European Journal of Medicinal Chemistry 45 (2010) 1854–1867

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original Article

# Novel quinoline and naphthalene derivatives as potent antimycobacterial agents

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ARTICLE INFO

*Article history:*
Received 25 November 2009
Received in revised form
8 January 2010
Accepted 12 January 2010
Available online 20 January 2010

*Keywords:*
ATP synthase
Naphthalene
Quinoline
TMC207
Mefloquine
Anti-tuberculosis drugs

ABSTRACT

We have designed and synthesized both the quinoline and naphthalene based molecules influenced by the unique structural make-up of mefloquine and TMC207, respectively. These compounds were evaluated for their anti-mycobacterial activity against drug sensitive *Mycobacterium tuberculosis* H37Rv *in vitro* at single-dose concentration (6.25 μg/mL). The compounds **22**, **23**, **26** and **27** inhibited the growth of *M. tuberculosis* H37Rv 99%, 90%, 98% and 91% respectively. Minimum inhibitory concentration of compounds **22**, **23**, **26** and **27** was found to be 6.25 μg/mL. Our molecular modeling and docking studies of designed compounds showed hydrogen bonding with Glu-61, Tyr-64 and Asn-190 amino acid residues at the putative binding site of ATP synthase, these interactions were coherent as shown by Mefloquine and TMC207, where hydrogen bonding was found with Tyr-64 and Glu-61 respectively. SAR analysis indicates importance of hydroxyl group and nature of substituents on piperazinyl-phenyl ring was critical in dictating the biological activity of newly synthesized compounds.



## 1. Introduction

Tuberculosis has become a primary health threat to the mankind. *Mycobacterium tuberculosis* is a very successful pathogen, which causes tuberculosis and is the greatest single infectious cause of mortality worldwide, killing approximately two million people annually [1]. It is estimated that, one third of world population is infected with latent TB [2]. The pathogenic synergy between TB and HIV is alarming [3–5]. HIV-positive patients are 50 times more susceptible to TB infection than that of HIV-negative individuals [6], also the progression rate of latent TB in HIV-positive patient is much more significant than those of the HIV-negative patient [1]. The emergence of multi-drug resistant TB (MDR-TB) [7] and extensive drug resistant TB (XDR-TB) [8] is a new threat to the public health [9] and has created an urgent need to develop new anti-mycobacterial therapeutics to treat this deadly disease. However, new anti-tubercular drugs with new mechanisms of action have not been developed in last 40 years. Quinoline-based compounds [10–13] and fluoroquinolones [14,15] are known to display anti-TB activity [10–13]. Quinoline-based well-known drug mefloquine is widely used for the prophylaxis of chloroquine-resistant *Plasmodium falciparum* malaria [16,17]. Mefloquine is also known for its antibacterial [18] and anti-tubercular activity [19–22] (H37Rv MIC range: 8–16 μg/mL or 21.1–42.2 μM) [23] and its analogs have displayed moderate [24] to submicromolar [25] anti-TB activity. Mefloquine and its derivatives are known to act as purine receptor antagonists [26] and it's only prokaryotic target known so far is $F_0F_1H^+$ ATPase in *Streptococcus pneumoniae* [27]. The possible reason of anti-TB activity of mefloquine might be due to sequence identity (~27%) and similarity (50%) of ATP synthase (subunit a and c, P63654 and P63691) of *M. tuberculosis* with the ATP synthase (subunit a and c, P0A2Y8 and P0A307; all sequences were retrieved from Uniprot database) of *S. pneumoniae*. Another possible reason of using mefloquine for treating intracellular pathogen could be its property, to reach 80 times greater

*Abbreviations:* ATP, adenosine triphosphate; DCM, dichloromethane; DMF, *N,N*-dimethyl formamide; DMSO, dimethyl sulphoxide; EAA, ethyl acetoacetate; GI, growth index; HIV, human immunodeficiency virus; $H_2O_2$, hydrogen peroxide; *m*-CPBA, *meta*-chloroperbenzoic acid; MDR, multi-drug resistance; MIC, minimum inhibitory concentration; mp, melting point; MeOH, methanol; NaH, sodium hydride; NBS, *N*-bromosuccinimide; NE, North-East; NMR, nuclear magnetic resonance; NW, North-West; $POCl_3$, phosphorus oxychloride; $PBr_3$, phosphorus tribromide; PPA, polyphosphoric acid; SAR, structure–activity relationship; SE, South-East; SW, South-West; TB, tuberculosis; THF, tetrahydorfuran; TLC, thin layer chromatography; WHO, World Health Organisation; XDR, extensive drug resistance; (NOTE: All amino acid numbering corresponds to *Mycobacterium tuberculosis* ATP synthase subunits A and C. Subunit type shown in superscript.).

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doi:10.1016/j.ejmech.2010.01.024

concentrations in tissues than the concentration achieved in serum and in addition has a long half-life [28]. Andries et al. have recently reported [29] a potent anti-TB molecule, diarylquinoline TMC207 and is targeted to the proton pump of *M. tuberculosis* ATP synthase and have inhibited mycobacterial growth effectively (H37Rv MIC of TMC207: 0.06 μg/mL or 0.01 μM). As mefloquine and TMC207 both target ATP synthase, we argued that a synthesis of new types of molecules incorporating the molecular features of both of mefloquine and TMC207 might produce a new "hit" against *M. tuberculosis*. Thus, we planned to synthesize two series of molecules based on this strategy (Fig. 1), modified quinoline series (compounds **9**–**19**) and modified naphthalene series (compounds **22**–**30**). Ramamurthy et al. reported [30] the synthesis and anti-tubercular activity of bioisosters *N*(2-naphthyl)glycine hydrazide analogs and *N*-(6-quinolyl)glycine hydrazide, and found that *N*(2-naphthyl)glycine hydrazide analogs possess potent inhibitory activity against *M. tuberculosis* H37Rv at concentrations ranging from 0.5 to 10.0 μg/mL whereas *N*-(6-quinolyl)glycine hydrazide analogs did not show anti-tubercular activity. A series of naphthalene-1,4-dione derivatives was synthesized and evaluated for their *in vitro* anti-mycobacterial activity against H37Rv strain and most effective compounds had MIC of 3.13 μg/mL and growth inhibition of 99% [31].

We have previously reported [32,33] design, synthesis and biological activity of novel quinoline derivatives against *M. tuberculosis*, based on molecular dissection (NE, SE and SW hemisphere modifications) of the TMC207 (Fig. 1). Our initial results showed that NE (hydroxyl and *N,N′* dimethyl amine) and SE (naphthyl) hemispheres are critical for anti-mycobacterial activity of TMC207. Different amine substitutions at NE, SE and SW hemispheres have also displayed good anti-mycobacterial activity [32,33]. We have also recently reported a new class of conformationally-constrained indeno[2,1-c]quinoline analogs [34] based on modification of SW and NW hemispheres of TMC207. Conformationally constrained indeno[2,1-c]quinoline analogs were designed (Fig. 2) to diminish the conformational flexibility which will decrease the entropic penalty for complex formation and enhance the binding affinity to the putative target ATP synthase by covalently locking the C4 center of the quinoline moiety in SW hemisphere with the C2′ center of the phenyl ring in NW hemisphere so as to enhance the binding affinity to the target. Most active compound from conformationally-constrained series is an oxime of indeno[2,1-c]quinoline which showed MIC of 0.39 μg/mL [34].

As a part of our on-going anti-TB research program, we herein report design, synthesis and anti-mycobacterial activity of novel quinoline and naphthalene derivatives influenced by structure of TMC207 and mefloquine (Fig. 1) to explore new class of potent anti-TB agents.

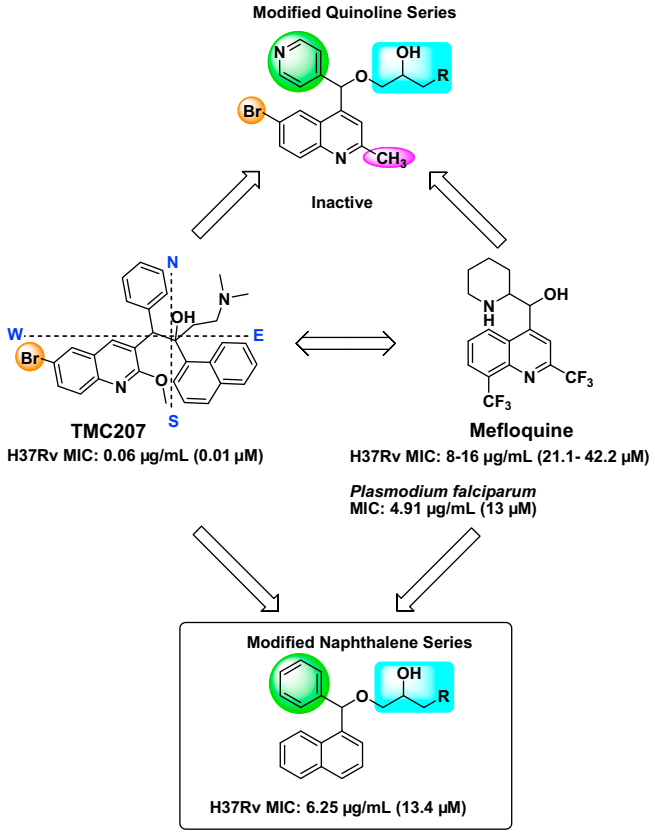



**Fig. 1.** Design of quinoline and naphthalene series based on Mefloquine and TMC207.

## 2. Chemistry

### 2.1. Synthesis of quinoline derivatives (9–19)

Quinoline derivatives (**9**–**19**) were prepared as shown in Scheme 1 and Scheme 2. 4-Bromoaniline (**1**) was heated with ethyl acetoacetate (EAA) and polyphosphoric acid (PPA) at 170 °C to give alcohol **2** (30%). Alcohol **2** when treated with $PBr_3$ in dry DMF gave 4,6-dibromo quinoline **3** in moderate yield (50%). 4,6-di-Bromoquinoline **3**, was subjected to *n*-BuLi treatment in dry THF at −78 °C followed by addition of pyridine-4-carboxaldehyde to give alcohol **4** (55%). We tried to synthesize epoxide **5** from alcohol **4** by two different methods. Alcohol **4** was treated with (a) *epi*-chlorohydrin in presence of dry DMF and NaH, and (b) *epi*-chlorohydrin in presence of dry acetone and $K_2CO_3$, but both the methods failed to give us desired key intermediate compound **5**. Then we changed the electrophile from *epi*-chlorohydrin to *epi*-bromohydrin. Alcohol **4** was treated with *epi*-bromohydrin in dry DMF in presence of NaH to obtain epoxide **5**, but yield was poor (3%). Hence we attempted to synthesize epoxide **5** from *O*-allyl ether **6**, followed by oxidation to give epoxide **5**. *O*-allyl ether **6** was synthesized in good yield (70%) from alcohol **4** by treating with allyl bromide and NaH in dry DMF. Epoxidation of *O*-allyl **6** with (a) *m*-CPBA in dry DCM and (b) 10% aq. NaOH in 30% $H_2O_2$ were tried, but were not successful. Again we devised our synthetic strategy to synthesize the target compounds **9**–**19** by exploiting halohydrin reaction on compound **6**. Compound **6** (Scheme 2) was initially treated with acetone:water (3:1, v/v) in presence of NBS to furnish compound **7** (12%) along with the undesirable di-bromo compound **8** in 38%. Yield of desired compound **7** was improved by changing the solvent system to THF:water (1:1, v/v) in presence of NBS to give compound **7** in 24% and di-bromo compound **8** in 32% yield. We optimized the yield of compound **7** by changing the solvent ratio of THF:water to 4:1, v/v and by adding a drop of conc. $H_2SO_4$ to obtain compound **7** in 45%

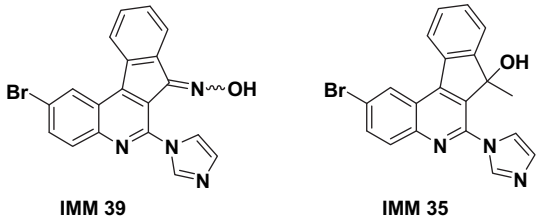
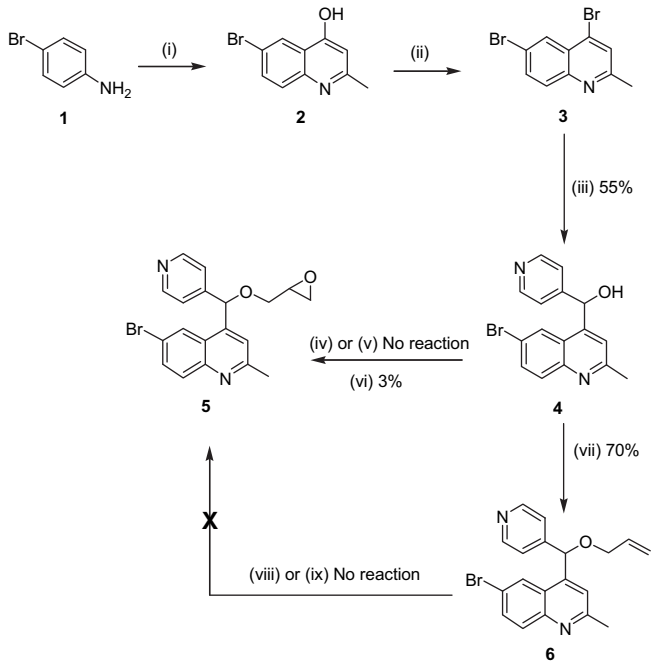



**Fig. 2.** Structures of conformationally constrained active molecules, oxime (**IMM 39**) and alcohol (**IMM 35**) [34].




**Scheme 1.** Reagents and conditions: (i) EAA, PPA, 170 °C, 6 h; 30% (ii) dry DMF, $PBr_3$ (2 eq), 0 °C; 8 h; 50% (iii) dry THF, *n*-BuLi (1.1 eq), −78 °C, pyridine-4-carboxaldehyde (1.5 eq), 30 min; 55% (iv) dry DMF, NaH (1.5 eq), *epi*-chlorohydrin (1.2 eq), rt, 2 h (v) dry Acetone, $K_2CO_3$ (1.2 eq), *epi*-chlorohydrin (1.2 eq), 80 °C, 2 h (vi) dry DMF, NaH (1.5 eq), *epi*-bromohydrin (2 eq), 0 °C to rt, 15 min; 3% (vii) dry DMF, NaH (1.5 eq), allyl bromide (1.2 eq), 0 °C, 30 min; 70% (viii) dry DCM, *m*-CPBA (3 eq), rt, 30 min (ix) 10% aq. NaOH, 30% v/v $H_2O_2$, rt, 24 h.

and compound **8** in 14%. It is known in the literature that the reactivity of NBS could be increased by adding catalytic amount of acid, which could form hydrogen bond with nitrogen, and thereby enhance the electrophilicity of the bromine [35]. This method gave us desired key intermediate compound **7** in sufficient quantity to proceed further in our synthetic scheme. Compound **7** (white solid) decomposes (becomes pinkish) after couple of weeks even after storing at −5 °C. Hence target compounds **9**–**19** (Fig. 3) were synthesized immediately from the key intermediate **7** by refluxing it with appropriate amine in a protic polar solvent, *iso*-propanol, and anhydrous $K_2CO_3$ for 10–12 h under nitrogen atmosphere in moderate yields (24–60%).

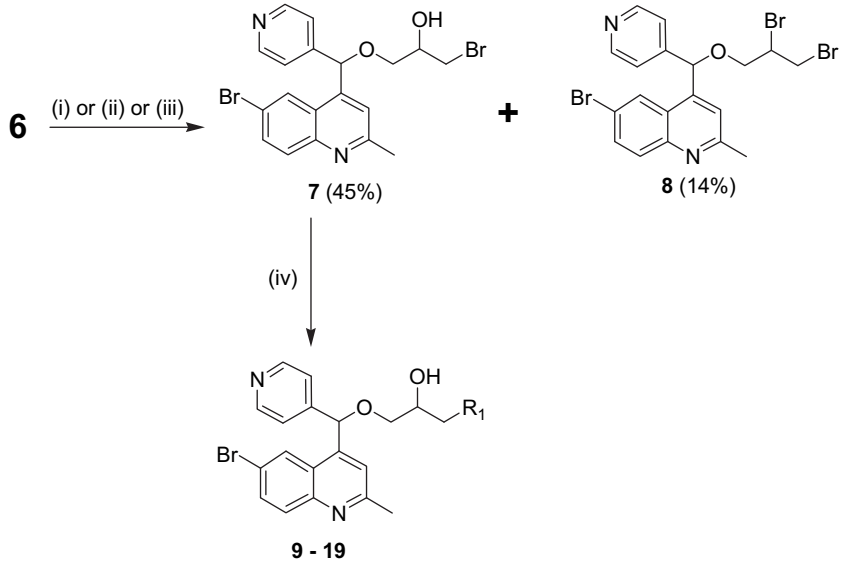
### 2.2. Synthesis of naphthalene derivatives (**22**–**30**)

Naphthalene series target molecules **22**–**30** were synthesized using procedure as shown in Scheme 3. Etherification of alcohol **20** [36] with *epi*-chlorohydrin using NaH as a base in dry DMF gave oxirane **21** (52%). Nucleophilic opening of the oxirane ring in **21** was carried out by treating compound **21** with appropriate aryl-piperazines [37] in refluxing *iso*-propanol for 16 h to furnish the target compounds **22**–**30** (Fig. 4) in moderate yields (23–44%).

## 3. Pharmacology

### 3.1. Antimycobacterial activity

Two different series of compounds **9**–**19** and **22**–**30** were evaluated for the anti-mycobacterial activity and the results are summarized in Table 1. These compounds were screened against *M. tuberculosis* H37Rv (ATCC 27294) in triplicate at the single concentration of 6.25 μg/mL for inhibitory activity by BACTEC 460 radiometric methods [38,39]. It was found that naphthalene series compounds (**22**–**30**) possess superior anti-TB activity than the quinoline series compounds (**9**–**19**). Graphs of growth index (GI) on the day basis for compounds **22**, **23**, **26** and **27** in comparison to Isoniazid were plotted as shown in Fig. 5. Graphs in Fig. 5 reveal that for compound **22** the mycobacterial load




**9**: $R_1$ = Imidazolyl (33%); **10**: $R_1$ = 1,2,4-trizolyl (24%); **11**: $R_1$ = Pyrazolyl (25%);
**12**: $R_1$ = 5-Amino-1,2,4-trizolyl (47%); **13**: $R_1$ = 3-Amino -1,2,4-trizolyl (24%);
**14**: $R_1$ = 1-(Pyridin-2-yl) piperazinyl (42%); **15**: $R_1$ = 3-Methyl pyrazolyl (25%);
**16**: $R_1$ = 2-Methoxy ethanamine (35%); **17**: $R_1$ = 2-(Methyl amino ethanol) (60%);
**18**: $R_1$ = 5-Amino- tetrazolyl (39%); **19**: $R_1$= Ethane-1,2-diamine (42%)

**Scheme 2.** Reagents and conditions: (i) Acetone:$H_2O$ (3:1), NBS (1.1 eq); rt, 1 h, for **7**, 12%; **8**, 38% (ii) THF:$H_2O$ (1:1), NBS (1.1 eq), rt, 1 h; for **7**, 24%; **8**, 32% (iii) THF:$H_2O$ (4:1), NBS (1.1 eq), $H_2SO_4$ (cat), rt, 30 min; for **7**, 45%; **8**, 14% (iv) 2-propanol, $R_1H$ (1 eq), reflux, 10–12 h; 24–60%.

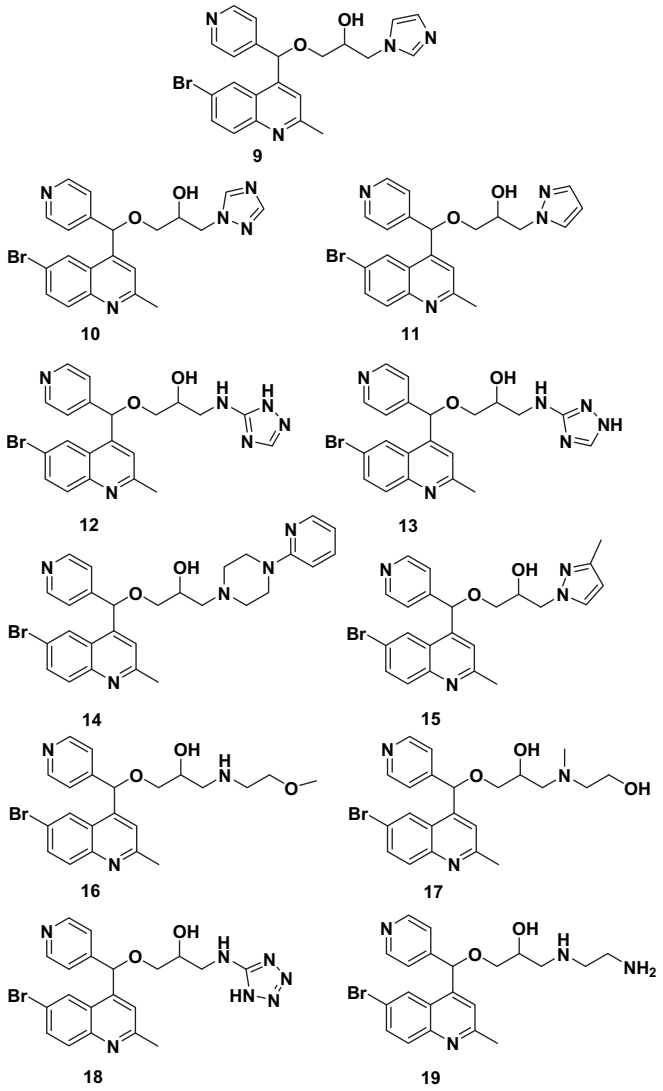



**Fig. 3.** Structures of quinoline series compounds (**9**–**19**).

never increased and showed gradual decrease from day 3 to day 11. Compounds **22**, **23**, **26** and **27** inhibited H37Rv 99% (±0.65), 90% (±2.40), 98% (±2.68) and 91% (±6.79) respectively (Table 1). Figs. 5 and 6 shows that compounds **22**, **23**, **26** and **27** possess good anti-mycobacterial activity and are comparable to standard first front-line drug Isoniazid at concentration 6.25 μg/mL and under identical experimental conditions. The activity profile of compounds **22**, **23**, **26** and **27** suggest that each compound has a bactericidal effect as there is no growth in treated control. Based on the primary growth inhibition activity, compounds **22**, **23**, **26** and **27** were selected to determine minimum inhibitory concentration (MIC) against H37Rv and was found to be 6.25 μg/mL for **22**, **23**, **26** and **27** (Table 2).

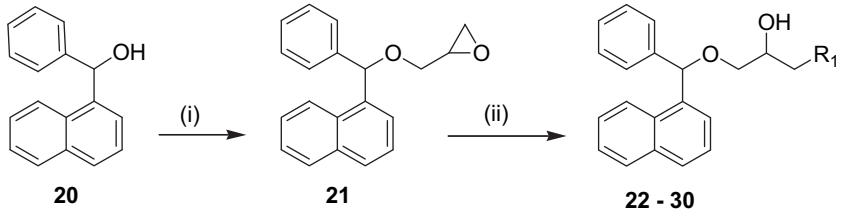
### 3.2. Cytotoxicity

Cell viability in the presence and absence of test compounds was determined by Mossman's MTT assay [40–42] at two different concentrations 1 and 10 μg/mL for the most active compounds (**22**, **23**, **26** and **27**) from our data set. The results are presented as percentage cell viability (Table 3). Cytotoxicity results of **22**, **23**, **26** and **27** (Table 3) suggest that these compounds are not cytotoxic to host cells at the given concentrations, except compound **23**, which is least safe (cell viability 64%) to human monocytic cells.

## 4. Results and discussion

Based on our strategy of modifying TMC207 having resemblance with Mefloquine we have presented new class of anti-TB compounds in order to understand SAR and develop new anti-TB compounds. Table 1 revels that quinoline based compounds did not show good anti-TB activity. Target compounds with heteroaromatic ring containing 2 to 4 nitrogen atoms (**9**, **10**, **11**, **12**, **13**, **15** and **18**), or aliphatic amines (**14**, **16**, **17** and **19**) did not show biological activity may be due to lack of proper interactions with crucial amino acids at the binding site.

It is interesting to note that the substituents on the piperazine-phenyl ring are playing important role in determining the biological activity of naphthalene series compounds **22**–**30**. From Table 1 it is clear that compound **22** having 3-methoxy and compound **23** having 2-methoxy group shows excellent activity (99% and 90% inhibition respectively). Change in the position of methoxy group in compounds **22** and **23** is not showing much effect on its anti-TB activity. When we have 3-trifluoro group on phenyl ring




**22**: $R_1$ = 4-(3-Methoxy-phenyl)-piperazin-1-yl (30%);
**23**: $R_1$ = 4-(2-Methoxy-phenyl)-piperazin-1-yl (42%);
**24**: $R_1$ =4-(3-Trifluromethyl-phenyl)-piperazin-1-yl (31%);
**25**: $R_1$ = 4-(3,4-Dichloro-phenyl)-piperazin-1-yl (39%);
**26**: $R_1$ = 4-Benzhydryl-piperazin-1-yl (37%);
**27**: $R_1$ = 4-Benzyl-piperazin-1-yl (44%);
**28**: $R_1$ = 4-(pyridin-2-yl)piperazin-1-yl (42%);
**29**: $R_1$ = 4-(4-Fluro-phenyl)-piperazin-1-yl (28%);
**30**: $R_1$ = 4-(4-Chloro-phenyl)-piperazin-1-yl (23%)

**Scheme 3.** Reagents and conditions: (i) dry DMF, NaH (1.2 eq), *epi*-chlorohydrin (2 eq), rt, 16 h; 52% (ii) 2-propanol, $R_1H$ (1 eq), reflux, 16 h; 23–44%.

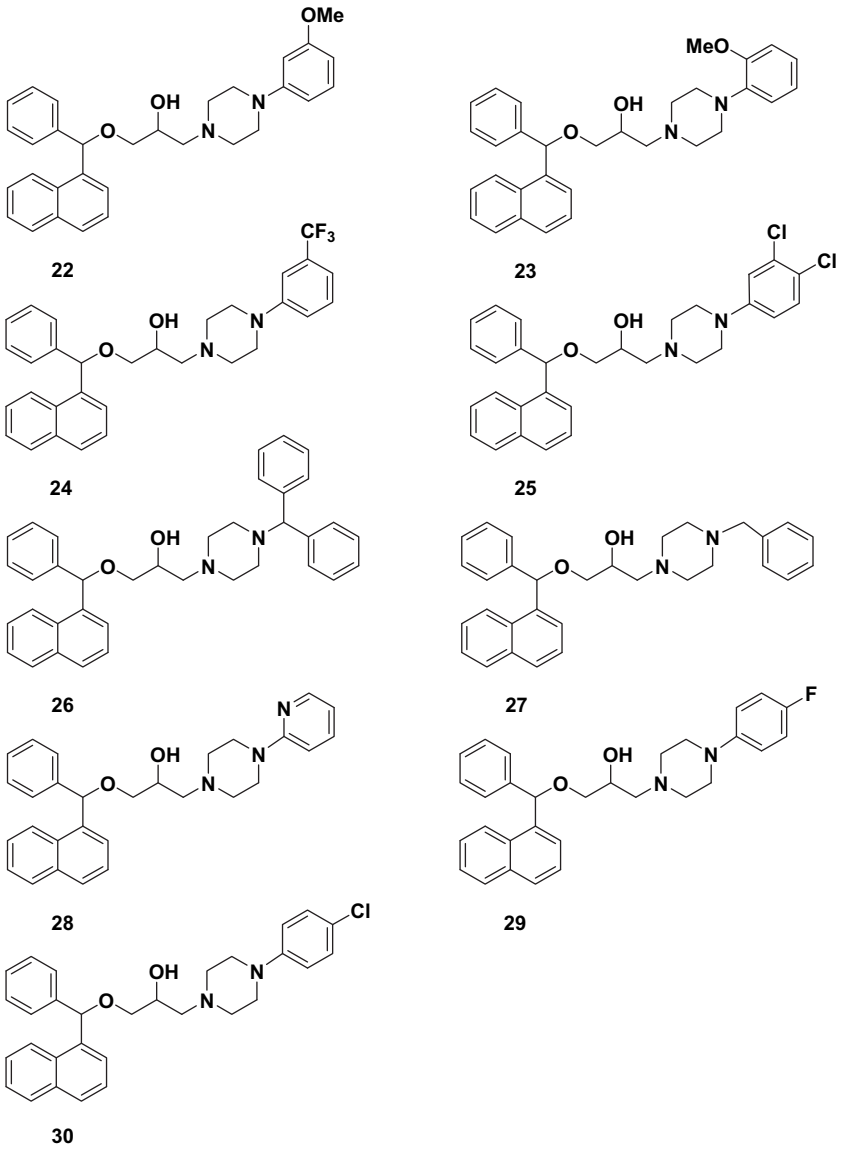



**Fig. 4.** Structures of naphthalene series compounds (**22**–**30**).

(compound **24**), biological activity is lost. Molecules having 4-fluoro (compound **29**), 4-chloro (compound **30**) and 3,4-dichloro group (compound **25**) on phenyl ring dose not show anti-TB activity. Also when phenyl ring is replaced by pyridyl ring in compound **28**, dose not display activity against *M. tuberculosis*. While molecules having benzhydryl group (compound **26**) and benzyl group (compound **27**) displays good activity. This analysis suggests that the electronic nature of substituent on piperazine-phenyl ring, probably modulates activity profile of these series of compounds. Substituents which increase electron density (methoxy) on the piperazine-phenyl ring (compounds **22** and **23**) or when phenyl ring is replaced by alkylaryl group (compounds **26** and **27**) molecules showed excellent activity. While electron withdrawing substituents on the piperazine-phenyl ring, like trifluoro (compound **24**), 3,4-dichloro (compound **25**), 4-fluoro (compound **29**) and 4-chloro (compound **30**) dose not show anti-TB activity. Similarly, compound **28** having pyridyl ring instead of phenyl ring was inactive, as it is known that the nitrogen polarizes the π-system of pyridine, resulting in decreased electron density on the ring carbons.

### 4.1. Docking studies

Designed molecules having fragmental similarity with TMC207 and Mefloquine were docked on previously known putative binding site of ATP synthase of *M. tuberculosis* [43]. The function of the ATP-synthase enzyme depends upon the ability of subunit a (81–250) and subunit c (1–81) to transfer proton through binding site residues [43]. The binding site of ATP synthase is composed of highly conserved and charged residues and located in between cavity formed by subunit a (Arg-186 and Asn-190) and subunit c (Glu-61, Tyr-64, Phe-65 and Leu-68). Docking study was carried out using Glide XP, which docks ligand accurately at the binding site [44] and details of docking procedure and methodology are given in Supplementary data. All molecules docked at the same binding site and in similar fashion. Their affinity towards the binding site can be judged by the energetic and structural features analysis at the binding site. The molecular docking studies showed that some compounds have high binding affinity, while some had low affinity towards binding site. The detailed analysis of docking energies (Table 4) and poses of the compounds helped us to find out the

**Table 1**
*In vitro* anti-mycobacterial activity against *M. tuberculosis* H37Rv (at 6.25 μg/mL).

| Compounds | % Inhibition | clogP |
|---|---|---|
| **9** | 7 | 2.0 |
| **10** | 10 | 1.72 |
| **11** | 9 | 2.40 |
| **12** | 22 | 2.14 |
| **13** | 15 | 2.41 |
| **14** | 4 | 3.48 |
| **15** | 8 | 2.67 |
| **16** | 19 | 2.14 |
| **17** | 13 | 2.03 |
| **18** | 20 | 1.11 |
| **19** | 5 | 0.97 |
| **22** | 99 | 5.73 |
| **23** | 90 | 5.73 |
| **24** | 11 | 6.96 |
| **25** | 4 | 7.32 |
| **26** | 98 | 7.42 |
| **27** | 91 | 6.07 |
| **28** | 23 | 4.83 |
| **29** | 14 | 6.10 |
| **30** | 5 | 6.67 |
| **Isoniazid** | 99 | −0.8[a] |

[a] From PubChem (http://pubchem.ncbi.nlm.nih.gov/).

possible reason for the difference in their bioactivity: Most active compound **22** (99% inhibition) showed lower −10.58 docking score. Visual analysis of the docked compound **22** (Fig. 7 A) showed that naphthalene nucleus resides in the pocket formed by the Glu-61 (2.288 Å), Tyr-64 (2.458 Å) and Phe-65 (2.523 Å), the phenyl ring adjacent to ethereal linkage fits in the close vicinity of Glu-61 (2.785 Å) and Tyr-64 (2.091 Å). Compound **22** showed crucial hydrogen bonding interaction of hydroxyl group with Asn-190 (2.130 Å). 3-Methoxy group of **22** on piperazine-phenyl ring showed additional weak interactions with the binding site residues, which contributed to the van der Walls and columbic interaction energies. Compound **23** (Fig. 7 B) is structurally similar to **22**, except difference between the position of methoxy group (on piperazine-phenyl ring) -*ortho* and –*meta* respectively. Although hydroxyl group of compound **23** made a hydrogen bonding interaction with a key amino acid residue Glu-61 (1.909 Å) (instead of Asn-190 in **22**), its docking score was −10.77 (−10.58 for **22**) showed good activity i.e. 90% inhibition, which is slightly less than **22**. From docking studies it can be concluded that shifting of methoxy group (from *meta* to *ortho*) leads to more restricted geometry (RMSD between **22** and **23** was 3.353 Å) than **22**, which might cause lesser interactions with the binding site residues and thus lead to possible slight decrease in the activity of compound **23**. Compound **27** having benzyl group on piperazine also followed similar binding pattern and its hydroxyl group showed hydrogen bonding interaction with Tyr-64 (2.063 Å) at the binding site. When benzyl group was replaced by bulkier benzhydryl group (compound **26**, Fig. 7 D), it docked in similar fashion making hydrogen bonding interaction of its hydroxyl group with Glu-61 (2.179 Å). Compound **27** showed 91% inhibition of *M. tuberculosis* while compound **26** showed 98% inhibition. Replacing benzyl group (compound **27**) on the piperazine ring by the bulkier benzhydryl group, leads to the extended geometry (RMSD between **26** and **27** was 2.737 Å) at the binding site and increase in interactions with the binding site, which could be the reason for higher docking score and better biological activity of **26** as compared to **27**. When the piperazine-phenyl ring had halogens as substituents (**24**, **25**, **29** and **30**) biological activity was dramatically reduced, although they docked in similar way (RMSD between **25** and **24**, **29**, **30** was 1.099 Å, 1.085 Å, 0.781 Å respectively). The docked complex of **25** (Fig. 7C), showed higher docking score (−6.67), higher EvdW (−5.98) and Ecoul (−0.81) interaction energies, in addition it lacked hydrogen bonding with any amino acid at the binding site. From docking study it can be seen that active compounds (**22**, **23**, **26** and **27**) have lower XP Glide docking score (−10.58, −10.77, −11.50 and −9.94 respectively) and lower interaction energies when compared with the inactive compound **25**. Thus for a compound to retain its biological activity, it should form crucial hydrogen bonding with critical amino acid (Glu-61, Tyr-64, Asn-190) residue at the binding site, Similar kind of interactions were observed with Mefloquine and TMC207, where they formed hydrogen bonding with Tyr-64 and Glu-61 binding site residues respectively. The lipophilic van der Walls (EvdW) and coulomb (Ecoul) interactions, were also found in accordance with biological activity. The docking study showed the importance of binding energies and hydrogen bonding between ligand and crucial amino acid residues of proton transfer chain for biological activity.

## 5. Conclusion

We have synthesized two series of molecules influenced by TMC207 and Mefloquine, among these compounds **22**, **23**, **26** and **27** were found to be active against *M. tuberculosis* on the basis of preliminary biological results through *in vitro* BACTEC-460 radiometric method. Naphthalene series compounds displayed excellent anti-mycobacterial activity as compared to quinoline series compounds and had MIC less than mefloquine. Nature of substituents on piperazine-phenyl ring in naphthalene series was found to play an important role in determining biological activity. Compounds having electron donating groups on piperazine-phenyl ring (naphthalene series) showed good anti-mycobacterial activity, while compounds having electron withdrawing groups on piperazine-phenyl ring were inactive. Docking calculations revealed that hydrogen bonding interactions played crucial role in demonstrating biological activity.

## 6. Experimental

### 6.1. Chemistry

All chemicals and reagents used were of reagent grade. Purification and drying of reagents and solvents was carried out according to literature procedure [45]. Thin layer chromatographic analyses were performed on E-Merck 60 F 254 precoated aluminum thin layer chromatographic plates. All air-sensitive reactions were carried out under nitrogen atmosphere. Melting points were determined on a Büchi melting point B-540 instrument and are uncorrected. $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker Biospin 400 MHz spectrometer in the indicated solvents (TMS as an internal standard). The values of chemical shifts are expressed in $\delta$ ppm and the coupling constants $J$ in hertz (Hz). Mass spectra were recorded on API 2000 LC/MS/MS system spectrometer.

#### 6.1.1. 6-Bromo-2-methylquinolin-4-ol (**2**)

*p*-Bromoaniline (5.0 g, 29.1 mmol), PPA (14.73 g, 43.7 mmol) and EAA (7.55 mL, 58.1 mmol) were heated at 170 °C for 6 h under nitrogen atmosphere. Reaction was allowed to come to room temperature and quenched with aqueous 20% NaOH solution so that pH becomes 7. Precipitated solid was washed with water (3 × 100 mL) and dried under vacuum to obtain pure white solid compound **2** (2.1 g, 30%); mp 257–260 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.33 (s, 3H, Ar–$CH_3$), 5.96 (s, 1H, Ar–H), 7.46 (d, $J$ = 8.8 Hz, 1H, Ar–H), 7.75 (dd, $J$ = 8.8, 2.4 Hz, 1H, Ar–H), 8.10 (d, $J$ = 2.4 Hz, 1H, Ar–H), 11.80 (br-s, 1H, $D_2O$ exchangeable, Ar–OH). $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): $\delta$ 19.5 (Ar–$CH_3$), 108.5 (Ar–C), 115.6 (Ar–C), 120.6 (Ar–C), 125.6 (Ar–C), 126.8 (Ar–C), 134.3 (Ar–C), 138.9

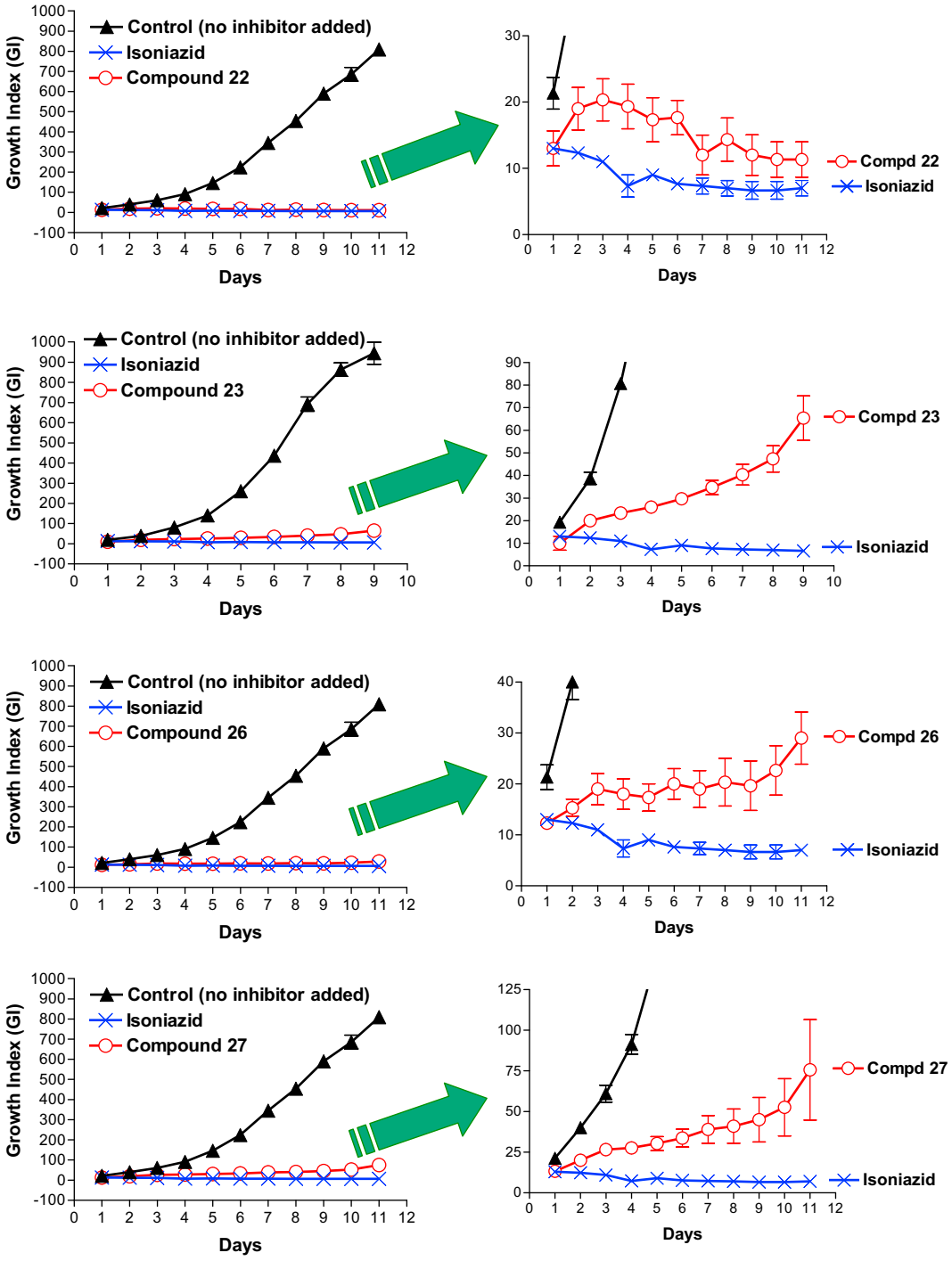



**Fig. 5.** Day-wise growth index of MTB after single-dose administration at the day-one of infection.

(Ar–C), 150.8 (Ar–C), 175.0 (Ar–C). ESI-MS *m*/*z* of 238.0, 240.0 $[M + H]^+$ was obtained for a calculated mass of 237.99, 239.98.

*6.1.2. 4,6-Dibromo-2-methylquinoline (**3**)*

6-Bromo-2-methylquinolin-4-ol (**2**, 0.100 g, 0.420 mmol) was dissolved in dry DMF (5 mL), $PBr_3$ (0.17 mL, 0.22 mmol) was added drop wise at 0 °C over 30 min under nitrogen atmosphere and stirred at room temperature for 8 h. Reaction was quenched by ice and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with water (2 × 10 mL), brine (1 × 10 mL), and dried over anhydrous sodium sulfate. Organic layer was filtered and concentrated under reduced pressure to obtain a sticky mass as a crude product. This crude product was purified by column chromatography (silica gel 100–200 mesh, eluent: 3% ethyl acetate in hexane) to afford pure **3** (0.062 g, 50%) as an off white solid, mp 94–96 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.69 (s, 3H, Ar–$CH_3$), 7.61 (s, 1H, Ar–H), 7.77 (dd, $J$ = 9.0, 2.1 Hz, 1H, Ar–H), 7.85 (d, $J$ = 9.0 Hz, 1H, Ar–H), 8.29 (d, $J$ = 2.1 Hz, 1H, Ar–H). $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 24.9 (Ar–$CH_3$), 120.9 (Ar–C), 126.4 (Ar–C), 127.1 (Ar–C), 128.6 (Ar–C), 130.7 (Ar–C), 132.5 (Ar–C), 133.7 (Ar–C), 146.8 (Ar–C), 159.2 (Ar–C). $[M + H]^+$ = for $C_{10}H_7Br_2N$. ESI-MS *m*/*z* of 301.80, 303.80 $[M + H]^+$ was obtained for a calculated mass of 301.90, 303.90.

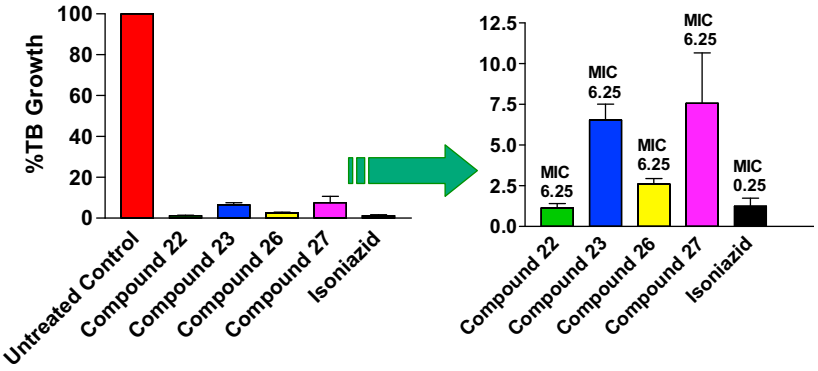



**Fig. 6.** % TB growth under influence of untreated control, compounds (**22**, **23**, **26** and **27**) and Isoniazid.

*6.1.3. (6-Bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methanol (**4**)*

*n*-Butyl lithium (1.6 M, 0.137 mL, 0.22 mmol) was added to the compound **3** (0.1 g, 0.33 mmol) in dry THF at −78 °C and stirred for 30 min. The solution of pyridine-4-carboxaldehyde (0.035 mL, 0.36 mmol) was added at −78 °C over 2 min, and stirred for 30 min. Reaction was quenched with aqueous $NH_4Cl$ (3 mL). Ice-cold water was added to reaction mixture and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with water (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous sodium sulfate. Organic layer was filtered and concentrated under reduced pressure to obtain a sticky mass as a crude product. This crude product was purified by column chromatography (Silica gel 100–200 mesh, eluent: 2.5% methanol in DCM) to afford **4** (0.056 g, 55%) as off white solid, mp 200–204 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 2.71 (s, 3H, Ar–$CH_3$), 4.63 (s, 1H, $D_2O$ exchangeable, OH), 6.37 (s, 1H, C<u>H</u>(OH)), 7.47 (dd, $J$ = 4.5, 1.6 Hz, 2H, Ar–H), 7.58 (s, 1H, Ar–H), 7.78 (dd, $J$ = 9.0, 2.1 Hz, 1H, Ar–H), 7.86 (d, $J$ = 9.0 Hz, 1H, Ar–H), 8.29 (d, $J$ = 2.1 Hz, 1H, Ar–H), 8.49 (dd, $J$ = 4.7, 1.6 Hz, 2H, Ar–H). $^{13}$C NMR (100.6 MHz, $CD_3OD$): $\delta$ 24.9 (Ar–$CH_3$), 72.3 (Ar–CHOH), 120.9 (Ar–C), 122.8 (Ar–C), 123.4 (Ar–C), 126.7 (Ar–C), 128.1 (Ar–C), 131.2 (Ar–C), 134.1 (Ar–C), 147.7 (Ar–C), 149.6 (Ar–C), 150.3 (Ar–C), 154.2 (Ar–C), 161.2 (Ar–C). ESI-MS $m/z$ of 329.00, 330.80 $[M + H]^+$ was obtained for a calculated mass of 329.03, 331.02.

*6.1.4. 6-Bromo-2-methyl-4-((oxiran-2-ylmethoxy) (pyridin-4-yl)methyl)quinoline (**5**)*

Compound **4** (0.5 g, 1.51 mmol) was dissolved in dry DMF (10 mL), *epi*-bromohydrin (0.26 mL, 3.03 mmol) was added, cooled to 0 °C, sodium hydride (0.054 g, 0.25 mmol) was added portion wise. Reaction was stirred at 0 °C for 30 min, quenched by ice and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with water (2 × 25 mL) and brine (2 × 25 mL). Organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to obtain a sticky mass as a crude product. Crude product was purified by column chromatography (silica gel 100–200 mesh, eluent: 1% MeOH in DCM) to give compound **5** (0.020 g, 3%) as a sticky mass. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.53 (dd, $J$ = 4.8, 2.7 Hz, 0.5H, epoxy–CH), 2.62 (dd, $J$ = 4.8, 2.7 Hz, 0.5H, epoxy–CH), 2.71 (s, 3H, Ar–$CH_3$), 2.75–2.82 (m, 1H, epoxy–$CH_2$), 3.16–3.27 (m, 1H, epoxy–$CH_2$), 3.34–3.48 (m, 1H, $OCH_2$), 3.81–3.91 (m, 1H, $OCH_2$), 5.95 (s, 1H, OCH), 7.22–7.32 (m, 2H, Ar–H), 7.33–7.42 (m, 1H, Ar–H), 7.69 (dd, $J$ = 9.0, 2.0 Hz, 1H, Ar–H), 7.87 (d, $J$ = 9.0 Hz, 1H, Ar–H), 8.10 (dd, $J$ = 9.3, 2.0 Hz, 1H, Ar–H), 8.51–8.85 (m, 2H, Ar–H). $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.4 (Ar–$CH_3$), 43.8 (epoxy–$CH_2$), 44.0 (epoxy–$CH_2$), 50.6 (epoxy–CH), 69.9 ($OCH_2$), 70.4 ($OCH_2$), 79.2 (Ar–CHO–), 79.3 (Ar–CHO–), 120.0 (Ar–C), 120.4 (Ar–C), 120.6 (Ar–C), 121.3 (Ar–C), 121.5 (Ar–C), 121.7 (Ar–C), 121.8 (Ar–C), 125.1 (Ar–C), 125.2 (Ar–C), 125.8 (Ar–C), 125.9 (Ar–C), 130.8 (Ar–C), 131.2 (Ar–C), 132.6 (Ar–C), 132.8 (Ar–C), 143.7 (Ar–C), 143.9 (Ar–C), 146.9 (Ar–C), 147.0 (Ar–C), 148.1 (Ar–C), 148.3 (Ar–C), 150.1 (Ar–C), 159.0 (Ar–C), 159.3 (Ar–C). ESI-MS $m/z$ of 384.90, 386.70 $[M + H]^+$ was obtained for a calculated mass of 385.06, 387.05.

*6.1.5. 4-(Allyloxy(pyridin-4-yl)methyl)-6-bromo-2-methylquinoline (**6**)*

Sodium hydride (0.007 g, 0.33 mmol) was added to solution of compound **4** (0.1 g, 0.30 mmol) in dry DMF (2 mL) at 0 °C and stirred for 30 min. Allyl bromide (0.041 mL, 0.45 mmol) was added at 0 °C and stirred at room temperature for 30 min. Reaction was quenched by ice and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with water (2 × 10 mL) followed by brine (1 × 10 mL) and dried over anhydrous sodium sulfate. Organic layer was filtered and concentrated under reduced pressure to obtain a sticky mass as a crude product. This crude product was purified by column chromatography (silica gel 100–200 mesh, eluent: 1% MeOH in DCM) to afford **6** (0.083 g, 70%) as off white solid, mp 118–120 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.73 (s, 3H, Ar–$CH_3$), 4.00–4.12 (m, 2H, $OCH_2$), 5.23–5.37 (m, 2H, CH=C<u>H</u>$_2$), 5.90 (s, 1H, OCH), 5.91–6.03 (m, 1H, $OCH_2$C<u>H</u>$CH_2$), 7.28 (d, $J$ = 6.0 Hz, 2H, Ar–H), 7.37 (s, 1H, Ar–H), 7.71 (dd, $J$ = 9.0, 2.0 Hz, 1H, Ar–H), 7.89 (d, $J$ = 7.9 Hz, 1H, Ar–H), 8.12 (d, $J$ = 2.0 Hz, 1H, Ar–H), 8.57 (dd, $J$ = 4.5, 1.5 Hz, 2H, Ar–H). $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.4 (Ar–$CH_3$), 70.4 ($OCH_2$), 77.9 (Ar–CHO–), 118.3 (<u>$CH_2$</u>=CH), 120.0 (Ar–C), 121.5 (Ar–C), 121.6 (Ar–C), 125.3 (Ar–C), 125.9 (Ar–C), 131.2 (Ar–C), 132.8 (Ar–C), 133.5 ($CH_2$ = <u>C</u>H$CH_2$O), 144.2 (Ar–C), 147.0 (Ar–C), 148.6 (Ar–C), 150.1 (Ar–C), 159.3 (Ar–C).

ESI-MS $m/z$ of 369.00, 370.80 $[M + H]^+$ was obtained for a calculated mass of 369.06, 371.06.

**Table 2**
MIC of compounds against *M. tuberculosis* H37Rv.

| Compounds | MIC (μg/mL) | MIC (μM/mL) |
|---|---|---|
| **22** | 6.25 | 12.96 |
| **23** | 6.25 | 12.96 |
| **26** | 6.25 | 11.53 |
| **27** | 6.25 | 13.41 |

**Table 3**
Cytotoxic effects of tested compounds on human monocytic cell line U937, 24 h and 72 h after treatment.

| Compounds | % Cell viability | | | |
|---|---|---|---|---|
| | 10 μg/mL | | 1 μg/mL | |
| | 24 h | 72 h | 24 h | 72 h |
| **22** | 82 | 63 | 100 | 100 |
| **23** | 81 | 62 | 81 | 64 |
| **26** | 74 | 70 | 93 | 79 |
| **27** | 77 | 74 | 77 | 71 |

**Table 4**
Glide docking energies of compounds **22**, **23**, **25**, **26** and **27**.

| Molecule | XP Glide Score | EvdW | Ecoul |
|---|---|---|---|
| **22** | −10.58 | −10.15 | −2.48 |
| **23** | −10.77 | −9.98 | −5.10 |
| **25** | −6.67 | −5.98 | −0.81 |
| **26** | −11.50 | −10.98 | −2.60 |
| **27** | −9.94 | −9.67 | −2.46 |

EvdW = lipophilic van der Waals energy (kcal/mol), Ecoul = coulomb energy (kcal/mol).

*6.1.6. 1-Bromo-3-((6-bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)propan-2-ol (**7**) and 6-bromo-4-((2,3-dibromopropoxy)(pyridin-4-yl)methyl)-2-methylquinoline (**8**)*

Compound **6** (0.1 g, 0.27 mmol) and *N*-bromosuccinimide (0.05 g, 0.32 mmol) was dissolved in THF:$H_2O$ (4:1, v/v, 10 mL), few drops of conc. sulphuric acid were added and stirred for 10 min. The reaction was quenched by water and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with water (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous sodium sulfate. Organic layer was filtered and concentrated under reduced pressure to obtain a sticky mass as a crude product. This crude product was purified by column chromatography (silica gel 100–200 mesh, eluent: 3% MeOH in DCM) to afford **7** (0.056 g, 45%) as off white solid and **8** (0.020 g, 14%) as a sticky solid.

Data for **7**: mp 75 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 2.67 (s, 1H, Ar–$CH_3$), 2.74 (s, 2H, Ar–$CH_3$), 3.40–3.74 (m, 2H, Br–$CH_2$), 3.75–3.90 (m, 2H, O–$CH_2$), 3.92–4.10 (m, 1 H, Br–$CH_2$), 4.15–4.30 (m, 1H, CH(OH)), 6.16 (s, 0.5H, OCH), 6.17 (s, 0.5H, OCH), 7.50 (d, $J$ = 4.8 Hz, 2H, Ar–H), 7.68 (s, 1H, Ar–H), 7.78 (dd, $J$ = 9.0, 2.0 Hz, 1H, Ar–H), 7.87 (d, $J$ = 9.0 Hz, 1H, Ar–H), 8.28–8.38 (m, 1H, Ar–H), 8.50 (d, $J$ = 4.0 Hz, 2H, Ar–H) total 18H in a diastereomeric ratio 2: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.3 (Ar–$CH_3$), 52.59 (CHOH), 52.65 (CHOH), 63.54 ($CH_2$–Br), 63.56 ($CH_2$–Br), 70.4 (O$CH_2$CHOH), 70.5 (O$CH_2$-CHOH), 79.74 (Ar–CHO–), 79.85 (Ar–CHO–), 120.19 (Ar–C), 120.21 (Ar–C), 121.5 (Ar–C), 121.62 (Ar–C), 121.65 (Ar–C), 121.8 (Ar–C), 125.07 (Ar–C), 125.12 (Ar–C), 125.7 (Ar–C), 125.91 (Ar–C), 125.95 (Ar–C), 131.0 (Ar–C), 132.90 (Ar–C), 132.93 (Ar–C), 143.47 (Ar–C), 143.52 (Ar–C), 143.6 (Ar–C), 146.82 (Ar–C), 146.9 (Ar–C), 148.26 (Ar–C), 148.3 (Ar–C), 149.9 (Ar–C), 159.26 (Ar–C), 159.28 (Ar–C). ESI-MS $m/z$ of 466.90, 469.00 $[M + H]^+$ was obtained for a calculated mass of 466.98, 468.98.

Data for **8**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.73 (s, 3H, Ar–$CH_3$), 2.78–3.93 (m, 3H, Br$CH_2$–CHBr, O$CH_2$CHBr), 3.97 (dd, $J$ = 10.6, 4.2 Hz, 0.5H, Br–CH), 4.04 (dd, $J$ = 10.4, 4.3 Hz, 0.5H, Br–CH), 4.26–4.34 (m, 1H, O$CH_2$CHBr), 5.92 (s, 1H, OCH), 7.25–7.32 (m, 2H, Ar–H), 7.35 (d, $J$ = 2.0 Hz, 1H, Ar–H), 7.67–7.75 (m, 1H, Ar–H), 7.86–7.95 (m, 1H, Ar–H), 8.12 (dd, $J$ = 9.8, 2.0 Hz, 1H, Ar–H), 8.55–8.63 (m, 2H, Ar–H). $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.4 (Ar–$CH_3$), 32.0 ($CH_2$–Br), 32.2 ($CH_2$–Br), 47.8 (CH–Br), 48.0 (CH–Br), 70.2 ($OCH_2$), 70.4 ($OCH_2$), 79.9 (Ar–CHO–), 120.3 (Ar–C), 121.5 (Ar–C), 121.6 (Ar–C), 121.8 (Ar–C), 122.0 (Ar–C), 122.7 (Ar–C), 125.2 (Ar–C), 126.0 (Ar–C), 126.1 (Ar–C), 131.2 (Ar–C), 133.0 (Ar–C), 143.2 (Ar–C), 147.1 (Ar–C), 147.8 (Ar–C), 147.9 (Ar–C), 150.2 (Ar–C), 159.3 (Ar–C). ESI-MS $m/z$ of 528.60, 530.50 $[M + H]^+$ was obtained for a calculated mass of 528.89, 530.89.

*6.1.7. Representative procedure A, for compounds **9**–**19**: 1-((6-bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)-3-(1H-imidazol-1-yl)propan-2-ol (**9**)*

Compound **7** (0.1 g, 0.21 mmol), imidazole (0.029 g, 0.42 mmol) and anhydrous potassium carbonate (0.059 g, 0.42 mmol) was refluxed in 2-propanol (8 mL) for 16 h. 2-Propanol was evaporated under reduced pressure to obtain sticky mass, which was diluted with ethyl acetate (20 mL) washed with water, brine (1 × 10 mL) and dried over anhydrous sodium sulfate. Organic layer was filtered

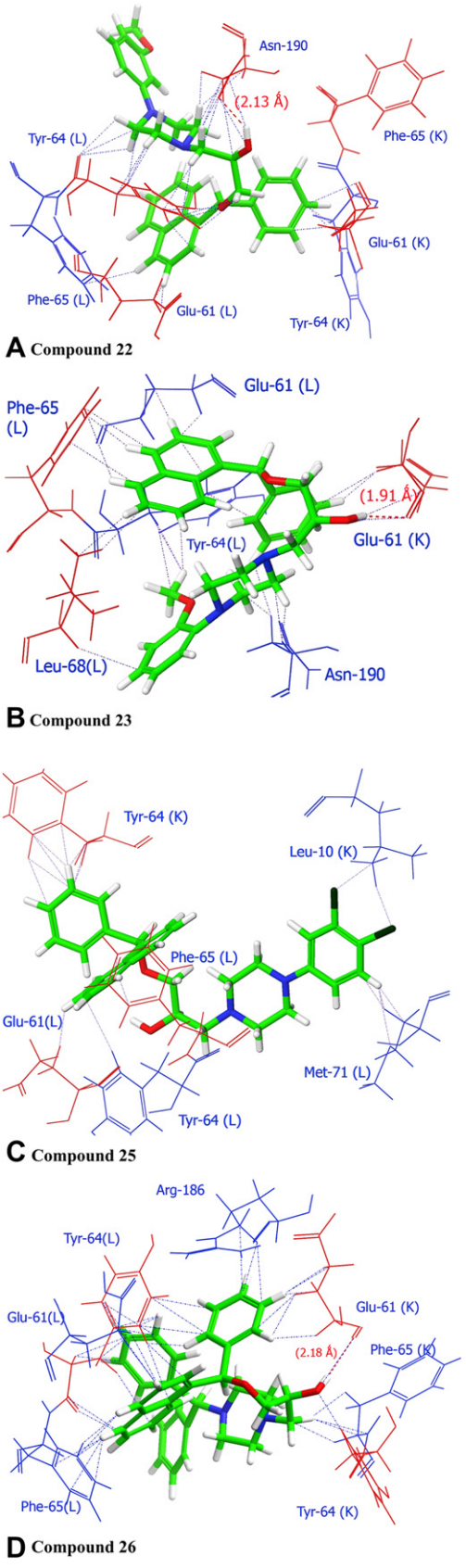



**Fig. 7.** Molecules **22**, **23**, **25** and **26** in the binding site of *M. tuberculosis* ATP synthase. EvdW and Ecoul interactions are shown in blue and hydrogen bonding in red color (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

and concentrated under reduced pressure to obtain sticky mass as a crude product. Crude product was purified by column chromatography (silica gel 100–200 mesh, eluent: 3.5% methanol in DCM) to afford **9** (0.032 g, 33%) as off white solid, mp 174–176 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 3H, Ar–$CH_3$), 3.33–3.76 (m, 3H, $OCH_2$ and 1H $D_2O$ exchangeable OH), 3.85–4.20 (m, 3H, $NCH_2$, CHOH), 5.88 (s, 0.5H, OCH), 5.90 (s, 0.5H, OCH), 6.86 (s, 2H, Ar–H), 7.15–7.47 (m, 4H, Ar–H), 7.63–7.80 (m, 1H, Ar–H), 7.80–8.00 (m, 1H, Ar–H), 8.09 (d, $J$ = 8.0 Hz, 1H, Ar–H), 8.55 (s, 2H, Ar–H) total 21H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 25.3 (Ar–$CH_3$), 50.5 (N–$CH_2$), 69.2 (CHOH), 71.3 ($OCH_2$), 80.0 (Ar–CHO–), 80.1 (Ar–CHO–), 119.8 (Ar–C), 120.1 (Ar–C), 121.5 (Ar–C), 121.6 (Ar–C), 121.7 (Ar–C), 125.0 (Ar–C), 125.8 (Ar–C), 128.3 (Ar–C), 131.1 (Ar–C), 132.9 (Ar–C), 137.4 (Ar–C), 143.6 (Ar–C), 146.9 (Ar–C), 148.3 (Ar–C), 150.0 (Ar–C), 159.3 (Ar–C). ESI-MS $m/z$ of 452.80, 455.00 $[M + H]^+$ was obtained for a calculated mass of 453.09, 455.09.

### 6.1.8. 1-((6-Bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)-3-(1H-1,2,4-triazol-1-yl) propan-2-ol (**10**)

Procedure A, yield 24%. Off white solid; mp 163–165 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 1.5H, Ar–$CH_3$), 2.72 (s, 1.5H, Ar–$CH_3$), 3.50–3.63 (m, 2H, $OCH_2$), 3.92 (br-s, 1H, $D_2O$ exchangeable, OH), 4.16–4.50 (m, 3H, $NCH_2$, CHOH), 5.89 (s, 1H, OCH), 7.19–7.33 (m, 3H, Ar–H), 7.64–7.77 (m, 1H, Ar–H), 7.82–7.88 (m, 2H, Ar–H), 8.00–8.20 (m, 2H, Ar–H), 8.56 (t, $J$ = 5.0 Hz, 2H, Ar–H) total 20H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 25.4 (Ar–$CH_3$), 52.4 (N–$CH_2$), 68.7 (CHOH), 71.2 ($OCH_2$), 79.96 (Ar–CHO–), 80.04 (Ar–CHO–), 120.2 (Ar–C), 121.40 (Ar–C), 121.43 (Ar–C), 121.6 (Ar–C), 125.1 (Ar–C), 125.8 (Ar–C), 131.15 (Ar–C), 131.2 (Ar–C), 132.9 (Ar–C), 143.46 (Ar–C), 143.54 (Ar–C), 144.0 (Ar–C), 144.1 (Ar–C), 146.87 (Ar–C), 146.89 (Ar–C), 146.94 (Ar–C), 148.1 (Ar–C), 149.8 (Ar–C), 149.9 (Ar–C), 150.0 (Ar–C), 150.1 (Ar–C), 151.7 (Ar–C), 151.8 (Ar–C), 159.2 (Ar–C), 159.3 (Ar–C). ESI-MS $m/z$ of 453.80, 455.90 $[M + H]^+$ was obtained for a calculated mass of 454.09, 456.09.

### 6.1.9. 1-((6-Bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)-3-(1H-pyrazol-1-yl) propan-2-ol (**11**)

Procedure A, yield 25%. Off white solid; mp 135–137 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.72 (s, 1.5H, Ar–$CH_3$), 2.73 (s, 1.5H, Ar–$CH_3$), 3.32–3.64 (m, 2H, $OCH_2$), 3.99–4.12 (br-s, 0.5H, $D_2O$ exchangeable, OH), 4.12–4.38 (m, 3.5H, 0.5H $D_2O$ exchangeable, $NCH_2$), 5.85 (s, 0.5H, Ar-CH-O-), 5.86 (s, 0.5H, Ar-CH-O-), 6.20 (t, $J$ = 2.0 Hz, 0.5H, Ar-H), 6.25 (t, $J$ = 2.0 Hz, 0.5H, Ar-H), 7.26–7.41 (m, 4H), 7.47 (d, $J$ = 2.0 Hz, 0.5H), 7.51 (d, $J$ = 2.0 Hz, 0.5H), 7.70 (dd, $J$ = 4.0, 2.0 Hz, 0.5H), 7.72 (dd, $J$ = 4.4, 2.0 Hz, 0.5H), 7.90 (dd, $J$ = 9.0, 3.3 Hz, 1H), 8.07 (dd, $J$ = 4.8, 2.0 Hz, 1H), 8.57 (d, $J$ = 5.9 Hz, 2H) total 21H in a diastereomeric ratio 1:1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 25.3 (Ar–$CH_3$), 53.9 (N–$CH_2$), 54.1 (N–$CH_2$), 69.6 (CHOH), 70.9 ($OCH_2$), 71.0 ($OCH_2$), 79.9 (Ar–CHO–), 105.4 (Ar–C), 105.5 (Ar–C), 120.06 (Ar–C), 120.08 (Ar–C), 121.5 (Ar–C), 121.6 (Ar–C), 121.7 (Ar–C), 125.1 (Ar–C), 125.8 (Ar–C), 125.82 (Ar–C), 125.9 (Ar–C), 130.5 (Ar–C), 131.10 (Ar–C), 131.16 (Ar–C), 131.20 (Ar–C), 132.7 (Ar–C), 132.8 (Ar–C), 139.7 (Ar–C), 139.74 (Ar–C), 143.6 (Ar–C), 143.7 (Ar–C), 146.9 (Ar–C), 147.0 (Ar–C), 148.2 (Ar–C), 150.0 (Ar–C), 159.2 (Ar–C), 159.25 (Ar–C). ESI-MS $m/z$ of 452.80, 454.90 $[M + H]^+$ was obtained for a calculated mass of 453.09, 455.09.

### 6.1.10. 1-(1H-1,2,4-Triazol-5-ylamino)-3-((6-bromo-2-methylquinolin-4-yl)(pyridin-4-yl) methoxy)propan-2-ol (**12**)

Procedure A, yield 47%. Off white solid; mp 199–201 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 0.75H, Ar–$CH_3$), 2.73 (s, 2.30H, Ar–$CH_3$), 3.45–3.70 (m, 2H, $CH_2NH$), 3.90–4.40 (m, 5H, $OCH_2$, CHOH, 2H $D_2O$ exchangeable OH, NH), 4.77 (d, $J$ = 7.2 Hz, 1H, $D_2O$ exchangeable, Ar–NH), 5.88 (s, 1H, OCH), 7.20–7.33 (m, 3H, Ar–H), 7.37–7.50 (m, 0.5H, Ar–H), 7.60–7.68 (m, 0.5H, Ar–H), 7.69–7.77 (m, 1H, Ar–H), 7.84–7.94 (m, 1H, Ar–H), 8.00–8.12 (m, 1H, Ar–H), 8.52–8.62 (m, 2H, Ar–H) total 21H in a diastereomeric ratio 1: 1.5. $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 25.3 (Ar–$CH_3$), 50.3 (HN–$CH_2$), 52.3 (HN–$CH_2$), 68.22 (CHOH), 68.28 (CHOH), 69.7 (CHOH), 71.4 ($OCH_2$), 71.5 ($OCH_2$), 71.52 ($OCH_2$), 71.57 ($OCH_2$), 79.8 (Ar–CHO–), 79.84 (Ar–CHO–), 120.1 (Ar–C), 120.21 (Ar–C), 121.6 (Ar–C), 125.1 (Ar–C), 125.71 (Ar–C), 125.76 (Ar–C), 125.8 (Ar–C), 130.9 (Ar–C), 131.1 (Ar–C), 132.9 (Ar–C), 143.13 (Ar–C), 143.16 (Ar–C), 143.7 (Ar–C), 146.7 (Ar–C), 146.8 (Ar–C), 148.03 (Ar–C), 148.05 (Ar–C), 148.17 (Ar–C), 148.3 (Ar–C), 148.4 (Ar–C), 149.8 (Ar–C), 149.9 (Ar–C), 159.27 (Ar–C), 159.29 (Ar–C), 163.3 (Ar–C). ESI-MS $m/z$ of 469.00, 471.40 $[M]^+$ was obtained for a calculated mass of 469.09, 471.09.

### 6.1.11. 1-(1H-1,2,4-Triazol-3-ylamino)-3-((6-bromo-2-methylquinolin-4-yl)(pyridin-4-yl) methoxy)propan-2-ol (**13**)

Procedure A, yield 24%. Off white solid; mp 179–182 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.68 (s, 1H, Ar–$CH_3$), 2.71 (s, 2H, Ar–$CH_3$), 3.46–3.67 (m, 2H, $NHCH_2$), 3.96–4.33 (m, 4H, $OCH_2$, CHOH, 1H $D_2O$ exchangeable OH), 4.91 (d, $J$ = 10.2 Hz, 1H $D_2O$ exchangeable, NH), 5.87 (s, 1H, OCH), 7.21–7.32 (m, 5H, 1H $D_2O$ exchangeable, Ar–NH), 7.40 (d, $J$ = 5.6 Hz, 0.5H, Ar–H), 7.60–7.76 (m, 1.5H, Ar–H), 7.83–7.92 (m, 1H, Ar–H), 8.01–8.10 (m, 1H, Ar–H), 8.48–8.59 (m, 2H, Ar–H) total 20H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 25.31 (Ar–$CH_3$), 25.38 (Ar–$CH_3$), 50.0 (HN–$CH_2$), 52.0 (HN–$CH_2$), 68.7 (CHOH), 70.03 (CHOH), 70.06 (CHOH), 71.03 (CHOH), 71.03 ($OCH_2$), 71.07 ($OCH_2$), 71.41 ($OCH_2$), 71.43 ($OCH_2$), 80.0 (Ar–CHO–), 120.18 (Ar–C), 120.21 (Ar–C), 121.45 (Ar–C), 121.49 (Ar–C), 121.5 (Ar–C), 121.6 (Ar–C), 121.65 (Ar–C), 125.03 (Ar–C), 125.05 (Ar–C), 125.09 (Ar–C), 125.7 (Ar–C), 125.82 (Ar–C), 125.85 (Ar–C), 131.0 (Ar–C), 131.22 (Ar–C), 131.26 (Ar–C), 132.9 (Ar–C), 143.2 (Ar–C), 143.4 (Ar–C), 143.54 (Ar–C), 143.58 (Ar–C), 143.6 (Ar–C), 146.7 (Ar–C), 146.94 (Ar–C), 146.99 (Ar–C), 147.9 (Ar–C), 148.1 (Ar–C), 148.3 (Ar–C), 149.9 (Ar–C), 150.1 (Ar–C), 155.51 (Ar–C), 159.2 (Ar–C), 159.29 (Ar–C), 159.33 (Ar–C), 163.4 (Ar–C). ESI-MS $m/z$ of 469.20, 471.30 $[M + H]^+$ was obtained for a calculated mass of 469.10, 471.10.

### 6.1.12. 1-((6-Bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)-3-(4-(pyridin-2-yl) piperazin-1-yl)propan-2-ol (**14**)

Procedure A, yield 42%. Off white solid; mp 149–151 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.35–2.56 (m, 4H, $CH_2N(CH_2)_2$), 2.67–2.95 (m, 5H, Ar–$CH_3$, $NCH_2CHOH$), 3.20–3.81 (m, 7H, $OCH_2$, $N(CH_2)_2$, 1H $D_2O$ exchangeable OH), 3.92–4.25 (m, 1H, CHOH), 5.97 (s, 0.5H, OCH), 5.98 (s, 0.5H, OCH), 6.62 (d, $J$ = 6.6 Hz, 2H, Ar–H), 7.22–7.40 (m, 3H, Ar–H), 7.40–7.58 (m, 1H, Ar–H), 7.67–7.83 (m, 1H, Ar–H), 7.85–8.03 (m, 1H, Ar–H), 8.06–8.33 (m, 2H, Ar–H), 8.59 (s, 2H, Ar–H) total 30H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 25.3 (Ar–$CH_3$), 45.1 (Py–N–$CH_2CH_2$), 52.9 (Py–N–$CH_2CH_2$), 60.43 (Py–N–$CH_2CH_2$), 60.47 (Py–N–$CH_2CH_2$), 66.10 (CHOH), 66.14 (CHOH), 71.9 ($OCH_2$), 72.1 ($OCH_2$), 79.9 (Ar–CHO–), 107.0 (Ar–C), 113.4 (Ar–C), 119.9 (Ar–C), 121.6 (Ar–C), 121.64 (Ar–C), 121.8 (Ar–C), 125.2 (Ar–C), 125.3 (Ar–C), 126.1 (Ar–C), 126.15 (Ar–C), 131.10 (Ar–C), 132.7 (Ar–C), 137.4 (Ar–C), 143.95 (Ar–C), 144.01 (Ar–C), 147.0 (Ar–C), 147.8 (Ar–C), 148.4 (Ar–C), 150.0 (Ar–C), 159.2 (Ar–C). ESI-MS $m/z$ of 548.40, 550.50 $[M + H]^+$ was obtained for a calculated mass of 548.17, 550.16.

### 6.1.13. 1-((6-Bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)-3-(3-methyl-1H-pyrazol-1-yl)propan-2-ol (**15**)

Procedure A, yield 25%. Off white solid; mp 144–146 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.15–2.23 (m, 3H, pyrazole–$CH_3$), 2.72 (s, 3H, Ar–$CH_3$), 3.27–3.70 (m, 2H, $OCH_2$), 3.97–4.37 (m, 4H, $NCH_2$, CHOH, 1H $D_2O$ exchangeable OH), 5.70–6.12 (m, 2H, OCH, pyrazole-H), 7.10–7.42 (m, 4H, Ar–H), 7.62–7.79 (m, 1H, Ar–H), 7.90 (d, $J$ = 9.0 Hz, 1H, Ar–H), 8.00–8.15 (m, 1H, Ar–H), 8.57 (s, 2H, Ar–H) total 23H in

a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 10.96 (Pyrazole–$CH_3$), 11.0 (Pyrazole–$CH_3$), 13.46 (Pyrazole–$CH_3$), 13.48 (Pyrazole–$CH_3$), 25.4 (Ar–$CH_3$), 50.2 (N–$CH_2$), 50.3 (N–$CH_2$), 53.5 (N–$CH_2$), 53.7 (N–$CH_2$), 69.8 (CHOH), 69.85 (CHOH), 70.7 ($OCH_2$), 70.9 ($OCH_2$), 70.98 ($OCH_2$), 71.01 ($OCH_2$), 79.97 (Ar–CHO–), 80.0 (Ar–CHO–), 80.1 (Ar–CHO–), 104.98 (Ar–C), 105.05 (Ar–C), 105.3 (Ar–C), 120.1 (Ar–C), 121.5 (Ar–C), 121.55 (Ar–C), 121.58 (Ar–C), 121.7 (Ar–C), 121.74 (Ar–C), 121.8 (Ar–C), 125.1 (Ar–C), 125.9 (Ar–C), 125.96 (Ar–C), 131.2 (Ar–C), 132.9 (Ar–C), 138.73 (Ar–C), 138.78 (Ar–C), 139.11 (Ar–C), 139.16 (Ar–C), 143.67 (Ar–C), 143.71 (Ar–C), 143.73 (Ar–C), 147.01 (Ar–C), 147.03 (Ar–C), 148.26 (Ar–C), 148.3 (Ar–C), 148.34 (Ar–C), 149.2 (Ar–C), 149.3 (Ar–C), 150.1 (Ar–C), 159.3 (Ar–C). ESI-MS *m*/*z* of 467.20, 469.30 $[M + H]^+$ was obtained for a calculated mass of 467.11, 469.11.

#### 6.1.14. 1-((6-Bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)-3-(2-methoxyethylamino)propan-2-ol (**16**)

Procedure A, yield 35%. Off white solid; mp 116–118 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.02 (br-s, 2H, $D_2O$ exchangeable, OH, NH), 2.55–2.95 (m, 7H, Ar–$CH_3$, $CH_2NHCH_2$), 3.32 (s, 3H, $OCH_3$), 3.40–3.70 (m, 4H, $OCH_2$, $CH_3OCH_2$), 3.89–4.09 (m, 1H, CHOH), 5.92 (s, 1H, OCH), 7.26–7.40 (m, 3H, Ar–H), 7.71 (dd, $J$ = 8.4, 1.9 Hz, 1H, Ar–H), 7.90 (d, $J$ = 9.0 Hz, 1H, Ar–H), 8.13 (dd, $J$ = 8.3, 1.9 Hz, 1H, Ar–H), 8.58 (d, $J$ = 5.7 Hz, 2H, Ar–H) total 26H in a diastereomeric ratio 1:1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.3 (Ar–$CH_3$), 48.7 (HN–$CH_2CH_2$), 51.66 (OHCH$CH_2$NH), 51.70 (OHCH$CH_2$NH), 58.7 ($OCH_3$), 67.9 (CHOH), 68.0 (CHOH), 70.6 ($CH_3OCH_2$), 72.2 ($OCH_2$CHOH), 79.9 (Ar–CHO–), 120.0 (Ar–C), 121.6 (Ar–C), 121.7 (Ar–C), 121.8 (Ar–C), 125.2 (Ar–C), 125.9 (Ar–C), 126.0 (Ar–C), 131.1 (Ar–C), 132.8 (Ar–C), 143.9 (Ar–C), 146.9 (Ar–C), 148.4 (Ar–C), 150.0 (Ar–C), 159.3 (Ar–C). ESI-MS *m*/*z* of 460.20, 462.00 $[M + H]^+$ was obtained for a calculated mass of 460.12, 462.12.

#### 6.1.15. 1-((6-Bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy)-3-((2-hydroxyethyl) (methyl)amino)propan-2-ol (**17**)

Procedure A, yield 60%. Viscous compound. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.32 (s, 4H, $NCH_3$, 1H $D_2O$ exchangeable, OH), 2.42–2.68 (m, 5H, $CH_2N(CH_3)CH_2$, 1H $D_2O$ exchangeable, OH), 2.72 (s, 1.5H, Ar–$CH_3$), 2.73 (s, 1.5H, Ar–$CH_3$), 3.43–3.68 (m, 4H, $OCH_2$, $OHCH_2$), 3.91–4.05 (m, 1H, CHOH), 5.93 (s, 1H, OCH), 7.25–7.32 (m, 3H, Ar–H), 7.69–7.74 (m, 1H, Ar–H), 7.89 (d, $J$ = 9.0 Hz, 1H, Ar–H), 8.14 (dd, $J$ = 6.5, 1.9 Hz, 1H, Ar–H), 8.58 (d, $J$ = 5.8 Hz, 2H, Ar–H) total 26H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.3 (Ar–$CH_3$), 42.5 (N–$CH_3$), 59.0 ($OHCH_2$), 59.5 ($NCH_2CH_2$), 60.3 ($NCH_2CHOH$), 60.4 ($NCH_2CHOH$), 67.3 (CHOH), 72.1 ($OCH_2$), 72.3 ($OCH_2$), 79.9 (Ar–CHO), 120.0 (Ar–C), 121.6 (Ar–C), 121.7 (Ar–C), 125.2 (Ar–C), 126.0 (Ar–C), 131.1 (Ar–C), 132.7 (Ar–C), 144.0 (Ar–C), 146.9 (Ar–C), 148.5 (Ar–C), 149.9 (Ar–C), 159.2 (Ar–C). ESI-MS *m*/*z* of 460.30, 462.00 $[M + H]^+$ was obtained for a calculated mass of 460.12, 462.12.

#### 6.1.16. 1-(1H-Tetrazol-5-ylamino)-3-((6-bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy) propan-2-ol (**18**)

Procedure A, yield 39%. Off white solid; mp 186–188 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.67 (br-s, 1H, $D_2O$ exchangeable, NH), 2.68 (s, 1H, Ar–$CH_3$), 2.72 (s, 2H, Ar–$CH_3$), 3.33–3.75 (m, 3H, $NHCH_2$, $OCH_2$), 4.25–4.49 (m, 2H, $OCH_2$, 1H $D_2O$ exchangeable, OH), 4.50–4.70 (m, 1H, CHOH), 5.15–5.35 (m, 1H, $D_2O$ exchangeable, tetrazole-NH), 5.75–5.95 (m, 1H, OCH), 7.05–7.24 (m, 2H, Ar–H), 7.26–7.45 (m, 1H, Ar–H), 7.55–7.75 (m, 1H, Ar–H), 7.76–7.95 (m, 1H, Ar–H), 7.96–8.20 (m, 1H, Ar–H), 8.42–8.62 (m, 2H, Ar–H) total 20H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.3 (Ar–$CH_3$), 48.8 (HN–$CH_2$), 55.3 (HN–$CH_2$), 68.6 (CHOH), 69.8 (CHOH), 70.7 ($OCH_2$), 79.8 (Ar–CHO–), 79.9 (Ar–CHO–), 120.2 (Ar–C), 121.4 (Ar–C), 121.44 (Ar–C), 121.49 (Ar–C), 121.6 (Ar–C), 121.7 (Ar–C), 124.9 (Ar–C), 125.0 (Ar–C), 125.6 (Ar–C), 129.6 (Ar–C), 130.9 (Ar–C), 131.1 (Ar–C), 132.9 (Ar–C), 132.95 (Ar–C), 143.3 (Ar–C), 143.46 (Ar–C), 143.5 (Ar–C), 146.8 (Ar–C), 146.84 (Ar–C), 148.06 (Ar–C), 148.1 (Ar–C), 149.8 (Ar–C), 149.9 (Ar–C), 149.96 (Ar–C), 159.3 (Ar–C), 165.3 (Ar–C), 166.1 (Ar–C). ESI-MS *m*/*z* of 470.20, 472.30 $[M + H]^+$ was obtained for a calculated mass of 470.09, 472.09.

#### 6.1.17. 1-(2-Aminoethylamino)-3-((6-bromo-2-methylquinolin-4-yl)(pyridin-4-yl)methoxy) propan-2-ol (**19**)

Procedure A, yield 42%. Off white solid; mp 107–109 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.10 (s, 1H, NH), 2.55–2.89 (m, 6H, Ar–$CH_3$, $NH_2CH_2$, OH), 2.90–3.10 (m, 2H, $NHCH_2$), 3.31–3.56 (m, 2H, $OCH_2$), 3.82–4.15 (m, 1H, CHOH), 4.46–5.20 (m, 4H, $NH_2$, $NHCH_2CHOH$), 5.80–6.05 (m, 1H, OCH), 7.28–7.43 (m, 3H, Ar–H), 7.55–7.78 (m, 1H, Ar–H), 7.80–7.94 (m, 1H, Ar–H), 8.04–8.23 (m, 1H, Ar–H), 8.41–8.68 (m, 2H, Ar–H) total 25H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 25.3 (Ar–$CH_3$), 40.0 ($NH_2$–$CH_2$), 49.0 (NH–$CH_2$), 51.8 (NH–$CH_2CHOH$), 68.6 (CHOH), 72.3 ($OCH_2$), 79.8 (Ar–CHO–), 119.9 (Ar–C), 121.6 (Ar–C), 121.7 (Ar–C), 125.1 (Ar–C), 126.0 (Ar–C), 131.2 (Ar–C), 132.7 (Ar–C), 143.9 (Ar–C), 146.9 (Ar–C), 148.4 (Ar–C), 150.0 (Ar–C), 159.3 (Ar–C). ESI-MS *m*/*z* of 445.00, 446.90 $[M + H]^+$ was obtained for a calculated mass of 445.12, 447.12.

#### 6.1.18. 2-((Naphthalen-1-yl(phenyl)methoxy)methyl)oxirane (**21**)

Alcohol **20** [36] (0.05 g, 0.21 mmol) was dissolved in dry DMF (0.5 mL), cooled to 0 °C, sodium hydride (0.006 g, 0.25 mmol) was added portion wise, cooling bath was removed and reaction was stirred at room temperature for 30 min. *epi*-Chlorohydrin (0.032 mL, 0.42 mmol) was added and stirring was continued for further 16 h at room temperature. Reaction mixture was concentrated under reduced pressure; ice-cold water was added and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with water (2 × 10 mL) and brine (1 × 10 mL). Organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a sticky mass as a crude product. This crude product was purified by column chromatography (silica gel 100–200 mesh, eluent: ethyl acetate, hexane; gradient elution) to give oxirane **21** (0.032 g, 52%) as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.56 (dd, $J$ = 5.0, 2.6 Hz, 0.5H, epoxy–$CH_2$), 2.66 (dd, $J$ = 5.0, 2.6 Hz, 0.5H, epoxy–$CH_2$), 2.77 (t, $J$ = 4.6 Hz, 0.5H, epoxy–$CH_2$), 2.80 (t, $J$ = 4.6 Hz, 0.5H, epoxy–$CH_2$), 3.22–3.30 (m, 1H, epoxy–CH), 3.52 (dd, $J$ = 11.4, 6.0 Hz, 0.5H, epoxy–$CH_2$), 3.57 (dd, $J$ = 11.5, 5.5 Hz, 0.5H, $OCH_2$), 3.82 (dd, $J$ = 2.9, 1.6 Hz, 0.5H, $OCH_2$), 3.85 (dd, $J$ = 2.9, 1.9 Hz, 0.5H, $OCH_2$), 6.17 (s, 1H, OCH), 7.23–7.30 (m, 1H, Ar–H), 7.31–7.37 (m, 2H, Ar–H), 7.42–7.55 (m, 5H, Ar–H), 7.66 (d, $J$ = 7.0 Hz, 1H, Ar–H), 7.81–7.92 (m, 2H, Ar–H), 8.08–8.17 (m, 1H, Ar–H) total 18H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 44.2 (epoxy $OCH_2$), 44.4 (epoxy $OCH_2$), 50.9 (epoxy OCH), 50.96 (epoxy OCH), 69.6 ($OCH_2$), 70.0 ($OCH_2$), 81.7 (OCH), 81.8 (OCH), 124.0 (Ar–C), 124.2 (Ar–C), 125.18 (Ar–C), 125.2 (Ar–C), 125.4 (Ar–C), 125.5 (Ar–C), 125.7 (Ar–C), 125.98 (Ar–C), 126.03 (Ar–C), 127.2 (Ar–C), 127.4 (Ar–C), 127.5 (Ar–C), 127.55 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.54 (Ar–C), 128.6 (Ar–C), 131.0 (Ar–C), 131.03 (Ar–C), 133.9 (Ar–C), 133.96 (Ar–C), 136.4 (Ar–C), 136.5 (Ar–C), 141.0 (Ar–C), 141.1 (Ar–C). ESI-MS *m*/*z* of 217.20 $[M - 73]^+$ was obtained for a calculated mass of 217.10.

#### 6.1.19. Representative procedure B, for compounds **22–30**: 1-(4-(3-methoxyphenyl)piperazin-1-yl)-3-(naphthalen-1-yl (phenyl)methoxy)propan-2-ol (**22**)

Oxirane **21** (0.05 g, 0.17 mmol) and 1-(3-methoxy phenyl)-piperazine (0.045 g, 0.17 mmol) were dissolved in 2-propanol

(5 mL) and the mixture was refluxed for 16 h. Reaction mixture was concentrated under reduced pressure to get thick liquid as a crude product. Crude product was purified by column chromatography (eluent: ethyl acetate, hexane; gradient elution) to obtain pure **22** (0.025 g, 30%) as a off-white sticky compound. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.45–2.65 (m, 4H, N–$CH_2$, piperazine–$CH_2$), 2.68–2.81 (m, 2H, piperazine–$CH_2$), 3.08–3.30 (m, 4H, piperazine–$CH_2$), 3.37–3.52 (m, 1H, $D_2O$ exchangeable, OH), 3.52–3.70 (m, 2H, $OCH_2$), 3.80 (s, 3H, $OCH_3$), 3.94–4.12 (m, 1H, OHC<u>H</u>), 6.10 (s, 0.5H, ArC<u>H</u>–O), 6.11 (s, 0.5H, ArC<u>H</u>–O), 6.32–6.50 (m, 2H, Ar–H), 6.53 (d, $J$ = 8.2 Hz, 1H, Ar–H), 7.18 (t, $J$ = 8.2 Hz, 1H, Ar–H), 7.23–7.30 (m, 1H, Ar–H), 7. 32 (t, $J$ = 7.5 Hz, 2H, Ar–H), 7.37–7.53 (m, 5H, Ar–H), 7.56–7.65 (m, 1H, Ar–H), 7.77–7.92 (m, 2H, Ar–H), 8.10–8.15 (m, 1H, Ar–H) total 34H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 49.0 (piperazine–$CH_2$), 53.2 (piperazine–$CH_2$), 55.1 ($OCH_3$), 60.7 ($NCH_2$), 66.4 (CHOH), 66.43 (CHOH), 71.7 ($OCH_2$), 71.8 ($OCH_2$), 82.1 (Ar–CHO–), 82.2 (Ar–CHO–), 102.4 (Ar–C), 104.4 (Ar–C), 108.8 (Ar–C), 124.2 (Ar–C), 125.2 (Ar–C), 125.5 (Ar–C), 125.6 (Ar–C), 125.7 (Ar–C), 125.96 (Ar–C), 125.98 (Ar–C), 127.3 (Ar–C), 127.5 (Ar–C), 128.3 (Ar–C), 128.52 (Ar–C), 128.55 (Ar–C), 128.7 (Ar–C), 129.74 (Ar–C), 131.05 (Ar–C), 131.08 (Ar–C), 133.96 (Ar–C), 133.98 (Ar–C), 136.67 (Ar–C), 136.73 (Ar–C), 141.2 (Ar–C), 152.5 (Ar–C), 160.5 (Ar–C). ESI-MS $m/z$ of 483.30 $[M + H]^+$ was obtained for a calculated mass of 483.26.

### 6.1.20. 1-(4-(2-Methoxyphenyl)piperazin-1-yl)-3-(naphthalen-1-yl(phenyl)methoxy)propan-2-ol (**23**)

Procedure B, yield 42%. Brownish sticky compound. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.42–2.70 (m, 4H, N–$CH_2$, piperazine–$CH_2$), 2.72–2.91 (m, 2H, piperazine–$CH_2$), 2.96–3.31 (m, 5H, 1H $D_2O$ exchangeable, piperazine–$CH_2$, OH), 3.55–3.68 (m, 2H, $OCH_2$), 3.85 (s, 3H, $OCH_3$), 3.95–4.10 (m, 1H, CHOH), 6.10 (s, 0.5H, Ar–CHO–), 6.11 (s, 0.5H, Ar–CHO–), 6.85 (d, $J$ = 7.8 Hz, 1H, Ar–H), 6.90–6.96 (m, 2H, Ar–H), 6.97–7.09 (m, 1H, Ar–H), 7.20–7.28 (m, 1H, Ar–H), 7.29–7.35 (m, 2H, Ar–H), 7.35–7.53 (m, 5H, Ar–H), 7.54–7.64 (m, 1H, Ar–H), 7.73–7.92 (m, 2H, Ar–H), 8.10 (d, $J$ = 6.7 Hz, 1H, Ar–H) total 34H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 50.6 (piperazine–$CH_2$), 53.4 (piperazine–$CH_2$), 55.3 (piperazine–$CH_2$), 60.8 (N–$CH_2$), 66.3 (CHOH), 66.36 (CHOH), 71.8 (O–$CH_2$), 71.9 (O–$CH_2$), 82.1 (Ar–CHO–), 111.1 (Ar–C), 118.1 (Ar–C), 120.9 (Ar–C), 122.9 (Ar–C), 124.24 (Ar–C), 124.27 (Ar–C), 125.2 (Ar–C), 125.5 (Ar–C), 125.7 (Ar–C), 125.73 (Ar–C), 125.95 (Ar–C), 125.97 (Ar–C), 127.3 (Ar–C), 127.5 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.52 (Ar–C), 128.7 (Ar–C), 131.09 (Ar–C), 131.12 (Ar–C), 133.97 (Ar–C), 133.98 (Ar–C), 136.74 (Ar–C), 136.79 (Ar–C), 141.1 (Ar–C), 141.25 (Ar–C), 141.26 (Ar–C), 152.2 (Ar–C). ESI-MS $m/z$ of 483.14 $[M + H]^+$ was obtained for a calculated mass of 483.26.

### 6.1.21. 1-(Naphthalen-1-yl(phenyl)methoxy)-3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propan-2-ol (**24**)

Procedure B, yield 31%. Sticky compound. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.43–2.64 (m, 4H, $NCH_2$, piperazine–$CH_2$), 2.68–2.82 (m, 2H, piperazine–$CH_2$), 2.90–3.40 (m, 5H, piperazine–$CH_2$, 1H $D_2O$ exchangeable, OH), 3.55–3.68 (m, 2H, $OCH_2$), 3.95–4.08 (m, 1H, CHOH), 6.10 (s, 0.5H, Ar–CHO–), 6.11 (s, 0.5H, Ar–CHO–), 6.90–7.06 (m, 1H, Ar–H), 7.06–7.16 (m, 2H, Ar–H), 7.20–7.29 (m, 1H, Ar–H), 7.30–7.39 (m, 3H, Ar–H), 7.40–7.54 (m, 5H, Ar–H), 7.55–7.63 (m, 1H, Ar–H), 7.77–7.92 (m, 2H, Ar–H), 8.03–8.17 (m, 1H, Ar–H) total 31H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 48.6 (piperazine–$CH_2$), 53.0 (piperazine–$CH_2$), 60.7 ($NCH_2$), 66.5 (CHOH), 66.6 (CHOH), 71.7 ($OCH_2$), 71.8 ($OCH_2$), 82.19 (Ar–CHO–), 82.21 (Ar–CHO–), 112.05 (Ar–C), 112.09 (Ar–C), 112.13 (Ar–C), 112.17 (Ar–C), 115.79 (Ar–C), 115.83 (Ar–C), 115.86 (Ar–C), 115.9 (Ar–C), 118.7 (Ar–C), 122.9 (Ar–C), 124.2 (Ar–C), 125.2 (Ar–C), 125.5 (Ar–C), 125.63 (Ar–C), 125.66 (Ar–C), 125.7 (Ar–C), 125.98 (Ar–C), 126.0 (Ar–C), 127.3 (Ar–C), 127.5 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.6 (Ar–C), 128.7 (Ar–C), 129.5 (Ar–C), 130.9 (Ar–C), 131.0 (Ar–C), 131.1 (Ar–C), 131.2 (Ar–C), 131.5 (Ar–C), 131.8 (Ar–C), 133.98 (Ar–C), 134.0 (Ar–C), 136.7 (Ar–C), 136.74 (Ar–C), 141.18 (Ar–C), 141.2 (Ar–C), 151.2 (Ar–C). ESI-MS $m/z$ of 520.90 $[M + H]^+$ was obtained for a calculated mass of 521.24.

### 6.1.22. 1-(4-(3,4-Dichlorophenyl)piperazin-1-yl)-3-(naphthalen-1-yl(phenyl)methoxy) propan-2-ol (**25**)

Procedure B, yield 39%. Sticky compound. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.35–2.62 (m, 5H, N–$CH_2$, piperazine –$CH_2$, 1H $D_2O$ exchangeable, OH), 2.65–2.75 (m, 2H, piperazine–$CH_2$), 3.07–3.20 (m, 4H, piperazine –$CH_2$), 3.55–3.68 (m, 2H, $OCH_2$), 3.95–4.06 (m, 1H, CHOH), 6.09 (s, 0.5H, Ar–CHO–), 6.10 (s, 0.5H, Ar–CHO–), 6.70 (dd, $J$ = 9.0, 2.8 Hz, 1H, Ar–H), 6.93 (d, $J$ = 2.8 Hz, 1H, Ar–H), 7.22–7.24 (m, 1H, Ar–H), 7.29–7.34 (m, 2H, Ar–H), 7.37–7.53 (m, 6H, Ar–H), 7.55–7.62 (m, 1H, Ar–H), 7.78–7.89 (m, 2H, Ar–H), 8.05–8.15 (m, 1H, Ar–H) total 30H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 48.6 (piperazine–$CH_2$) 52.9 (piperazine–$CH_2$), 60.6 ($NCH_2$), 66.5 (CHOH), 66.54 (CHOH), 71.7 ($OCH_2$), 71.75 ($OCH_2$), 82.15 (Ar–CHO–), 82.17 (Ar–CHO–), 115.2 (Ar–C), 117.1 (Ar–C), 122.1 (Ar–C), 124.2 (Ar–C), 125.2 (Ar–C), 125.5 (Ar–C), 125.6 (Ar–C), 125.7 (Ar–C), 125.97 (Ar–C), 125.98 (Ar–C), 127.3 (Ar–C), 127.5 (Ar–C), 128.3 (Ar–C), 128.53 (Ar–C), 128.57 (Ar–C), 128.7 (Ar–C), 130.3 (Ar–C), 131.03 (Ar–C), 131.06 (Ar–C), 132.7 (Ar–C), 133.95 (Ar–C), 133.97 (Ar–C), 136.63 (Ar–C), 136.7 (Ar–C), 141.13 (Ar–C), 141.14 (Ar–C), 150.5 (Ar–C).

ESI-MS $m/z$ of 521.10 $[M + H]^+$ was obtained for a calculated mass of 521.18.

### 6.1.23. 1-(4-Benzhydrylpiperazin-1-yl)-3-(naphthalen-1-yl(phenyl)methoxy)propan-2-ol (**26**)

Procedure B, yield 37%. Off-white sticky solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.00–2.57 (m, 9H, $NCH_2$, piperazine–$CH_2$, 1H $D_2O$ exchangeable, OH), 2.55–2.69 (m, 2H, piperazine –$CH_2$), 3.48–3.59 (m, 2H, O–$CH_2$), 3.89–4.00 (m, 1H, CHOH), 4.19 (s, 1H, NCH), 6.06 (s, 0.5H, Ar–CHO–), 6.07 (s, 0.5H, Ar–CHO–), 7.13–7.19 (m, 2H, Ar–H), 7.20–7.25 (m, 4H, Ar–H), 7.26–7.32 (m, 3H, Ar–H), 7.36–7.49 (m, 9H, Ar–H), 7.52 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.75–7.88 (m, 2H, Ar–H), 8.02–8.10 (m, 1H, Ar–H) total 38H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 51.9 (piperazine–$CH_2$), 53.5 (piperazine–$CH_2$), 60.7 ($NCH_2$), 66.20 (CHOH), 66.26 (CHOH), 71.8 ($OCH_2$), 71.9 ($OCH_2$), 76.14 (NCH), 82.1 (Ar–CHO–), 124.23 (Ar–C), 124.26 (Ar–C), 125.2 (Ar–C), 125.5 (Ar–C), 125.66 (Ar–C), 125.71 (Ar–C), 125.92 (Ar–C), 125.94 (Ar–C), 126.9 (Ar–C), 127.3 (Ar–C), 127.4 (Ar–C), 127.8 (Ar–C), 128.2 (Ar–C), 128.3 (Ar–C), 128.43 (Ar–C), 128.47 (Ar–C), 128.5 (Ar–C), 128.6 (Ar–C), 131.09 (Ar–C), 131.11 (Ar–C), 133.95 (Ar–C), 133.97 (Ar–C), 136.7 (Ar–C), 136.8 (Ar–C), 141.3 (Ar–C), 142.66 (Ar–C), 142.67 (Ar–C).

ESI-MS $m/z$ of 542.80 $[M]^+$ was obtained for a calculated mass of 542.29.

### 6.1.24. 1-(4-Benzylpiperazin-1-yl)-3-(naphthalen-1-yl(phenyl)methoxy)propan-2-ol (**27**)

Procedure B, yield 44%. Sticky-compound. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.21–2.57 (m, 9H, N–$CH_2$, piperazine –$CH_2$, 1H $D_2O$ exchangeable, OH), 2.58–2.74 (br-s, 2H, piperazine–$CH_2$), 3.49 (s, 2H, O–$CH_2$), 3.53–3.63 (m, 2H, $CH_2$), 3.87–4.02 (m, 1H, CHOH), 6.07 (s, 0.5H, Ar–CHO–), 6.08 (s, 0.5H, Ar–CHO–), 7.19–7.29 (m, 5H, Ar–H), 7.29–7.35 (m, 3H, Ar–H), 7.35–7.49 (m, 5H, Ar–H), 7.55 (d, $J$ = 7 Hz, 1H, Ar–H), 7.73–7.89 (m, 2H, Ar–H), 7.99–8.11 (m, 1H, Ar–H) total 34 H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 53.0 (piperazine–$CH_2$), 60.7 ($NCH_2$), 63.0 ($OCH_2$), 66.2 (CHOH), 66.3 (CHOH), 71.8 (OCPh), 71.9(OCPh), 82.1 (Ar–CHO–), 124.25 (Ar–C), 124.27 (Ar–C), 125.2 (Ar–C), 125.5 (Ar–C), 125.7 (Ar–

C), 125.72 (Ar–C), 125.94 (Ar–C), 125.96 (Ar–C), 127.0 (Ar–C), 127.3 (Ar–C), 127.5 (Ar–C), 128.2 (Ar–C), 128.3 (Ar–C), 128.48 (Ar–C), 128.51 (Ar–C), 128.7 (Ar–C), 129.2 (Ar–C), 131.1 (Ar–C), 131.12 (Ar–C), 134.0 (Ar–C), 136.7 (Ar–C), 136.8 (Ar–C), 138.0 (Ar–C), 141.3 (Ar–C).

ESI-MS *m*/*z* of 467.21 $[M + H]^+$ was obtained for a calculated mass of 467.27.

*6.1.25. 1-(Naphthalen-1-yl(phenyl)methoxy)-3-(4-(pyridin-2-yl)piperazin-1-yl)propan-2-ol (**28**)*

Procedure B, yield 42%. Sticky-solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.37–2.60 (m, 4H, $NCH_2$, piperazine–$CH_2$), 2.64–2.76 (m, 2H, piperazine–$CH_2$), 3.45–3.66 (m, 7H, piperazine–$CH_2$, $OCH_2$, 1H $D_2O$ exchangeable, OH), 3.95–4.07 (m, 1H, CHOH), 6.08 (s, 0.5H, Ar–CHO–), 6.09 (s, 0.5H, Ar–CHO–), 6.61 (dd, $J$ = 7.0, 5.8 Hz, 2H, Ar–H), 7.20–7.24 (m, 1H, Ar–H), 7.27–7.34 (m, 2H, Ar–H), 7.36–7.51 (m, 6H, Ar–H), 7.53–7.61 (m, 1H, Ar–H), 7.75–7.87 (m, 2H, Ar–H), 8.03–8.11 (m, 1H, Ar–H), 8.14–8.23 (m, 1H, Ar–H) total 31H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 45.1 (piperazine–$CH_2$), 53.0 (piperazine–$CH_2$), 60.8 ($NCH_2$), 66.3 (CHOH), 66.4 (CHOH), 71.7 ($OCH_2$), 71.75 ($OCH_2$), 82.06 (Ar–CHO–), 82.08 (Ar–CHO–), 107.0 (Ar–C), 113.3 (Ar–C), 124.1 (Ar–C), 125.1 (Ar–C), 125.5 (Ar–C), 125.6 (Ar–C), 125.7 (Ar–C), 125.90 (Ar–C), 125.91 (Ar–C), 127.2 (Ar–C), 127.4 (Ar–C), 128.2 (Ar–C), 128.44 (Ar–C), 128.47 (Ar–C), 128.6 (Ar–C), 130.97 (Ar–C), 131.0 (Ar–C), 133.87 (Ar–C), 133.89 (Ar–C), 136.61 (Ar–C), 136.68 (Ar–C), 137.4 (Ar–C), 141.1 (Ar–C), 147.8 (Ar–C), 159.3 (Ar–C).

ESI-MS *m*/*z* of 454.30 $[M + H]^+$ was obtained for a calculated mass of 454.25.

*6.1.26. 1-(4-(4-Fluorophenyl)piperazin-1-yl)-3-(naphthalen-1-yl(phenyl)methoxy)propan-2-ol (**29**)*

Procedure B, yield 28%. Sticky-solid. $^1$H NMR (400 MHz, $CDCl_3$): 2.45–2.59 (m, 4H, $NCH_2$, piperazine–$CH_2$), 2.69–2.80 (m, 2H, piperazine–$CH_2$), 2.97–3.30 (m, 5H, piperazine –$CH_2$, 1H $D_2O$ exchangeable, OH), 3.53–3.67 (m, 2H, $OCH_2$), 3.94–4.08 (m, 1H, CHOH), 6.09 (s, 0.5H, Ar–CHO–), 6.10 (s, 0.5H, Ar–CHO–), 6.82–6.89 (m, 2H, Ar–H), 6.92–7.00 (m, 2H, Ar–H), 7.26–7.28 (m, 1H, Ar–H), 7.29–7.35 (m, 2H, Ar–H), 7.37–7.52 (m, 5H, Ar–H), 7.52–7.62 (m, 1H, Ar–H), 7.78–7.91 (m, 2H, Ar–H), 8.04–8.14 (m, 1H, Ar–H) total 31H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 50.1 (piperazine–$CH_2$), 53.2 (piperazine–$CH_2$), 60.7 ($NCH_2$), 66.4 (CHOH), 66.5 (CHOH), 71.7 ($OCH_2$), 71.8 ($OCH_2$), 82.13 (Ar–CHO–), 82.14 (Ar–CHO–), 115.3 (Ar–C), 115.5 (Ar–C), 117.7 (Ar–C), 117.8 (Ar–C), 124.2 (Ar–C), 125.2 (Ar–C), 125.5 (Ar–C), 125.6 (Ar–C), 125.7 (Ar–C), 125.94 (Ar–C), 125.97 (Ar–C), 127.3 (Ar–C), 127.5 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.54 (Ar–C), 128.7 (Ar–C), 131.04 (Ar–C), 131.07 (Ar–C), 133.94 (Ar–C), 133.96 (Ar–C), 136.7 (Ar–C), 136.73 (Ar–C), 141.16 (Ar–C), 141.17 (Ar–C), 147.7 (Ar–C), 147.8 (Ar–C), 155.9 (Ar–C), 158.3 (Ar–C).

ESI-MS *m*/*z* of 471.10 $[M + H]^+$ was obtained for a calculated mass of 471.24.

*6.1.27. 1-(4-(4-Chlorophenyl)piperazin-1-yl)-3-(naphthalen-1-yl(phenyl)methoxy)propan-2-ol (**30**)*

Procedure B, yield 23%. Sticky-solid. $^1$H NMR (400 MHz, $CDCl_3$): 2.43–2.60 (m, 4H, $NCH_2$, piperazine–$CH_2$), 2.64–2.80 (m, 2H, piperazine–$CH_2$), 3.04–3.21 (m, 4H, piperazine–$CH_2$), 3.53–3.66 (m, 2H, $OCH_2$), 3.94–4.08 (m, 1H, CHOH), 6.08 (s, 0.5H, Ar–CHO–), 6.09 (s, 0.5H, Ar–CHO–), 6.75–6.86 (m, 2H, Ar–H), 7.15–7.23 (m, 2H, Ar–H), 7.26–7.28 (m, 1H, Ar–H), 7.29–7.34 (m, 2H, Ar–H), 7.35–7.41 (m, 2H, Ar–H), 7.42–7.52 (m, 3H, Ar–H), 7.54–7.61 (m, 1H, Ar–H), 7.80 (d, $J$ = 8.0 Hz, 1H, Ar–H), 7.83–7.89 (m, 1H, Ar–H), 8.03–8.12 (m, 1H, Ar–H) total 31H in a diastereomeric ratio 1: 1. $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 48.9 (piperazine–$CH_2$), 52.9 (piperazine–$CH_2$), 60.6 ($NCH_2$), 66.3 (CHOH), 66.4 (CHOH), 71.6 ($OCH_2$), 71.7 ($OCH_2$), 82.05 (Ar–CHO–), 82.06 (Ar–CHO–), 117.1 (Ar–C), 124.1 (Ar–C), 124.3 (Ar–C), 125.1 (Ar–C), 125.5 (Ar–C), 125.6 (Ar–C), 125.64 (Ar–C), 125.9 (Ar–C), 125.91 (Ar–C), 127.2 (Ar–C), 127.4 (Ar–C), 128.2 (Ar–C), 128.4 (Ar–C), 128.5 (Ar–C), 128.6 (Ar–C), 128.8 (Ar–C), 130.97 (Ar–C), 131.0 (Ar–C), 133.87 (Ar–C), 133.89 (Ar–C), 136.61 (Ar–C), 136.67 (Ar–C), 141.1 (Ar–C), 149.6 (Ar–C).

ESI-MS *m*/*z* of 487.10 $[M + H]^+$ was obtained for a calculated mass of 487.22.

### 6.2. Biological methods

#### 6.2.1. Microbiology

All compounds **9**–**19**, **22**–**30** and drug references were dissolved in DMSO at a concentration of 6.25 μg/mL and were stored at ~4 °C until used.

#### 6.2.2. Cytotoxicity

The cells (human monocytic cell line U937) were plated in flat-bottomed 96 well plates ($1 \times 10^5$ cells/mL), cultured for 1 h in controlled atmosphere ($CO_2$ 5% at 37 °C), and non-adherent cells were washed by gentle flushing with RPMI 1640. Adherent cells were cultured in the presence of medium alone, Tween 20 (3%) (live and dead controls, respectively) or different concentration of compounds (depending upon the solubility) in a triplicate assay (Table 3). After completion of the experiment protocol 10 μL of MTT solution (5 mg/mL solution in Phosphate Buffer Saline) was added in each well. Plates were incubated for 3 h in $CO_2$ incubator at 37 °C. Then 100 μL solubilizing solution (0.4 M HCl in isopropanol) was added to solubilize the formazan crystals formed by the surviving cells. Finally the absorbance was read at 600 nm in a micro plate reader (Bio-Rad-i Mark) using acidified isopropanol as blank.

## Acknowledgement

We thank Dr. Anjlina Wali, Institute of Molecular Medicine, for cytotoxicity study of compounds. We thank Uppsala University, Sweden for valuable scientific support through JC. Generous financial support from the European Union (Project No. 222965, Project name: New approaches to target Tuberculosis, Call identifier: FP7-Health-2007-B) and TCG Life Sciences, Kolkata for funding the collaboration are also gratefully acknowledged.

## Appendix. Supplementary data

Supplementary material associated with this paper can be found, in the online version, at doi:10.1016/j.ejmech.2010.01.024.

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