyl-1-benzofuran-2-yl)azetidin-1-yl]-3-oxoprop-1-en-1-yl}-1,8-naphthyridin-2(1*H*)-one); C score: (consensus score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score

(Figs. 2A, B, 4A, B) binds very efficiently and interacts with the same amino acid, Tyr158 and co-factor NAD^+, through hydrogen-bonding. The Figs. 2C and 4C suggest that the hydrophobic amino acids, Ile194, Trp230, Pro193, Phe97, Met98, Trp222, Pro99, Leu218, Met103, Ala157, Pro156, Met155, Trp160, Met161, Ile215, Met199 and Ala198 block/well surrounded to the quinoline inhibitor and are well conserved in ENR family (He *et al*., 2006; Luckner *et al*., 2010). Based on Figs. 3 and 5 it can be concluded that compounds bind very effectively at binding site of ENR pocket.

ENR from *Escherichia coli*

Crystal structure of *E. coli* enoyl reductase in complex with NAD and AEA16 were further used to understand the binding mode of quinoline derivatives in ENR active site. According to the crystal structure of **5d** and **8a** (blue color) with the ENR (PDB ID 4JX8), the carbonyl functionality participates into two hydrogen bonds, one with the Tyr156 amino acid and another with co-factor NAD^+. Methoxy group at second position of quinoline moiety makes one hydrogen bond with co-factor NAD^+ but loses the interaction with Ala95, that of ligand AEA16 (green color) make four hydrogen bonds, two nitrogens of naphthyridinone moiety make two hydrogen bonds with Ala95 and bridge carbonyl group make one hydrogen bond with Try156 amino acid and another with co-factor NAD^+ (Figs. 6A, B, 8A, B). Figures 7 and 9 show the hydrophobic amino acids Phe94, Ala95, Pro96, Leu100, Pro191, Ile192, Leu195, Ala196, Ala197 and Ile200 well surrounded to molecules, that of Figs. 7 and 9 display the exact binding site of compounds with secondary structure using MOLCAD application. Figure 10 depicts the all

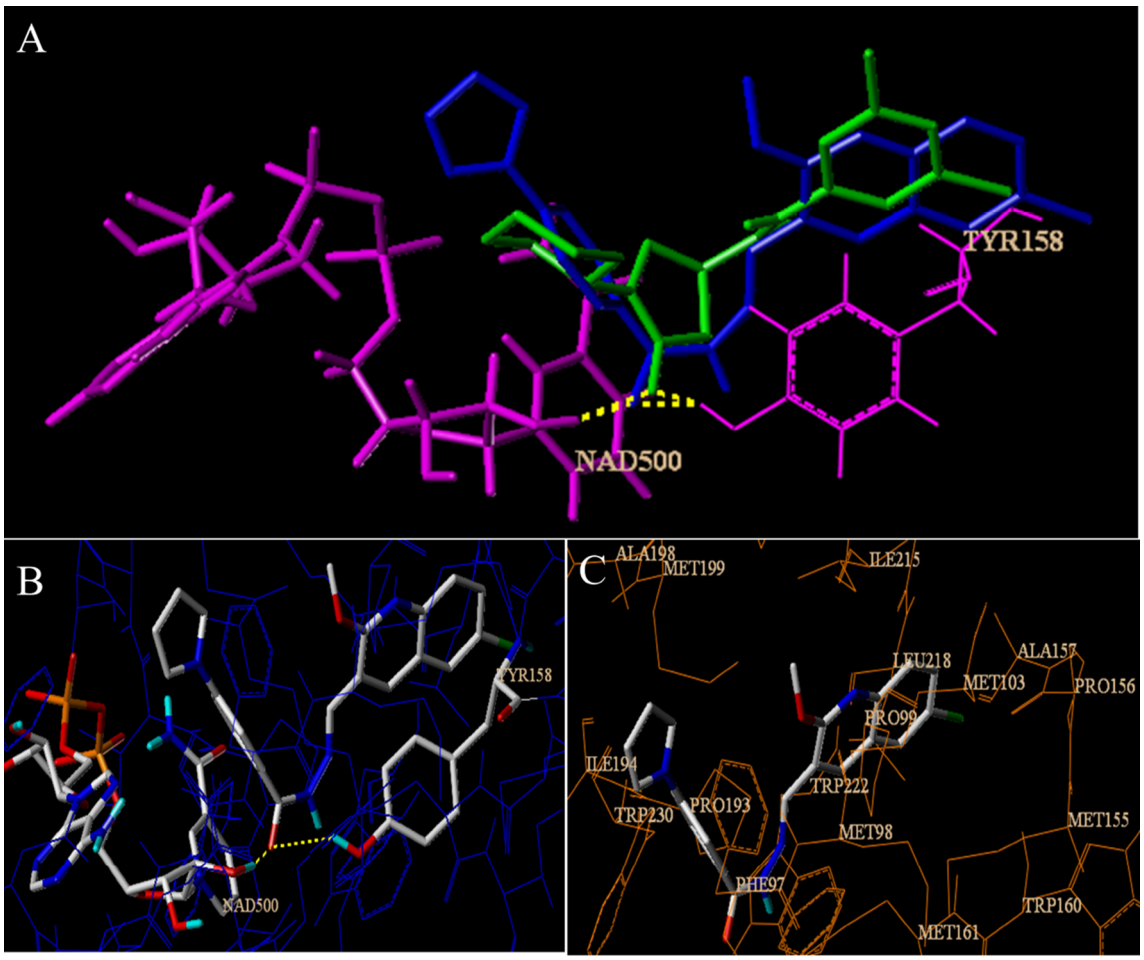


Fig. 2 **A** Details of the interactions between the pyrrolidine carboxamide (*green*) and **5b** (*Blue*) at ENR-binding site, hydrogen bonds were indicated by *dash lines*; **B** Details of interaction between compound **5b** and InhA; **C** hydrophobic amino acid residue surrounded to molecule (Color figure online)

compounds at active site of ENR and Fig. 10A, B for ENR from *M. tuberculosis* and *E. coli*, respectively. No outliner compound at active site, which concludes the binding of all compounds in ENR.

In conclusion, in vitro studies demonstrated that **5c** and **5d** exhibited promising anti-TB activity and compounds **7c**, **8a**, **8b**, **8d** and **9c** showed significant antibacterial activity, that of molecular modeling and docking studies suggest that compounds **5b**, **5c**, **5d** and **8a** interacted with ENR more significantly; hence, these compounds can be further developed/optimize to improve their anti-TB as well as antibacterial activities.

Experimental procedures

Molecular docking using Surflex-Dock

The Surflex-Dock was applied to study molecular docking by using an empirical scoring function and a patented search engine to dock ligands into a protein's binding site (Sybyl-X 2.0, 2012). The crystal structure of *M. tuberculosis* enoyl reductase (InhA) complexed with 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide and crystal structure of *E. coli* enoyl reductase in complex with NAD and AEA16 was retrieved from the RCSB Protein Data Bank (PDB entry codes: 2H7M and 4JX8). All ligands and water molecules in ENR have been deleted except co-factor NAD^+, and the essential hydrogen atoms were added as well as united atom Amber7FF9902 were assigned for the protein. Protomol, a representation of a ligand making every potential interaction with the binding site, was applied to guide molecular docking, and other parameters were established by default in the software. The previously minimized ligands (energy minimization of each structure was performed using the SYBYL energy minimizer Tripos force field and Gasteiger-Hückel charge) were docked into corresponding protein's binding site by an empirical scoring function and a patented search engine in Surflex-Dock (Jain 1996, 2003). Surflex-Dock scores

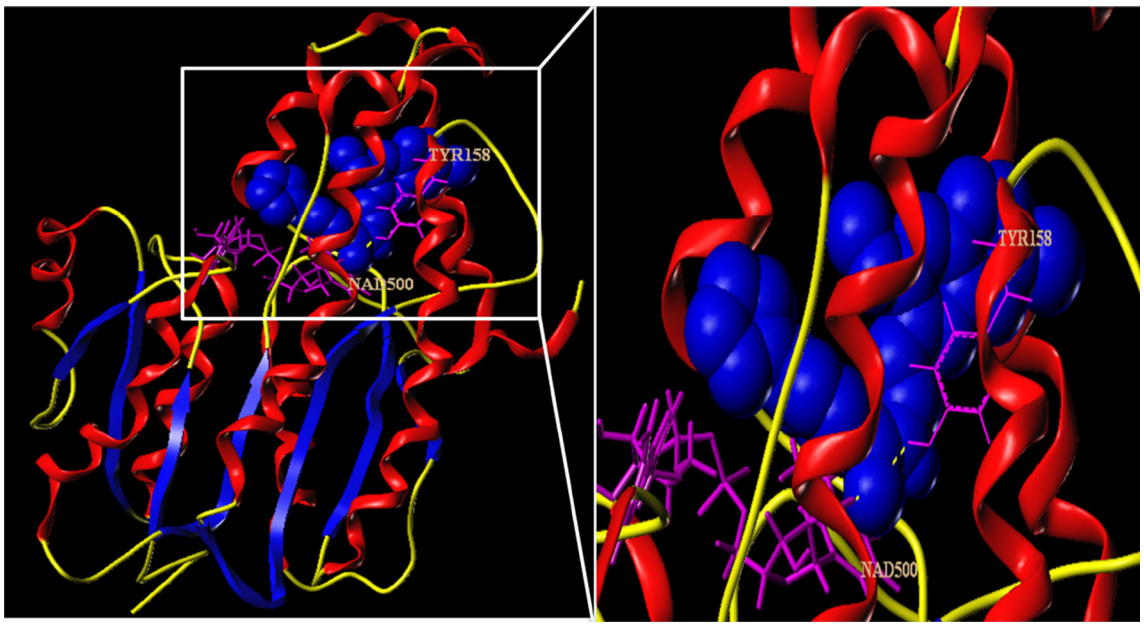


Fig. 3 Binding site for compound **8a**

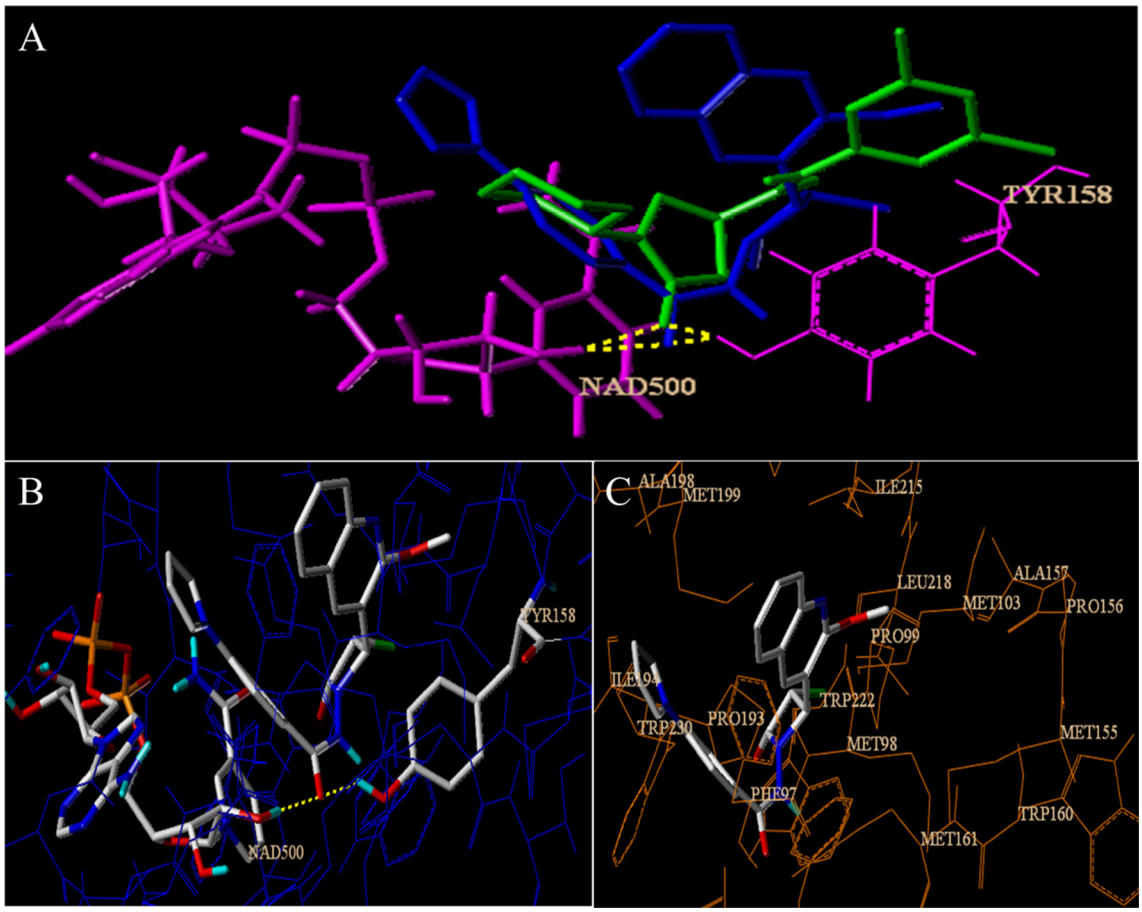


Fig. 4 **A** Details of the interactions between the pyrrolidine carboxamide (*green*) and **8a** (*blue*) at ENR-binding site, hydrogen bonds were indicated by *dash lines*; **B** Details of interaction between compound **8a** and InhA; **C** hydrophobic amino acid residue surrounded to molecule (Color figure online)

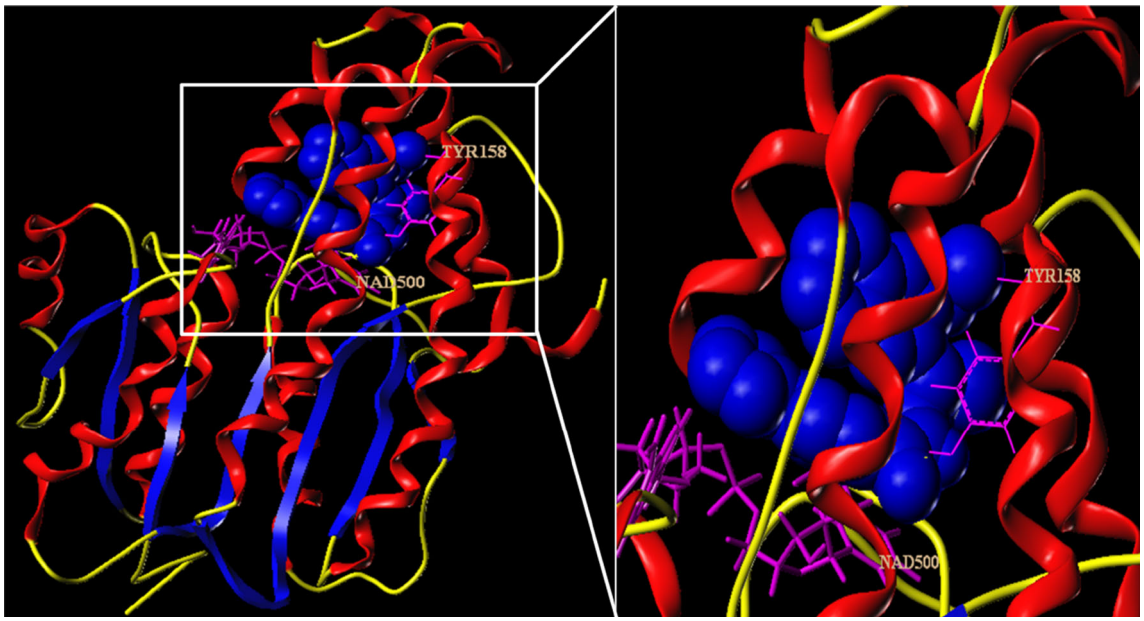


Fig. 5 Binding site for compound **8a**

(total scores) were expressed in kcal/mol units to represent binding affinities. Then, the MOLCAD (Molecular Computer Aided Design) program was employed to visualize the binding mode between the protein and ligand. MOL CAD calculates and exhibits the surfaces of channels and cavities, as well as the separating surface between protein subunits.

Chemistry protocols

Chemicals used in the synthesis of the titled compounds were purchased from Sigma-Aldrich, S. D. Fine-Chem Limited and Spectrochem Pvt. Ltd. All the solvents were of reagent grade and when necessary, they were purified and dried by the standard methods. Melting points (M.p.) of the synthesized compounds were determined on Shital Scientific Industries (Mumbai, India) melting point apparatus and are uncorrected; infrared spectra were recorded on a Bruker spectrophotometer using KBr pellets. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker 300 MHz and Bruker AVANCE III 500 MHz instruments using DMSO-d_6/$CDCl_3$ as a solvent and TMS as an internal standard; chemical shifts are expressed as δ values (ppm). The J values are expressed in Hertz (Hz). Mass spectra (MS) were taken in JEOL GCMATE II GC-Mass spectrometer under electron impact ionization (EI) technique. Microanalyses of the compounds were also performed on Leco Tru Spec CHNS Analyzer to estimate C, H and N elements. All the new compounds exhibited spectral data that are consistent with the proposed structures and the microanalysis data are within ±0.4 % of the theoretical values. Analytical thin-layer chromatography (TLC) was performed on precoated TLC sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany), visualized by long- and short-wavelength UV lamps. Chromatographic purifications were performed on Merck aluminum oxide (70–230 mesh) and Merck silica gel (70–230 mesh).

General procedure for the synthesis of 6-substituted -2-chloroquinoline-3-carbaldehydes ***2a–d*** (Meth-Cohn *et al.,* 1981) Dimethylformamide 9.6 mL (0.125 mol) was cooled to 0 °C, and phosphoryl chloride 32.2 mL (0.35 mol) was added drop-wise with stirring. To this solution was added substituted acetanilide **1a–d** (0.05 mol) and the reaction mixture was refluxed for 16–17 h. Reaction completion was monitored by TLC. The reaction mixture was poured into ice water (300 mL) and stirred for 30 min at 0–10 °C. The resulting suspension was filtered and washed with water to give the intermediates **2a–d**.

General procedure for the synthesis of 6-substituted -2-methoxyquinoline-3-carbaldehydes ***3a–d*** To a solution of potassium hydroxide (1 g, 0.00178 mol) in 50 mL of methanol was added 6-substituted-2-chloroquinoline-3-carbaldehydes **2a–d** (0.0131 mol). The mixture was heated cautiously at 100–110 °C for 3 h. After completion of the reaction, the resulting mixture was then cooled and poured onto 200 g of crushed ice. The solid product obtained was filtered, washed with water, dried and purified by column chromatography (Pet. ether/Ethyl acetate 8:2).

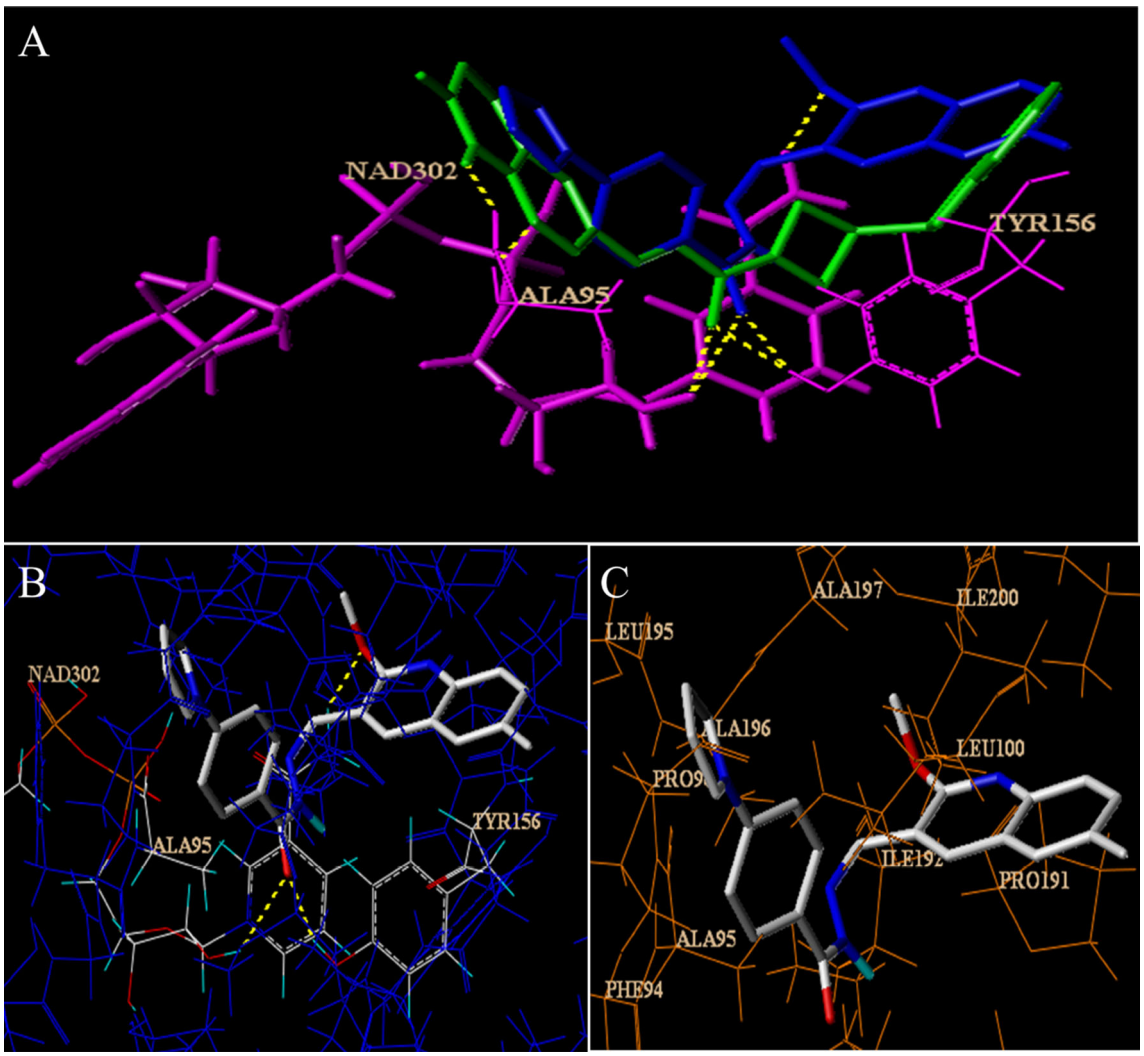


Fig. 6 **A** Details of the interactions between the AEA16 (*green*) and **5d** (*blue*) at ENR-binding site, hydrogen bonds were indicated by *dash lines*; **B** Details of interaction between compound **5d** and FabI; **C** hydrophobic amino acid residue surrounded to molecule (Color figure online)

*2-Methoxyquinoline-3-carbaldehyde (**3a**)* (Kuethe *et al.*, 2005) Compound **3a** was obtained as white solid. Yield 57 %, M.p. 112–114 °C, $R_f = 0.63$ (Silica gel, 70 % *n*-Hexane in 20 % Ethyl acetate and 10 % Chloroform); IR (KBr) ν_{max}: cm^{-1}: 2982 (C–H aromatic), 1689 (C=O), 1619 (C=C), 1600 (C=N), 1441 (C–H aliphatic), 1259 (C–O–C ether stretching); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.49 (s, 1H, *CHO*), 8.60 (s, 1H, C_4–*H*), 7.89 (m, 2H, C_5 and C_8–*H*), 7.75 (t, 1H, C_6–*H*), 7.46 (t, 1H, C_7–*H*), 4.21 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 189.32 (CHO), 161.22 (C_2), 148.97 (C_9), 139.98 (C_4), 132.54 (C_7), 129.73 (C_5), 127.29 (C_8), 125.02 (C_{10}), 124.39 (C_6), 120.06 (C_3), 53.81 (OCH_3); MS (EI) *m/z*: found 188.74 (M + 1); calcd. 187. 06. Anal. Calcd for $C_{11}H_9NO_2$; Calc: C, 70.58; H, 4.85; N, 7.48; found: C, 70.30; H, 4.86; N, 7.50.

6-Chloro-2-methoxyquinoline-3-carbaldehyde *(**3b**)* Compound **3b** was obtained as white solid. Yield 79 %, M.p. 145–147 °C, $R_f = 0.59$ (Silica gel, 70 % *n*-Hexane in 20 % Ethyl acetate and 10 % Chloroform); IR (KBr) ν_{max}: cm^{-1}: 3049 (C–H aromatic), 1690 (C=O), 1601 (C=N), 1420 (C–H aliphatic), 1259 (C–O–C ether stretching), 774 (C–Cl); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.32 (s, 1H, *CHO*), 8.72 (s, 1H, C_4–*H*), 8.23 (d, 1H, C_8–*H*), 7.81 (m, 2H, C_5 and C_7–*H*), 4.11 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 188.94 (CHO), 161.35 (C_2), 147.30 (C_9), 138.79 (C_4), 133.09 (C_7), 130.47 (C_6), 128.82 (C_{10}), 128.10 (C_8), 124.96 (C_5), 120.63 (C_3), 53.98 (OCH_3); MS (EI) *m/z*: found 221.64 (M^+), 223.64 $(M + 2)^+$; calcd. 221.02. Anal. Calcd for $C_{11}H_8ClNO_2$; Calc: C, 59.61; H, 3.64; N, 6.32; found: C, 59.37; H, 3.65; N, 6.29.

*6-Bromo-2-methoxyquinoline-3-carbaldehyde(**3c**)* Compound **3c** was obtained as white solid. Yield 76 %, M.p. 142–144 °C, $R_f = 0.57$ (Silica gel, 70 % *n*-Hexane in 20 % Ethyl acetate and 10 % Chloroform); IR (KBr) ν_{max}:

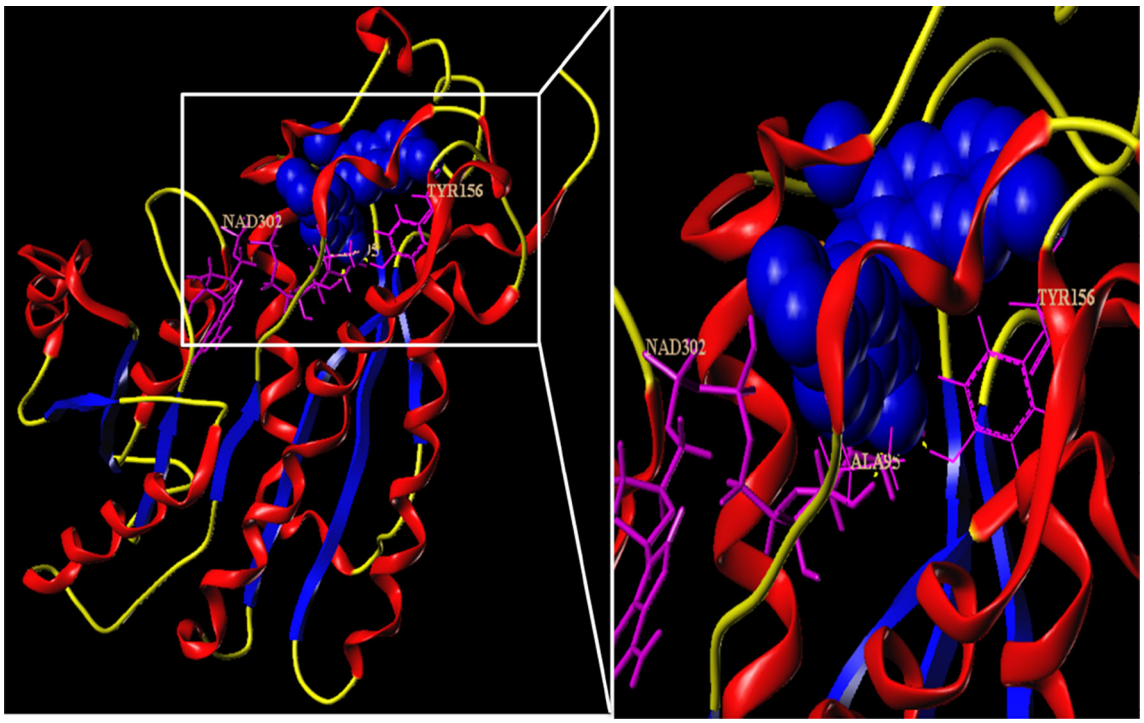


Fig. 7 Binding site for compound **5d**

cm^{-1}: 3004 (C–H aromatic), 1688 (C=O), 1614 (C=N), 1470 (C–H aliphatic), 1262 (C–O–C ether stretching), 529 (C–Br); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.47 (s, 1H, *CHO*), 8.49 (s, 1H, C_4–*H*), 8.00 (d, 1H, C_8–*H*), 7.80 (d, 1H, C_5–*H*), 7.76 (d, 1H, C_7–*H*), 4.19 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 188.93 (CHO), 161.42 (C_2), 147.57 (C_9), 138.74 (C_4), 135.65 (C_7), 131.43 (C_5), 128.99 (C_8), 125.55 (C_{10}), 120.61 (C_3), 118.24 (C_6), 54.01 (OCH_3); MS (EI) *m/z:* found 264.09 (M^+), 266.09 (M + 2) $^+$; calcd. 264.97. Anal. Calcd for $C_{11}H_8BrNO_2$; Calc: C, 49.65; H, 3.03; N, 5.26; found: C, 49.84; H, 3.02; N, 5.24.

*2-Methoxy-6-methylquinoline-3-carbaldehyde(**3d**)* Compound **3d** was obtained as white solid. Yield 80 %, M.p. 94–96 °C, R_f = 0.64 (Silica gel, 70 % *n*-Hexane in 20 % Ethyl acetate and 10 % Chloroform); IR (KBr) ν_{max}: cm^{-1}: 2996 (C–H aromatic), 1687 (C=O), 1599 (C=N), 1460 (C–H aliphatic), 1252 (C–O–C ether stretching); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.46 (s, 1H, *CHO*), 8.50 (s, 1H, C_4–*H*), 7.78 (d, 1H, C_8–*H*), 7.60 (m, 2H, C_5 and C_7–*H*), 4.18 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 189.27 (CHO), 160.71 (C_2), 147.23 (C_9), 139.20 (C_4), 134.66 (C_6 and C_7), 128.52 (C_5), 126.89 (C_8), 124.23 (C_{10}), 119.81 (C_3), 53.68 (OCH_3), 21.17 (CH_3); MS (EI) *m/z*: found 201.22 (M^+); calcd. 201.08. Anal. Calcd for $C_{12}H_{11}NO_2$; Calc: C, 71.63; H, 5.51; N, 6.96; found: C, 71.90; H, 5.49; N, 6.98.

*General procedure for the synthesis of N′-[(6-substituted-2-methoxyquinolin-3-yl) methylene]isonicotinohydrazides **4a–d*** A mixture of **3a–d** (0.005 mol) and isoniazid (0.005 mol) in ethanol (20 mL) was refluxed for 4–6 h in the presence of few drops of glacial acetic acid. The completion of reaction was detected by TLC. Solvent was evaporated under reduced pressure and poured onto crushed ice, and the resultant solid was recrystallized from ethanol and DMF mixture to give the products.

*N′-[(2-Methoxyquinolin-3-yl)methylene]isonicotinohydrazide (**4a**)* Compound **4a** was obtained as pale yellow solid. Yield 66 %, M.p. 216–218 °C, R_f = 0.62 (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3187 (N–H), 3033 (C–H aromatic), 1671 (C=O), 1617 (C=N), 1589 (C=C), 1471 (C–H aliphatic), 1293 (C–O–C ether stretching); ^{1}H NMR (DMSO, 500 MHz) δ: 12.28 (s, 1H, *NH*), 8.83 (s, 1H, C_4–*H*), 8.81 (d, 1H, C_8–*H*), 8.80 (d, 1H, C_5–*H*), 8.77 (s, 1H, *CH=N*), 8.08 (d, 1H, pyridine-C_5–*H*), 7.88 (dd, 2H, pyridine-C_2 and C_6–*H*), 7.81 (d, 1H, pyridine-C_3–*H*), 7.74 (t, 1H, C_7–*H*), 7.49 (t, 1H, C_6–*H*), 4.09 (s, 3H, OCH_3); ^{13}C NMR (DMSO, 125 MHz) δ: 162.01 (C_2), 159.83 (C=O), 150.85 (C_9), 146.78 (pyridine-C_2 and C_6), 143.65 (CH=N), 140.68 (pyridine-C_4), 135.23 (C_4), 131.33 (C_7), 129.33 (C_5), 127.01 (C_8), 125.31 (C_6), 125.21 (C_{10}), 122.00 (pyridine-C_3 and C_5), 118.78 (C_3), 54.20 (OCH_3); MS (EI) *m/z:* found 306.32 (M^+); calcd. 306.11. Anal.

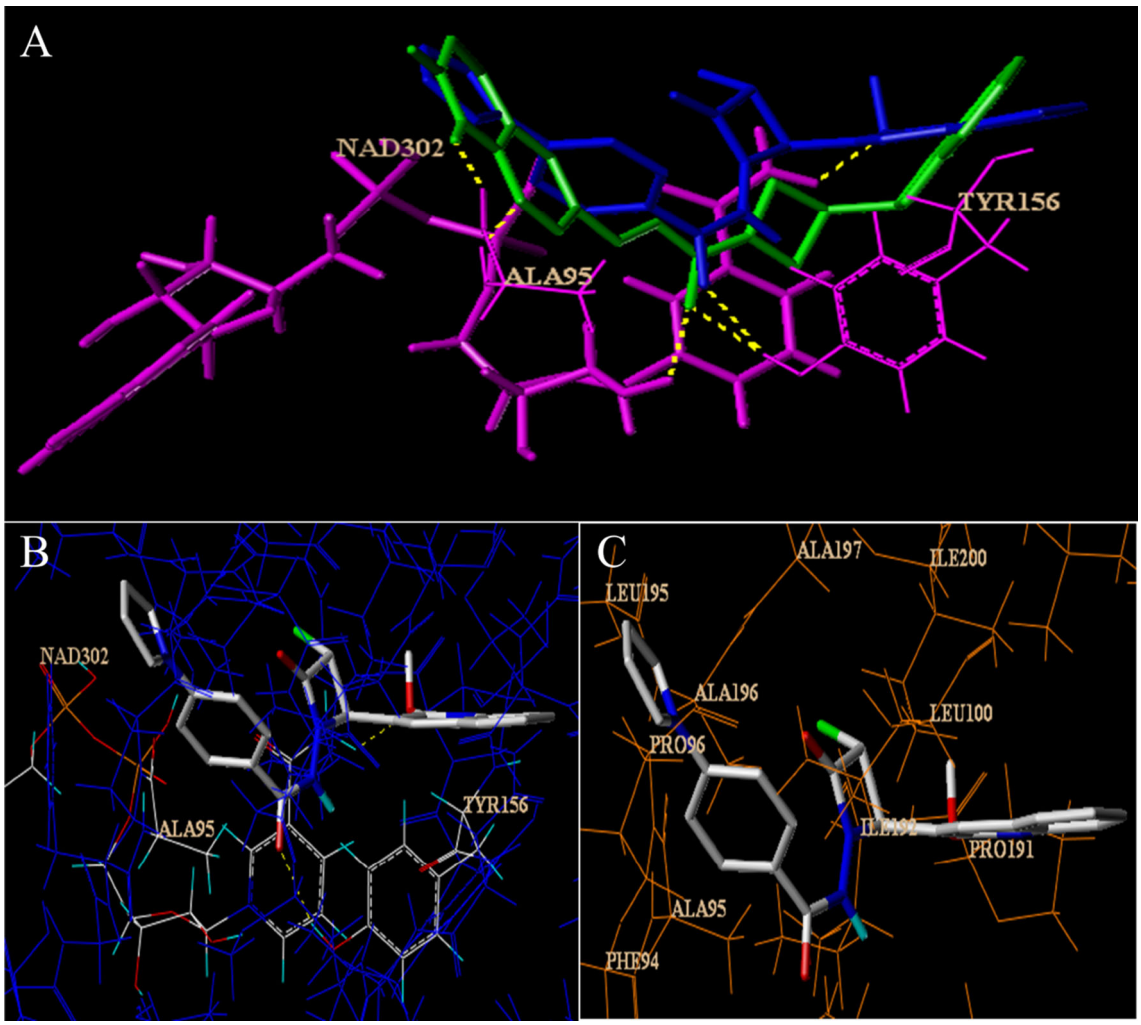


Fig. 8 **A** Details of the interactions between the AEA16 (*green*) and **8a** (*blue*) at ENR-binding site, hydrogen bonds were indicated by *dash lines*; **B** Details of interaction between compound **8a** and FabI; **C** hydrophobic amino acid residue surrounded to molecule (Color figure online)

Calcd for $C_{17}H_{14}N_4O_2$; Calc: C, 66.66; H, 4.61; N, 18.29; found: C, 66.39; H, 4.62; N, 18.36.

*N′-[(6-Chloro-2-methoxyquinolin-3-yl)methylene]isonicotinohydrazide (**4b**)* Compound **4b** was obtained as pale yellow solid. Yield 69 %, M.p. 238–240 °C, $R_f = 0.61$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3238 (N–H), 3043 (C–H aromatic), 1659 (C=O), 1616 (C=N), 1555 (C=C), 1458 (C–H aliphatic), 1290 (C–O–C ether stretching); ^{1}H NMR (DMSO, 500 MHz) δ: 12.30 (s, 1H, *NH*), 8.81 (d, 2H, C_4–*H* and C_8–*H*), 8.76 (s, 1H, *CH=N*), 8.23 (d, 2H, pyridine-C_2 and C_6–*H*), 7.87 (m, 2H, pyridine-C_3 and C_5–*H*), 7.81 (d, 1H, C_7–*H*), 7.71 (dd, 1H, C_5–*H*), 4.09 (s, 3H, *OCH_3*); ^{13}C NMR (DMSO, 125 MHz) δ: 162.04 (C_2), 160.13 (C=O), 150.86 (C_9), 145.24 (pyridine-C_2 and C_6), 143.28 (CH=N), 140.61 (pyridine-C_4), 134.42 (C_4), 131.45 (C_7), 129.36 (C_6), 128.98 (C_8), 127.94 (C_{10}), 126.08 (C_5), 122.00 (pyridine-C_3 and C_5), 119.84 (C_3), 54.37 (OCH_3); MS (EI) *m/z:* found 340.75 (M^+), 342.75 (M + 2) $^+$; calcd. 340.07. Anal. Calcd for $C_{17}H_{13}ClN_4O_2$; Calc: C, 59.92; H, 3.85; N, 16.44; found: C, 59.71; H, 3.86; N, 16.38.

*N′-[(6-Bromo-2-methoxyquinolin-3-yl)methylene]isonicotinohydrazide (**4c**)* Compound **4c** was obtained as pale yellow solid. Yield 68 %, M.p. 233–235 °C, $R_f = 0.57$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3183 (N–H), 3036 (C–H aromatic), 1656 (C=O), 1620 (C=N), 1545 (C=C), 1461 (C–H aliphatic), 1260 (C–O–C ether stretching), 675 (C–Br); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.46 (s, 1H, *NH*), 9.37 (s, 1H, *CH=N*), 8.68–8.85 (m, 2H, pyridine-C_2 and C_6–*H*), 8.24 (d, 1H, C_7–*H*), 7.92 (s, 1H, C_5–*H*), 7.71–7.92 (m, 4H, C_4 and C_8–*H* and pyridine-C_3 and C_5–*H*), 4.11 (s, 3H, *OCH_3*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.00 (C_2), 159.74 (C=O), 150.00 (C_9), 149.00 (pyridine-C_2 and C_6), 144.00 (CH=N),

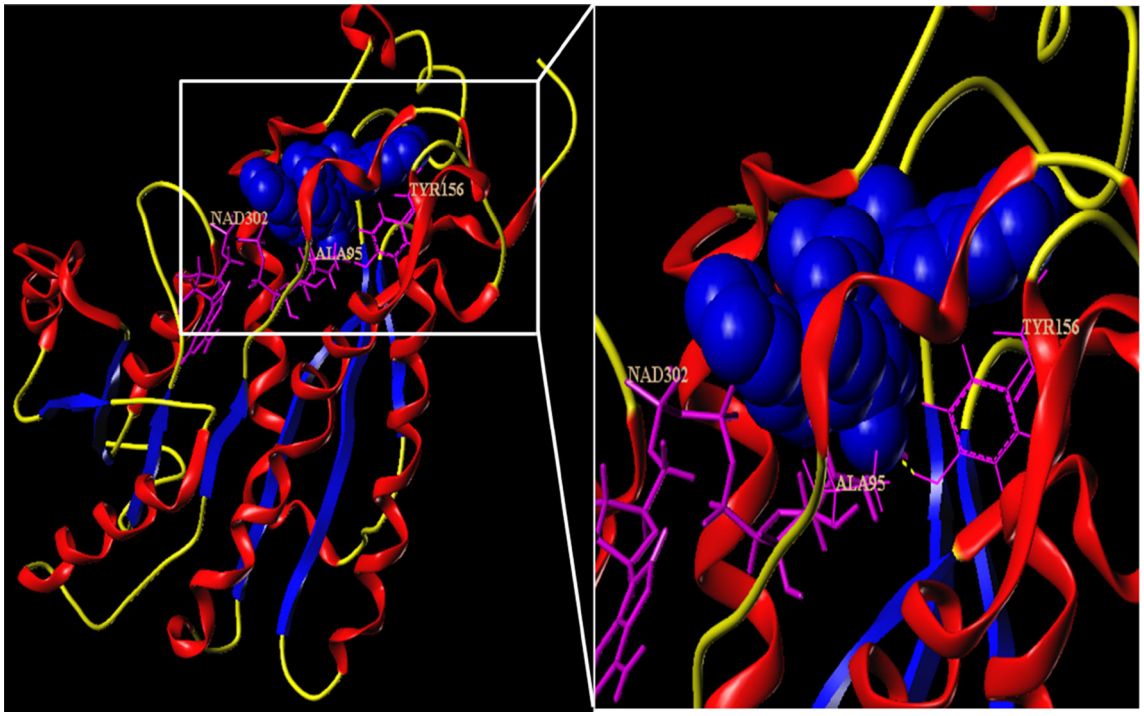


Fig. 9 Binding site for compound **8a**

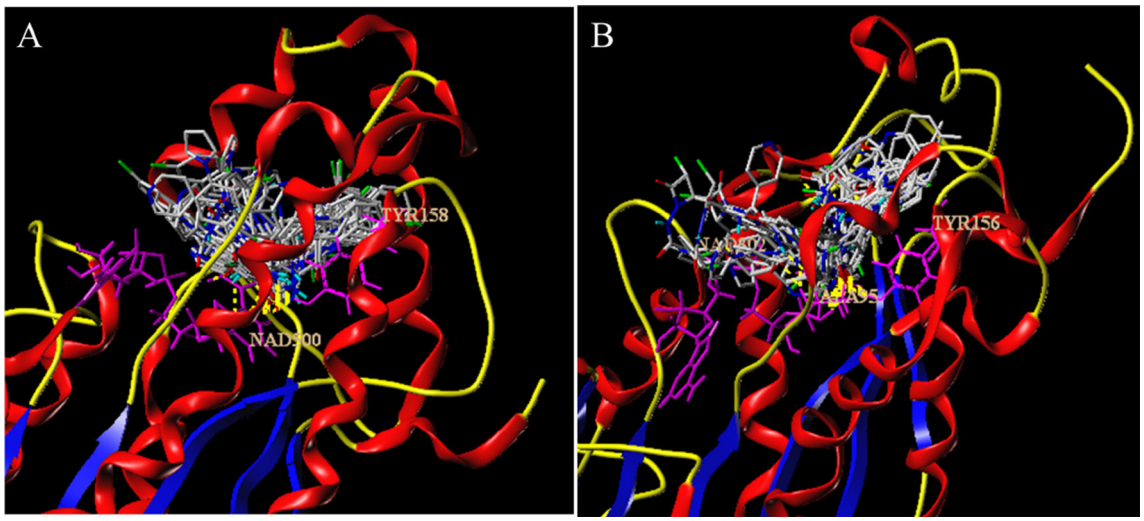


Fig. 10 Crystalline structure of all compounds at ENR active site **A** from *M. tuberculosis* **B** from *E. coli*

140.00 (pyridine-C_4) 135.00 (C_4), 134.05 (C_7), 128.81 (C_8), 125.00 (C_{10}), 121.00 (pyridine-C_3 and C_5), 118.08 (C_6), 53.95 (OCH_3); MS (EI) *m/z:* found 384.21 (M^+), 386.21 (M + 2) $^+$; calcd. 384.02. Anal. Calcd for $C_{17}H_{13}BrN_4O_2$; Calc: C, 53.00; H, 3.40; N, 14.54; found: C, 53.20; H, 3.39; N, 14.49.

*N′-[(2-Methoxy-6-methylquinolin-3-yl)methylene]isonicotinohydrazide (**4d**)* Compound **4d** was obtained as pale yellow solid. Yield 85 %, M.p. 228–230 °C, $R_f = 0.67$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3229 (N–H), 3070 (C–H aromatic), 1662 (C=O), 1605 (C=N), 1555 (C=C), 1455 (C–H aliphatic), 1290 (C–O–C ether stretching); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.26 (s, 1H, *NH*), 8.81 (t, 3H, C_8–*H* and pyridine-C_2 and C_6–*H*), 8.65 (s, 1H, *CH*=*N*), 7.87 (m, 2H, pyridine-C_3 and C_5–*H*), 7.82 (s, 1H, C_4–*H*), 7.71 (d, 1H, C_7–*H*), 7.56 (dd, 1H, C_5–*H*), 4.07 (s, 3H, *OCH*$_3$), 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 166.67 (C_2), 164.04 (C=O), 155.19 (C_9),

150.40 (pyridine-C_2 and C_6), 148.71 (CH=N), 145.44 (pyridine-C_4), 139.26 (C_4), 139.07 (C_6), 137.70 (C_7), 132.48 (C_8), 131.59 (C_5), 129.79 (C_{10}), 126.71 (pyridine-C_3 and C_5), 123.27 (C_3), 58.60 (OCH_3), 26.12 (CH_3); MS (EI) *m/z:* found 320.35 (M^+); calcd. 320.13. Anal. Calcd for $C_{18}H_{16}N_4O_2$.; Calc: C, 67.49; H, 5.03; N, 17.49; found: C, 67.74; H, 5.01; N, 17.54.

*General procedure for synthesis of N′-[(6-substituted-2-methoxyquinolin-3-yl) methylene]-4-(1H-pyrrol-1-yl)benzohydrazides **5a–d*** A mixture of **3a–d** (0.005 mol) and 4-(1*H*-pyrrol-1-yl)benzohydrazide (0.005 mol) (Joshi *et al*., 2008) in ethanol (20 mL) was refluxed for 4–6 h in the presence of few drops of glacial acetic acid. The completion of reaction was detected by TLC. Solvent was evaporated under reduced pressure and poured onto crushed ice, and the resultant solid was recrystallized from ethanol and DMF mixture to give the products.

*N′-[(2-Methoxyquinolin-3-yl)methylene]-4-(1H-pyrrol-1-yl) benzohydrazide (**5a**)* Compound **5a** was obtained as yellow solid. Yield 72 %, M.p. 239–241 °C, $R_f = 0.68$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3217 (N–H), 3054 (C–H aromatic), 1651 (C=O), 1610 (C=N), 1559 (C=C), 1473 (C–H aliphatic), 1271 (C–O–C ether stretching); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 12.10 (s, 1H, *NH*), 8.84 (s, 1H, C_4–*H*), 8.76 (s, 1H, *CH=N*), 8.08 (d, 2H, phenyl-C_2 and C_6–*H*), 7.95 (s, 1H, C_5–*H*), 7.81 (t, 3H, C_8–*H* and phenyl-C_3 and C_5–*H*), 7.72 (t, 1H, C_7–*H*), 7.54 (dd, 2H, pyrrole-C_2 and C_5–*H*), 7.49 (t, 1H, C_6–*H*), 6.34 (dd, 2H, pyrrole-C_3 and C_4–*H*), 4.10 (s, 3H, *OCH_3*); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 162.63 (C_2), 159.82 (C=O), 146.63 (C_9), 142.82 (CH=N), 142.22 (phenyl-C_4), 134.87 (C_4), 131.13 (C_7), 129.88 (phenyl-C_3 and C_5), 129.76 (phenyl-C_2 and C_6), 129.22 (C_5 and phenyl-C_1), 127.00 (C_8), 125.26 (C_6 and C_{10}), 119.51 (C_3), 118.96 (pyrrole-C_2 and C_5), 111.70 (pyrrole-C_3 and C_4), 54.16 (OCH_3); MS (EI) *m/z:* found 370.40 (M^+); calcd. 370.14. Anal. Calcd for $C_{22}H_{18}N_4O_2$; Calc: C, 71.34; H, 4.90; N, 15.13; found: C, 71.62; H, 4.89; N, 15.07.

*N′-[(6-Chloro-2-methoxyquinolin-3-yl)methylene]-4-(1H-pyrrol-1-yl)benzohydrazide (**5b**)* Compound **5b** was obtained as yellow solid. Yield 82 %, M.p. 253–255 °C, $R_f = 0.65$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3210 (N–H), 3055 (C–H aromatic), 1648 (C=O), 1608 (C=N), 1550 (C=C), 1463 (C–H aliphatic), 1253 (C–O–C ether stretching), 721 (C–Cl); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.13 (s, 1H, *NH*), 8.82 (s, 1H, C_4–*H*), 8.76 (s, 1H, *CH=N*), 8.23 (s, 1H, C_5–*H*), 8.07 (d, 2H, phenyl-C_2 and C_6–*H*), 7.92 (m, 1H, C_8–*H*), 7.69–7.82 (m, 4H, pyrrole-C_2 and C_5–*H* and phenyl-C_3 and C_5–*H*), 7.54 (t, 1H, C_7–*H*), 6.34 (dd, 2H, pyrrole-C_3 and C_4–*H*), 4.10 (s, 3H, *OCH_3*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 166.00 (C_2), 159.75 (C=O), 145.00 (C_9), 141.05 (CH=N), 140.00 (phenyl-C_4), 138.00 (C_4), 131.27 (C_7), 131.00 (phenyl-C_1), 130.17 (C_6), 129.00 (C_8), 128.60 (phenyl-C_3 and C_5), 127.03 (phenyl-C_2 and C_6), 125.00 (C_{10}), 121.00 (C_5), 119.04 (pyrrole-C_2 and C_5), 117.00 (C_3), 111.58 (pyrrole-C_3 and C_4), 53.90 (OCH_3); MS (EI) *m/z*: found 404.85 (M^+), 406.10 $(M + 2)^+$; calcd. 404.10. Anal. Calcd for $C_{22}H_{17}ClN_4O_2$; Calc: C, 64.27; H, 4.23; N, 13.84; found: C, 64.52; H, 4.21; N, 13.89.

*N′-[(6-Bromo-2-methoxyquinolin-3-yl)methylene]-4-(1H-pyrrol-1-yl)benzohydrazide (**5c**)* Compound **5c** was obtained as yellow solid. Yield 60 %, M.p. 248–250 °C, $R_f = 0.63$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3218 (N–H), 3050 (C–H aromatic), 1655 (C=O), 1607 (C=N), 1562 (C=C), 1461 (C–H aliphatic), 1265 (C–O–C ether stretching); ^{1}H NMR (DMSO, 500 MHz) δ: 12.13 (s, 1H, *NH*), 8.81 (s, 1H, C_4–*H*), 8.74 (s, 1H, *CH=N*), 8.36 (s, 1H, C_5–*H*), 8.07 (d, 2H, C_7 and C_8–*H*), 7.72–7.81 (m, 4H, C_2, C_3, phenyl-C_5 and C_6–*H*), 7.54 (dd, 2H, pyrrole-C_2 and C_5–*H*), 6.34 (dd, 2H, pyrrole-C_3 and C_4–*H*), 4.09 (s, 3H, *OCH_3*); ^{13}C NMR (DMSO, 125 MHz) δ: 162.65 (C_2), 160.17 (C=O), 145.31 (C_9), 142.85 (CH=N), 141.86 (phenyl-C_4), 133.98 (C_4), 133.82 (C_7), 131.04 (phenyl-C_2 and C_5), 129.90 (C_8), 129.68 (phenyl-C_2 and C_6), 126.72 (C_5), 120.15 (C_{10}), 119.51 (C_6), 118.95 (pyrrole-C_2 and C_5), 117.62 (C_3), 111.71 (pyrrole-C_3 and C_4), 54.35 (OCH_3); MS (EI) *m/z:* found 448.30 (M^+), 450.30 $(M + 2)^+$; calcd. 448.05. Anal. Calcd for $C_{22}H_{17}BrN_4O_2$; Calc: C, 58.81; H, 3.81; N, 12.47; found: C, 58.58; H, 3.82; N, 12.51.

*N′-[(2-Methoxy-6-methylquinolin-3-yl)methylene]-4-(1H-pyrrol-1-yl)benzohydrazide (**5d**)* Compound **5d** was obtained as yellow solid. Yield 80 %, M.p. 236–238 °C, $R_f = 0.71$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3212 (N–H), 3040 (C–H aromatic), 1655 (C=O), 1606 (C=N), 1562 (C=C), 1458 (C–H aliphatic), 1266 (C–O–C ether stretching); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.09 (s, 1H, *NH*), 8.82 (s, 1H, C_4–*H*), 8.64 (s, 1H, *CH=N*), 8.07 (d, 2H, C_7–*H*), 7.95 (s, 1H, C_5–*H*), 7.70–7.82 (m, 4H, phenyl-C_2, C_3, C_5, C_6–*H*), 7.56 (dd, 3H, C_8–*H* and pyrrole-C_2, C_5–*H*), 6.34 (d, 2H, pyrrole-C_3 and C_4–*H*), 4.08 (s, 3H, *OCH_3*), 2.89 (s, 3H, *CH_3*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 167.82 (C_2), 164.02 (C=O), 149.92 (C_9), 147.63 (CH=N), 139.05 (phenyl-C_4), 138.96 (C_4), 134.56 (C_6), 132.16 (C_7), 131.55 (phenyl-C_3 and C_5), 129.76 (phenyl-C_1, C_2 and C_6), 127.00 (C_8), 126.00 (C_5), 123.79 (C_{10}), 123.45 (pyrrole-C_2 and C_5), 116.24 (C_3), 111.50 (pyrrole-C_3 and C_4) 58.44 (OCH_3), 26.12 (CH_3); MS (EI) *m/z:* found 384.44 (M^+); calcd. 384.16. Anal. Calcd for $C_{23}H_{20}N_4O_2$; Calc: C, 71.86; H, 5.24; N, 14.57; found: C, 71.57; H, 5.26; N, 14.51.

General procedure for synthesis of N′-[(6-substituted-2-chloroquinolin-3-yl) methylene]isonicotinohydrazides ***6a–d*** (Khalil *et al*., 1993) A mixture of **2a–d** (0.005 mol) and isoniazid (0.005 mol) in ethanol (20 mL) was refluxed for 4–6 h in the presence of few drops of glacial acetic acid. The completion of reaction was detected by TLC. Solvent was evaporated under reduced pressure and poured onto crushed ice, and the resultant solid was recrystallized from ethanol and DMF mixture to give the products.

*N′-[(2-Chloroquinolin-3-yl) methylene]isonicotinohydrazide (**6a**)* (Khalil *et al*., 1993) Compound **6a** was obtained as yellow solid. Yield 71 %, M.p. 229–231 °C, $R_f = 0.71$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3179 (N–H), 3053 (C–H aromatic), 1652 (C=O), 1619 (C=N), 1589 (C=C), 1486 (C–H aliphatic), 727 (C–Cl); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.46 (s, 1H, *NH*), 8.57–8.98 (m, 4H, C_4, C_5, C_8–*H* and *CH=N*), 8.27 (d, 1H, pyridine-C_5–*H*), 7.50–8.01 (m, 5H, C_6, C_7–*H* and pyridine-C_2, C_3, C_6–*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 162.23 (C=O), 150.89 (C_2), 148.98 (C_9), 147.74 (pyridine-C_2 and C_6), 144.56 (CH=N), 140.54 (pyridine-C_4), 136.44 (C_4), 132.43 (C_7), 129.58 (C_5), 128.39 (C_8), 128.11 (C_6), 127.31 (C_{10}), 126.33 (C_3), 122.02 (pyridine-C_3 and C_5); MS (EI) *m/z:* found 310.74 (M^+), 312.74 $(M + 2)^+$; calcd. 310.06. Anal. Calcd for $C_{16}H_{11}ClN_4O$; Calc: C, 61.84; H, 3.57; N, 18.03; found: C, 61.60; H, 3.58; N, 18.10.

*N′-[(2,6-Dichloroquinolin-3-yl)methylene]isonicotinohydrazide (**6b**)* Compound **6b** was obtained as yellow solid. Yield 70 %, M.p. 262–264 °C, $R_f = 0.68$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3177 (N–H), 3055 (C–H aromatic), 1656 (C=O), 1589 (C=N), 1545 (C=C), 1479 (C–H aliphatic), 667 (C–Cl); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.42 (s, 1H, *NH*), 8.40–8.98 (m, 2H, C_4, C_5–*H*), 8.28 (d, 1H, C_8–*H*), 8.20 (s, 1H, *CH=N*), 7.40–8.08 (m, 5H, C_7–*H* and pyridine-C_2, C_3, C_5, C_6–*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.12 (C=O), 151.57 (C_2), 148.92 (C_9), 146.22 (pyridine-C_2 and C_6), 144.23 (CH=N), 140.12 (pyridine-C_4), 135.12 (C_4), 131.29 (C_7), 128.47 (C_5), 128.32 (C_8), 128.09 (C_6), 127.25 (C_{10}), 126.23 (C_3), 121.18 (pyridine-C_3 and C_5); MS (EI) *m/z:* found 344.81 (M^+), 346.81 $(M + 2)^+$; calcd. 344.02. Anal. Calcd for $C_{16}H_{10}Cl_2N_4O$; Calc: C, 55.67; H, 2.92; N, 16.23; found: C, 55.44; H, 2.93; N, 16.16.

*N′-[(6-Bromo-2-chloroquinolin-3-yl) methylene]isonicotinohydrazide (**6c**)* Compound **6c** was obtained as yellow solid. Yield 77 %, M.p. 267–269 °C, $R_f = 0.67$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3174 (N–H), 3046 (C–H aromatic), 1656 (C=O), 1586 (C=N), 1545 (C=C), 1477 (C–H aliphatic), 702 (C–Cl); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.10 (s, 1H, *NH*), 8.40–8.98 (m, 2H, C_4, C_5–*H*), 8.24 (d, 1H, C_8–*H*), 8.26 (s, 1H, *CH=N*), 7.48–8.16 (m, 5H, C_7–*H* and pyridine-C_2, C_3, C_5, C_6–*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.88 (C=O), 151.56 (C_2), 149.22 (C_9), 147.56 (pyridine-C_2 and C_6), 145.64 (CH=N), 140.19 (pyridine-C_4), 137.24 (C_4), 132.87 (C_7), 129.23 (C_5), 128.55 (C_8), 128.18 (C_6), 127.39 (C_{10}), 126.54 (C_3), 123.63 (pyridine-C_3 and C_5); MS (EI) *m/z:* found 387.31 (M^+), 389.31 $(M + 2)^+$; calcd. 387.97. Anal. Calcd for $C_{16}H_{10}BrClN_4O$; Calc: C, 49.32; H, 2.59; N, 14.38; found: C, 49.50; H, 2.58; N, 14.32.

*N′-[(2-Chloro-6-methylquinolin-3-yl) methylene]isonicotinohydrazide (**6d**)* (Bawa *et al*., 2009) Compound **6d** was obtained as yellow solid[38]. Yield 80.72 %, M.p. 246–248 °C, $R_f = 0.75$ (Silica gel, 80 % Benzene in Acetonitrile); IR (KBr) ν_{max}: cm^{-1}: 3195 (N–H), 3066 (C–H aromatic), 1680 (C=O), 1595 (C=N), 1503 (C=C), 1370 (C–H aliphatic), 756 (C–Cl); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.12 (s, 1H, *NH*), 8.54–8.96 (m, 2H, C_4, C_5–*H*), 8.32 (d, 1H, C_8–*H*), 8.28 (s, 1H, *CH=N*), 7.42–8.10 (m, 5H, C_7–*H* and pyridine-C_2, C_3, C_5, C_6–*H*), 2.32 (s, 1H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 166.54 (C=O), 152.52 (C_2), 149.78 (C_9), 146.88 (pyridine-C_2 and C_6), 144.87 (CH=N), 141.42 (pyridine-C_4), 138.42 (C_4), 133.74 (C_7), 130.32 (C_5), 128.86 (C_8), 128.16 (C_6), 127.10 (C_{10}), 126.45 (C_3), 122.42 (pyridine-C_3 and C_5), 21.50 (CH_3); MS (EI) *m/z:* found 324.77 (M^+), 326.77 $(M + 2)^+$; calcd. 324.08. Anal. Calcd for $C_{17}H_{13}ClN_4O$; Calc: C, 62.87; H, 4.03; N, 17.25; found: C, 63.12; H, 4.01; N, 17.32.

General procedure for the synthesis of N-(3-chloro-2-(2-methoxy-6-substitutedquinolin-3-yl)-4-oxoazetidin-1-yl) isonicotinamides ***7a–d****, N-(3-chloro-2-(6-substituted-2-methoxyquinolin-3-yl)-4-oxoazetidin-1-yl)-4-(1H-pyrrol-1-yl)benzamides* ***8a–d*** *and N-(3-chloro-2-(2-chloro-6-substitutedquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamides* ***9a–d*** To a solution of appropriate **4a–d** or **5a–d** or **6a–d** (0.01 mol) and triethylamine (5-6 drops) in dry benzene (50 mL) was added in monochloroacetylchloride (0.015 mol) at 50 °C. The reaction mixture was stirred for 40 min at room temperature and refluxed for 7 h. Reaction completion was monitored by TLC. The reaction mixture was filtered to remove triethylamine hydrogen chloride, and the resultant solution was poured onto crushed ice with constant stirring. The solid thus obtained was recrystallized from methanol and purified by column chromatography (Pet. ether/Ethyl acetate 7:3).

*N-(-3-Chloro-2-(2-methoxyquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamides (**7a**)* Compound **7a** was obtained as yellow solid. Yield 29 %, M.p. 280–282 °C, $R_f = 0.72$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3152 (NH), 2962(C–H aromatic), 1743 (β-lactam-C=O), 1690 (C=O), 1622 (C=C), 1418 (C–H

aliphatic), 1336 (C–N), 1242 (C–O–C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.20 (s, 1H, *NH*), 8.86 (s, 1H, C_4–*H*), 8. 80 (d, 1H, C_8–*H*), 8.70 (d, 1H, C_5–*H*), 7.68–8.40 (m, 4H, pyridine-C_2–*H* C_3–*H*, C_5–*H* and C_6–*H*), 7.70 (t, 1H, C_7–*H*), 7.42 (t, 1H, C_6–*H*), 4.56 (d, 1H, $J = 1.7$ Hz, *CH–Cl*), 4.40 (d, 1H, $J = 1.6$ Hz, *CH–N*), 3.98 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.12 (NH–C=O), 157.78 (β-lactam-C=O), 154.56 (C_2), 150.06 (pyridine-C_2 and C_6), 144.56 (C_9), 137.56 (pyridine-C_4), 134.02 (C_4), 132.26 (C_6), 130.46 (C_7), 127.12 (C_8), 126.23 (C_5), 124.22 (C_{10}), 122.46 (C_3), 120.26 (pyridine-C_3 and C_5), 116.88 (β-lactam-C_3), 91.02 (β-lactam-C_2), 52.18 (OCH_3); MS (EI) *m/z:* found 382.01 (M^+), 384.01 $(M + 2)^+$; calcd. 382.08. Anal. Calcd for $C_{19}H_{15}ClN_4O_3$; Calc: C, 59.61; H, 3.95; N, 14.64; found: C, 59.41; H, 3.96; N, 14.69.

*N-(3-Chloro-2-(6-chloro-2-methoxyquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamides (**7b**)* Compound **7b** was obtained as yellow solid. Yield 33 %, M.p. 290–292 °C, $R_f = 0.71$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3145 (NH), 2948 (C–H aromatic), 1740 (β-lactam-C=O), 1692 (C=O), 1620 (C=C), 1421 (C–H aliphatic), 1342 (C–N), 1246 (C–O–C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.10 (s, 1H, *NH*), 8.88 (s, 1H, C_4–*H*), 8. 82 (d, 1H, C_8–*H*), 8.78 (d, 1H, C_5–*H*), 7.61–8.48 (m, 4H, pyridine-C_2–*H* C_3–*H*, C_5–*H* and C_6–*H*), 7.58 (d, 1H, C_7–*H*), 4.50 (d, 1H, $J = 1.5$ Hz, *CH–Cl*), 4.42 (d, 1H, $J = 1.6$ Hz, *CH–N*), 4.10 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.56 (NH–C=O), 157.64 (β-lactam-C=O), 155.41 (C_2), 151.46 (pyridine-C_2 and C_6), 147.42 (C_9), 139.78 (pyridine-C_4), 135.54 (C_4), 134.26 (C_6), 131.75 (C_7), 128.45 (C_8), 126.23 (C_5), 125.46 (C_{10}), 123.88 (C_3), 120.89 (pyridine-C_3 and C_5), 118.32 (β-lactam-C_3), 90.80 (β-lactam-C_2), 52.10 (OCH_3); MS (EI) *m/z:* found 416.25 (M^+), 418.25 $(M + 2)^+$; calcd. 416.04. Anal. Calcd for $C_{19}H_{14}Cl_2N_4O_3$; Calc: C, 54.69; H, 3.38; N, 13.43; found: C, 54.47; H, 3.39; N, 13.37.

*N-(2-(6-Bromo-2-methoxyquinolin-3-yl)-3-chloro-4-oxoazetidin-1-yl)isonicotinamides (**7c**)* Compound **7c** was obtained as yellow solid. Yield 31 %, M.p. 255–257 °C, $R_f = 0.74$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3113 (NH), 2928 (C–H aromatic), 1745 (β-lactam-C=O), 1694 (C=O), 1621 (C=C), 1411 (C–H aliphatic), 1339 (C–N), 1242 (C–O–C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.20 (s, 1H, *NH*), 8.89 (s, 1H, C_4–*H*), 8. 79 (d, 1H, C_8–*H*), 8.70 (d, 1H, C_5–*H*), 7.65–8.52 (m, 4H, pyridine-C_2–*H* C_3–*H*, C_5–*H* and C_6–*H*), 7.48 (d, 1H, C_7–*H*), 4.52 (d, 1H, $J = 1.7$ Hz, *CH–Cl*), 4.41 (d, 1H, $J = 1.7$ Hz, *CH–N*), 4.02 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.12 (NH–C=O), 159.88 (β-lactam-C=O), 156.10 (C_2), 151.22 (pyridine-C_2 and C_6), 145.78 (C_9), 139.45 (pyridine-C_4), 135.42 (C_4), 134.23 (C_6), 131.86 (C_7), 127.12 (C_8), 126.84 (C_5), 125.66 (C_{10}), 123.46 (C_3), 121.78 (pyridine-C_3 and C_5), 118.56 (β-lactam-C_3), 92.26 (β-lactam-C_2), 52.46 (OCH_3); MS (EI) *m/z:* found 459.70 (M^+), 461.70 $(M + 2)^+$; calcd. 459.99. Anal. Calcd for $C_{19}H_{14}BrClN_4O_3$; Calc: C, 49.43; H, 3.06; N, 12.13; found: C, 49.62; H, 3.05; N, 12.08.

*N-(3-Chloro-2-(2-methoxy-6-methylquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamide (**7d**)* Compound **7d** was obtained as yellow solid. Yield 30 %, M.p. 316–318 °C, $R_f = 0.81$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3115 (NH), 2924 (C–H aromatic), 1738 (β-lactam-C=O), 1680 (C=O), 1574 (C=C), 1451 (C–H aliphatic), 1348 (C–N), 1259 (C–O–C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.68 (s, 2H, C_8–*H* and *NH*), 7.92 (S, 1H, C_4–*H*), 7.68–7.65 (m, 2H, pyridine-C_2–*H* and C_6–*H*), 7.44–7.41 (m, 2H, pyridine-C_3–*H* and C_5–*H*), 7.26 (s, 1H, C_7–*H*), 7.19 (s, 1H, C_5–*H*), 4.50 (d, 1H, $J = 1.7$ Hz, *CH–Cl*), 4.42 (d, 1H, $J = 1.6$ Hz, *CH–N*), 3.95 (s, 3H, OCH_3), 1.18 (S, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.00 (NH–C=O), 158.92 (β-lactam-C=O), 155.00 (C_2), 150.35 (pyridine-C_2 and C_6), 145.61 (C_9), 138.14 (pyridine-C_4), 134.43 (C_4), 133.10 (C_6), 131.94 (C_7), 127.95 (C_8), 126.75 (C_5), 124.29 (C_{10}), 123.00 (C_3), 120.65 (pyridine-C_3 and C_5), 117.44 (β-lactam-C_3), 91.25 (β-lactam-C_2), 53.78 (OCH_3), 29.70 (CH_3); MS (EI) *m/z:* found 396.83 (M^+), 398.83 $(M + 2)^+$; calcd. 396.10. Anal. Calcd for $C_{20}H_{17}ClN_4O_3$; Calc: C, 60.53; H, 4.32; N, 14.12; found: C, 60.77; H, 4.31; N, 14.17.

*N-(3-Chloro-2-(2-methoxyquinolin-3-yl)-4-oxoazetidin-1-yl)-4-(1H-pyrrol-1-yl)benzamide (**8a**)* Compound **8a** was obtained as yellow solid. Yield 29 %, M.p. 254–256 °C, $R_f = 0.77$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3133 (NH), 2935 (C–H aromatic), 1735 (β-lactam-C=O), 1685 (C=O), 1616 (C=C), 1458 (C–H aliphatic), 1338 (C–N), 1255 (C–O–C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.62 (s, 1H, *NH*), 8.86 (s, 1H, C_4–*H*), 8.10 (d, 2H, phenyl-C_2 and C_6–*H*), 7.95–7.81 (m, 4H, C_5–*H*, C_8–*H* and phenyl-C_3 and C_5–*H*), 7.70 (t, 1H, C_7–*H*), 7.50 (dd, 2H, pyrrole-C_2 and C_5–*H*), 7.46 (t, 1H, C_6–*H*), 6.32 (dd, 2H, pyrrole-C_3 and C_4–*H*), 4.53 (d, 1H, $J = 4.2$ Hz, *CH–Cl*), 4.35 (d, 1H, $J = 4.1$ Hz, *CH–N*), 4.02 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 164.55 (NH–C=O), 160.23 (β-lactam-C=O), 157.41 (C_2), 151.55 (phenyl-C_4), 146.25 (C_9), 136.28 (C_4), 134.56 (C_6), 132.77 (C_7), 131.59 (phenyl-C_3 and C_5), 129.87 (phenyl-C_1, C_2 and C_6), 128.02 (C_8), 126.73 (C_5), 125.17 (C_{10}), 123.09 (C_3), 121.88 (pyrrole-C_2 and C_5), 119.12 (pyrrole-C_3 and C_4), 116.00 (β-lactam-C_3), 90.57 (β-lactam-C_2), 53.56 (OCH_3); MS (EI) *m/z:* found 446.89 (M^+), 448.89 $(M + 2)^+$; calcd. 446.11. Anal. Calcd for $C_{24}H_{19}ClN_4O_3$; Calc: C, 64.50; H, 4.29; N, 12.54; found: C, 64.75; H, 4.27; N, 12.49.

*N-(3-Chloro-2-(6-chloro-2-methoxyquinolin-3-yl)-4-oxoazetidin-1-yl)-4-(1H-pyrrol-1-yl)benzamide (**8b**)* Compound **8b** was obtained as yellow solid. Yield 32 %, M.p. 294–296 °C, $R_f = 0.75$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3120 (NH), 2915 (C–H aromatic), 1742 (β-lactam-C=O), 1680 (C=O), 1612 (C=C), 1469 (C–H aliphatic), 1340 (C–N), 1250 (C–O–C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.80 (s, 1H, *NH*), 8.80 (s, 1H, C_4–*H*), 8.10 (d, 2H, phenyl-C_2 and C_6–*H*), 7.86–7.98 (m, 2H, C_5–*H* and C_8–*H*), 7.66–7.80 (m, 4H, pyrrole-C_2 and C_5–*H* and phenyl-C_3 and C_5–*H*), 7.56 (t, 1H, C_7–*H*), 6.33 (dd, 2H, pyrrole-C_3 and C_4–*H*), 4.52 (d, 1H, $J = 4.2$ Hz, *CH–Cl*), 4.39 (d, 1H, $J = 4.2$ Hz, *CH–N*), 4.12 (s, 3H, *OCH_3*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.89 (NH–C=O), 162.48 (β-lactam-C=O), 157.59 (C_2), 153.26 (phenyl-C_4), 148.53 (C_9), 137.41 (C_4), 135.09 (C_6), 132.55 (C_7), 132.09 (phenyl-C_3 and C_5), 131.88 (phenyl-C_1, C_2 and C_6), 129.00 (C_8), 127.02 (C_5), 125.77 (C_{10}), 123.35 (C_3), 121.22 (pyrrole-C_2 and C_5), 120.01 (pyrrole-C_3 and C_4), 117.25 (β-lactam-C_3), 92.29 (β-lactam-C_2), 53.00 (OCH_3); MS (EI) *m/z:* found 480.33 (M^+), 482.33 $(M + 2)^+$; calcd. 480.08. Anal. Calcd for $C_{24}H_{18}Cl_2N_4O_3$; Calc: C, 59.89; H, 3.77; N, 11.64; found: C, 60.11; H, 3.76; N, 11.68.

*N-(2-(6-Bromo-2-methoxyquinolin-3-yl)-3-chloro-4-oxoazetidin-1-yl)-4-(1H-pyrrol-1-yl)benzamide (**8c**)* Compound **8c** was obtained as yellow solid. Yield 32 %, M.p. 289–291 °C, $R_f = 0.71$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3110 (NH), 2921 (C–H aromatic), 1743 (β-lactam-C=O), 1666 (C=O), 1617 (C=C), 1467 (C–H aliphatic), 1335 (C–N), 1254 (C–O–C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.56 (s, 1H, *NH*), 8.80 (s, 1H, C_4–*H*), 8.12–8.44 (m, 3H, C_5, C_7 and C_8–*H*), 7.70–7.89 (m, 4H, phenyl-C_2, C_3, C_5 and C_6–*H*), 7.60 (dd, 2H, pyrrole-C_2 and C_5–*H*), 6.34 (dd, 2H, pyrrole-C_3 and C_4–*H*), 4.50 (d, 1H, $J = 4.3$ Hz, *CH–Cl*), 4.32 (d, 1H, $J = 4.2$ Hz, *CH–N*), 4.10 (s, 3H, *OCH_3*); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 164.01 (NH–C=O), 163.09 (β-lactam-C=O), 159.29 (C_2), 155.56 (phenyl-C_4), 149.51 (C_9), 139.77 (C_4), 137.41 (C_6), 133.03 (C_7), 132.22 (phenyl-C_3 and C_5), 130.26 (phenyl-C_1, C_2 and C_6), 129.01 (C_8), 127.03 (C_5), 125.43 (C_{10}), 123.00 (C_3), 121.16 (pyrrole-C_2 and C_5), 119.00 (pyrrole-C_3 and C_4), 115.62 (β-lactam-C_3), 95.01 (β-lactam-C_2), 55.12 (OCH_3); MS (EI) *m/z:* found 524.78 (M^+), 526.78 $(M + 2)^+$; calcd. 524.03. Anal. Calcd for $C_{24}H_{18}BrClN_4O_3$; Calc: C, 54.82; H, 3.45; N, 10.66; found: C, 54.60; H, 3.46; N, 10.70.

*N-(3-Chloro-2-(2-methoxy-6-methylquinolin-3-yl)-4-oxoazetidin-1-yl)-4-(1H-pyrrol-1-yl)benzamide (**8d**)* Compound **8d** was obtained as yellow solid. Yield 30 %, M.p. 218–220 °C, $R_f = 0.85$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3038 (NH), 2950 (C–H aromatic), 1736 (β-lactam-C=O), 1666 (C=O), 1576 (C=C), 1457 (C–H aliphatic), 1398 (C–N), 1257 (C–O–C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.56 (s, 1H, *NH*), 8.81 (s, 1H, C_4–*H*), 8.10 (d, 2H, C_7–*H*), 7.92 (s, 1H, C_5–*H*), 7.70–7.78 (m, 4H, phenyl-C_2, C_3, C_5, C_6–*H*), 7.52 (dd, 3H, C_8–*H* and pyrrole-C_2, C_5–*H*), 6.32 (d, 2H, pyrrole-C_3 and C_4–*H*), 4.52 (d, 1H, $J = 4.3$ Hz, *CH–Cl*), 4.34 (d, 1H, $J = 4.3$ Hz, *CH–N*), 4.10 (s, 3H, *OCH_3*), 2.89 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.03 (NH–C=O), 161.11 (β-lactam-C=O), 157.00 (C_2), 151.82 (phenyl-C_4), 146.62 (C_9), 135.61 (C_4), 134.21 (C_6), 131.77 (C_7), 130.52 (phenyl-C_3 and C_5), 129.53 (phenyl-C_1, C_2 and C_6), 127.39 (C_8), 125.79 (C_5), 124.21 (C_{10}), 122.89 (C_3), 120.93 (pyrrole-C_2 and C_5), 117.21 (pyrrole-C_3 and C_4), 113.12 (β-lactam-C_3), 93.00 (β-lactam-C_2), 54.10 (OCH_3), 27.55 (CH_3); MS (EI) *m/z:* found 460.91 (M^+), 462.91 $(M + 2)^+$; calcd. 460.13. Anal. Calcd for $C_{25}H_{21}ClN_4O_3$; Calc: C, 65.15; H, 4.59; N, 12.16; found: C, 64.89; H, 4.60; N, 12.11.

*N-(3-Chloro-2-(2-chloroquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamide (**9a**)* Compound **9a** was obtained as yellow solid. Yield 30 %, M.p. 284–286 °C, $R_f = 0.78$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3140 (N–H), 2939 (C–H aromatic), 1732 (β-lactam-C=O), 1678 (C=O), 1628 (C=C), 1462 (C–H aliphatic), 1344 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.40 (s, 1H, *NH*), 8.80 (d, 1H, C_8–*H*), 8.40–8.78 (m, 3H, C_4, C_5 C_6–*H*), 7.42–8.22 (m, 5H, C_7–*H* and pyridine-C_2, C_3, C_5, C_6–*H*), 4.58 (d, 1H, $J = 1.5$ Hz, *CH–Cl*), 4.42 (d, 1H, $J = 1.6$ Hz, *CH–N*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.22 (NH–C=O), 155.32 (β-lactam-C=O), 153.45 (C_2), 151.67 (pyridine-C_2 and C_6), 145.63 (C_9), 138.12 (pyridine-C_4), 135.66 (C_4), 132.62 (C_6), 131.02 (C_7), 126.84 (C_8), 126.12 (C_5), 124.65 (C_{10}), 122.20 (C_3), 121.87 (pyridine-C_3 and C_5), 115.34 (β-lactam-C_3), 90.30 (β-lactam-C_2); MS (EI) *m/z:* found 386.00 (M^+), 388.00 $(M + 2)^+$; calcd. 386.03 Anal. Calcd for $C_{18}H_{12}Cl_2N_4O_2$; Calc: C, 55.83; H, 3.12; N, 14.47; found: C, 56.05; H, 3.11; N, 14.41.

*N-(3-Chloro-2-(2,6-dichloroquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamide (**9b**)* Compound **9b** was obtained as yellow solid. Yield 37 %, M.p. 276–278 °C, $R_f = 0.75$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3130 (N–H), 2935 (C–H aromatic), 1734 (β-lactam-C=O), 1685 (C=O), 1630 (C=C), 1459 (C–H aliphatic), 1351 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.45 (s, 1H, *NH*), 8.78 (d, 1H, C_8–*H*), 8.42–8.72 (m, 2H, C_4, C_5–*H*), 7.44–8.33 (m, 5H, C_7–*H* and pyridine-C_2, C_3, C_5, C_6–*H*), 4.56 (d, 1H, $J = 1.7$ Hz, *CH–Cl*), 4.37 (d, 1H, $J = 1.6$ Hz, *CH–N*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.89 (NH–C=O), 156.22 (β-lactam-C=O), 156.66 (C_2), 150.26 (pyridine-C_2 and C_6), 146.69 (C_9), 140.56 (pyridine-C_4), 134.56 (C_4), 133.96 (C_6), 130.88 (C_7), 128.01 (C_8), 126.87 (C_5), 124.56 (C_{10}),

123.06 (C_3), 121.68 (pyridine-C_3 and C_5), 119.22 (β-lactam-C_3), 90.02 (β-lactam-C_2); MS (EI) *m/z:* found 419.66 (M^+), 421.66 $(M + 2)^+$; calcd. 419.99. Anal. Calcd for $C_{18}H_{11}Cl_3N_4O_2$; Calc: C, 51.27; H, 2.63; N, 13.29; found: C, 51.47; H, 2.62; N, 13.34.

*N-(2-(6-Bromo-2-chloroquinolin-3-yl)-3-chloro-4-oxoazetidin-1-yl)isonicotinamide (**9c**)* Compound **9c** was obtained as yellow solid. Yield 28 %, M.p. 302–304 °C, $R_f = 0.74$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3115 (N–H), 2926 (C–H aromatic), 1736 (β-lactam-C=O), 1695 (C=O), 1622 (C=C), 1411 (C–H aliphatic), 1411 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.52 (s, 1H, *NH*), 8.81 (d, 1H, C_8–*H*), 8.34–8.68 (m, 2H, C_4, C_5–*H*), 7.36–8.20 (m, 5H, C_7–*H* and pyridine-C_2, C_3, C_5, C_6–*H*), 4.62 (d, 1H, $J = 1.7$ Hz, *CH–Cl*), 4.32 (d, 1H, $J = 1.6$ Hz, *CH–N*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.65 (NH–C=O), 157.46 (β-lactam-C=O), 155.44 (C_2), 150.78 (pyridine-C_2 and C_6), 144.56 (C_9), 138.22 (pyridine-C_4), 134.86 (C_4), 133.16 (C_6), 130.56 (C_7), 127.86 (C_8), 126.26 (C_5), 124.62 (C_{10}), 122.54 (C_3), 120.86 (pyridine-C_3 and C_5), 117.84 (β-lactam-C_3), 92.65 (β-lactam-C_2); MS (EI) *m/z:* found 463.12 (M^+), 465.12 $(M + 2)^+$; calcd. 463.94. Anal. Calcd for $C_{18}H_{11}BrCl_2N_4O_2$; Calc: C, 46.38; H, 2.38; N, 12.02; found: C, 46.19; H, 2.38; N, 12.06.

*N-(3-Chloro-2-(2-chloro-6-methylquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamide (**9d**)* Compound **9d** was obtained as yellow solid. Yield 33 %, M.p. 274–276 °C, $R_f = 0.81$ (Silica gel, 70 % Ethyl acetate in *n*-Hexane); IR (KBr) ν_{max}: cm^{-1}: 3128 (N–H), 2928 (C–H aromatic), 1733 (β-lactam-C=O), 1682 (C=O), 1624 (C=C), 1455 (C–H aliphatic), 1345 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.60 (s, 1H, *NH*), 8.88 (d, 1H, C_8–*H*), 8.44–8.80 (m, 2H, C_4, C_5–*H*), 7.42–8.39 (m, 5H, C_7–*H* and pyridine-C_2, C_3, C_5, C_6–*H*), 4.58 (d, 1H, $J = 1.6$ Hz, *CH–Cl*), 4.33 (d, 1H, $J = 1.5$ Hz, *CH–N*), 2.30 (s, 1H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.12 (NH–C=O), 157.32 (β-lactam-C=O), 155.24 (C_2), 151.84 (pyridine-C_2 and C_6), 144.46 (C_9), 137.34 (pyridine-C_4), 134.78 (C_4), 132.26 (C_6), 131.20 (C_7), 127.02 (C_8), 126.72 (C_5), 124.56 (C_{10}), 122.52 (C_3), 121.65 (pyridine-C_3 and C_5), 116.49 (β-lactam-C_3), 92.40 (β-lactam-C_2), 27.46 (CH_3); MS (EI) *m/z:* found 400.25 (M^+), 402.25 $(M + 2)^+$; calcd. 400.05. Anal. Calcd for $C_{19}H_{14}Cl_2N_4O_2$; Calc: C, 56.87; H, 3.52; N, 13.96; found: C, 56.64; H, 3.53; N, 13.90.

Biological assay

Antibacterial activity (Goto *et al*., 1981; NCCLS, 1985) and antimycobacterial activity (Franzblau *et al*., 1998) assays were performed following a protocol previously reported.

Cytotoxicity analysis; all the synthesized products were analyzed for cytotoxicity using neutral red uptake by using Vero-C1008 cell line at various concentrations ranging from 0.01 to 0.1 μg/ml, none of them were found toxic. Hence the activities of the above synthesized compounds were not due to cytotoxicity of the compounds.

Conclusion

In the present research, we have reported the synthesis of a new series of Schiff base and azetidinone derivatives of quinoline along with spectral data as well as antibacterial and antitubercular activities. Compounds **5c** and **5d** having –CH=N–NH–C(=O)– moiety were found to be more active than azetidinones against all studied microorganisms. A marked increase was observed in antibacterial and antitubercular activities when the chlorine atom was replaced by methoxy group, indicating the relevance of methoxy group to exhibit biological activity. Molecular docking of different inhibitors into enoyl ACP-reductase enzyme suggested that compounds **5b**, **5c**, **5d** and **8a** bind to Tyr158 amino acid and co-factor NAD^+ promisingly, same as that of pyrrolidine carboxamide against MTB. That of same compounds shown binding to Tyr156 amino acid and co-factor NAD^+ in ENR active site of *E. coli*. The results of this study can be utilized to further optimize in order to improve the potency and selectivity for ENR enzyme by varying the basic skeleton.

In summary, our results on the biological screening of the compounds offered an excellent framework that may lead to the discovery of new potent anti-infective agents. Additional molecular docking study involving topoisomerase II and transamidase will offer better insights to understand the detailed binding interactions and the mechanism, this work will be undertaken in the near future.

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