Synthetic Communications ›
An International Journal for Rapid Communication of Synthetic Organic Chemistry
Volume 49, 2019 - Issue 4

Articles

Dicationic liquid mediated synthesis of tetrazoloquinolinyl methoxy phenyl 4-thiazolidinones and their antibacterial and antitubercular evaluation

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Pages 587-601 | Received 10 Oct 2018, Published online: 29 Jan 2019

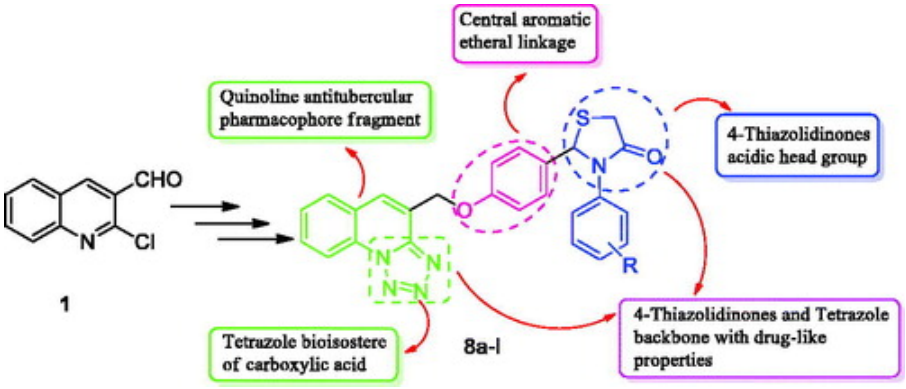
Cite this article https://doi.org/10.1080/00397911.2018.1564928

Abstract

In a search of new potentially active antitubercular agents here we have synthesized 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones (**8a-l**) and evaluated their antibacterial, particularly antitubercular activity. These have been conveniently synthesized by performing one-pot cyclocondensation of 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde, anilines and mercaptoacetic acid in dicationic ionic liquid, (3-methyl-1-[3-(methyl-1*H*-imidazolium-1-yl)propyl]-1*H*-imidazolium dibromide

characterized by their spectral analyses. These compounds have been screened for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis H37Ra* and *Mycobacterium bovis* (BCG). The compounds **8a**, **8c,** and **8e** exhibited notable *in vitro* antitubercular activity compare to the reference, Rifampicin. Molecular docking study has also been performed to know the binding mode of these analogs in to the active site of DprE1 enzyme. The synthesized compounds were also evaluated for their *in vitro* antibacterial activity and amongst them compound **8k** has shown moderate activity against both gram-negative and gram-positive bacterial strains.

Graphical Abstract



Keywords: Antibacterial activity antitubercular activity cytotoxicity dicationic ionic liquid molecular docking 4-thiazolidinones tetrazolo[1,5-a]quinoline

Introduction

Several research reports have narrated the seriousness of tuberculosis (TB) as infectious disease, caused by bacterial pathogens belonging to the *Mycobacterium tuberculosis*.[1] World Health Organization (WHO) has declared tuberculosis as global health crisis.[2] The existing drugs available for treating TB are finding difficulty to cure the patients having multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).[3] It is most challenging situation to treat TB when it is accompanying with (HIV) infection.[4] Present clinical treatment for the tuberculosis disease is co-administrating first-line drugs, that is isoniazid (INH), rifampicin (RMP), ethambutol (EMB) and pyrazinamide (PAZ) for months

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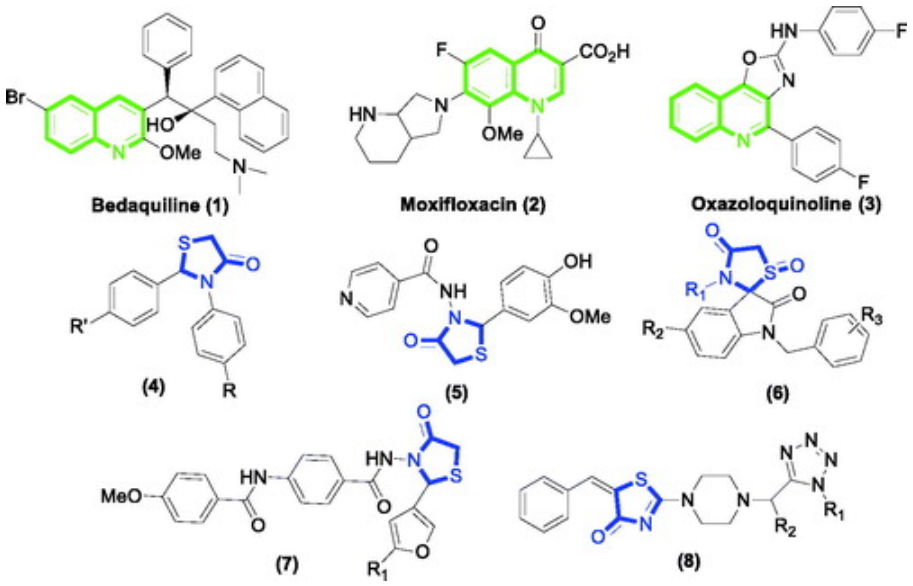
mode of treatment has several side effects and tuberculosis strains are becoming resistant to these drug regimens. Therefore, tuberculosis is a devastating problem whose control and treatment are becoming complicated, including substantially long course therapy and noncompliance by the patient.[8] Hence there is an urgency and growing need for the new class of chemical compounds with diverse and unique structural features to treat this disease efficiently.

Quinoline moiety is found in large variety of naturally occurring compounds and is an useful synthon having diverse pharmacological properties.[9-11] The quinoline class of compounds have displayed promising activity against resistant tuberculosis. [12-15] Quinoline derivatives have been found to inhibit mycobacterial growth effectively. Recently new entities bearing quinolinyl scaffold have been synthesized and evaluated for anti-tubercular activity. Some of them, namely bedaquiline (TMC207) **1,** [16] a diarylquinoline, moxifloxacin **2** [17] and oxazoloquinoline **3**,[18] (Fig. 1), have exhibited significant *in vitro* antitubercular activity against *Mycobacterium tuberculosis, H37Rv*. The fusion of quinoline and tetrazole ring is known to enhance the biological activities.[19] In particular, tetrazolo[1,5-*a*]quinoline-4-carbaldehyde serves as a key synthetic intermediate for the synthesis of medicinally valuable compounds.[20-23] Recently the synthesis and antitubercular activity of tetrazoloquinoline-rhodanine and quinolidine-rhodanine conjugates have been reported.[24, 25] A significant number of compounds bearing the phenyl ring joined by ether linker to quinolines are found to enhance anti-*Mycobacterium tuberculosis H37Rv* activity and provide path to develop new antitubercular drugs.[26-29]

Figure 1. Quinoline and 4-Thiazolidinone scaffolds possessing antitubercular activity.



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4-Thiazolidinones are well explored as therapeutic agents [30-32] and some of the candidates (**4-8,** Fig. 1) of this class have displayed potential activity against *Mycobacterium tuberculosis.* [33-39]

In search of newer bioactive heterocyclic agents with antihyperglycemic and anti-tubercular properties [40-46] already we synthesized 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones and reported their antidiabetic activity.[47] Considering the antitubercular activity displayed by hetryl rings like quinoline, 4-thiazolidinones and aryl ethereal group, here we thought that the recently synthesized 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones (**8a-l**), are having all these scaffolds in one molecular architectural frame and they may be better candidates to treat tubercular infection. In view of this here we synthesized and the screened 4-thiazolidinones (**8a-l**) and reported their antitubercular activity.

To provide more convenient synthetic protocol for obtaining new 4-thiazolidinones (**8a-l**) here an alternative and safer route has also been developed. In this alternative route one-pot cyclocondensation of 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde, anilines and mercaptoacetic has been carried in nonvolatile dicationic ionic liquid (DCIL), $C_3(MIM)_2$-2Br and obtained 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones (**8a-l**) with better yields.

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Results and discussion

Chemistry

In our earlier report,[47] we have carried one-pot cyclocondensation of newly synthesized aldehyde (**5**), aryl amines (**6a-l**) and mercapto acetic acid (**7**) in PEG-400, and obtained moderate yields of the title 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones (**8a-l**) after heating the reaction content at 110 °C for 2 h. To provide alternative reaction conditions for this cyclocondensation here we used dicationic ionic liquid, 3-methyl-1-[3-(methyl-1*H*-imidazolium-1-yl)propyl]-1*H*-imidazolium dibromide [$C_3(MIM)_2$-2Br], derived from condensing 2 moles of 1-methylimidazole and 1 mole of 1,3-dibromopropane as medium and catalyst.[48,49] It was noted that the one-pot cyclocondensation in the dicationic ionic liquid has undergone completion within 1 h at 80 °C giving 81-92% yield of the titled 4-thiazolidinones (**8a-l**) (Scheme 1a,b, Table 1). The rate acceleration in this modified protocol is attributed to the dual role of dicationic ionic liquid as a dipolar medium and catalyst.

Scheme 1. Syntheses of (a) (4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde and (b) 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones.

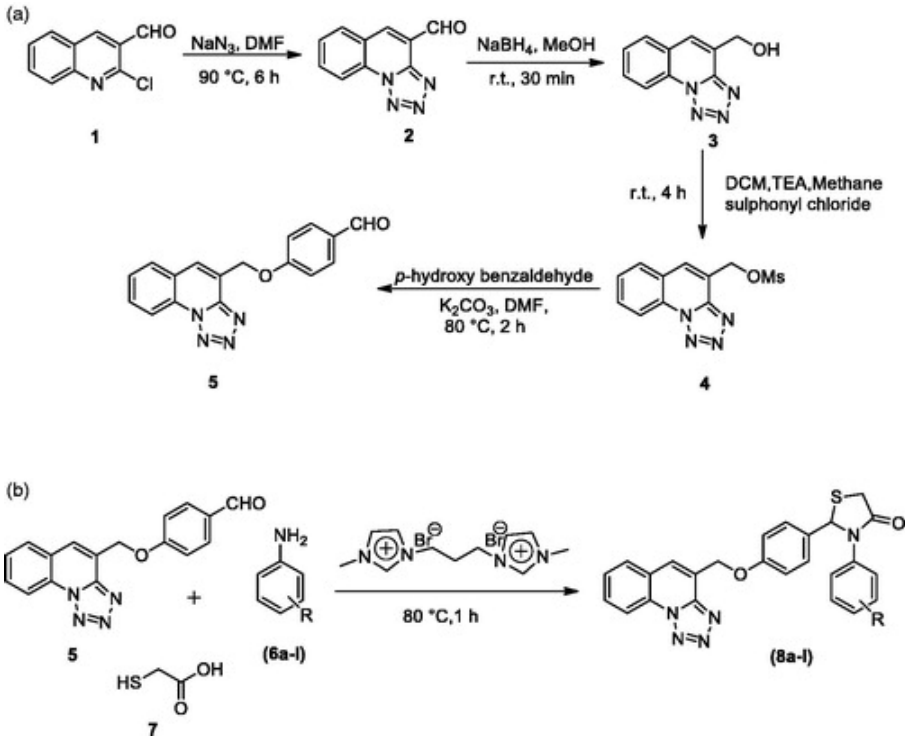

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Table 1. Synthesis of 3-substitutedphenyl-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl) thiazolidin-4-ones [a] (**8a-l**).

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The dicationic ionic liquid, (3-methyl-1-[3-(methyl-1*H*-imidazolium-1-yl)propyl]-1*H*-imidazolium dibromide [$C_3(MIM)_2$-2Br]) was found to be safer and excellent medium for the present substrates and reagents. The dicationic ionic liquid has ability to easily solubilize the substrate and reagents to make their saturated solutions before commencing the cyclocondensation. That could be one of the factors which may be assisting the rate enhancement of the condensation. This dicationic ionic liquid might have been displaying catalytical behaviors, enhancing overall yield of the reaction. Imidazolyl cations of the DCIL may enhance electrophilic character of the carbonyl carbon of the aldehyde and hence favoring the attack of nucleophilic amino nitrogen of anilines (a). The rapid proton abstraction by bromide anions from the intermediates might have been resulted into rapid formation of Schiff bases (b). The nucleophilicity of mercapto group of thioglycolic acid would have been enhanced because of hydrogen bonding with bromide anions of the dicationic ionic liquid and that might be assisting for its easy addition on imino carbon of the Schiff bases (c) (proposed mechanism is depicted in Fig. S1 and incorporated in Supporting Information (SI)). The physical data of 4-thiazolidinones (**8a-l**) is incorporated in Table 1.

All the synthesized intermediates and titled products have been thoroughly characterized, using their ^{1}H NMR, 13C NMR and HRMS spectral data. The ^{1}H NMR spectrum of compound **8a** displayed characteristics peak for a pair of doublet at *δ* 3.92 and 3.99 ppm, due to the geminal coupling between two hydrogens of S-CH_2-C=O, a sharp singlet at *δ* 6.09 ppm, corresponds to proton of N-CH-S, and singlet at *δ* 5.55 ppm due to methylene proton. The presence of three characteristics carbon signals are observed at *δ* 33.6, 65.3 and 171 ppm in 13C NMR spectrum of compound **8a** owing to carbons of S-CH_2-CO, N-CH-S and C=O groups, respectively, confirming the presence of a 4-thiazolidinone ring in **8a**. The HRMS spectrum of compound **8a** further strengthen the structure as it displays $[M + H]^+$ ion peak at *m/z* 454.1329 in consistent with its molecular formula $C_{25}H_{20}N_5O_2S$.

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All the synthesized compounds were screened for their *in vitro* antitubercular activity against Dormant *Mycobacterium bovis* BCG (ATCC 35734) and *Mycobacterium tuberculosis H37Ra* (ATCC 25177). Primary screening was done at three concentrations 30, 10, 3 µg/mL. Those compounds which have shown more than 90% inhibition at 30 µg/mL using an established XRMA (for *M. tuberculosis*) as well as NR (Nitrate reductase for *M. bovis* BCG) assays were considered for further evaluation.[50,51] All the compounds displayed promising activity against *M. bovis* BCG and moderate activity against *M. tuberculosis H37Ra* (Table 2). Among them, compounds **8a**, **8c** and **8e** showed good antitubercular activity against *M. bovis* BCG, which is better than first-line antitubercular drug, pyrazinamide (MIC 20 µg/mL). The compound **8e** has shown MIC 3.80 µg/mL against *M. bovis* BCG and 20.34 µg/mL against *M. tuberculosis H37Ra*.

Table 2. Antitubercular evaluation, cytotoxicity study and docking scores of 3-substitutedphenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones (**8a-l**).

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All the compounds which are active for anti-tubercular activity was further assayed for their *in vitro* cytotoxicity against HeLa (Human cervical cancer cell line), using paclitaxel as positive control.[52-54] Except **8i** all the compounds were found to have MIC above 30 on HeLa cells (Table 2). Compound **8i** has an MIC value of 15.46. Hence, other than **8i,** remaining all the compounds have good antitubercular activity with low cytotoxicity on the HeLa cell lines. These results indicate a selective inhibition toward *Mycobacterium tuberculosis.*

Antibacterial activity

To check the specificity of (**8a-l**) for mycobacteria, IC_{90} and IC_{50} of these compounds against Gram positive and Gram-negative bacteria were also estimated (Table 3). Gram-positive bacteria, *S. aureus* and *B.subtilis*, and gram-negative bacteria, *E.coli* and *P. aeruginosa*, have shown higher resistance with an MIC >100 µg/mL for all the compounds (**8a-l**). However, compound **8k** was found to be more active against both gram-negative and gram-positive bacterial strains with MIC between 46 and 95 µg/mL. It was observed that the MICs of **8a, 8c** and **8e** are up to 32 folds higher against the bacteria than that of mycobacteria, indicating

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greater specificity of these compounds towards mycobacteria.[55]

Table 3. Antibacterial evaluation of 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones (**8a-l**).

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Molecular docking study

Molecular docking provides a powerful tool in understanding different types of interactions that govern the binding of a molecule to the biological receptor. In order to rationalize the observed antitubercular activity and to understand the binding interactions of the 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones at the molecular level, a molecular docking study was carried out with the DprE1 enzyme. The binding conformations of 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones into the active site of DprE1 enzyme were predicted using the Glide (Grid-Based Ligand Docking with Energetic) program incorporated in the Schrodinger molecular modeling package (Schrödinger, LLC, New York, NY, 2015).[56] The crystal structure of DprE1 enzyme [PDB entry code: 4FDO, complexed with the inhibitor, Resolution: 2.40Å] 32 was obtained from the Protein Data Bank (http://www.rcsb.org).

In the recent years, molecular modeling tools like docking have become very important to identify the potential targets for different ligands and the associated thermodynamic interactions with the target enzyme governing the inhibition of the target microorganism especially in the absence of available resources to carry out the experimental studies.

Mycobacterium tuberculosis has a special cell wall arrangement, with layers of outer lipids, mycolic acid, polysaccharides (arabinogalactan), peptidoglycan, plasma membrane, lipoarabinomannan (LAM), and phosphatidylinositol mannoside. Decaprenylphosphoryl-β-D-ribose-20-epimerase (DprE1) is an oxidase involved in the biosynthesis of decaprenylphosphoryl-D-arabinose (DPA). DPA is the only known donor of D-arabinofuranosyl residues for the synthesis of arabinogalactans-basic precursor for bacterial cell wall synthesis. DprE1 along with decaprenylphosphoryl 2-ketoribose reductase (DprE2) catalyzes the

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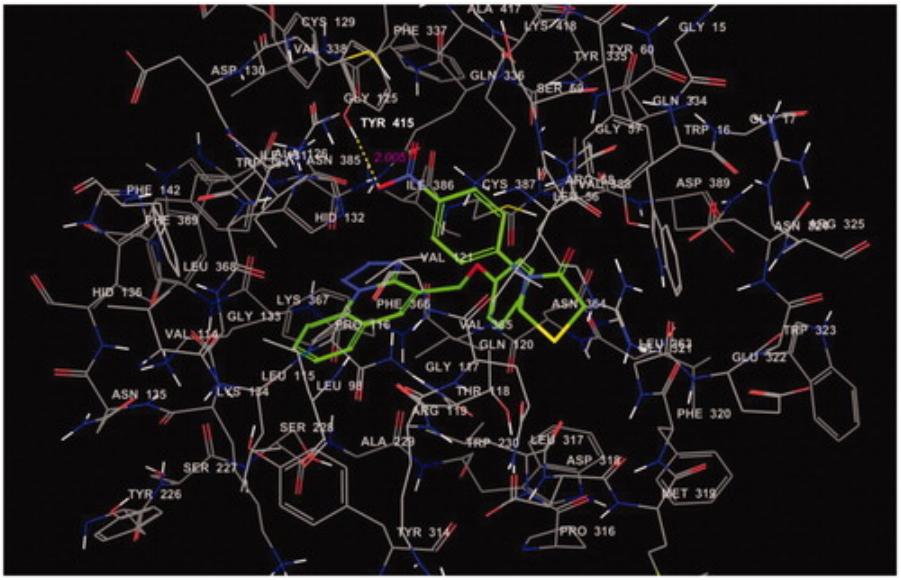
essential component for cell growth and survival, making it a potential drug target and has been shown to be a highly druggable target that can be inhibited by a wide variety of chemical structures.[58, 59] Following the discovery of the nitrobenzothiazinone, (BTZ043) that binds covalently to DprE1, there has been a growing interest in this target.[60]

Molecular docking study revealed that all the 3-substituted phenyl-2-(4-(tetrazolo [1, 5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones were successfully docked into the active site of DprE1 with varying degree of affinities and their complexation was stabilized by formation of several steric and electrostatic interactions. Their docking scores ranged from −8.57 to −6.58 while the docking score for the native ligand was found to be −7.95 indicating that these compounds could be optimized as a pertinent starting points for lead optimization (Table 2). A statistically significant harmony was observed between the experimental antitubercular activity and the molecular docking scores, wherein the active compounds showed higher docking scores while those with relatively low inhibition were also predicted to have a lower score. A detailed per-residue interaction analysis between the protein and the 3-substituted phenyl-2-(4-(tetrazolo [1, 5-*a*] quinolin-4-ylmethoxy) phenyl) thiazolidin-4-ones was carried out to identify the most significantly interacting residues. However, for the sake of brevity we have elucidated this analysis only for one of the most active analog **8e** (Fig. 2).

Figure 2. Binding mode of **8e** into the active site of DprE1.



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The compound **8e** showed the highest binding affinity with a docking score of −8.57 and a good interaction energy that is −60.51kcal/mol. The per-residue interaction analysis revealed that, the ligand adopted a stable binding pose within the active site of DprE1 enzyme by forming various Van der Waals and electrostatic interactions. Extensive van der Waals interactions were observed between tetrazolo[1,5-*a*]quinoline nucleus and Cys387 (−1.278 kcal/mol), Ile 386 (−1.004 kcal/mol), Asn 385(−2.041 kcal/mol), Phe 369 (−1.522 kcal/mol), Lys 367 (−2.675 kcal/mol), Phe 366(−1.140 kcal/mol), Val 365 (−3.142 kcal/mol), Gln 336 (−2.356 kcal/mol), Leu 317 (−3.857 kcal/mol), Tyr 314 (−1.190 kcal/mol), Gly 133(−1.201 kcal/mol) and His 132(−4.201 kcal/mol) residues. The tetrazolo[1,5-*a*]quinoline moiety was further stabilized in the active site through favorable electrostatic interaction with Gln 336 (−1.125 kcal/mol) and a close pi-pi stacking interaction with His132. The central phenyl ring bridging the tetrazolo[1,5-*a*]quinoline scaffold with 4-thiazolidinones counterpart was involved in significant van der Waals interactions with Lys418 (−2.754 kcal/mol), Ala 417 (−1.092 kcal/mol) and Gly 117 (−3.345 kcal/mol) residues and additional favorable electrostatic interaction with Lys 418 (−1.685 kcal/mol) and Asp 318 (−2.405 kcal/mol). The 4-thiazolidinone ring was involved in significant van der Waals interactions with Tyr 60 (−3.316073), Arg 58 (−1.79192) and Trp 16 (−3.064106) residues while the 4-nitro substituted phenyl ring showed favorable van der Waals interactions with Tyr 415 (−1.571 kcal/mol), Ile131 (−1.354 kcal/mol), Val 121 (−1.419 kcal/mol), Thr 118 (−2.943 kcal/mol), Pro 116 (−3.353 kcal/mol**),** Ser 59 (−1.161 kcal/mol) residues in the active site. Furthermore the oxygen atom of nitro functional group formed a hydrogen bond (2.005Å) with the Tyr415 residue contributing to the stability of **8e** within the active site of DprE1. Such hydrogen bonds serve as an “anchor” guiding the 3D space position of a molecule within the active site. The per-residue ligand interaction energy distribution showed that the van der Waals contacts were more prevalent over the electrostatic contribution in the overall binding of **8e**. So on the basis of the biological activity data and the molecular docking results, it can be concluded that these 3-substituted phenyl-2-(4-(tetrazolo [1, 5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones have the potential to be developed as lead compounds in the antitubercular drug design strategy.

Conclusion

We have developed a convenient and high yielding one-pot multi- component synthetic route

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from freshly prepared 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde using dicationic ionic liquid, (3-methyl-1-[3-(methyl-1*H*-imidazolium-1-yl)propyl]-1H-imidazolium dibromide [$C_3(MIM)_2$-2Br]) as medium and catalyst. Among the synthesized 4-thiazolidinones, the compounds **8a**, **8c** and **8e** have displayed notable *in vitro* antitubercular activity against *Mycobacterium bovis* BCG (ATCC 35734) and *Mycobacterium tuberculosis H37Ra* (ATCC 25177) with tolerable cytotoxicity. The molecular docking study has supported that these derivatives have a high affinity towards mycobacterial DprE1 enzyme which will provide a strong platform for new structure-based drug design efforts. A more detail study of the pharmacological profile of the noticeable compounds, **8a**, **8e** and **8c,** are underway. This will help in generating a library of analogs of the series as potential antitubercular agents.

Experimental

Material and methods

Chemicals and solvents, required were procured from Merck, Spectrochem and S. D. Fine chem. Melting points were determined in open capillary and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Avance 300-500 (FT-NMR) and Bruker DRX-300 instruments, respectively, using $CDCl_3$/DMSO-d_6 as solvents and TMS as an internal standard. Chemical shifts are in δ (ppm). High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) ESI-HRMS instrument and mass spectra on JEOL-Accu TOF DART-MS-T 100Lc. The purity of the synthesized compounds was measured by thin-layer chromatography (TLC) using Merck silica gel 60F_{254} aluminum sheet and hexane:ethyl acetate as eluent.

General procedure for the synthesis of tetrazolo[1,5-a]quinolin-4-ylmethyl methanesulfonate (4)

Tetrazolo[1,5-*a*]quinolin-4-ylmethanol (**3**) (7 g, 0.035 mol) was dissolved in dichloromethane (DCM) (70 ml). To this solution triethylamine (TEA) (7.39 ml, 0.053 mol) was added and the solution was stirred for 30 min. To this stirred solution methane sulfonyl chloride (3.1 ml, 0.039 mol) was added in portions at 0-5 °C and then stirred for 4 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After 4 h of the reaction, solvent was removed from the reaction mass under reduced pressure. The residue was poured on crushed ice. Thus obtained solid was filtered, washed with water and dried. It was crystallized and used for the

Tetrazolo[**1,5-a]quinolin-4-ylmethyl methanesulfonate** (**4**) as off-white solid and obtained with 82% yield, mp 169-171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 2.05 (s, 3H, methyl), 5.12 (s, 2H, methylene) and 7.75-8.71(m, 5H, Quinoline-H).

General procedure for the synthesis of 4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)benzaldehyde (5)

A mixture of 4-hydroxy benzaldehyde (1.89 g, 0.015mol) and potassium carbonate (2.90 g 0.021 mol) was stirred in DMF (30 ml) for 30 min at 90 °C. To this, tetrazolo[1,5-*a*]quinolin-4-ylmethyl 4-methylbenzenesulfonate (**4**) (5 g, 0.014 mol) was added and further the reaction mass was stirred at 90 °C. The progress of the reaction was monitored by thin-layer chromatography (TLC). After 2 h the reaction mass was allowed to cool and poured on crushed ice. The obtained solid was filtered, washed with water, dried and crystallized using ethanol.

4-(Tetrazolo[1,5-a]quinolin-4-ylmethoxy)benzaldehyde (**5**) as off-white solid and obtained with 76% yield, mp 159-161 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 5.70 (s, 2H), 7.21-8.72 (m, 9H, Ar-H and Quinoline-H, merged peaks) and 9.93 (s, 1H, aldehydic); ^{13}C-NMR ($CDCl_3$, 125 MHz) *δ* 64.72 (CH_2), 115.15, 116.88, 121.73, 123.85, 128.32, 129.14, 129.95, 130.26, 130.8, 131.26, 132.18, 146.06, 162.74, 190.24 (C=O); HRMS (ESI) $[M + Na]^+$ calculated for $C_{17}H_{12}N_4NaO_2$ 327.0858, found 327.0875 and $[M + K]^+$ calculated for $C_{17}H_{12}N_4KO_2$ 343.0597, found 343.0615.

General procedure for the synthesis of 3-phenyl-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (8a-l)

A mixture of 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde **(5)** (1 g, 0.0032 mol), aryl amines **(6a-l)** (0.30 g, 0.0032 mol) and mercaptoacetic acid **(7)** (0.90 g, 0.0098 mol) was heated in dicationic ionic liquid, $[C_3(MIM)_2\text{-}2Br]$ (5 ml) at 80 °C. The progress of the reaction was monitored on thin layer chromatography (TLC). After 1 h heating at 80 °C, the reaction mass was allowed to cool at rt. and poured in ice cold water and neutralized with $NaHCO_3$. Thus obtained crude products were filtered and crystallized from ethanol.

3-Phenyl-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8a**) as off white solid and was obtained via cyclocondensation reaction between aldehyde **5**, aniline and mercaptoacetic acid in 1 h with 89% yield, mp 121-123 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 3.92 (d, *J* = 16 Hz, 1H, methylene), 3.99 (d, *J* = 16 Hz, 1H methylene), 5.55 (s, 2H, methylene), 6.09 (s, 1H,

MHz) δ 33.59 (CH_2), 64.56 (CH_2), 65.31 (CH), 115.12, 116.86, 120.13, 122.36, 123.95, 124.83, 125.93, 127.23, 128.29, 128.83, 129.08, 129.16, 129.75, 131.08, 132.41, 137.51, 146.17, 158.31, 167.32, 171.59 (C=O); HRMS $(ESI)^+$ $[M + H]^+$ calculated for $C_{25}H_{20}N_5O_2S$ 454.1338, found 454.1329.

Supplemental material

Supplemental Material

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Acknowledgements

Authors are thankful to Professor D. B. Ingle for his invaluable discussions and guidance. Authors are also very much grateful to CSIR-National Chemical Laboratory, Pune for providing screening data of synthesized compounds. One of the authors ARD is also grateful to Wockhardt Research Centre, Aurangabad and Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, for awarding research fellowship.

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