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Design, synthesis and antimycobacterial evaluation of 1-(4-(2-substitutedthiazol-4-yl)phenethyl)-4-(3-(4-substitutedpiperazin-1-yl) alkyl)piperazine hybrid analogues

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ABSTRACT

A series of twenty six new 1-(4-(2-substitutedthiazol-4-yl)phenethyl)-4-(3-(4-substitutedpiperazin-1-yl)alkyl)piperazine analogues were synthesized by seven steps and evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. Among the tested compounds, **7j**, **7p**, and **7r** exhibited moderate activity (MIC = 6.25 μg/mL) and compounds **7a**, **7f**, **7g**, **7n** and **7v** exhibited good activity (MIC = 3.125 μg/mL), while **7h** displayed excellent activity (MIC = 1.56 μg/mL) by inhibiting 99% growth of *M. tuberculosis* $H_{37}Rv$ strain. In addition, all the active compounds were subjected to cytotoxic studies against mouse macrophage (RAW264.7) cell lines and the selectivity index values for most of the compounds is >**10** indicating suitability of compounds in an endeavour to attain lead molecule for further drug development.

1. Introduction

Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2012, 8.6 million people fell ill with TB and 1.3 million died from TB. Over 95% of TB deaths occur in low and middle income countries, and it is among the top three causes of death for women aged 15 to 44. People falling ill with TB each year is declining, although very slowly. An estimated 22 million lives saved through use of Directly Observed Therapy Shortcourse and the Stop TB strategy recommended by World Health Organization [1]. Detection of Multi-Drug resistant TB (MDR-TB) patients is increasing every year as a result of scanty treatment and once TB organisms acquire resistance they can spread from person to person in the same way as drug-sensitive TB. The biggest increases were in India, South Africa and Ukraine. Also, emergence of extensively drug-resistant TB (XDR-TB) and Rifampicin-resistant TB has still deteriorated the TB treatment by not responding to the standard six month treatment with first-line anti-TB drugs and can take two years or more to treat with drugs that are less effective, more toxic and more expensive [2]. Efforts have been steered to manipulate the biological processes of existing drugs for effective development of new chemical entities against TB as a rational approach.

Ascribable to complexity and toxicity of the current TB drug regimens and emergence of various forms of drug resistant TB warranted the scientific community to focus on exploring novel chemotherapeutical agents. As TB is an inevitable disease among HIV patients, it is identified that current TB drugs (Rifabutin, Rifampicin and Rifapentine) interact with the antiretroviral drugs [3] taken by HIV positive people; hence it is essential to scrutinize cost effective, less toxic chemical entities preferably with new biochemical pathways to shorten treatment time, and to interrupt drug–drug interaction.

2-Aminothiazoles are well acknowledged potential therapeutic agents viz. antiviral, NPY_5 antagonists, PGE_2 inhibitors, anticancer, opiod receptor agonists, antimycobacterial, anti-inflammatory, antiprion etc., [4–11]. The wide applicability of thiazole framework in drug discovery is attributed to the use of inexpensive starting materials and adoption of simple synthetic strategy to wangle diverse molecules. In particular, nitazoxanide (NTZ) and its active metabolite tizoxanide (TIZ) are known to inhibit replicative and non-replicative *Mycobacterium tuberculosis* (MTB) [12]. Some of the drugs based on aminothiazoles moiety are depicted in Fig. 1.

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In addition, Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) and the National Institutes of Health, Molecular Libraries Screening Centres Network disclosed encouraging results from an MTB whole-cell high-throughput assay and identified aminothiazoles as an important core which is depicted in Fig. 2 [9,13–15]. Few research groups synthesized various 2-(2-hydrazinyl)thiazole derivatives and reported good activity against MTB strain $H_{37}Rv$ [16–18]. Similarly, Makam et al., reported 2-(2-hydrazinyl)thiazole derivatives which are structurally similar to thiolactomycin using rational hybrid approach with good anti-TB activity [19]. Sridhar et al., synthesized N^1-hydroxy-*N*-(4*H*,5*H*-naphtho[1,2-*d*]thiazol-2-yl)methanimidamide analogues which inhibit MTB methionine aminopeptidases [20]. Ranjith et al., synthesized (2-aminothiazol-4-yl)methyl 3-(2-cyanoethyl)benzoate and found to exhibit good anti-TB activity than isoniazid against MTB $H_{37}Rv$, *Mycobacterium Smegmatis* (ATCC 19420), *Mycobacterium Fortuitum* (ATCC 19542) and MDR-TB strains [21]. Meissner et al., synthesized 3-bromo-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide derivatives which inhibit MTB $H_{37}Rv$ strain at 0.008 μg/mL [9]. Very recently, Pieroni et al., synthesized *N*-substituted-2-aminothiazole derivatives and clearly briefed the structure activity relationship emphasizing on the mandatory of aminomethyl group at second position of thiazole [22].

MTB cells wrap a protective sheath on the cell wall composed of complex carbohydrates, proteins and glycolipids [23] making most of the drugs very complicated to penetrate through this thick, non-permeable, hydrophobic barrier which defies current treatment. This being one of the greatest challenges put forward to the scientists while designing a drug. Piperazine linkers have made vast impact on drug discovery process as they have ability to increase the lipophilicity of the molecule to a greater extent. Bogatcheva et al., synthesized various diamine linked moieties and reported good *in vitro* and *in vivo* anti-tubercular activity against MTB $H_{37}Rv$ strain [24]. Huang et al., synthesized 2-methyl benzothiazoles which inhibited the growth of MTB $H_{37}Rv$ strain at 1.4 μM [25].

With this collective information and encouraged by our recent anti-TB results emphasizing on molecular hybridization approach [26–28] we drew a synthetic stratagem (Fig. 2) to fit all these imperative pharmacophoric groups into one distinct scaffold and synthesized 1-(4-(2-substitutedthiazol-4-yl)phenethyl)-4-(3-(4-substitutedpiperazin-1-yl)alkyl)piperazine analogues.

2. Chemistry

We synthesized 1-(4-(2-substitutedthiazol-4-yl)phenethyl)-4-(3-(4-substitutedpiperazin-1-yl)alkyl)piperazine analogues as sketched in Fig. 3. We adopted reported procedure with slight modification to prepare 4-(4-(2-chloroethyl)phenyl)-2-substitutedthiazole (**3**) [29], then **3** was coupled with anhydrous piperazine in *N*,*N*-dimethylformamide (DMF) at 100 °C for 3 h to give 1-(4-(2-substitutedthiazol-4-yl)phenethyl)piperazine (**4**). Compound 4-(4-(4-(2-substitutedthiazol-4-yl)phenethyl)piperazin-1-yl)alkan-1-ol (**5**) was obtained by coupling **4** with bromoalkanols in the presence of triethylamine (TEA) and DMF at 100 °C for 3 h; further heating **5** at 120 °C with 40% hydrobromic acid for 2 h fetched 1-(4-(2-substitutedthiazol-4-yl)phenethyl)-4-(n-bromoalkyl)piperazine (**6**). Subsequently various substituted piperazines were coupled with **6** at 120 °C for 3 h using TEA and DMF to achieve title compounds (**7a**–**z**). All the title compounds displayed multiplet in the range 2.75–2.95 ppm and 3.45–3.65 ppm corresponding to piperazine (–CH_2–) protons. Characteristic aromatic proton (C-5) of thiazole ring resonated in the range 6.50–6.75 ppm. Both analytical and spectral data (^{1}H NMR, ^{13}C NMR, IR and HRMS) of all the synthesized compounds were confirmed and employed further for their antimycobacterial evaluation.

3. Results and discussion

3.1. Antimycobacterial activity

All the synthesized compounds were tested for their ability to inhibit the growth of MTB $H_{37}R_V$ strain by Microplate Alamar Blue Assay (MABA). Isoniazid and Rifampicin were used as the positive drug standard. The *in vitro* antimycobacterial test results of title compounds are tabulated in Table 1 as minimum inhibitory concentration (MIC) and the activity ranges between 1.56 and >6.25 μg/mL. Compounds with MIC ≤6.25 μg/mL were further subjected to cytotoxicity studies. Amongst the series, compounds **7j**, **7p** and **7r** inhibit 99% growth of MTB $H_{37}Rv$ strain at a concentration 6.25 μg/mL whereas compounds **7a**, **7f**, **7g**, **7n** and **7v** inhibit 99% growth of MTB $H_{37}Rv$ strain at a concentration 3.125 μg/mL. Compound **7h** emerged as the most promising candidate by inhibiting 99% growth of MTB $H_{37}Rv$ strain at a concentration 1.56 μg/mL.

Among the synthesized compounds electron releasing groups like phenyl and benzhydryl piperazine with propyl and butyl linker respectively, bearing *N*-methylthiazol-2-amine backbone were found to be inactive (**7c** and **7i**, MIC = 50 μg/mL). Next, keeping propyl linker intact we synthesized 2-methylthiazole moiety bearing phenyl piperazine (**7e**) which exhibited 2 fold increase in the activity (MIC = 25 μg/mL). Subsequently an alkyl chain was increased to fetch compound **7b** which exhibited similar activity

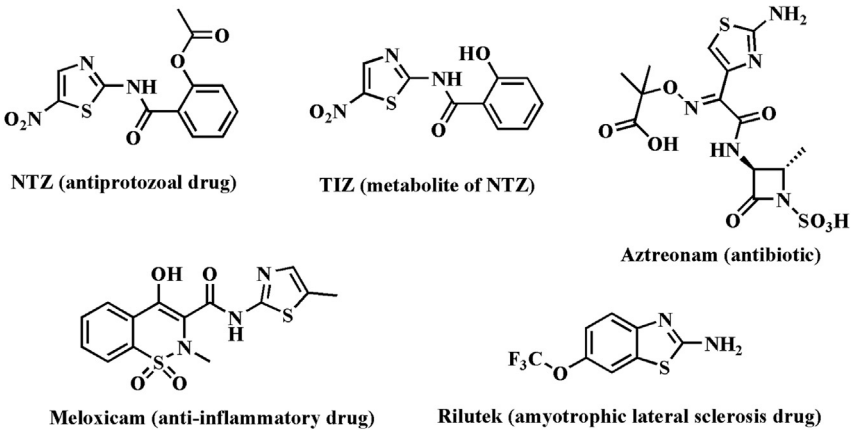


Fig. 1. Drugs currently in use based on 2-aminothiazole skeleton.

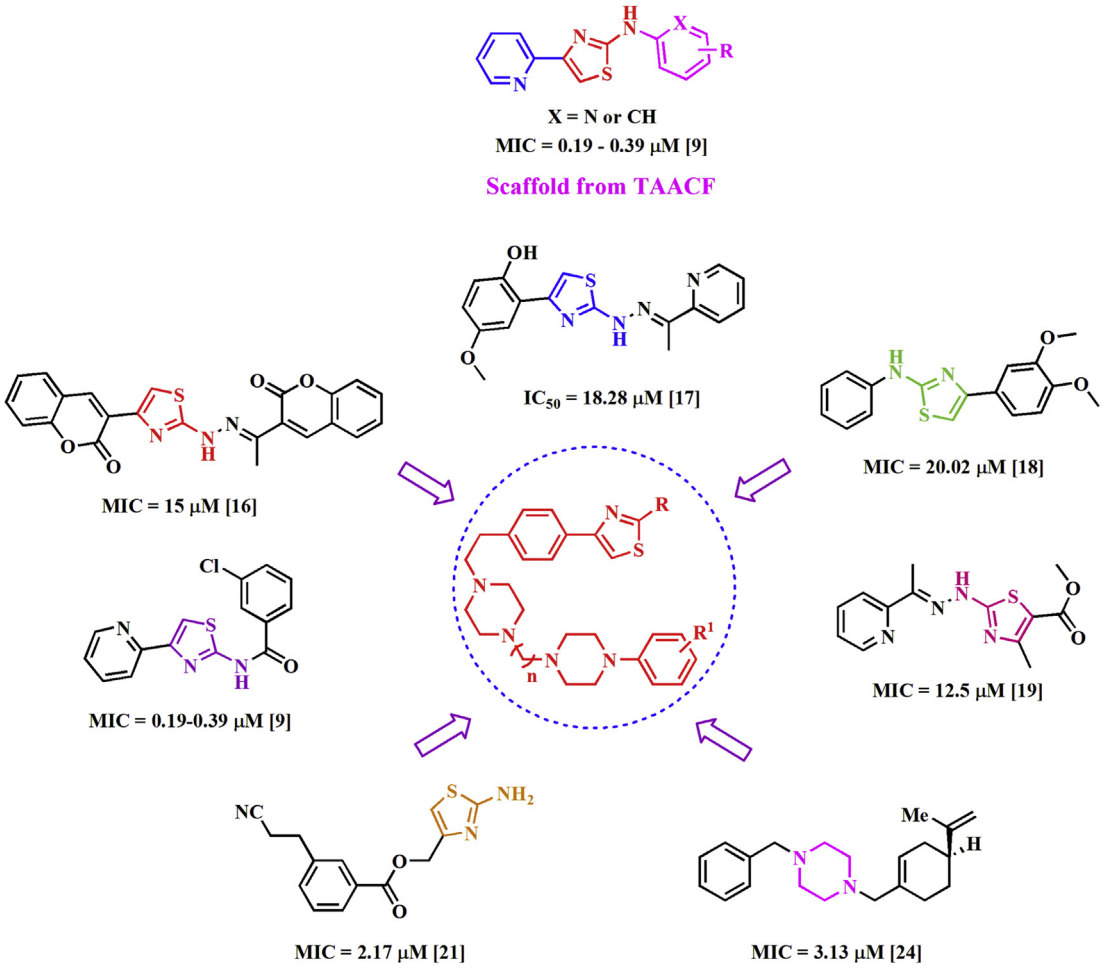


Fig. 2. Scaffold from TAACF high-throughput screening campaign and design strategy to achieve title compounds.

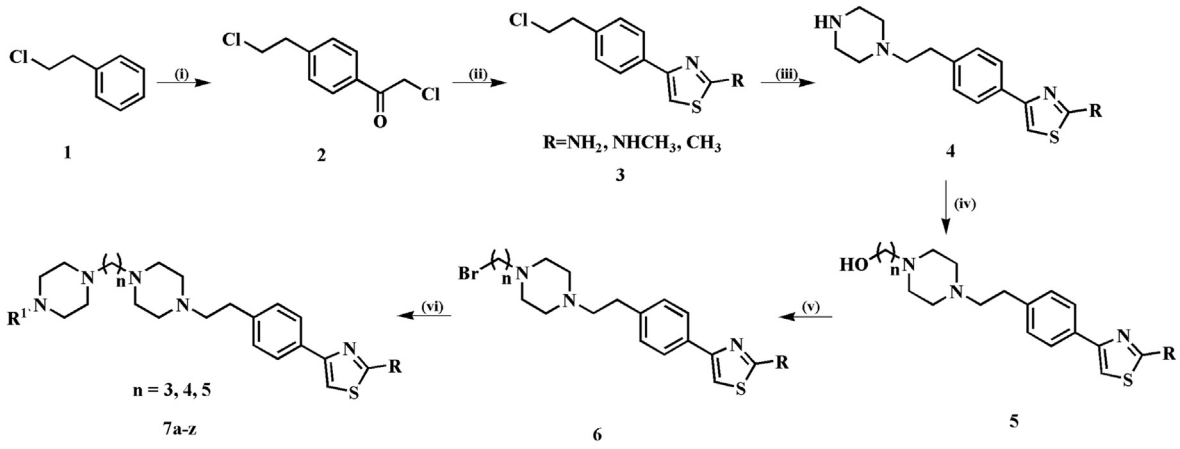
(MIC = 25 μg/mL). With this increased activity, butyl link tailored to phenyl group and *N*-methylthiazol-2-amine backbone leading to **7d**, amplified the activity further by 2 fold (MIC = 12.5 μg/mL). Switching from aminothiazoles to 2-methylthiazole with benzhydryl-piperazine and propyl linker exhibited significant activity (**7j**, MIC = 6.25 μg/mL). Notably, compounds with phenyl and benzhydryl piperazine tagged 2-aminothiazoles with propyl and butyl linker respectively exhibited good activity (**7a**, **7f** and **7g**, MIC = 3.125 μg/mL). Eventually, compound **7h** comprising *N*-methylthiazol-2-amine attached to benzhydryl piperazine through propyl link emerged as a potential candidate by inhibiting the MTB H_{37}Rv strain at 1.56 μg/mL. In general, compounds with electron withdrawing groups were found to be inactive except compound **7n** bearing *N*-methylthiazol-2-amine attached to 2-chlorophenyl piperazine through butyl link exhibited good activity (MIC = 3.125 μg/mL). On the other hand, employing 2-pyridyl piperazine led to compound **7v** consisting 2-aminothiazole backbone through propyl linker which exhibited good activity (MIC = 3.125 μg/mL). Structure–activity relationship evidently indicates the necessity of 2-aminomethyl group at 2nd position of thiazole which might involve in hydrogen bonding to a greater extent to exhibit good activity.

3.2. Cytotoxicity assay

RAW 264.7 cell lines derived from BALB/c mice maintain many of the properties of macrophages including nitric oxide production and phagocytosis. As MTB generally reside and multiply inside the macrophages, so to carry out the cytotoxicity against RAW 264.7 cells is imperative to scrutinize the selectivity of compounds against MTB rather than host macrophage. Hence the active compounds **7a**, **7f**, **7g**, **7h**, **7j**, **7n**, **7p**, **7r** and **7v** were subjected to *in vitro* cytotoxicity studies by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The IC_{50} and selectivity index (SI) values are tabulated in Table 2. The SI is defined as the ratio of the IC_{50} to the MIC (MTB H_{37}Rv strain). SI value >10 indicates that the compound may be considered for further studies. Tested active compounds exhibited percentage growth inhibitions of RAW 264.7 cells in the range of 31.76–46.43% at a concentration 50 μg/mL. Among the tested compounds, **7j**, **7p** and **7r** exhibited toxicity (SI ≥ 7) and compounds **7a**, **7f**, **7g**, **7n** and **7v** exhibited non-toxic (SI ≥ 15). Nevertheless, most active compound **7h** (SI ≥ 30) found to be safe for further studies and emerged as more potent molecule of the series. These encouraging results imply the suitability of compounds in an endeavour to attain lead molecule for further drug development.

4. Conclusion

In conclusion, our preliminary anti-tubercular screening results earmarked us to fine-tune the architecture of 2-aminothiazole framework to fetch desired pharmacophoric features that might be explored to evaluate various drug resistant forms of TB. We



Reagents and conditions: (i) $ClCH_2COCl$ (1.2 eq), $AlCl_3$ (2 eq), CH_2Cl_2 0ºC - rt, 1h (ii) $RCSNH_2$ (1 eq), acetone, reflux, 3h (iii) anhydrous piperazine (3 eq), Et_3N (1 eq), KI (0.2 eq), DMF, 100ºC, 3h (iv) bromoalkanols (1.2 equiv), Et_3N (1.5 eq), DMF, 100ºC, 3h (v) HBr (40% aqueous) (0.6 eq), TBAB (0.3 eq), neat, 120ºC, 2h (vi) substituted piperazines (1.2 eq), Et_3N (2 eq), DMF, 120ºC, 3h

Fig. 3. Synthetic strategy to achieve title compounds.

disclose that integrating *N*-methyl-4-(4-(2-(piperazin-1-yl)ethyl) phenyl)thiazol-2-amine to benzhydryl piperazine through propyl linker emerged as a prospective candidate by inhibiting the MTB $H_{37}Rv$ strain at concentration 1.56 μg/mL (**7h**).

Table 1
Antimycobacterial activities of compound **7a**–**z** against MTB $H_{37}Rv$ strain.

Compound no.	R^1	*n*	R	MIC (μg/mL) against MTB $H_{37}Rv$
7a	Ph	3	NH_2	3.125
7b	Ph	4	NH_2	25
7c	Ph	3	$NHCH_3$	50
7d	Ph	4	$NHCH_3$	12.5
7e	Ph	3	CH_3	25
7f	$(Ph)_2CH$	3	NH_2	3.125
7g	$(Ph)_2CH$	4	NH_2	3.125
7h	$(Ph)_2CH$	3	$NHCH_3$	1.56
7i	$(Ph)_2CH$	4	$NHCH_3$	50
7j	$(Ph)_2CH$	3	CH_3	6.25
7k	2-ClPh	3	NH_2	50
7l	2-ClPh	4	NH_2	50
7m	2-ClPh	3	$NHCH_3$	12.5
7n	2-ClPh	4	$NHCH_3$	3.125
7o	2-ClPh	3	CH_3	50
7p	4-NO_2Ph	3	NH_2	6.25
7q	4-NO_2Ph	4	NH_2	12.5
7r	4-NO_2Ph	5	NH_2	6.25
7s	4-NO_2Ph	3	$NHCH_3$	12.5
7t	4-NO_2Ph	4	$NHCH_3$	50
7u	4-NO_2Ph	3	CH_3	50
7v	2-Py	3	NH_2	3.125
7w	2-Py	4	NH_2	12.5
7x	2-Py	3	$NHCH_3$	12.5
7y	2-Py	4	$NHCH_3$	25
7z	2-Py	3	CH_3	50
Isoniazid				0.05
Rifampicin				0.1

5. Experimental section

5.1. Materials and methods

Chemicals and solvents were procured from commercial sources and are analytically pure. Thin-layer chromatography (TLC) was carried out on aluminium-supported silica gel plates (Merck 60 F254) with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel (Merck 230–400 mesh). ^1H NMR spectra and ^{13}C NMR spectra were recorded at 300 MHz using a Bruker AV 300 spectrometer or 400 MHz using a Bruker AV 400 spectrometer (Bruker CO., Switzerland) in $CDCl_3$ or DMSO-D_6 solution with tetramethylsilane as the internal standard, and chemical shift values (δ) are given in ppm. Microwave reactions were performed in closed vessel using Biotage Initiator microwave synthesizer (Uppsala, Sweden). IR spectra were recorded on a FT-IR spectrometer (Schimadzu) and peaks are reported in cm^{-1}. Melting points were determined on an electro thermal melting point apparatus (Stuart-SMP30) in open capillary tubes and are uncorrected. High-resolution mass spectra

Table 2
IC_{50} (μg/mL) and selectivity index (SI) values of active compounds.

Compound	MIC (μg/mL) in MTB $H_{37}Rv$	% Cell inhibition at 50 μg/mL	IC_{50} (μg/mL) approximation	SI value IC_{50}/MIC
7a	3.125	35.62	>50	>15
7f	3.125	38.42	>50	>15
7g	3.125	46.43	>50	>15
7h	1.56	31.76	>50	>30
7j	6.25	42.8	>50	>7
7n	3.125	40.4	>50	>15
7p	6.25	36.46	>50	>7
7r	6.25	44.6	>50	>7
7v	3.125	38.1	>50	>15

(HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Elemental analysis was carried out on Elementar (vario MICRO cube, Hanau, Germany).

5.2. Preparation of **4**

To a suspension of **3** (1 eq) in DMF was added KI (0.2 eq), TEA (1 eq) and stirred for 15 min at room temperature (rt). To the resultant mixture anhydrous piperazine (3 eq) was added and heated at 100 °C for 3 h. Completion of the reaction was monitored by TLC using 20% MeOH in DCM as mobile phase. After the reaction was complete, DMF was evaporated under vacuo and added 5 mL of water. Compound was extracted using EtOAc (3 × 5 mL). Combined organic layers were washed with saturated brine solution, dried over anhydrous sodium sulphate and evaporated in vacuo. The crude residue was purified by column chromatography (MeOH/DCM) to get compounds **4**.

5.3. Preparation of **5**

To a solution of **4** (1 eq) in DMF was added bromoalkanol (1.2 eq), TEA (1.5 eq) and heated at 100 °C for 3 h. Completion of the reaction was monitored by TLC using 20% MeOH in DCM as mobile phase. After the reaction was complete, DMF was evaporated under vacuo and added 5 mL of water. Compound was extracted using EtOAc (3 × 5 mL). Combined organic layers were washed with saturated brine solution, dried over anhydrous sodium sulphate and evaporated in vacuo. The crude residue was purified by column chromatography (MeOH/DCM) to get compounds **5**.

5.4. Preparation of **6**

To a suspension of **5** (1 eq) in 40% aq. HBr (0.6 eq) was added TBAB (0.3 eq) and heated at 120 °C for 2 h. Completion of the reaction was monitored by TLC using 5% MeOH in DCM as mobile phase. After the reaction was complete, added 5 mL of water. Compound was extracted using EtOAc (3 × 5 mL). Combined organic layers were washed with saturated brine solution, dried over anhydrous sodium sulphate and evaporated in vacuo. The crude residue was purified by column chromatography (MeOH/DCM) to get compounds **6**.

5.5. Synthesis of title compounds (**7a**–**z**)

To a solution of **6** (1 eq) in DMF and TEA (2 eq) was added substituted piperazine (1.2 eq) and heated at 120 °C for 3 h. Completion of the reaction was monitored by TLC using 20% MeOH in DCM as mobile phase. After the reaction was complete, DMF was evaporated under vacuo and added 5 mL of water. Compound was extracted using EtOAc (3 × 5 mL). Combined organic layers were washed with saturated brine solution, dried over anhydrous sodium sulphate and evaporated in vacuo. The crude residue was purified by column chromatography (MeOH/DCM) to get compounds **7a**–**z**.

5.5.1. 4-(4-(2-(4-(3-(4-phenylpiperazin-1-yl)propyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7a**)

Yield = 83%; Off white solid, m.p. 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.18 Hz, 2H), 7.33 (d, J = 7.3 Hz, 2H), 7.21 (m, 2H), 6.89 (m, 3H), 6.68 (s, 1H), 5.52 (b, 2H), 3.58 (m, 4H), 3.37 (m, 2H), 2.86 (m, 4H), 2.63 (m, 8H), 2.42 (m, 6H), 2.17 (m, 2H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 169.61, 152.86, 150.23, 143.65, 133.87, 128.91, 128.12, 127.53, 124.05, 102.11, 100.67, 60.86, 58.92, 56.11, 55.81, 51.34, 32.12, 24.61, 20.19, 12.87. IR (KBr, ν_{max}) cm^{-1}: 3436, 3407 (NH stretch); 3071, 3033 (aromatic C–H stretch); 2849, 2761 (aliphatic C–H stretch); 1638 (C–S stretch); 1612, 1595 (aromatic C=C stretch); 1272 (aliphatic C–N stretch); 838 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{28}H_{39}N_6S$ calculated: 491.2957, found: 491.2983 $(M+H)^+$; Anal. Calculated for $C_{28}H_{38}N_6S$: C 68.53, H 7.81, N 17.13, S 6.53; found: C 68.46, H 7.63, N 17.22, S 6.47.

5.5.2. 4-(4-(2-(4-(4-(4-phenylpiperazin-1-yl)butyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7b**)

Beige solid (86%); m.p. 192–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.18 Hz, 2H), 7.29 (d, J = 7.3 Hz, 2H), 7.19 (m, 2H), 6.86 (m, 3H), 6.64 (s, 1H), 5.49 (b, 2H), 3.53 (m, 4H), 3.27 (m, 2H), 2.76 (m, 4H), 2.58 (m, 8H), 2.36 (m, 6H), 1.96 (m, 4H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 168.89, 151.83, 150.04, 142.92, 133.09, 128.15, 127.26, 126.28, 124.82, 101.69, 100.07, 59.37, 58.39, 56.81, 55.13, 51.61, 30.72, 25.56, 21.63, 12.06, 11.42. IR (KBr, ν_{max}) cm^{-1}: 3440, 3410 (NH stretch); 3065, 3027 (aromatic C–H stretch); 2842, 2753 (aliphatic C–H stretch); 1647 (C–S stretch); 1603, 1590 (aromatic C=C stretch); 1261 (aliphatic C–N stretch); 823 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{29}H_{41}N_6S$ calculated: 505.3113, found: 505.3133 $(M+H)^+$; Anal. Calculated for $C_{29}H_{40}N_6S$: C 69.01, H 7.99, N 16.65, S 6.35; found: C 69.10, H 7.78, N 16.88, S 6.42.

5.5.3. N-methyl-4-(4-(2-(4-(3-(4-phenylpiperazin-1-yl)propyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7c**)

Beige solid (79%); m.p. 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.18 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H), 7.27 (m, 2H), 6.78 (m, 3H), 6.59 (s, 1H), 4.96 (b, 1H), 3.61 (m, 4H), 2.92 (m, 4H), 2.81 (m, 8H), 2.47 (s, 3H), 2.38 (m, 8H), 1.79 (m, 2H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 167.83, 151.62, 150.02, 144.68, 134.62, 129.26, 128.77, 127.62, 124.33, 102.15, 100.99, 61.83, 59.09, 56.44, 55.22, 51.88, 34.29, 32.14, 24.90, 20.48, 11.94. IR (KBr, ν_{max}) cm^{-1}: 3418 (NH stretch); 3059, 3033 (aromatic C–H stretch); 2837, 2747 (aliphatic C–H stretch); 1629 (C–S stretch); 1611, 1583 (aromatic C=C stretch); 1263 (aliphatic C–N stretch); 827 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{29}H_{41}N_6S$ calculated: 505.3113, found: 505.3129 $(M+H)^+$; Anal. Calculated for $C_{29}H_{40}N_6S$: C 69.01, H 7.99 N 16.65, S 6.35; found: C 69.10, H 7.81, N 16.77, S 6.44.

5.5.4. N-methyl-4-(4-(2-(4-(4-(4-phenylpiperazin-1-yl)butyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7d**)

Pale yellow solid (81%); m.p. 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.18 Hz, 2H), 7.42 (d, J = 7.3 Hz, 2H), 7.28 (m, 2H), 6.83 (m, 3H), 6.61 (s, 1H), 4.82 (b, 1H), 3.58 (m, 4H), 2.87 (m, 4H), 2.72 (m, 8H), 2.51 (s, 3H), 2.37 (m, 8H), 2.11 (m, 2H), 1.92 (m, 2H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 168.12, 152.41, 151.83, 145.22, 135.21, 128.16, 127.72, 126.15, 124.11, 101.83, 100.54, 61.13, 59.85, 56.05, 55.24, 52.47, 34.25, 32.63, 25.35, 21.37, 12.88, 11.26. IR (KBr, ν_{max}) cm^{-1}: 3421 (NH stretch); 3072, 3011 (aromatic C–H stretch); 2834, 2768 (aliphatic C–H stretch); 1671 (C–S stretch); 1623, 1597 (aromatic C=C stretch); 1268 (aliphatic C–N stretch); 836 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{30}H_{43}N_6S$ calculated: 519.3270, found: 519.3251 $(M+H)^+$; Anal. Calculated for $C_{30}H_{42}N_6S$: C 69.46, H 8.16, N 16.20, S 6.18; found: C 69.23, H 8.22, N 16.11, S 6.09.

5.5.5. 1-(4-(2-methylthiazol-4-yl)phenethyl)-4-(3-(4-phenylpiperazin-1-yl)propyl)piperazine (**7e**)

Off white solid (75%); m.p. 201–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.18 Hz, 2H), 7.45 (d, J = 7.3 Hz, 2H), 7.32 (m, 2H), 6.73 (m, 3H), 6.58 (s, 1H), 3.58 (m, 6H), 2.87 (t, J = 4.7 Hz, 2H), 2.72 (m, 6H), 2.51 (t, J = 3.8 Hz, 2H), 2.41 (s, 3H), 2.34 (m, 8H), 1.86 (m, 2H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 167.51, 153.83, 151.53, 146.66, 134.73, 128.16, 127.14, 126.62, 124.94, 102.35, 100.26, 60.83, 58.45, 56.11, 55.35, 52.17, 35.22, 31.62, 26.62, 21.88, 11.83. IR (KBr, ν_{max})

cm^{-1}: 3058, 3019 (aromatic C–H stretch); 2862, 2782 (aliphatic C–H stretch); 1667 (C–S stretch); 1629 (thiazole CH_3 C–C stretch), 1612, 1582 (aromatic C=C stretch); 1277 (aliphatic C–N stretch); 848 (para disubstituted benzene); HRMS: (ESI *m/z*) for $C_{29}H_{40}N_5S$ calculated: 490.3004, found: 490.3023 $(M+H)^+$; Anal. Calculated for $C_{29}H_{39}N_5S$: C 71.12, H 8.03, N 14.30, S 6.55; found: C 71.09, H 8.10, N 14.23, S 6.49.

*5.5.6. 4-(4-(2-(4-(3-(4-benzhydrylpiperazin-1-yl)propyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7f**)*

White solid (72%); m.p. 168–170 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, $J = 11.9$ Hz, 2H), 7.41 (d, $J = 7.4$ Hz, 4H), 7.26 (t, $J = 7.1$ Hz, 4H), 7.17 (dd, $J = 12.2$, 7.4 Hz, 4H), 6.66 (s, 1H), 5.34 (b, 2H), 4.21 (s, 1H), 3.42 (m, 4H), 3.29 (m, 2H), 2.89 (m, 4H), 2.58 (m, 8H), 2.37 (m, 6H), 1.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.54, 151.09, 142.70, 139.75, 132.70, 128.91, 128.49, 127.90, 126.94, 126.05, 102.11, 60.21, 59.03, 56.55, 56.52, 53.40, 53.06, 52.95, 51.68, 33.21, 24.15, 23.96, 19.76, 13.72. IR (KBr, ν_{max}) cm^{-1}: 3482, 3426 (NH stretch); 3088, 3061 (aromatic C–H stretch); 2877, 2728 (aliphatic C–H stretch); 1651 (C–S stretch); 1612, 1587 (aromatic C=C stretch); 1278 (aliphatic C–N stretch); 844 (para disubstituted benzene); HRMS: (ESI *m/z*) for $C_{35}H_{45}N_6S$ calculated: 581.3426, found: 581.3418 $(M+H)^+$; Anal. Calculated for $C_{35}H_{44}N_6S$: C 72.37, H 7.64, N 14.47, S 5.52; found: C 72.44, H 7.70, N 14.53, S 5.64.

*5.5.7. 4-(4-(2-(4-(4-(4-benzhydrylpiperazin-1-yl)butyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7g**)*

Beige solid (81%); m.p. 175–177 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, $J = 11.4$ Hz, 2H), 7.39 (d, $J = 7.1$ Hz, 4H), 7.29 (t, $J = 6.9$ Hz, 4H), 7.19 (dd, $J = 11.9$, 7.6 Hz, 4H), 6.68 (s, 1H), 5.33 (b, 2H), 4.18 (s, 1H), 3.48 (m, 4H), 3.36 (m, 2H), 2.92 (m, 4H), 2.51 (m, 8H), 2.46 (m, 6H), 1.92 (m, 2H), 1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.41, 151.01, 141.66, 138.99, 133.45, 127.78, 127.32, 126.67, 126.23, 126.01, 104.43, 62.77, 60.96, 57.49, 56.83, 54.97, 53.76, 51.87, 50.54, 34.39, 25.75, 23.54, 18.44, 14.56, 13.96. IR (KBr, ν_{max}) cm^{-1}: 3440, 3410 (NH stretch); 3065, 3027 (aromatic C–H stretch); 2842, 2753 (aliphatic C–H stretch); 1647 (C–S stretch); 1603, 1590 (aromatic C=C stretch); 1261 (aliphatic C–N stretch); 823 (para disubstituted benzene); HRMS: (ESI *m/z*) for $C_{36}H_{47}N_6S$ calculated: 595.3583, found: 595.3577 $(M+H)^+$; Anal. Calculated for $C_{36}H_{46}N_6S$: C 72.69, H 7.79, N 14.13, S 5.39; found: C 72.60, H 7.74, N 14.18, S 5.27.

*5.5.8. 4-(4-(2-(4-(3-(4-benzhydrylpiperazin-1-yl)propyl)piperazin-1-yl)ethyl)phenyl)-N-methylthiazol-2-amine (**7h**)*

Pale yellow solid (88%); m.p. 193–195 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (t, $J = 11.4$ Hz, 2H), 7.41 (d, $J = 7.1$ Hz, 4H), 7.26 (t, $J = 6.9$ Hz, 4H), 7.12 (dd, $J = 11.9$, 7.6 Hz, 4H), 6.65 (s, 1H), 5.23 (b, 1H), 4.19 (s, 1H), 3.45 (m, 4H), 3.36 (m, 2H), 2.88 (m, 4H), 2.79 (s, 3H), 2.71 (m, 3H), 2.62 (m, 8H), 2.38 (m, 7H), 1.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.01, 152.67, 141.87, 139.34, 132.12, 128.26, 127.23, 126.77, 125.23, 124.22, 101.82, 61.82, 58.62, 56.66, 55.52, 53.85, 53.06, 52.24, 51.23, 32.77, 29.45 25.72, 24.15, 19.24, 12.72. IR (KBr, ν_{max}) cm^{-1}: 3422 (NH stretch); 3061, 3038 (aromatic C–H stretch); 2887, 2725 (aliphatic C–H stretch); 1637 (C–S stretch); 1611, 1578 (aromatic C=C stretch); 1268 (aliphatic C–N stretch); 851 (para disubstituted benzene); HRMS: (ESI *m/z*) for $C_{36}H_{47}N_6S$ calculated: 595.3583, found: 595.3571 $(M+H)^+$; Anal. Calculated for $C_{36}H_{46}N_6S$: C 72.69, H 7.79, N 14.13, S 5.39; found: C 72.60, H 7.74, N 14.18, S 5.27.

*5.5.9. 4-(4-(2-(4-(4-(4-benzhydrylpiperazin-1-yl)butyl)piperazin-1-yl)ethyl)phenyl)-N-methylthiazol-2-amine (**7i**)*

Off white solid (77%); m.p. 211–212 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (t, $J = 11.8$ Hz, 2H), 7.43 (d, $J = 7.6$ Hz, 4H), 7.33 (t, $J = 7.2$ Hz, 4H), 7.26 (dd, $J = 11.7$, 7.9 Hz, 4H), 6.75 (s, 1H), 5.23 (b, 1H), 4.13 (s, 1H), 3.47 (m, 2H), 2.99 (m, 4H), 2.63 (m, 8H), 2.49 (s, 3H), 2.39 (m, 8H), 2.13 (m, 2H), 1.75 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.22, 151.61, 141.42, 138.26, 132.77, 128.15, 127.72, 126.15, 125.01, 124.31, 102.72, 60.62, 58.15, 56.26, 55.15, 53.63, 53.12, 52.67, 50.83, 32.21, 29.12, 25.53, 24.11, 20.28, 12.12, 11.68. IR (KBr, ν_{max}) cm^{-1}: 3431 (NH stretch); 3072, 3043 (aromatic C–H stretch); 2878, 2716 (aliphatic C–H stretch); 1641 (C–S stretch); 1621, 1582 (aromatic C=C stretch); 1271 (aliphatic C–N stretch); 846 (para disubstituted benzene); HRMS: (ESI *m/z*) for $C_{37}H_{49}N_6S$ calculated: 609.3739, found: 609.3721 $(M+H)^+$; Anal. Calculated for $C_{37}H_{48}N_6S$: C 72.99, H 7.95, N 13.80, S 5.27; found: C 72.82, H 7.91, N 13.87, S 5.22.

*5.5.10. 1-(4-(2-methylthiazol-4-yl)phenethyl)-4-(3-(4-benzhydrylpiperazin-1-yl)propyl)piperazine (**7j**)*

Brown solid (76%); m.p. 208–210 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, $J = 11.9$ Hz, 2H), 7.41 (d, $J = 7.4$ Hz, 4H), 7.26 (t, $J = 7.1$ Hz, 4H), 7.17 (dd, $J = 12.2$, 7.4 Hz, 4H), 6.66 (s, 1H), 4.32 (s, 1H), 3.52 (m, 2H), 2.98 (m, 4H), 2.75 (s, 3H), 2.61 (m, 8H), 2.36 (m, 8H), 1.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.12, 154.86, 143.15, 140.82, 133.34, 129.24, 128.15, 127.26, 126.72, 125.74, 104.89, 61.83, 60.73, 57.83, 57.32, 54.26, 53.54, 52.62, 51.15, 34.63, 25.65 24.72, 21.56, 19.58, 14.22. IR (KBr, ν_{max}) cm^{-1}: 3061, 3022 (aromatic C–H stretch); 2872, 2779 (aliphatic C–H stretch); 1663 (C–S stretch); 1633 (thiazole-CH_3 C–C stretch), 1622, 1587 (aromatic C=C stretch); 1266 (aliphatic C–N stretch); 853 (para disubstituted benzene); HRMS: (ESI *m/z*) for $C_{36}H_{46}N_5S$ calculated: 580.3474, found: 580.3466 $(M+H)^+$; Anal. Calculated for $C_{36}H_{45}N_5S$: C 74.57, H 7.82, N 12.08, S 5.53; found: C 74.52, H 7.90, N 12.07, S 5.48.

*5.5.11. 4-(4-(2-(4-(3-(4-(2-chlorophenyl)piperazin-1-yl)propyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7k**)*

Pale yellow solid (85%); m.p. 152–154 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.31 (dd, $J = 14.4$, 3.8 Hz, 3H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 7.7$ Hz, 1H), 6.67 (s, 1H), 5.25 (b, 2H), 3.39 (m, 2H), 3.22 (m, 4H), 2.78 (m, 2H), 2.52 (m, 12H), 2.36 (m, 4H), 1.83 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.03, 158.61, 149.36, 140.71, 133.88, 132.16, 129.82, 128.16, 127.11, 126.47, 123.71, 121.81, 110.88, 61.39, 59.27, 57.72, 55.87, 53.83, 52.04, 50.82, 31.61, 24.76, 18.72, 16.16, 13.67. IR (KBr, ν_{max}) cm^{-1}: 3451, 3409 (NH stretch); 3078, 3033 (aromatic C–H stretch); 2855, 2759 (aliphatic C–H stretch); 1656 (C–S stretch); 1612, 1595 (aromatic C=C stretch); 1288 (aliphatic C–N stretch); 846 (para disubstituted benzene); 745 (ortho disubstituted benzene); 680 (aromatic C–Cl stretch); HRMS: (ESI *m/z*) for $C_{28}H_{38}ClN_6S$ calculated: 525.2567, found: 525.2558 $(M+H)^+$; Anal. Calculated for $C_{28}H_{37}ClN_6S$: C 64.04, H 7.10, Cl 6.75, N 16.00, S 6.11; found: C 64.00, H 7.09, Cl 6.67, N 16.10, S 6.05.

*5.5.12. 4-(4-(2-(4-(4-(4-(2-chlorophenyl)piperazin-1-yl)butyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7l**)*

Off white solid (71%); m.p. 148–150 °C; δ 7.71 (d, $J = 8.1$ Hz, 2H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.37 (dd, $J = 14.4$, 3.8 Hz, 3H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.17 (d, $J = 7.7$ Hz, 1H), 6.68 (s, 1H), 5.27 (b, 2H), 3.42 (m, 2H), 3.27 (m, 4H), 2.86 (m, 2H), 2.61 (m, 12H), 2.35 (m, 4H), 1.76 (m, 2H), 1.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.16, 157.96, 149.13, 141.67, 134.67, 132.84, 129.67, 128.71, 127.82, 126.87, 123.22, 121.64, 110.11, 60.92, 58.61, 57.24, 55.15, 53.72, 52.55, 50.26, 32.82, 25.72, 19.26, 15.17, 12.72, 11.67. IR (KBr, ν_{max}) cm^{-1}: 3466, 3423 (NH stretch); 3066, 3024 (aromatic C–H stretch); 2867, 2762 (aliphatic C–H stretch); 1448 (C–S stretch); 1654, 1611 (aromatic C=C stretch); 1273 (aliphatic C–N stretch); 844 (para disubstituted benzene); 748 (ortho disubstituted benzene); 679 (aromatic C–Cl stretch); HRMS: (ESI *m/z*) for $C_{29}H_{40}ClN_6S$ calculated: 539.2724, found: 539.2745 $(M+H)^+$; Anal. Calculated for $C_{29}H_{39}ClN_6S$: C

64.60, H 7.29, Cl 6.58, N 15.59, S 5.95; found: C 64.53, H 7.25, Cl 6.67, N 15.50, S 5.87.

*5.5.13. 4-(4-(2-(4-(3-(4-(2-chlorophenyl)piperazin-1-yl)propyl) piperazin-1-yl)ethyl)phenyl)-N-methylthiazol-2-amine (**7m**)*

Brown solid (78%); m.p. 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.27 (dd, J = 14.4, 3.8 Hz, 3H), 7.07 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.63 (s, 1H), 5.17 (b, 1H), 3.42 (m, 2H), 3.29 (m, 4H), 2.66 (m, 2H), 2.45 (m, 12H), 2.36 (s, 3H), 2.29 (m, 4H), 1.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.23, 157.42, 148.55, 139.78, 132.11, 131.35, 129.15, 128.66, 127.75, 126.34, 122.86, 120.58, 111.25, 60.36, 59.70, 57.58, 54.44, 52.68, 51.95, 50.26, 32.36, 24.97, 23.32, 18.37, 16.88, 13.37. IR (KBr, ν_{max}) cm^{-1}: 3412 (NH stretch); 3046, 3028 (aromatic C–H stretch); 2874, 2717 (aliphatic C–H stretch); 1623 (C–S stretch); 1609, 1584 (aromatic C=C stretch); 1276 (aliphatic C–N stretch); 857 (para disubstituted benzene); 739 (ortho disubstituted benzene); 681 (aromatic C–Cl stretch); HRMS: (ESI m/z) for $C_{29}H_{40}ClN_6S$ calculated: 539.2724, found: 539.2728 $(M+H)^+$; Anal. Calculated for $C_{29}H_{39}ClN_6S$: C 64.60, H 7.29, Cl 6.58, N 15.59, S 5.95; found: C 64.63, H 7.25, Cl 6.67, N 15.50, S 5.87.

*5.5.14. 4-(4-(2-(4-(4-(4-(2-chlorophenyl)piperazin-1-yl)butyl) piperazin-1-yl)ethyl)phenyl)-N-methylthiazol-2-amine (**7n**)*

Pale yellow solid (80%); m.p. 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.32 (dd, J = 14.4, 3.8 Hz, 3H), 7.12 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.61 (s, 1H), 5.22 (b, 1H), 3.39 (m, 2H), 3.14 (m, 4H), 2.78 (m, 2H), 2.59 (m, 12H), 2.49 (s, 3H), 2.38 (m, 4H), 2.05 (m, 2H), 1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.16, 156.82, 149.62, 139.16, 133.21, 131.83, 129.93, 128.41, 127.18, 126.67, 123.26, 120.11, 110.82, 60.43, 58.34, 56.05, 53.83, 52.22, 51.43, 50.34, 33.66, 24.57, 23.26, 18.82, 16.23, 13.71, 11.78. IR (KBr, ν_{max}) cm^{-1}: 3446 (NH stretch); 3052, 3034 (aromatic C–H stretch); 2866, 2723 (aliphatic C–H stretch); 1634 (C–S stretch); 1612, 1591 (aromatic C=C stretch); 1283 (aliphatic C–N stretch); 851 (para disubstituted benzene); 743 (ortho disubstituted benzene); 677 (aromatic C–Cl stretch); HRMS: (ESI m/z) for $C_{30}H_{42}ClN_6S$ calculated: 553.2880, found: 553.2859 $(M+H)^+$; Anal. Calculated for $C_{30}H_{41}ClN_6S$: C 65.13, H 7.47, Cl 6.41, N 15.19, S 5.80; found: C 65.28, H 7.35, Cl 6.47, N 15.22, S 5.85.

*5.5.15. 1-(4-(2-methylthiazol-4-yl)phenethyl)-4-(3-(4-(2-chlorophenyl)piperazin-1-yl)propyl)piperazine (**7o**)*

Beige solid (74%); m.p. 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.8 Hz, 1H), 7.25 (dd, J = 14.4, 3.8 Hz, 3H), 7.05 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.63 (s, 1H), 3.33 (m, 2H), 3.16 (m, 4H), 2.86 (m, 2H), 2.71 (s, 3H), 2.65 (m, 12H), 2.48 (m, 4H), 1.46 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.81, 155.04, 149.09, 139.78, 132.64, 130.63, 129.04, 128.77, 127.62, 126.42, 123.79, 120.43, 111.80, 59.95, 56.35, 53.30, 52.82, 52.53, 50.91, 33.09, 24.24, 23.54, 19.80, 19.32, 13.71. IR (KBr, ν_{max}) cm^{-1}: 3078, 3031 (aromatic C–H stretch); 2886, 2785 (aliphatic C–H stretch); 1676 (C–S stretch); 1643 (thiazole-CH_3 C–C stretch), 1631, 1586 (aromatic C=C stretch); 1278 (aliphatic C–N stretch); 847 (para disubstituted benzene); 737 (ortho disubstituted benzene); 674 (aromatic C–Cl stretch); HRMS: (ESI m/z) for $C_{29}H_{39}ClN_5S$ calculated: 524.2615, found: 524.2633 $(M+H)^+$; Anal. Calculated for $C_{29}H_{38}ClN_5S$: C 66.45, H 7.31, Cl 6.76, N 13.36, S 6.12; found: C 66.38, H 7.35, Cl 6.27, N 13.22, S 6.25.

*5.5.16. 4-(4-(2-(4-(3-(4-(4-nitrophenyl)piperazin-1-yl)propyl) piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7p**)*

Yellow solid (69%); m.p. 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 9.3 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 3.0 Hz, 2H), 6.77 (d, J = 9.3 Hz, 2H), 6.61 (s, 1H), 5.53 (b, 2H), 3.57 (m, 6H), 2.78 (m, 2H), 2.66 (m, 6H), 2.51 (m, 6H), 2.45 (m, 4H), 1.53 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.32, 158.63, 155.37, 138.93, 136.38, 131.70, 129.37, 127.12, 126.49, 111.44, 110.49, 60.48, 58.70, 57.25, 56.42, 54.74, 52.26, 44.96, 33.06, 25.70, 22.47, 18.58, 10.64. IR (KBr, ν_{max}) cm^{-1}: 3462, 3417 (NH stretch); 3087, 3029 (aromatic C–H stretch); 2861, 2753 (aliphatic C–H stretch); 1658 (C–S stretch); 1632, 1609 (aromatic C=C stretch); 1549, 1367 (NO_2 stretch); 1277 (aliphatic C–N stretch); 836 (para disubstituted benzene); 809 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{28}H_{38}N_7O_2S$ calculated: 536.2808, found: 536.2811 $(M+H)^+$; Anal. Calculated for $C_{28}H_{37}N_7O_2S$: C 62.78, H 6.96, N 18.30, O 5.97, S 5.99; found: C 62.59, H 6.85, N 18.42, O 5.89, S 5.85.

*5.5.17. 4-(4-(2-(4-(4-(4-(4-nitrophenyl)piperazin-1-yl)butyl) piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7q**)*

Yellow solid (71%); m.p. 193–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 9.3 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 3.0 Hz, 2H), 6.72 (d, J = 9.3 Hz, 2H), 6.62 (s, 1H), 5.52 (b, 2H), 3.65 (m, 6H), 2.71 (m, 2H), 2.63 (m, 6H), 2.52 (m, 6H), 2.43 (m, 4H), 1.74 (m, 2H), 1.43 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.89, 157.75, 154.78, 138.37, 136.70, 131.36, 129.48, 127.70, 126.33, 110.23, 109.60, 60.37, 58.26, 57.27, 56.18, 54.29, 52.80, 44.22, 33.25, 24.32, 23.72, 22.19, 19.49, 11.93. IR (KBr, ν_{max}) cm^{-1}: 3457, 3406 (NH stretch); 3076, 3016 (aromatic C–H stretch); 2871, 2765 (aliphatic C–H stretch); 1661 (C–S stretch); 1644, 1607 (aromatic C=C stretch); 1546, 1372 (NO_2 stretch); 1259 (aliphatic C–N stretch); 843 (para disubstituted benzene); 812 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{29}H_{40}N_7O_2S$ calculated: 550.2964, found: 550.2954 $(M+H)^+$; Anal. Calculated for $C_{29}H_{39}N_7O_2S$: C 63.36, H 7.15, N 17.84, O 5.82, S 5.83; found: C 63.49, H 7.28, N 17.72, O 5.77, S 5.75.

*5.5.18. 4-(4-(2-(4-(5-(4-(4-nitrophenyl)piperazin-1-yl)pentyl) piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7r**)*

Yellow solid (79%); m.p. 187–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 9.3 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 3.0 Hz, 2H), 6.69 (d, J = 9.3 Hz, 2H), 6.59 (s, 1H), 5.46 (b, 2H), 3.57 (m, 6H), 2.65 (m, 2H), 2.53 (m, 6H), 2.46 (m, 6H), 2.41 (m, 4H), 1.61 (m, 4H), 1.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.62, 157.38, 155.21, 137.69, 136.75, 131.87, 130.43, 127.26, 126.19, 110.61, 110.04, 61.72, 58.83, 57.86, 56.47, 54.38, 52.23, 45.52, 33.69, 25.68, 24.32, 23.37, 22.93, 19.72, 12.26. IR (KBr, ν_{max}) cm^{-1}: 3463, 3413 (NH stretch); 3084, 3023 (aromatic C–H stretch); 2864, 2751 (aliphatic C–H stretch); 1678 (C–S stretch); 1637, 1603 (aromatic C=C stretch); 1545, 1361 (NO_2 stretch); 1261 (aliphatic C–N stretch); 851 (para disubstituted benzene); 807 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{30}H_{42}N_7O_2S$ calculated: 564.3121, found: 564.3143 $(M+H)^+$; Anal. Calculated for $C_{30}H_{41}N_7O_2S$: C 63.91, H 7.33, N 17.39, O, 5.68, S 5.69; found: C 63.89, H 7.38, N 17.42, O 5.57, S 5.65.

*5.5.19. N-methyl-4-(4-(2-(4-(3-(4-(4-nitrophenyl)piperazin-1-yl) propyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7s**)*

Yellow solid (73%); m.p. 181–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 9.3 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 3.0 Hz, 2H), 6.75 (d, J = 9.3 Hz, 2H), 6.61 (s, 1H), 5.22 (s, 1H), 3.61 (m, 6H), 2.74 (m, 2H), 2.67 (m, 6H), 2.59 (m, 6H), 2.57 (s, 3H), 2.47 (m, 4H), 1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.24, 156.16, 154.27, 138.77, 136.37, 131.48, 130.55, 128.74, 127.33, 111.47, 110.37, 60.16, 59.72, 57.23, 56.16, 54.77, 52.73, 45.48, 33.77, 29.58, 24.37, 23.25, 19.32, 11.69. IR (KBr, ν_{max}) cm^{-1}: 3447 (NH stretch); 3076, 3037 (aromatic C–H stretch); 2854, 2718 (aliphatic C–H stretch); 1645 (C–S stretch); 1609, 1586 (aromatic C=C stretch); 1531, 1367 (NO_2 stretch); 1278 (aliphatic C–N stretch); 842 (para disubstituted benzene); 812 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{29}H_{40}N_7O_2S$ calculated: 550.2964, found: 550.2951 $(M+H)^+$; Anal.

Calculated for $C_{29}H_{39}N_7O_2S$: C 63.36, H 7.15, N 17.84, O 5.82, S 5.83; found: C 63.49, H 7.28, N 17.72, O 5.77, S 5.89.

*5.5.20. N-methyl-4-(4-(2-(4-(4-(4-nitrophenyl)piperazin-1-yl) butyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7t**)*

Yellow solid (78%); m.p. 189–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9.3 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 3.0 Hz, 2H), 6.93 (d, J = 9.3 Hz, 2H), 6.63 (s, 1H), 5.26 (s, 1H), 3.42 (m, 6H), 2.79 (m, 2H), 2.69 (m, 6H), 2.56 (m, 6H), 2.52 (s, 3H), 2.43 (m, 4H), 2.01 (m, 2H), 1.46 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.01, 156.96, 154.25, 139.43, 137.97, 132.94, 130.66, 127.27, 126.16, 112.28, 110.78, 61.82, 59.83, 57.7 4, 56.46, 53.27, 52.49, 45.72, 33.28, 29.39, 24.82, 23.29, 19.77, 13.23, 11.62. IR (KBr, ν_{max}) cm^{-1}: 3456 (NH stretch); 3087, 3041 (aromatic C–H stretch); 2844, 2721 (aliphatic C–H stretch); 1656 (C–S stretch); 1631, 1595 (aromatic C=C stretch); 1527, 1362 (NO_2 stretch); 1286 (aliphatic C–N stretch); 852 (para disubstituted benzene); 806 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{30}H_{42}N_7O_2S$ calculated: 564.3121, found: 564.3139 $(M+H)^+$; Anal. Calculated for $C_{30}H_{41}N_7O_2S$: C 63.91, H 7.33, N 17.39, O 5.68, S 5.69; found: C 63.89, H 7.39, N 17.42, O 5.85, S 5.73.

*5.5.21. 1-(4-(2-methylthiazol-4-yl)phenethyl)-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)propyl)piperazine (**7u**)*

Pale yellow solid (73%); m.p. 177–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 9.3 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 3.0 Hz, 2H), 6.81 (d, J = 9.3 Hz, 2H), 6.61 (s, 1H), 3.49 (m, 6H), 2.81 (m, 2H), 2.76 (s, 3H), 2.63 (m, 6H), 2.58 (m, 6H), 2.44 (m, 4H), 1.46 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.84, 155.02, 154.85, 139.89, 138.39, 132.61, 129.04, 126.41, 125.96, 112.61, 111.81, 60.06, 59.15, 56.42, 56.31, 53.01, 52.68, 46.99, 33.19, 24.23, 23.94, 19.80, 19.34, 13.71. IR (KBr, ν_{max}) cm^{-1}: 3122, 3076 (aromatic C–H stretch); 2867, 2726 (aliphatic C–H stretch); 1662 (C–S stretch); 1639 (thiazole-CH_3 C–C stretch); 1628, 1597 (aromatic C=C stretch); 1523, 1356 (NO_2 stretch); 1276 (aliphatic C–N stretch); 844 (para disubstituted benzene); 807 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{29}H_{39}N_6O_2S$ calculated: 535.2855, found: 535.2862 $(M+H)^+$; Anal. Calculated for $C_{29}H_{38}N_6O_2S$: C 65.14, H 7.16, N 15.72, O 5.98, S 6.00; found: C 65.29, H 7.20, N 15.62, O 5.88, S 6.07.

*5.5.22. 4-(4-(2-(4-(3-(4-(pyridin-2-yl)piperazin-1-yl)propyl) piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7v**)*

White solid (84%); m.p. 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, J = 4.9, 1.2 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.47 (ddd, J = 8.8, 7.2, 2.0 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 6.83–6.49 (m, 3H), 5.45 (s, 2H), 3.59–3.51 (m, 4H), 2.81 (dd, J = 9.9, 6.3 Hz, 2H), 2.74–2.59 (m, 6H), 2.59–2.48 (m, 8H), 2.47–2.39 (m, 4H), 1.82–1.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.49, 159.53, 151.14, 147.93, 139.75, 137.48, 132.71, 128.92, 126.05, 113.31, 107.10, 102.11, 60.22, 56.67, 56.60, 53.12, 53.05, 52.96, 45.17, 33.24, 24.14. IR (KBr, ν_{max}) cm^{-1}: 3461, 3421 (NH stretch); 3136, 3071 (aromatic C–H stretch); 2875, 2733 (aliphatic C–H stretch); 1658 (C–S stretch); 1631, 1602 (aromatic C=C stretch); 1284 (aliphatic C–N stretch); 846 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{27}H_{38}N_7S$ calculated: 492.2909, found: 492.2912 $(M+H)^+$; Anal. Calculated for $C_{27}H_{37}N_7S$: C 65.95, H 7.58, N 19.94, S 6.52; found: C 65.89, H 7.50, N 19.82, S 6.57.

*5.5.23. 4-(4-(2-(4-(4-(4-(pyridin-2-yl)piperazin-1-yl)butyl) piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7w**)*

Off white solid (77%); m.p. 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 4.7, 1.1 Hz, 1H), 7.78 (d, J = 7.9 Hz, 2H), 7.61 (ddd, J = 8.1, 6.9, 1.8 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 6.72–6.56 (m, 3H), 5.39 (s, 2H), 3.55–3.47 (m, 4H), 2.77 (dd, J = 9.7, 6.6 Hz, 2H), 2.68–2.54 (m, 6H), 2.49–2.36 (m, 8H), 2.33–2.26 (m, 4H), 1.91–1.72 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.22, 160.23, 152.64, 149.17, 140.88, 139.25, 133.66, 129.34, 127.61, 114.43, 108.19, 103.51, 61.83, 57.37, 56.11, 53.84, 52.83, 51.24, 46.24, 34.77, 26.49, 24.92. IR (KBr, ν_{max}) cm^{-1}: 3458, 3419 (NH stretch); 3142, 3081 (aromatic C–H stretch); 2879, 2719 (aliphatic C–H stretch); 1655 (C–S stretch); 1619, 1593 (aromatic C=C stretch); 1292 (aliphatic C–N stretch); 839 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{28}H_{40}N_7S$ calculated: 506.3066, found: 506.3059 $(M+H)^+$; Anal. Calculated for $C_{28}H_{39}N_7S$: C 66.50, H 7.77, N 19.39, S 6.34; found: C 66.67, H 7.62, N 19.42, S 6.47.

*5.5.24. N-methyl-4-(4-(2-(4-(3-(4-(pyridin-2-yl)piperazin-1-yl) propyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7x**)*

Beige solid (71%); m.p. 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.7, 1.5 Hz, 1H), 7.11 (d, J = 7.8 Hz, 2H), 7.49 (ddd, J = 8.1, 6.7, 1.7 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 6.92–6.53 (m, 3H), 5.37 (s, 1H), 3.54–3.43 (m, 4H), 2.93 (dd, J = 9.7, 5.8 Hz, 2H), 2.72–2.63 (m, 6H), 2.53–2.45 (m, 8H), 2.38–2.27 (m, 7H), 1.78–1.66 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.89, 158.95, 152.44, 148.21, 138.62, 138.11, 133.84, 129.15, 127.84, 114.37, 108.26, 103.44, 59.51, 57.72, 55.94, 53.32, 52.73, 51.22, 46.53, 34.35, 29.83 26.62. IR (KBr, ν_{max}) cm^{-1}: 3426 (NH stretch); 3161, 3102 (aromatic C–H stretch); 2883, 2725 (aliphatic C–H stretch); 1671 (C–S stretch); 1625, 1598 (aromatic C=C stretch); 1282 (aliphatic C–N stretch); 847 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{28}H_{40}N_7S$ calculated: 506.3066, found: 506.3041 $(M+H)^+$; Anal. Calculated for $C_{28}H_{39}N_7S$: C 66.50, H 7.77, N 19.39, S 6.34; found: C 66.66, H 7.82, N 19.44, S 6.49.

*5.5.25. N-methyl-4-(4-(2-(4-(4-(4-(pyridin-2-yl)piperazin-1-yl) butyl)piperazin-1-yl)ethyl)phenyl)thiazol-2-amine (**7y**)*

Off white solid (73%); m.p. 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 5.1, 1.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.72 (ddd, J = 7.6, 6.2, 1.3 Hz, 1H), 7.34 (d, J = 7.6 Hz, 2H), 6.61–6.54 (m, 3H), 5.41 (s, 1H), 3.53–3.41 (m, 4H), 2.68 (dd, J = 9.2, 6.7 Hz, 2H), 2.55–2.47 (m, 6H), 2.43–2.37 (m, 8H), 2.29–2.23 (m, 7H), 1.92–1.86 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.44, 161.56, 151.62, 150.67, 141.34, 140.87, 134.12, 130.73, 128.81, 115.99, 109.44, 104.33, 60.52, 56.84, 55.73, 54.24, 53.45, 51.73, 46.87, 35.41, 27.16, 25.84, 24.21. IR (KBr, ν_{max}) cm^{-1}: 3422 (NH stretch); 3157, 3104 (aromatic C–H stretch); 2877, 2713 (aliphatic C–H stretch); 1679 (C–S stretch); 1644, 1587 (aromatic C=C stretch); 1273 (aliphatic C–N stretch); 851 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{29}H_{42}N_7S$ calculated: 520.3222, found: 520.3234 $(M+H)^+$; Anal. Calculated for $C_{29}H_{41}N_7S$: C 67.02, H 7.95, N 18.86, S 6.17; found: C 67.16, H 7.88, N 18.94, S 6.19.

*5.5.26. 1-(4-(2-methylthiazol-4-yl)phenethyl)-4-(3-(4-(pyridin-2-yl)piperazin-1-yl)propyl)piperazine (**7z**)*

Off white solid (79%); m.p. 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, J = 4.9, 1.2 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.47 (ddd, J = 8.8, 7.2, 2.0 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 6.83–6.49 (m, 3H), 5.45 (s, 2H), 3.59–3.51 (m, 4H), 2.81 (dd, J = 9.9, 6.3 Hz, 2H), 2.74–2.59 (m, 6H), 2.59–2.48 (m, 8H), 2.47–2.39 (m, 4H), 1.82–1.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.49, 159.53, 151.14, 147.93, 139.75, 137.48, 132.71, 128.92, 126.05, 113.31, 107.10, 102.11, 60.22, 56.67, 56.60, 53.12, 53.05, 52.96, 45.17, 33.24, 24.14. IR (KBr, ν_{max}) cm^{-1}: 3164, 3096 (aromatic C–H stretch); 2869, 2710 (aliphatic C–H stretch); 1682 (C–S stretch); 1639 (thiazole-CH_3 C–C stretch); 1612, 1592 (aromatic C=C stretch); 1281 (aliphatic C–N stretch); 844 (para disubstituted benzene); HRMS: (ESI m/z) for $C_{28}H_{39}N_6S$ calculated: 491.2957, found: 491.2967 $(M+H)^+$; Anal. Calculated for $C_{28}H_{38}N_6S$: C 68.53, H 7.81, N 17.13 S, 6.53; found: C 68.46, H 7.74, N 17.24, S 6.45.

5.6. Anti-tubercular activity against MTB $H_{37}R_V$ strain

The antimycobacterial activities of title compounds **7a**–**z** were evaluated against MTB H_{37}Rv strain using MABA [30,31]. 200 μL of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates to minimize evaporation of the medium in the test wells during incubation. The wells in rows B to G in columns 3 to 11 received 100 μl of 7H9GC broth. 100 μL of 2 × drug solutions were added to the wells in rows B to G in columns 2 and 3. By using a multichannel pipette, 100 μl was transferred from column 3 to column 4, and the contents of the wells were mixed well. Identical serial 1:2 dilutions were continued through column 10, and 100 μl of excess medium was discarded from the wells in column 10. 100 μL of MTB inoculum was added to the wells in rows B to G in columns 2 to 10. 100 μL of medium to B11 and C11 (media control), 100 μL of MTB inoculum to D11 and E11 and 100 μL of MTB inoculum with 3–5% DMSO to F11 and G11 (solvent control) were added. The plates were sealed with parafilm and were incubated at 37 °C for 5 days. 50 μL of a freshly prepared 1:1 mixture of 10 x Alamar Blue (Accumed International, Westlake, Ohio) reagent and 10% Tween 80 were added to well D11. The plates were reincubated at 37 °C for 24 h. If well D11 turned pink, the reagent mixture was added to all wells in the microplate (if the well remained blue, the reagent mixture would be added to another control well and the result would be read on the following day). The microplates were resealed with parafilm and were incubated for an additional 24 h at 37 °C, and the colours of all wells were recorded. A blue colour in the well was interpreted as no growth, and a pink colour was scored as growth. A few wells appeared violet after 24 h of incubation, but they invariably changed to pink after another day of incubation and thus were scored as growth (while the adjacent blue wells remained blue). The MIC was defined as the lowest drug concentration which prevented a colour change from blue to pink.

5.7. Cytotoxicity assay

Most active compounds **7a**, **7f**, **7g**, **7h**, **7j**, **7n**, **7p**, **7r** and **7v** were further examined for toxicity in a RAW 264.7 cell line at the concentration 50 μg/mL. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay [32].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.07.067.

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