Chapter V

Design, synthesis and biological evaluation of new substituted sulfonamide tetrazole derivatives as anti-tubercular agents

Chapter 5

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5.1. Introduction

1,2,4 triazoles and their base derivatives correspond to an interesting class of compounds possessing a wide spectrum of biological activities. Number of 1,2,4 triazole containing ring systems exhibited anti-tubercular [1-3], antibacterial [4-6], anticancer [7, 8], antiviral [9, 10] and antifungal activities [11-13]. Based on the incorporation of various substitutents into 1,2,4 triazole ring their heterocyclic derivatives lead to compounds with enhanced biological activities. Thompson *et al.,* reported (7*S*)-2-nitro-7-((4-(trifluoromethoxy)benzyl)oxy)-5a,6,7,8,9a,10-hexahydro-5*H*-pyrano[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyridine derivatives which inhibited MTB H37RV strain with MIC ranging from 112-128 µM [14]. Krishna and co-workers published (*E*)-4-(benzylideneamino)-3-(2-(2,6-dichlorophenylamino)benzyl)-1-(morpholinomethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione derivatives which showed anti-TB activity ranging from 0.2-25 µM against MTB H37RV strain [15]. Klimesova's group reported 1,2,4-triazole 3-benzylsulfanyl derivatives which exhibited MTB activity with MIC ranging from 32-250 µM. Pattan *et al*., reported 4-(3-mercapto-5- substituted 1*H*-1,2,4-triazol-4-yl)benzenesulfonamide compounds which inhibited MTB H37Rv strain at 25.0 µg/mL [16]. Suresh Kumar *et al.,* reported 4-substituted- 5-(4-isopropylthiazol-2-yl)-4*H*-1,2,4-triazole-3-thiols which exhibited MIC ranging from 4-125 µg/mL against MTB H37RV [17]. Khanage *et al*., reported 6-(substitutedaryl)-4-(3,5-diphenyl-*1H*-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol derivatives which inhibited MTB H37Rv strain at 0.156 µg/mL [17]. 1,2,4 triazole based anti-TB agents are portrayed in **figure 5.1**.

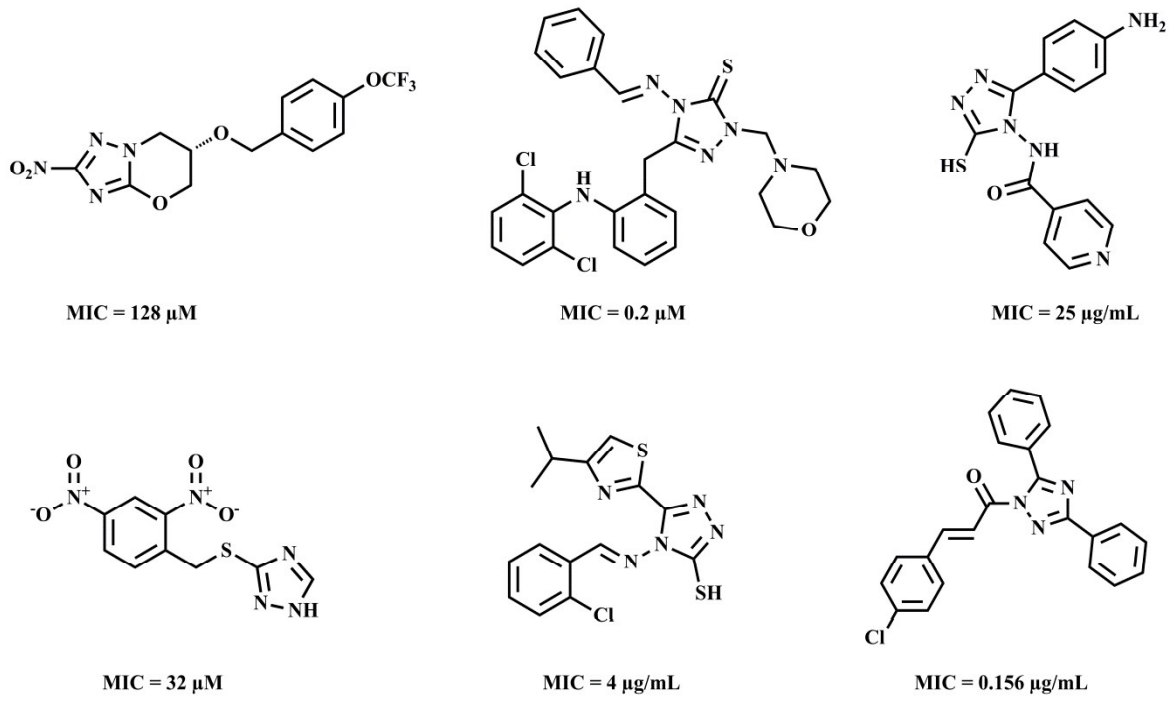


Figure 5.1: Some of the1,2,4 triazole based anti-tubercular agents.

Tetrazoles and its derivatives are known for biological activities such as antibacterial, anti-inflammatory, antifungal, antiviral, anti-TB, antinociceptive, hypoglycemic and anti-cancer [18]. The tetrazole ring is resistant to biological degradation and therefore used as isosteric substituents of various functional groups [19]. Indeed, substituted tetrazoles have similar p*Ka* values to that of corresponding carboxylic acid [20]. Further, tetrazole analogues increase lipophilicity facilitating easier crossing of compounds across the plasma membrane [19]. Karabanovich's group reported 1- and 2-alkyl-5-[(3,5-dinitrobenzyl)sulfanyl]-2*H*-tetrazole derivatives and their selenium bioisosteres with highest antimycobacterial activity, with MIC values 0.37-0.46 µg/mL against MTB CNCTC My 331/88 [21]. Chauhan and co-researchers reported a novel series of thiazolone piperazine tetrazole derivatives with MICs ranging from 1.56 -12.5 µg/mL [19]. Mohite *et al.,* reported 3-chloro-4-(substituted phenyl)- 1-{[2-oxo-2-(5-phenyl-1*H*-tetrazol-1-yl) ethyl] amino} azetidin-2-one derivatives with MIC values ranging from 10.0-0.156 µg/mL against MTB H37Rv [18]. Tetrazole based anti-TB agents are depicted in **figure 5.2**.

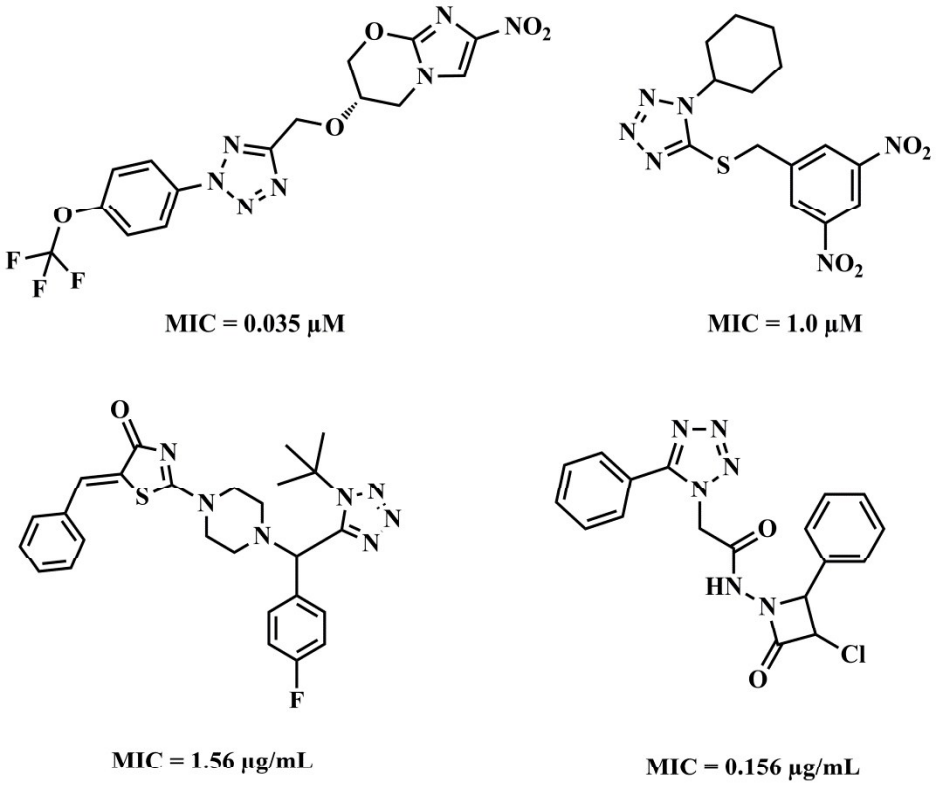


Figure 5.2: Some of the tetrazole based anti-tubercular agents.

Aryl sulfonamide derivatives display enhanced antibacterial and anti-TB activity. Lipophilicity is an important parameter related to membrane permeation of compounds in biological systems [22]. Thomas *et al.,* reported 1-[1-(quinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methyl sulphonamides with MIC values 0.625-100 µg/mL [23]. Ranjith *et al.,* reported *N*-(4-(4-chloro-1*H*-imidazol-1- yl)-3-methoxyphenyl)sulfonamide derivatives as anti-TB agents with MIC values ranging from 0.625-5.0 µg/mL againt MTB H37Rv [24]. Nagesh *et al.,* reported series of 3-(4-(substitutedsulfonyl)piperazin-1-yl)benzo[*d*]isoxazole analogues with MIC ranging from 3.125 to ≥50 µg/mL [25] and novel 6-(piperazin-1-yl)phenanthridine amide and sulphonamide analogues exhibiting MIC between 1.56 to ≥50 µg/mL were reported [26]. Sulfonamide based anti-TB compounds are displayed in **figure 5.3.**

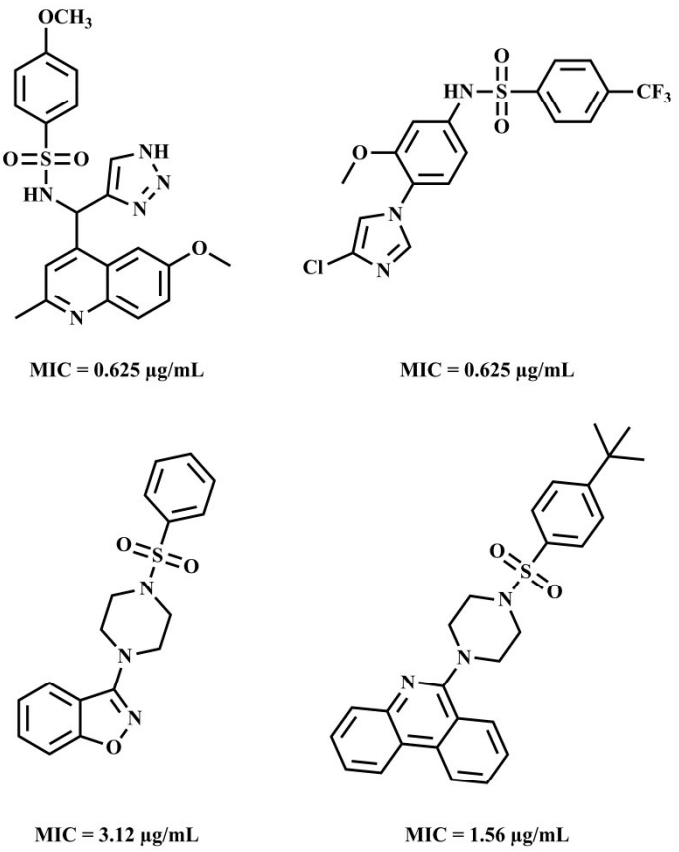


Figure 5.3: Some of the sulfonamide based anti-tubercular agents.

With this collective information and confident by our recent anti-TB results emphasizing on molecular hybridization approach, we drew a synthetic stratagem to knit all these imperative pharmacophoric groups into one single scaffold and synthesized 2-(2,4-dihalophenyl)-1-(4-(1-(substitutedsulfonyl)-1*H*-tetrazol-5-yl)phenoxy)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol and 2-(2,4-dihalo)-1-(2-methoxy-4-(1-(substitutedsulfonyl)-1*H*-tetrazol-5-yl)phenoxy)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol analogues (**Figure 5.4**).

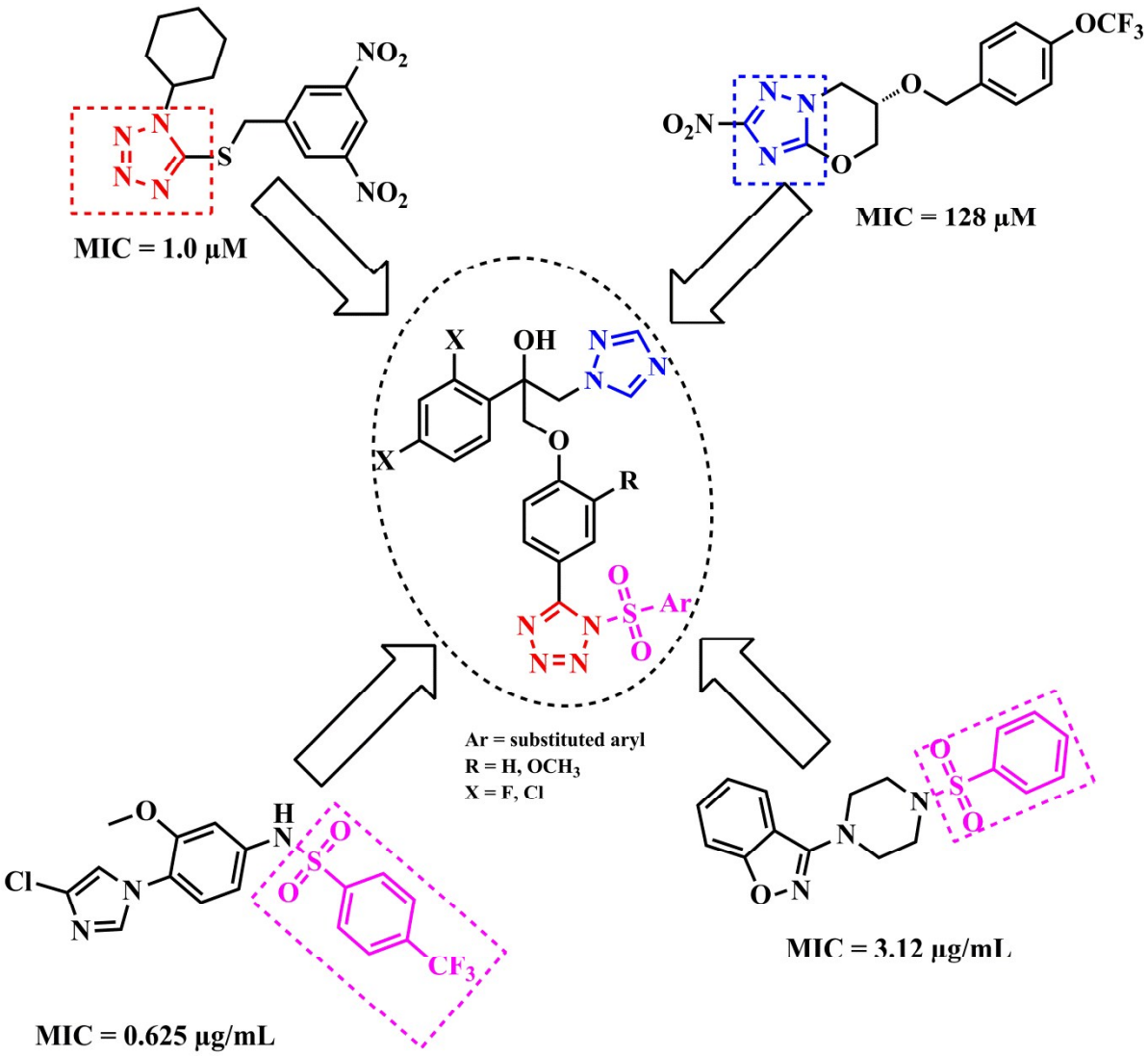


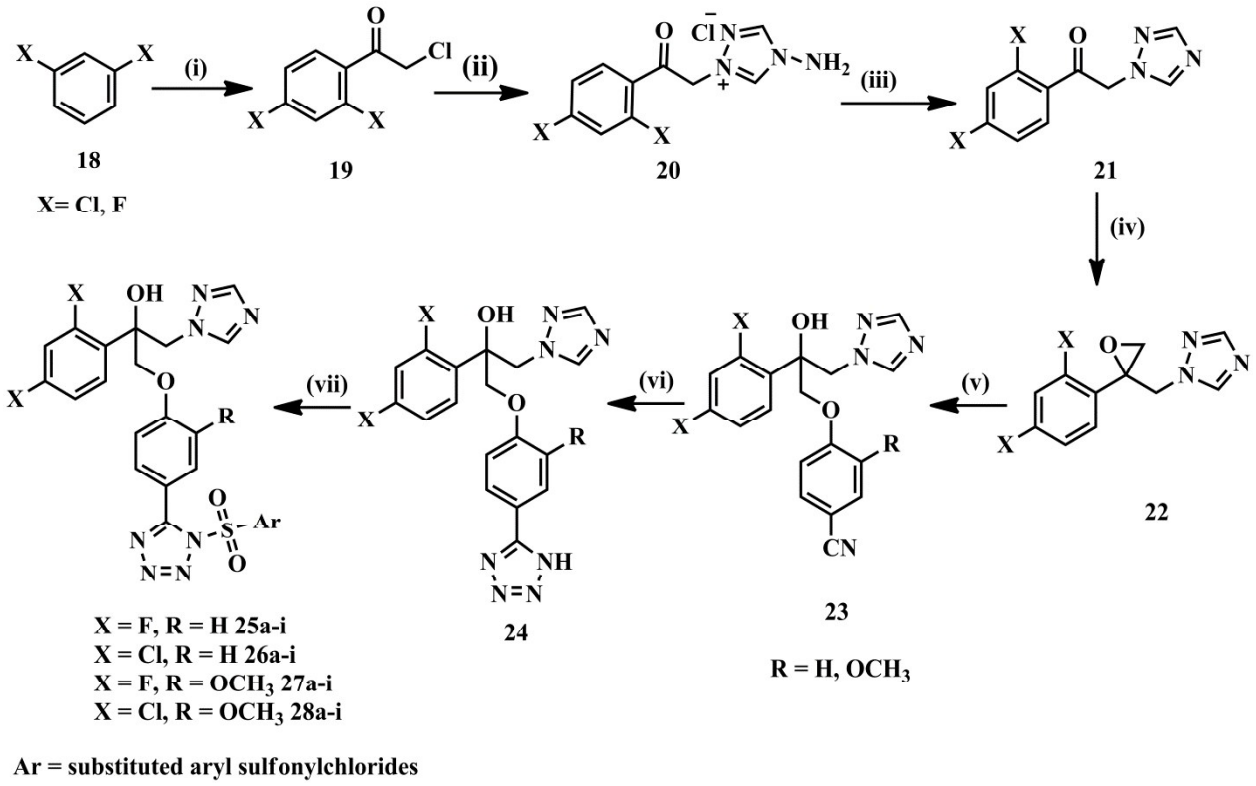
Figure 5.4: Design strategy to achieve title compounds

5.2. Results and Discussion

5.2.1. Chemistry

The designed molecules were synthesized in seven steps as sketched in **Scheme 5.1**. Initially, we prepared 2-chloro-1-(2,4-dihalophenyl)ethanone (**19**) from dihalobenzene (dichlorobenzene or diflourobezene), chloroacetylchloride, and $AlCl_3$ *via* Friedel craft acylation. Treatment of **19** with 4-amino-4*H*-1,2,4-triazole in acetonitrile yielded 4-amino-1-(2-(2,4-dihalophenyl)-2-oxoethyl)-4*H*-1,2,4-triazol-1-ium chloride salt (**20**). Compound **20** on deamination followed by 1.5N HCl, $NaNO_2$ yielded compound **21**. Corey-Chaykovsky epoxidation of **21** using trimethylsulfoxonium

iodide and NaOH yielded epoxide **22** [27]. Compound **22** on treatment with 4-hydroxybenzonitrile/4-hydroxy-3-methoxybenzonitrile in the presence K_2CO_3 and TBAB resulted in compound **23** [28]. Conversion of cyano compound **23** to tetrazole **24** was carried out using trimethylsilyl azide and TBAB.$3H_2O$ in the sealed tube [29]. The title tetrazole containing substituted aryl sulfonyls (**25a-i, 26a-i, 27a-i** & **28a-i**) were synthesized from **24** by varying substituted aryl sulfonylchlorides in the presence of TEA in dichloromethane.



Scheme 5.1: Synthetic protocol of tetrazole sulfonamides.

Reagents and conditions: (i) $ClCH_2COCl$ (1.2 eq), $AlCl_3$ (2.0 eq), DCE, 60 ºC, 12 h. (ii) 4-amino-4*H*-1,2,4-triazole (1.2 eq), ACN, 80 ºC, 16 h. (iii) 1.5N HCl, $NaNO_2$ (1.2 eq), 0 ºC, 1 h (iv) TMSI (1.2 eq), 20% NaOH (1.0 eq), toluene, 60 ºC, 12 h. (v) 4-hydroxybenzonitrile/4-hydroxy-3-methoxybenzonitrile (1.3 eq), K_2CO_3 (3.0 eq), TBAB (0.1 eq), EtOAc, 80 ºC, 12 h. (vi) $TMSN_3$ (1.2 eq), TBAB.$3H_2O$ (1.0 eq), 12 h. (vii) substituted aryl sulfonylchlorides (1.3 eq), TEA (3.0 eq), DCM, rt, 16 h.

In this synthesis, cyano compound (**23**) to tetrazole compound (**24**) conversation was confirmed by disappearance of IR signal at 2224 cm^{-1} (cyano peak). Structures of **25a-i, 26a-i, 27a-i** & **28a-i** was further substantiated through ^{1}H NMR and mass spectrometry. All the synthesized compounds displayed doublets of doublets in the range 4.36–4.95 ppm corresponding to their enantiotopic (–CH_2–) protons, singlet in the range 3.65–3.87 ppm corresponding to –OCH_3 proton, and protons of 1,2,4-triazole ring resonated in the range 7.8–8.2 and 8.3–8.5 ppm. Both analytical and spectral data (^{1}H NMR, ^{13}C NMR, IR and LCMS) of all the synthesized compounds confirmed the obtained structures.

5.2.2 Antimycobacterial activity

All the synthesized compounds were tested for their ability to inhibit the growth of MTB H37RV by MABA [30-32]. Isoniazid, Rifampicin and Ethambutol were used as the positive drug controls. The antimycobacterial test results of synthesized compounds are represented in the **Table 5.1** as minimum inhibitory concentration ranging from 0.78 to ≥25 µg/mL. Compounds with MIC ≤ 6.25 µg/mL were further subjected to cytotoxicity studies.

Table 5.1: Result of Antimycobacterial screening of title compounds

Entry	X	R	Ar	MIC in µM against MTB H37Rv (µg/mL)
25a	F	H	Phenyl	5.78 (3.12)
25b	F	H	4-Methylphenyl	11.29 (6.25)
25c	F	H	4-Fluorophenyl	2.79 (1.56)
25d	F	H	4-Bromophenyl	5.04 (3.12)
25e	F	H	4-Methoxyphenyl	5.47 (3.12)
25f	F	H	4-Nitrophenyl	2.66 (1.56)
25g	F	H	4-*ter*-butylphenyl	10.49 (6.25)
25h	F	H	2-bromothiophene	4.99 (3.12)

25i	F	H	4-trifluoromethoxyphenyl	10.02 (6.25)
26a	Cl	H	Phenyl	43.67 (25)
26b	Cl	H	4-Methylphenyl	5.32 (3.12)
26c	Cl	H	4-Fluorophenyl	1.32 (0.78)
26d	Cl	H	4-Bromophenyl	9.59 (6.25)
26e	Cl	H	4-Methoxyphenyl	10.37 (6.25)
26f	Cl	H	4-Nitrophenyl	20.24 (12.5)
26g	Cl	H	4-*ter*-butylphenyl	2.48 (1.56)
26h	Cl	H	2-bromothiophene	19.01 (12.5)
26i	Cl	H	4-trifluoromethoxyphenyl	38.08 (25.0)
27a	F	OCH_3	Phenyl	5.47 (3.12)
27b	F	OCH_3	4-Methylphenyl	10.70 (6.25)
27c	F	OCH_3	4-Fluorophenyl	10.63 (6.25)
27d	F	OCH_3	4-Bromophenyl	4.81 (3.12)
27e	F	OCH_3	4-Methoxyphenyl	2.60 (1.56)
27f	F	OCH_3	4-Nitrophenyl	20.34 (12.5)
27g	F	OCH_3	4-*ter*-butylphenyl	2.49 (1.56)
27h	F	OCH_3	2-bromothiophene	2.38 (1.56)
27i	F	OCH_3	4-trifluoromethoxyphenyl	4.77 (3.12)
28a	Cl	OCH_3	Phenyl	41.49 (25)
28b	Cl	OCH_3	4-Methylphenyl	5.06 (3.12)
28c	Cl	OCH_3	4-Fluorophenyl	10.07 (6.25)

28d	Cl	OCH_3	4-Bromophenyl	2.28 (1.56)
28e	Cl	OCH_3	4-Methoxyphenyl	9.88 (6.25)
28f	Cl	OCH_3	4-Nitrophenyl	4.81 (3.12)
28g	Cl	OCH_3	4-*ter*-butylphenyl	18.98 (12.5)
28h	Cl	OCH_3	2-bromothiophene	2.26 (1.56)
28i	Cl	OCH_3	4-trifluoromethoxyphenyl	9.10 (6.25)
Ethambutol	-	-	-	7.63 (1.56)
Isoniazid	-	-	-	0.036 (0.05)
Rifampicin	-	-	-	0.12 (0.10)

Structure activity relationship of compounds 25a-i & 26a-i

For structure activity relationship (SAR) study, among the nine compounds which contained 1,3 difluorobenzene skeleton, we varied it with 3 electron donating *para* substituted sulfonyl chlorides, 4 electron withdrawing *para* substituted sulfonylchlorides and one heterocyclic sulfonylchloride. SAR for both the series is explained with respect to unsubstituted compounds (**25a** and **26a**).

Among the 1,3 difluorobezene derivatives, the unsubstituted benzene sulfonylchloride compound (**25a**) exhibited MTB MIC value of 3.12 μg/mL. Electron releasing methyl and tertiary butyl groups reduced (**25b, 25g**) the activity by two folds (MIC = 6.25 μg/mL) but the presence of electron releasing methoxy group in the *para* position did not impact the activity (**25e,** MIC = 3.12 μg/mL). Presence of electron withdrawing groups showed major impact on the activity. Nitro group in compound **25f** at *para* position enhanced the activity by two folds (MIC =1.56 μg/mL), while the electron withdrawing -OCF_3 decreased the activity by two folds (**25i,** MIC = 6.25 μg/mL). With the presence of electron withdrawing fluoro the activity was enhanced by two folds **25c** (MIC =1.56 μg/mL); replacing with bromo group had no effect on the activity. With introduction of heterocyclic sulfonylchloride (2-bromothiophene) the activity (**25h**) remained unaltered (MIC = 3.12 μg/mL).

Among the synthesized, 1,3 dichlorobenzene derivatives **26a-i, 26a,** unsubstituted benzene sulfonyl chloride compound exhibited activity with MIC = 25 μg/mL. With the introduction of electron withdrawing groups at the *para* position on phenyl ring the activity increased. Presence of methyl group enhanced the activity by eight folds (**26b,** MIC = 3.12 μg/mL) but with presence of tertiary butyl group activity was enhanced by sixteen fold (**26g**, MIC = 1.56 μg/mL). Presence of the electron releasing methoxy increased the activity by four folds (**26e**, MIC = 6.25 μg/mL). With electron withdrawing -OCF_3 the activity remained unaltered (**26i**, MIC = 25 μg/mL). Presence of the withdrawing nitro increased the activity by two folds (**26f**, MIC = 12.5 μg/mL). Introduction of fluoro at *para* position drastically enhanced the activity by thirty two folds (**26c**, MIC = 0.78 μg/mL) but with the presence of bromo (**26d**, MIC = 6.25 μg/mL) activity increased four folds. With heterocyclic sulfonylchloride (2-bromothiophene) activity increased by two fold in **26h** (MIC = 12.5 μg/mL).

SAR of compounds 27a-i & 28a-i

For SAR study, among the nine compounds which contained 1,3 difluorobenzene skeleton, we varied it with 3 electron donating *para* substituted sulfonyl chlorides, 4 electron withdrawing *para* substituted sulfonylchlorides and one heterocyclic sulfonylchloride. SAR for both the series is explained with respect to unsubstituted compounds (**27a** and **28a**).

In these 1,3 difluorobezene derivatives, the unsubstituted benzene sulfonylchloride compound (**27a**) exhibited MTB MIC value of 3.12 μg/mL. Electron releasing methoxy and tertiary butyl groups enhanced (**27e, 27g**) the activity by two folds (MIC = 1.56 μg/mL) but the presence of methyl group in **27b** at the *para* position led to decrease in the activity by two folds (MIC = 6.25 μg/mL). Electron withdrawing groups showed major impact on the activity. Presence of Nitro group in compound **27f** at *para* position decreased the activity by four folds (MIC =12.5 μg/mL), when the electron withdrawing group -OCF_3 was introduced no much change in the activity was observed. Presence of electron withdrawing fluoro decreased the activity by two folds in compound **27c** (MIC = 6.25 μg/mL); replacing with bromo group had no effect on the activity spectrum. With introduction of heterocyclic sulfonylchloride (2-bromothiophene) the activity (**27h**) increased by two folds (MIC = 1.56 μg/mL).

Among the synthesized 1,3 dichlorobenzene derivatives **28a-i, 28a,** unsubstituted benzene sulfonyl chloride compound exhibited activity with MIC = 25 µg/mL. With the introduction of electron withdrawing groups at the *para* position on phenyl ring the activity increased. Introduction of electron withdrawing $–OCF_3$ exhibited four folds increase in activity (**28i,** MIC = 6.25 µg/mL). Hopping to $-NO_2$ group improved the activity by eight folds (**28f,** MIC = 3.12 µg/mL). In this series, introduction of electron donating groups like tertiary butyl, methyl and methoxy resulted in increase of activity. With the introduction of tertiary butyl group activity increased by two folds in **28g** (MIC = 12.5 µg/mL); varying with methyl group at the *para* position in **28b** the activity increased by eight folds (MIC = 3.12 µg/mL). With $–OCH_3$ at the *para* position (**28e**) the activity increased by four folds (MIC = 6.25 µg/mL). Introduction of fluoro at the *para* position in **28c** led to increase in activity by four folds (MIC = 6.25 µg/mL), whereas changing to bromo at the *para* position the MTB activity was enhanced by sixteen folds in **28d** (MIC = 1.56 µg/mL). With heterocyclic sulfonylchloride (2-bromothiophene) activity drastically increased by sixteen fold in **28h** (MIC = 1.56 µg/mL).

5.2.3. Cytotoxicity

Overall, anti-TB results indicate that the 1,3 difluorobenzene derivatives **(25a-r)** exhibited better anti-TB activity than the 1,3 dichlorobenzene derivatives **(26a-r)** as all twenty eight compounds exhibited anti-TB activity MIC ≤ 12.5 µg/mL. The compounds with MIC ≤ 6.25 µg/mL were subjected to *in vitro* cytotoxicity studies by MTT assay method against CHO-K1 cell lines at a concentration 100 µM [33]. The IC_{50} and selectivity index (SI) values are tabulated in **Table 5.2** and the results imply the suitability of the compounds in further drug development for TB.

Table 5.2: IC_{50} (µg/mL) and selectivity index (SI) values of active compounds

Entry	MIC (µg/mL) in MTB H37Rv	IC_{50} (µg/mL) approximation	[a]SI values IC_{50}/MIC
25a	3.12	>150	>48
25b	6.25	>150	>24
25c	1.56	>150	>96
25d	3.12	>150	>48
25f	1.56	123.45	79
25g	6.25	82.55	13

25h	3.12	>150	>48
25i	6.25	>150	>24
26b	3.12	>150	>48
26c	0.78	>150	>192
26d	6.25	96.69	15
26e	6.25	>150	>24
26g	1.56	>150	>96
27a	3.12	>150	>48
27b	6.25	>150	>24
27c	6.25	>150	>24
27d	3.12	38.12	12
27e	1.56	>150	>96
27g	1.56	>150	>96
27h	1.56	>150	>96
27i	3.12	58.12	18
28b	3.12	>150	>48
28c	6.25	>150	>24
28d	1.56	>150	>96
28e	6.25	>150	>24
28f	3.12	>150	>48
28h	1.56	>150	>96
28i	6.25	>150	>24

[a] Selectivity index

5.3. Conclusion

Our preliminary anti-TB results encourage us to engineer the chemical structure of 1,2,4 triazole containing tetrazole with sulfonyl groups to generate essential pharmacophoric features that could lead to the synthesis of a promising candidate to develop anti-TB agents. We proved that incorporating sulfonyl group in the pharmacophore plays a pivotal role in the activity profile. *In vitro* anti tubercular screening results indicate that ten compounds **25a, 25d, 25e, 25h, 26b, 27a, 27d, 27i, 28b** and **28f** showed moderate activity (MIC = 3.12 µg/mL). Eight compounds **25c, 25f, 26g, 27e, 27g, 27h, 28d** and **28h** displayed good anti-TB activity (MIC = 1.56 µg/mL). Compound **26c** exhibited excellent anti-TB activity (MIC = 0.78µg/mL). Most of the compounds did not show toxicity (SI value >13). Detailed *in vivo* studies of compounds **25a-i, 26a-i, 27a-i** &

28a-i further structural modification in 1,2,4 triazoles and tetrazoles need to be explored in future.

5.4. Experimental Section:

5.4.1. Materials and methods

Chemicals and solvents were purchased 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 100-200 mesh). ^{1}H 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. 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. Mass spectra (ESI-MS) were recorded on Schimadzu MS/ESI mass spectrometer.

5.4.2. Chemistry

***Representative procedure for the synthesis of compound* 19**

To a solution of 1,3-difluorobenzene/1,3-dichlorobenzene (1.0 eq) in 1,2-dichloroethane (DCE), anhydrous aluminum chloride (2.0 eq) was added at 25 to 30 °C and stirred for 30 min. The reaction mixture was then cooled to 0 °C and chloroacetyl chloride (1.2 eq) in DCE was added into it over a period of 30 min at 0 to 10 °C. The reaction mixture was then stirred at 60 °C for 12 h and diluted with DCE and poured into 5% hydrochloric acid (50 ml) at 0 to 5 °C. The product was extracted with DCE (2 ×50 ml) and the combined organic layer was washed with 5% aqueous $NaHCO_3$ solution (20 ml), water (2 × 20 ml), brine (20 ml) and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to yield the product **19**, as yellow solid; yield (80%).

***Representative procedure for the synthesis of compound* 20**

To a solution of compound **19** (1.0 eq) in acetonitrile (ACN), 4-amino-4*H*-1,2,4-triazole (1.2 eq) was added and stirred for 16 h, at 80 ºC. The reaction mixture was then cooled to room temperature and filtered. The solid was washed with ethyl ether to afford the light yellow salt (**20**).

***Representative procedure for the synthesis of compound* 21**

The compound **20** was dissolved in 1.5N hydrochloric acid. To this solution was obtained an aqueous solution of sodium nitrite (1.2 eq) was added drop wise and the reaction mixture was stirred for 1 h at 0 ºC to room temperature. Aqueous ammonia was used to adjust to neutral P^H. The precipitated solid was filtered to afford 87% white product **21**.

***Representative procedure for the synthesis of compound* 22**

To a solution of **21** (1.0 eq) in toluene, was added trimethylsulfoxonium iodide (1.2 eq) followed by the addition of 20% sodium hydroxide solution. The reaction mixture was then heated at 60 °C for 12 h. After the reaction was over, it was diluted with toluene and poured into chilled water. The organic layer was washed with water, brine solution dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give compound **22** as light brown oil; yield 64%.

***Representative procedure for the synthesis of compound* 23**

To a solution of compound **22** (1.0 eq) in ethyl acetate, K_2CO_3 (3.0 eq) and tetra-butyl ammonium bromide (TBAB) (0.1 eq) were added. The reaction mixture was allowed to stir under reflux for 12 h under nitrogen atmosphere. It was then cooled to room temperature, diluted with water, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography using pet ether-ethyl acetate (40:60) as eluent. Yield; 82% (white solid).

***Representative procedure for the synthesis of compound* 24**

To a screw capped vial equipped with a magnetic stirrer were added TBAB.$3H_2O$ (1.0 eq), compound **23** (1.0 eq) and $TMSN_3$ (1.2 eq), and the resulting mixture was heated under vigorous

stirring at 85 ºC for 18 h. The crude reaction mixture was transferred into a separatory funnel with 20 mL of ethyl acetate, and TBAF was removed by washing the organic phase with a 1 M HCl aqueous solution The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to furnish pure intermediate compound **24** as a white solid in 88% yield.

***Representative procedure for the synthesis of compounds* 25a-i, 26a-i, 27a-i & 28a-i**

1-(4-(1*H*-tetrazol-5-yl)phenoxy)-2-(2,4-dihalophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol/2-(2,4-dihalophenyl)-1-(2-methoxy-4-(1*H*-tetrazol-5-yl)phenoxy)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (**24**) (1.0 eq) was dissolved in dichloromethane then triethylamine (3.0 eq), and substituted aryl sulfonylchloride (1.3 eq) were added. Resultant mixture was stirred at room temperature for 16 h. After the reaction was complete as indicated by TLC, compound was extracted using DCM. Combined organic layers were washed with saturated brine solution, dried over anhydrous sodium sulphate and evaporated in vacuo. The crude products were purified over silica gel column chromatography [MeOH / DCM (2 – 6%)] to afford required compounds **25a-i, 26a-i, 27a-i** & **28a-i**.

***2-(2,4-difluorophenyl)-1-(4-(1-(phenylsulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (25a)**

White solid (85%); m.p. 133-135 ºC; IR (KBr) υ_{max} / cm^{-1} 3520, 3041, 2844, 1614, 1527, 1415,1362, 1152, 823.^{1}H NMR (300MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.83 (s, 1H), 6.98 – 7.80 (m, 12H), 6.45 (s, 1H), 4.72 (dd, J = 14.4, 28.4 Hz, 2H), 4.30 (dd, J = 13.2, 38.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.03, 158.28, 154.35, 150.74, 145.28, 136.99, 133.70, 133.50, 133.11, 131.42, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 121.72, 114.53, 75.09, 71.20. EI-MS *m/z* 540 $(M+H)^+$; Anal. Calcd for $C_{24}H_{19}F_2N_7O_4S$: (%) C, 53.43; H, 3.55; N, 18.17; Found: C, 53.45; H, 3.56; N, 18.19.

***2-(2,4-difluorophenyl)-1-(4-(1-tosyl-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1yl)propan-2-ol* (25b)**

Pale yellow solid (77%); m.p. 141-143 ºC; IR (KBr) υ_{max} / cm^{-1} 3540, 3031, 2854, 1624, 1522, 1425, 1360, 1150, 820, 720. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.83 (s, 1H), 6.98 – 7.80 (m, 11H), 6.45 (s, 1H), 4.72 (dd, J = 14.4, 28.4 Hz, 2H), 4.30 (dd, J = 13.2, 38.8 Hz, 2H),

2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.03, 158.28, 154.35, 150.74, 145.28, 136.99, 133.70, 133.50, 133.11, 131.42, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 121.72, 114.53, 75.09, 71.20, 27.8. EI-MS *m/z* 554 $(M+H)^+$; Anal. Calcd for $C_{25}H_{21}F_2N_7O_4S$: (%) C, 53.24; H, 3.82; N, 17.71; Found: C, 53.25; H, 3.85; N, 17.73.

***2-(2,4-difluorophenyl)-1-(4-(1-((4-fluorophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (25c)**

Pale yellow solid (98%); m.p. 130-132 ºC; IR (KBr) υ_{max} / cm^{-1} 3544, 3040, 2854, 1614, 1522, 1425, 1361, 1141, 1075, 818, 721. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.83 (s, 1H), 7.00 – 7.80 (m, 11H), 6.49 (s, 1H), 4.82 (dd, J = 14.1, 27.4 Hz, 2H), 4.30 (dd, J = 13.2, 38.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 162.04, 161.03, 158.28, 150.74, 145.28, 136.99, 133.70, 133.50, 133.11, 131.42, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 121.72, 114.53, 75.09, 71.20. EI-MS: *m/z* 558 $(M+H)^+$; Anal. Calcd for $C_{24}H_{18}F_3N_7O_4S$: (%) C, 51.70; H, 3.25; N, 17.59; Found: C, 51.73; H, 3.26; N, 17.62.

***1-(4-(1-((4-bromophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (25d)**

Pale yellow solid (78%); m.p. 126-128 ºC; (KBr) υ_{max} / cm^{-1} 3545, 3020, 2850, 1605, 1528, 1425, 1375, 1145, 825, 720, 512. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.82 (s, 1H), 6.92 – 7.98 (m, 11H), 6.51 (s, 1H), 4.95 (dd, J = 14.1, 27.4 Hz, 2H), 4.49 (dd, J = 13.2, 38.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.74, 161.73, 159.28, 150.74, 145.28, 136.99, 133.70, 133.50, 136.61, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 125.56, 121.72, 114.53, 75.09, 71.20. EI-MS: *m/z* 617 $(M+H)^+$, 619 $(M+H)^{+2}$; Anal. Calcd for $C_{24}H_{18}BrF_2N_7O_4S$: (%) C, 46.61; H, 2.94; N, 15.85; Found: C, 46.63; H, 2.95; N, 15.86.

***2-(2,4-difluorophenyl)-1-(4-(1-((4-methoxyphenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (25e)**

Off white solid (77%); m.p. 130-131 ºC; IR (KBr) υ_{max} / cm^{-1} 3533, 3020, 2855, 1603, 1520, 1430, 1365, 1140, 1073, 835, 717. ^{1}H NMR (300 MHz, DMSO-d_6) δ. 8.32 (s, 1H), 7.82 (s, 1H), 6.92 – 7.98 (m, 11H), 6.48 (s, 1H), 4.93 (dd, J = 14.9, 26.4 Hz, 2H), 4.35 (dd, J = 13.2, 38.1 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.47, 161.99, 159.98, 154.77, 151.74,

145.28, 139.45, 136.99, 133.50, 136.61, 131.38, 29.97, 128.06, 127.05, 126.51, 125.56, 121.72, 114.53, 78.89, 72.10, 59.65. EI-MS: *m/z* 570 $(M+H)^+$; Anal. Calcd for $C_{25}H_{21}F_2N_7O_5S$: (%) C, 52.73; H, 3.72; N, 17.22; Found: C, 52.75; H, 3.75; N, 17.83.

***2-(2,4-difluorophenyl)-1-(4-(1-((4-nitrophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (25f)**

Yellow solid (68%); m.p. 139-141 ºC; IR (KBr) υ_{max} / cm^{-1} 3542, 3023, 2845, 1601, 1510, 1430, 1365, 1259, 1145, 1070, 830, 715. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.12 (s, 1H), 6.82 – 8.25 (m, 11H), 6.51 (s, 1H), 4.95 (dd, J = 14.1, 27.4 Hz, 2H), 4.49 (dd, J = 13.2, 38.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.74, 161.73, 159.28, 154.35, 150.74, 145.28, 136.99, 133.70, 133.50, 136.61, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 124.56, 121.72, 114.53, 71.20. EI-MS *m/z* 585 $(M+H)^+$; Anal. Calcd for $C_{24}H_{18}F_2N_8O_6S$: (%) C, 49.33; H, 3.10; N, 19.17; Found: C, 49.35; H, 3.11; N, 19.19.

***1-(4-(1-((4-(tert-butyl)phenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (25g)**

Off white solid (93%); m.p. 143-144 ºC; IR (KBr) υ_{max} / cm^{-1} 3540, 3020, 2843, 1606, 1516, 1430, 1365, 1145, 1075, 813, 722. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.98 (s, 1H), 6.98 – 7.80 (m, 11H), 6.45 (s, 1H), 4.72 (dd, J = 14.4, 28.4 Hz, 2H), 4.30 (dd, J = 13.2, 38.8 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.03, 158.48, 154.35, 150.74, 145.28, 136.99, 133.70, 133.50, 133.11, 131.42, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 121.72, 114.53, 75.09, 71.20, 35.12, 30.63. EI-MS *m/z* 596 $(M+H)^+$; Anal. Calcd for $C_{28}H_{27}F_2N_7O_4S$: (%) C, 56.46; H, 4.57; N, 16.47; Found: C, 56.47; H, 4.59; N, 16.49.

***1-(4-(1-((5-bromothiophen-2-yl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (25h)**

Pale yellow solid (87%); m.p. 125-127 ºC; IR (KBr) υ_{max} / cm^{-1} 3543, 3022, 2845, 1678, 1510, 1432, 1360, 1145, 804, 721, 513. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.82 (s, 1H), 7.03 – 7.69 (m, 9H), 6.37 (s, 1H), 4.95 (dd, J = 14.1, 28.4 Hz, 2H), 4.35 (dd, J = 12.9, 39.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.74, 160.93, 159.48, 158.35, 151.84, 143.66, 136.99, 131.87, 131.37, 130.23, 129.55, 129.33, 128.69, 114.53, 111.98, 110.87,105.67, 98.87, 75.09,

68.20. EI-MS *m/z* 623 $(M+H)^{+1}$, 625 $(M+H)^{+2}$; Anal. Calcd for $C_{22}H_{16}BrF_2N_7O_4S_2$: (%) C, 42.32; H, 2.58; N, 15.70; Found: C, 42.34; H, 2.59; N, 15.71.

***2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-(4-(1-((4-(trifluoromethoxy)phenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)propan-2-ol* (25i)**

Off white solid (76%); m.p. 140-142 ºC; IR (KBr) υ_{max} / cm^{-1} 3530, 3024, 2825, 1605, 1525, 1434, 1368, 1140, 1070, 803, 720. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.80 (s, 1H), 7.00 – 8.10 (m, 11H), 6.45 (s, 1H), 4.85 (dd, J = 14.7, 27.8 Hz, 2H), 4.37 (dd, J = 13.6, 9.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.54, 161.23, 158.56, 150.98, 146.38, 137.29, 133.80, 133.86, 133.70, 133.76, 131.87, 131.15, 130.45, 128.67, 127.24, 126.45, 125.87, 121.45, 114.53, 72.20, 59.12. EI-MS *m/z* 623 $(M+H)^+$; Anal. Calcd for $C_{26}H_{18}F_5N_7O_5S$: (%) C, 48.16; H, 2.91; N, 15.72; Found: C, 48.17; H, 2.92; N, 15.73.

***2-(2,4-dichlorophenyl)-1-(4-(1-(phenylsulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26a)**

White solid (88%); m.p. 120-121 ºC; IR (KBr) υ_{max} / cm^{-1} 3520, 3043, 2840, 1615, 1520, 1415, 1362, 1155, 805, 655. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.83 (s, 1H), 7.63 (s, 1H), 6.98 – 7.80 (d, 11H), 6.50 (s, 1H), 4.98 (dd, J = 14.4, 28.9 Hz, 2H), 4.41 (dd, J =13.3, 38.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.25, 161.03, 158.28, 154.35, 150.74, 145.28, 136.99, 133.70, 133.50, 131.42, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 121.72, 114.53, 75.09, 71.20. EI-MS *m/z* 572 $(M+H)^+$; Anal. Calcd for $C_{24}H_{19}Cl_2N_7O_4S$: (%) C, 50.36; H, 3.36; N, 17.13; Found: C, 50.37; H, 3.38; N, 17.38.

***2-(2,4-dichlorophenyl)-1-(4-(1-tosyl-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26b)**

Brown solid (86%); m.p. 133-135 ºC; IR (KBr) υ_{max} / cm^{-1} 3545, 3035, 2855, 1624, 1520, 1425, 1360, 1150, 812, 722, 608. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 6.95 – 7.82 (d, 10H), 6.44 (s, 1H), 4.96 (dd, J = 14.7, 28.5 Hz, 2H), 4.44 (dd, J = 13.7, 38.9 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.23, 158.14, 154.55, 150.74, 145.26, 136.99, 133.79, 133.57, 131.62, 131.56, 130.87, 130.23, 129.97, 128.06, 127.05, 126.51,

121.72, 114.53, 75.09, 71.20, 27.8. EI-MS *m/z* 586 $(M+H)^+$; Anal. Calcd for $C_{25}H_{21}Cl_2N_7O_4S$: (%) C, 51.21; H, 3.61; N, 16.73; Found: C, 51.23; H, 3.62; N, 16.74.

***2-(2,4-dichlorophenyl)-1-(4-(1-((4-fluorophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26c)**

Off white solid (87%); m.p 133-135 ºC; IR (KBr) υ_{max} / cm^{-1} 3538, 3035, 2844, 1614, 1520, 1428, 1361, 1151, 1075, 820, 717, 601. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 6.98 – 7.82 (d, 10H), 6.50 (s, 1H), 4.89 (dd, *J* = 14.9, 28.4 Hz, 2H), 4.39 (dd, *J* = 13.5, 38.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.23, 162.55, 158.99, 151.01, 150.34, 145.87, 137.10, 133.65, 133.99, 132.62, 131.67, 130.99, 129.67, 128.78, 127.58, 126.68, 121.92, 114.63, 75.19, 71.20. EI-MS *m/z* 590 $(M+H)^+$; Anal. Calcd for $C_{24}H_{18}Cl_2FN_7O_4S$: (%) C, 48.82; H, 3.08; N, 16.61; Found: C, 48.83; H, 3.10; N, 16.62.

***1-(4-(1-((4-bromophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26d)**

Pale yellow solid (88%); m.p. 127-129 ºC; IR (KBr) υ_{max} / cm^{-1} 3535, 3018, 2856, 1605, 1525, 1421, 1365, 1136, 815, 713, 608, 510. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.82 (s, 1H), 7.69 (s, 1H), 6.92 – 7.98 (d, 10H), 6.51 (s, 1H), 4.95 (dd, *J* = 14.1, 27.4 Hz, 2H), 4.49 (dd, *J* = 13.2, 38.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.74, 161.73, 159.28, 150.74, 145.28, 136.99, 133.70, 133.50, 136.61, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 125.56, 121.72, 114.53, 75.09, 71.20. EI-MS *m/z* 649 $(M+H)^{+1}$, 651 $(M+H)^{+2}$; Anal. Calcd for $C_{24}H_{18}BrCl_2N_7O_4S$: (%) C, 44.26; H, 2.79; N, 15.05; Found: C, 44.27; H, 2.80; N, 15.06.

***2-(2,4-dichlorophenyl)-1-(4-(1-((4-methoxyphenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26e)**

Off white solid (70%); m.p. 130-132 ºC; IR (KBr) υ_{max} / cm^{-1} 3538, 3029, 2855, 1603, 1527, 1420, 1361, 1132, 812, 711, 610. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.82 (s, 1H), 6.99 – 7.98 (d, 10H), 6.48 (s, 1H), 4.93 (dd, *J* = 14.9, 26.4 Hz, 2H), 4.35 (dd, *J* = 13.2 Hz, 38.1 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.47, 162.99, 161.88, 159.98, 154.77, 151.74, 145.28, 139.45, 136.99, 133.50, 136.61, 131.38, 129.97, 128.06, 127.05, 126.51,

125.56, 121.72, 114.53, 72.10, 59.65. EI-MS *m/z* 602 $(M+H)^+$; Anal. Calcd for $C_{24}H_{18}BrCl_2N_7O_4S$: (%) C, 44.26; H, 2.79; N, 15.05; Found: C, 44.27; H, 2.80; N, 15.06.

***2-(2,4-dichlorophenyl)-1-(4-(1-((4-nitrophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26f)**

Yellow solid (68%); m.p. 134-136 ºC; IR (KBr) υ_{max} / cm^{-1} 3545, 3030, 2875, 1606, 1515, 1431, 1364, 1259, 1135, 1070, 815, 715, 610. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.12 (s, 1H), 7.80 (s, 1H), 6.82 – 8.25 (d, 10H), 6.49 (s, 1H), 4.93 (dd, J = 14.9, 27.6 Hz, 2H), 4.40 (dd, J = 13.5, 38.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.94, 161.63, 159.28, 150.74, 145.38, 136.79, 133.80, 133.50, 136.61, 131.38, 130.23, 129.97, 128.16, 127.25, 126.55, 124.66, 122.72, 115.53, 75.09, 72.20. EI-MS *m/z* 617 $(M+H)^+$; Anal. Calcd for $C_{24}H_{18}Cl_2N_8O_6S$: (%) C, 46.69; H, 2.94; N, 18.15; Found: C, 46.70; H, 2.95; N, 18.16.

***1-(4-(1-((4-(tert-butyl)phenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26g)**

Pale yellow solid (76%); m.p. 123-125 ºC; IR (KBr) υ_{max} / cm^{-1} 3548, 3030, 2853, 1604, 1522, 1419, 1362, 1130, 811, 604. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 6.95 – 7.82 (d, 10H), 6.44 (s, 1H), 4.93 (dd, J = 14.6, 28.9 Hz, 2H), 4.47 (dd, J = 13.4, 38.2 Hz, 2H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.23, 161.03, 158.28, 154.55, 150.74, 145.26, 136.99, 133.79, 133.57, 131.62, 131.56, 130.87, 129.02, 128.12, 127.45, 126.51, 121.72, 114.53, 75.09, 71.20, 35.12, 30.63. EI-MS *m/z* 628 $(M+H)^+$; Anal. Calcd for $C_{28}H_{27}Cl_2N_7O_4S$: (%) C, 53.51; H, 4.33; N, 15.60; Found: C, 53.52; H, 4.34; N, 15.61.

***1-(4-(1-((5-bromothiophen-2-yl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (26h)**

Pale yellow solid (89%); m.p. 141-143 ºC; IR (KBr) υ_{max} / cm^{-1} 3544, 3026, 2845, 1670, 1510, 1431, 1360, 1145, 804, 720, 608, 509. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 7.06 – 7.79 (d, 8H), 6.49 (s, 1H), 4.95 (dd, J = 14.2, 29.1 Hz, 2H), 4.32 (dd, J = 12.3, 39.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.99, 161.83, 159.48, 158.35, 151.84, 143.66, 136.99, 131.87, 131.37, 130.23, 129.55, 129.33, 128.69, 114.53, 111.98, 110.87,105.67,

98.87, 75.19, 68.65. EI-MS *m/z* 655 $(M+H)^{+1}$, 657 $(M+H)^{+2}$; Anal. Calcd for $C_{22}H_{16}BrCl_2N_7O_4S_2$: (%) C, 40.20; H, 2.45; N, 14.92; Found: C, 40.22; H, 2.46; N, 14.93.

***2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-(4-(1-((4-(trifluoromethoxy)phenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)propan-2-ol* (26i)**

Off White solid (85%); m.p. 144-145 ºC; IR (KBr) υ_{max} / cm^{-1} 3540, 3025, 2845, 1605, 1525, 1410, 1360, 1133, 812, 715, 610. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 6.98 – 7.82 (d, 10H), 6.49 (s, 1H), 4.79 (dd, *J* = 14.4, 28.9 Hz, 2H), 4.35 (dd, *J* = 13.9, 38.1 Hz, 2H) ^{13}C NMR (100MHz, DMSO-d_6) δ 164.34, 162.55, 158.99, 155.20, 150.34, 145.87, 137.10, 133.65, 133.99, 132.62, 131.67, 130.99, 129.67, 128.78, 127.58, 126.68, 121.92, 114.63, 79.43, 75.19, 72.40. EI-MS *m/z* 656 $(M+H)^+$; Anal. Calcd for $C_{25}H_{18}Cl_2F_3N_7O_5S$: (%) C, 45.74; H, 2.76; N, 14.94; Found: C, 45.76; H, 2.77; N, 14.95.

***2-(2,4-difluorophenyl)-1-(2-methoxy-4-(1-(phenylsulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27a)**

Off white solid (79%); m.p. 125-127 ºC; IR (KBr) υ_{max} / cm^{-1} 3520, 3041, 2844, 1614, 1527, 1415, 1362, 1152, 823.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 7.87 (s, 1H), 7.60 (s, 1H), 7.01 – 7.96 (m, 10H), 6.50 (s, 1H), 5.10 (dd, *J* = 14.9, 26.9 Hz, 2H), 4.49 (dd, *J* = 13.9, 38.3 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.78, 161.03, 158.28, 154.39, 150.74, 151.76, 145.28, 136.99, 133.70, 133.50, 131.38, 130.93, 129.56, 128.26, 127.77, 126.97, 121.72, 114.53, 87.67,72.19, 69.11, 57.89. EI-MS *m/z* 570 $(M+H)^+$; Anal. Calcd for $C_{25}H_{21}F_2N_7O_5S$: (%) C, 52.72; H, 3.72; N, 17.22; Found: C, 52.73; H, 3.74; N, 17.23.

***2-(2,4-difluorophenyl)-1-(2-methoxy-4-(1-tosyl-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27b)**

Pale yellow solid (83%); m.p. 133-134 ºC; IR (KBr) υ_{max} / cm^{-1} 3540, 3031, 2854, 1624, 1522, 1425, 1360, 1150, 820, 720. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.79 (s, 1H), 7.68 (s, 1H), 6.95 – 7.91 (m, 9H), 6.43 (s, 1H), 4.99 (dd, *J* = 14.9, 26.4 Hz, 2H), 4.52 (dd, *J* =13.5, 38.9 Hz, 1H), 4.33 (dd, *J* =12.7, 37.3 Hz, 1H), 3.90 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.67, 161.87, 158.45, 154.58, 150.87, 151.99, 145.67, 141.87, 136.67, 132.98, 133.67, 131.12, 130.43, 129.54, 128.65, 127.86, 126.99, 121.67, 114.85, 85.63, 72.77, 69.68,

58.89, 21.3. EI- MS *m/z* 584 $(M+H)^+$; Anal. Calcd for $C_{26}H_{23}F_2N_7O_5S$: (%) C, 53.51; H, 3.97; N, 16.80; Found: C, 53.53; H, 3.98; N, 16.82.

***2-(2,4-difluorophenyl)-1-(4-(1-((4-fluorophenyl)sulfonyl)-1H-tetrazol-5-yl)-2-methoxyphenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27c)**

Pale yellow solid (82%); m.p. 117-118 ºC IR (KBr) υ_{max} / cm^{-1} 3544, 3040, 2854, 1614, 1522, 1425, 1361, 1141, 1075, 818, 721. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.83 (s, 1H), 7.00 – 7.80 (m, 9H), 6.91 (s, 1H), 6.49 (s, 1H), 4.79 (dd, J = 14.7, 27.4 Hz, 2H), 4.45 (dd, J = 13.3, 38.5 Hz, 1H), 4.28 (dd, J = 13.1, 37.8 Hz, 1H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.12, 163.50, 161.23, 158.28, 154.67, 151.74, 145.28, 133.10, 133.54, 133.65, 131.66, 131.38, 130.23, 129.97, 128.06, 127.15, 126.76, 121.79, 114.56, 75.76, 72.88, 55.19, 53.89. EI-MS *m/z* 588 $(M+H)^+$; Anal. Calcd for $C_{25}H_{20}F_3N_7O_5S$: (%) C, 51.11; H, 3.43; N, 16.69; Found: C, 51.12; H, 3.45; N, 16.70.

***1-(4-(1-((4-bromophenyl)sulfonyl)-1H-tetrazol-5-yl)-2-methoxyphenoxy)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27d)**

White solid (81%); m.p. 155-157 ºC; (KBr) υ_{max} / cm^{-1} 3545, 3020, 2855, 1600, 1528, 1425, 1374, 1145, 825, 720, 510. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.83 (s, 1H), 7.00 – 7.80 (m, 9H), 6.91 (s, 1H), 6.49 (s, 1H), 4.79 (dd, J = 14.7, 27.4 Hz, 2H), 4.45 (dd, J = 13.3, 38.5 Hz, 1H), 4.28 (dd, J = 13.1, 37.8 Hz, 1H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.12, 163.50, 161.23, 158.28, 154.67, 151.74, 145.28, 133.10, 133.54, 133.65, 131.66, 131.38, 130.23, 129.97, 128.06, 127.15, 126.76, 121.79, 114.56, 75.76, 72.88, 55.19, 53.89. EI-MS *m/z* 647 $(M+H)^{+1}$, 649 $(M+H)^{+2}$; Anal. Calcd for $C_{25}H_{20}BrF_2N_7O_5S$: (%) C, 46.31; H, 3.11; N, 15.12; Found: C, 46.32; H, 3.13; N, 15.13.

***2-(2,4-difluorophenyl)-1-(2-methoxy-4-(1-((4-methoxyphenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27e)**

Off white solid (83%); m.p. 129-131 ºC; IR (KBr) υ_{max} / cm^{-1} 3535, 3025, 2850, 1605, 1518, 1435, 1364, 1145, 1070, 830, 715.^{1}H NMR (400MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.90 (s, 1H), 6.91 (s, 1H), 6.99 – 7.97 (m, 9H), 4.87 (dd, J = 14.6, 26.7 Hz, 2H), 4.30 (dd, J =13.6, 37.9 Hz, 2H), 3.78 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.45, 162.47, 161.88,

159.98, 154.77, 151.74, 145.28, 139.45, 136.99, 133.50, 136.61, 131.38, 129.97, 128.06, 127.05, 126.51, 125.56, 121.72, 114.53, 83.15, 78.89, 72.10, 60.10, 58.90. EI-MS *m/z* 600 $(M+H)^+$; Anal. Calcd for $C_{26}H_{23}F_2N_7O_6S$: (%) C, 52.08; H, 3.87; N, 16.35; Found: C, 52.12; H, 3.89; N, 16.36.

***2-(2,4-difluorophenyl)-1-(2-methoxy-4-(1-((4-nitrophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27f)**

Yellow solid (71%); m.p. 150-151 ºC; ; IR (KBr) υ_{max} / cm^{-1} 3542, 3023, 2845, 1601, 1510, 1430, 1365, 1259, 1145, 1070, 830, 715. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.21 (s, 1H), 6.98 – 8.20 (m, 9H), 6.50 (s, 1H), 4.96 (dd, J = 14.3 Hz, 27.9 Hz, 2H), 4.50 (dd, J = 13.6 Hz, 38.6 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.64, 162.73, 159.43, 154.7, 150.87, 145.87, 136.92, 136.61, 133.66, 133.52, 131.38, 130.28, 129.92, 128.06, 127.55, 126.67, 124.99, 121.34, 114.88, 86.45,78.34, 72.01, 58.99 EI-MS *m/z* 615 $(M+H)^+$; Anal. Calcd for $C_{25}H_{20}F_2N_8O_7S$: (%) C, 48.86; H, 3.28; N, 18.23; Found: C, 48.89; H, 3.29; N, 18.25.

***1-(4-(1-((4-(tert-butyl)phenyl)sulfonyl)-1H-tetrazol-5-yl)-2-methoxyphenoxy)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27g)**

Pale yellow solid (85%); m.p. 118-120 ºC IR (KBr) υ_{max} / cm^{-1} 3540, 3021, 2840, 1605, 1515, 1432, 1365, 1145, 1070, 810, 720.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.98 (s, 1H), 7.79 (s, 1H), 6.98 – 7.80 (m, 10H), 6.48 (s, 1H), 4.68 (dd, J = 14.4, 28.4 Hz, 2H), 4.34 (dd, J = 13.2, 38.8 Hz, 2H), 3.81 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.03, 158.48, 154.35, 150.74, 145.28, 136.99, 133.70, 133.50, 133.11, 131.42, 131.38, 130.23, 129.97, 128.06, 127.05, 126.51, 121.72, 114.53,87.12, 75.09, 71.20, 65.43, 35.12, 30.63. EI-MS *m/z* 626 $(M+H)^+$; Anal. Calcd for $C_{29}H_{29}F_2N_7O_5S$: (%) C, 55.67; H, 4.67; N, 15.67; Found: C, 55.69; H, 4.68; N, 15.69.

***1-(4-(1-((5-bromothiophen-2-yl)sulfonyl)-1H-tetrazol-5-yl)-2-methoxyphenoxy)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27h)**

Pale yellow solid (87%); m.p. 135-136 ºC IR (KBr) υ_{max} / cm^{-1} 3543, 3022, 2844, 1678, 1515, 1432, 1365, 1145, 805, 721, 515. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.88 (s, 1H), 7.68 (s, 1H), 7.13 – 7.80 (m, 7H), 6.45 (s, 1H), 4.95 (dd, J = 14.6, 28.9 Hz, 2H), 4.39 (dd, J =

12.4, 39.0 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.32, 163.89, 162.23, 159.55, 158.43, 154.77, 151.67, 143.45, 136.87, 132.87, 131.87, 130.93, 129.85, 129.63, 128.79, 114.55, 111.57, 111.83, 105.67, 98.89, 75.59, 69.20, 59.80 EI-MS *m/z* 653 $(M+H)^+$, 655 $(M+H)^{+2}$; Anal. Calcd for $C_{23}H_{18}BrF_2N_7O_5S_2$: (%) C, 55.67; H, 4.67; N, 15.67; Found: C, 55.69; H, 4.68; N, 15.69.

***2-(2,4-difluorophenyl)-1-(2-methoxy-4-(1-((4-(trifluoromethoxy)phenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (27i)**

Off White solid (85%); m.p. 144-145 ºC; IR (KBr) υ_{max} / cm^{-1} 3530, 3024, 2825, 1605, 1525, 1434, 1368, 1140, 1070, 803, 720. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 6.98 – 7.82 (d, 9H), 6.49 (s, 1H), 4.68 (dd, *J* = 14.4, 28.4 Hz, 2H), 4.34 (dd, *J* = 13.2, 38.8 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.87, 162.55, 158.99, 155.20, 153.78, 150.34, 145.87, 137.10, 133.65, 133.99, 132.62, 131.67, 130.99, 129.67, 129.12, 128.78, 127.58, 126.68, 121.92, 114.63, 83.54, 75.19, 72.40, 56.78. EI-MS m/z 654 $(M+H)^+$; Anal. Calcd for $C_{26}H_{20}F_5N_7O_6S$: (%) C, 47.78; H, 3.08; N, 15.00; Found: C, 47.79; H, 3.10; N, 15.01.

***2-(2,4-dichlorophenyl)-1-(2-methoxy-4-(1-(phenylsulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (28a)**

Brown solid (78%); m.p. 156-158 ºC; IR (KBr) υ_{max} / cm^{-1} 3525, 3040, 2839, 1614, 1525, 1418, 1362, 1150, 803, 650. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.54 (s, 1H), 6.81 – 7.88 (d, 9H), 6.50 (s, 1H), 5.01 (dd, *J* = 14.0, 27.1 Hz, 1H), 4.81 (dd, *J* = 13.7, 26.9 Hz, 1H), 4.81 (dd, *J* = 14.1, 27.1 Hz, 1H), 4.51 (dd, *J* = 13.6, 38.8 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.32, 161.23, 159.39, 154.77, 151.94, 151.56, 145.47, 137.10, 133.68, 133.70, 131.54, 130.89, 129.76, 128.47, 127.87, 127.97, 124.76, 121.99, 115.53, 82.76, 72.34, 69.16, 57.99. EI-MS *m/z* 602 $(M+H)^+$; Anal. Calcd for $C_{25}H_{21}Cl_2N_7O_5S$: (%) C, 49.84; H, 3.51; N, 16.27; Found: C, 49.86; H, 3.52; N, 16.28.

***2-(2,4-dichlorophenyl)-1-(2-methoxy-4-(1-tosyl-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (28b)**

Off white solid (80%); m.p. 136-137 ºC; IR (KBr) υ_{max} / cm^{-1} 3545, 3030, 2854, 1624, 1522, 1425, 1360, 1151, 810, 722, 605. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.80 (s, 1H), 7.76 (s, 1H), 7.45 (s, 1H), 6.97 – 7.95 (d, 8H), 6.49 (s, 1H), 4.91 (dd, *J* = 14.6, 26.9 Hz, 2H), 4.49 (dd, *J* = 13.9, 37.9 Hz, 2H), 3.78 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.78, 164.76, 162.77, 159.55, 154.76, 150.75, 151.34, 145.86, 136.97, 132.18, 133.97, 132.12, 130.73, 129.94, 128.55, 127.57, 126.86, 121.89, 115.85, 86.12, 72.67, 69.78, 58.79, 29.49. EI-MS *m/z* 616 $(M+H)^+$; Anal. Calcd for $C_{26}H_{23}Cl_2N_7O_5S$: (%) C, 50.66; H, 3.76; N, 15.90; Found: C, 50.21; H, 3.77; N, 15.91.

***2-(2,4-dichlorophenyl)-1-(4-(1-((4-fluorophenyl)sulfonyl)-1H-tetrazol-5-yl)-2-methoxyphenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (28c)**

Pale yellow solid (82%); m.p. 151-153 ºC; IR (KBr) υ_{max} / cm^{-1} 3538, 3035, 2844, 1614, 1520, 1428, 1361, 1151, 1075, 820, 717, 601. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.89 (s, 1H), 7.66 (s, 1H),6.85 (s, 1H), 7.16 – 7.80 (d, 8H), 6.35 (s, 1H), 5.02 (dd, *J* = 14.8, 27.6 Hz, 1H), 4.87 (dd, *J* = 13.7, 38.5 Hz, 1H), 4.67 (dd, *J* = 13.3, 38.1 Hz, 1H), 4.52 (dd, *J* = 13.1, 37.9 Hz, 1H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.60, 161.83, 158.58, 154.77, 151.94, 145.48, 138.80, 133.10, 133.54, 133.65, 131.66, 131.38, 130.23, 129.97, 128.06, 127.15, 126.76, 121.79, 114.56, 85.17, 75.76, 71.88, 57.89. EI-MS *m/z* 620 $(M+H)^+$; Anal. Calcd for $C_{25}H_{20}Cl_2FN_7O_5S$: (%) C, 48.40; H, 3.25; N, 15.80; Found: C, 48.41; H, 3.27; N, 15.81.

***1-(4-(1-((4-bromophenyl)sulfonyl)-1H-tetrazol-5-yl)-2-methoxyphenoxy)-2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (28d)**

Off white solid (82%); m.p. 129-130 ºC; IR (KBr) υ_{max} / cm^{-1} 3535, 3019, 2855, 1601, 1525, 1421, 1364, 1135, 815, 710, 608, 508. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.96 (s, 1H), 7.86 (s, 1H), 6.79 (s, 1H), 7.61 (s, 1H), 7.16 – 7.80 (d, 8H), 6.45 (s, 1H), 5.18 (dd, *J* = 14.9, 28.0 Hz, 1H), 4.85 (dd, *J* = 13.85, 37.9 Hz, 1H), 4.66 (dd, J = 13.7, 37.4 Hz, 1H), 4.46 (dd, *J* = 13.1, 37.5 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.20, 161.63, 158.68, 154.97, 151.84, 145.58, 138.79, 133.18, 133.84, 133.75, 131.76, 131.48, 130.33, 129.87, 128.66, 127.45, 126.87, 121.80, 114.56, 87.21,75.76, 71.88, 57.89. EI-MS m/z 679 $(M+H)^+$, 681 $(M+H)^{+2}$; Anal. Calcd for $C_{25}H_{20}BrCl_2N_7O_5S$: (%) C, 44.07; H, 2.96; N, 14.39; Found: C, 44.18; H, 2.97; N, 14.39.

2-(2,4-dichlorophenyl)-1-(2-methoxy-4-(1-((4-methoxyphenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol **(28e)**

Pale yellow solid (82%); m.p. 144-146 ºC; IR (KBr) υ_{max} / cm^{-1} 3538, 3029, 2855, 1603, 1527, 1420, 1361, 1132, 812, 711, 610.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.79 (s, 1H), 7.66 (s, 1H), 6.85 (s, 1H), 7.12–7.90 (d, 8H), 6.45 (s, 1H), 5.12 (dd, J = 14.3 Hz, 27.1 Hz, 1H), 4.87 (dd, J = 13.72, 37.6 Hz, 2H), 4.67 (dd, J = 13.72, 37.4 Hz, 1H), 4.57 (dd, J = 13.62, 37.7 Hz, 1H), 3.91 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.78, 163.10, 162.90, 161.89, 158.77, 154.87, 151.74, 145.88, 138.82, 133.40, 133.64, 133.15, 131.36, 131.88, 129.67, 128.36, 127.65, 126.46, 121.99, 114.66, 75.76, 71.88, 60.86, 57.89. EI-MS *m/z* 632 $(M+H)^+$; Anal. Calcd for $C_{26}H_{23}Cl_2N_7O_6S$: (%) C, 49.37; H, 3.67; N, 15.50; Found: C, 49.38; H, 3.69; N, 15.51.

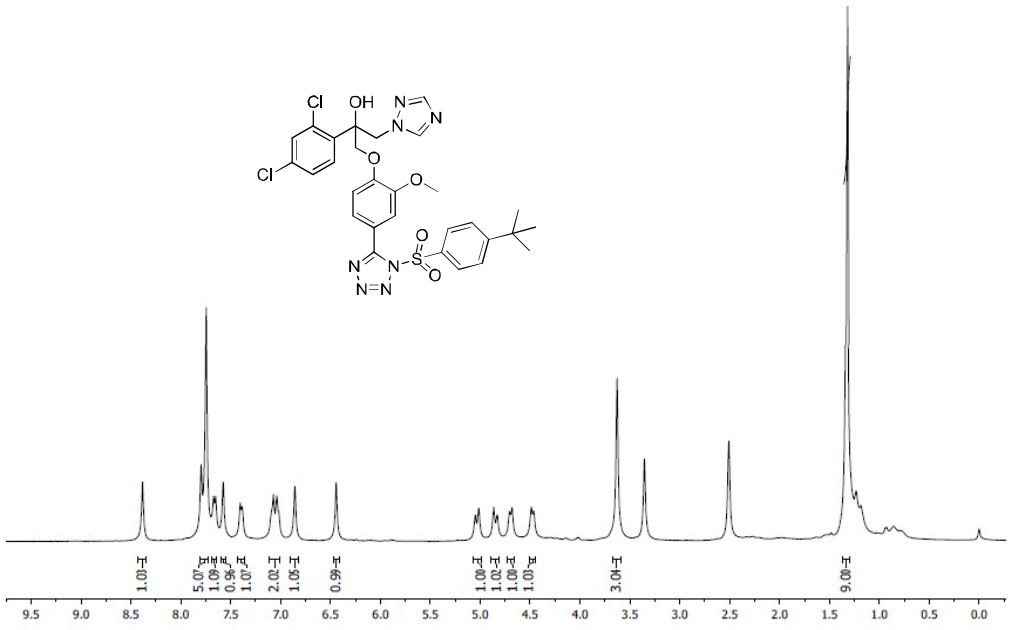
2-(2,4-dichlorophenyl)-1-(2-methoxy-4-(1-((4-nitrophenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol **(28f)**

Yellow solid (76%); m.p. 133-134 ºC; IR (KBr) υ_{max} / cm^{-1} 3545, 3030, 2875, 1606, 1515, 1431, 1364, 1259, 1135, 1070, 815, 714, 608. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 6.89 (s, 1H), 6.98 – 7.95 (d, 8H), 6.50 (s, 1H), 5.10 (dd, J = 14.3, 27.9 Hz, 1H), 4.81 (dd, J =13.6, 38.6 Hz, 1H), 4.65 (dd, J = 13.5, 38.3 Hz, 1H), 4.51 (dd, J = 13.4, 38.2 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.12, 163.64, 162.73, 159.43, 154.7, 150.87, 145.87, 136.92, 136.61, 133.66, 133.52, 131.38, 130.28, 129.92, 128.06, 127.55, 126.67, 124.99, 121.34, 114.88, 78.34, 72.01, 58.99. EI-MS *m/z* 647 $(M+H)^+$; Anal. Calcd for $C_{25}H_{20}Cl_2N_8O_7S$: (%) C, 46.38; H, 3.11; N, 17.31; Found: C, 46.39; H, 3.12; N, 17.33.

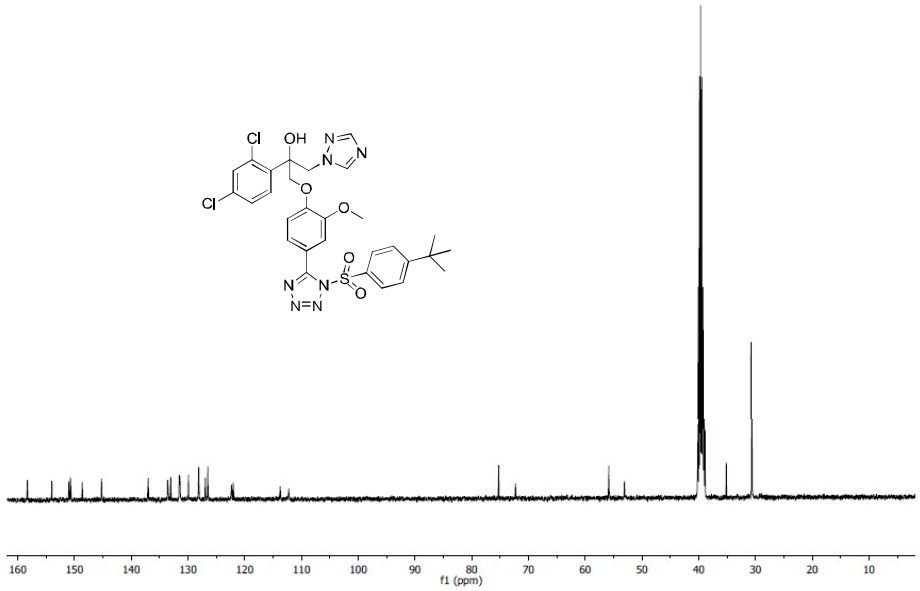
1-(4-(1-((4-(tert-butyl)phenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol **(28g)**

Pale yellow solid (71%); m.p. 120-121 ºC; IR (KBr) υ_{max} / cm^{-1} 3548, 3030, 2853, 1604, 1522, 1419, 1362, 1130, 811, 604. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.88 (s, 1H), 7.79 (s, 1H), 6.89 (s, 1H), 6.98 – 7.80 (d, 8H), 6.50 (s, 1H), 5.07 (dd, J = 14.8, 27.9 Hz, 1H), 4.84 (dd, J = 14.1, 38.5 Hz, 1H), 4.64 (dd, J = 14.0, 38.3 Hz, 1H), 4.49 (dd, J = 14.1, 38.5 Hz, 1H), 3.62 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.13, 158.88, 154.65, 150.84, 147.12,

145.88, 142.12, 137.01, 133.55, 133.78, 133.56, 131.89, 131.87, 130.93, 129.97, 128.76, 127.25, 126.61, 121.82, 114.73, 87.12, 75.19, 71.90, 35.82, 30.99. EI-MS *m/z* 658 $(M+H)^+$; Anal. Calcd for $C_{29}H_{29}Cl_2N_7O_5S$: (%) C, 52.89; H, 4.44; N, 14.89; Found: C, 52.91; H, 4.45; N, 14.90.



^{1}H NMR spectrum (400MHz, DMSO-d_6) of compound **28g.**



^{13}C NMR spectrum (100 MHz, DMSO-d_6) of compound **28g.**

1-(4-(1-((5-bromothiophen-2-yl)sulfonyl)-1H-tetrazol-5-yl)-2-methoxyphenoxy)-2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol **(28h)**

Pale yellow solid (83%); m.p. 119-121 ºC; IR (KBr) υ_{max} / cm^{-1} 3544, 3026, 2845, 1670, 1510, 1431, 1360, 1145, 804, 720, 608, 509. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.28 (s, 1H),7.78 (s,1H), 6.89 (s,1H), 7.13–7.91 (d, 6H), 6.47 (s, 1H), 5.01 (dd, J = 14.7 Hz, 28.9 Hz, 1H), 4.82 (dd, J = 12.9, 39.2 Hz, 2H), 4.66 (dd, J = 12.5, 39.0 Hz, 2H), 4.52 (dd, J = 12.9, 39.2 Hz, 1H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.12, 163.89, 162.23, 159.55, 158.43, 151.67, 143.45, 136.87, 132.87, 131.87, 130.93, 129.85, 129.63, 128.79, 114.55, 111.57, 111.83, 105.67, 98.89, 86.12,75.59, 69.20, 59.80. EI-MS *m/z* 685 $(M+H)^+$, 687 $(M+H)^{+2}$; Anal. Calcd for $C_{23}H_{18}BrCl_2N_7O_5S_2$: (%) C, 40.19; H, 2.64; N, 14.26; Found: C, 40.20; H, 2.65; N, 14.37.

2-(2,4-dichlorophenyl)-1-(2-methoxy-4-(1-((4-(trifluoromethoxy)phenyl)sulfonyl)-1H-tetrazol-5-yl)phenoxy)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol **(28i)**

Pale yellow solid (85%); m.p. 144-145 ºC; IR (KBr) υ_{max} / cm^{-1} 3540, 3021, 2843, 1603, 1520, 1410, 1361, 1130, 810, 715, 608. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41(s, 1H), 7.80 (s, 1H),

7.69 (s, 1H), 6.95 (s, 1H), 7.28 – 7.82 (d, 8H), 6.49 (s, 1H), 5.09 (dd, J = 14.4, 28.9 Hz, 1H), 4.85 (dd, J = 13.9, 37.1 Hz, 1H), 4.70 (dd, J = 14.9, 37.9 Hz, 1H), 4.49 (dd, J = 15.1, 37.4 Hz, 1H), 3.61 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.75, 164.65, 162.55, 160.12, 158.99, 155.20, 150.34, 145.87, 141.43, 137.10, 133.65, 133.99, 132.62, 131.67, 130.99, 129.67, 128.78, 127.58, 126.68, 121.92, 114.63, 86.1, 75.19, 72.40. EI-MS *m/z* 686 $(M+H)^+$; Anal. Calcd for $C_{27}H_{22}Cl_2F_3N_7O_7S$: (%) C, 45.49; H, 2.94; N, 14.28; Found: C, 45.50; H, 2.95; N, 14.29.

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

The antimycobacterial activities of title compounds **25a-i, 26a-i, 27a-i** and **28a-i** were evaluated against MTB H_{37}Rv (ATCC 27294) strain by using MABA [30-32]. Ethambutol, Isoniazid and Rifampcin are used as positive controls. Compound stock solutions were prepared in DMSO at a concentration of 100 µL and the final test concentrations ranged from 25 to 0.78 µg/mL. 200 mL 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 colors of all wells were recorded. A blue color in the well was interpreted as no growth, and a pink color 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 color change from blue to pink [32].

5.4.3. CHO-K1 Cytotoxicity

Standard MTT assay (Sigma Aldrich) was applied according to the manufacturer´s protocol on Chinese hamster ovary (CHO-K1) cell lines. The cells were cultured according to ECACC recommended conditions and seeded in a density of 8×10^3, 12×10^3 per well respectively for CHO-K1 cells. Cells were exposed to test compounds for 48 hours, then the medium was replaced for a medium containing 100 μM of MTT and cells were allowed to produce formazan for another approximately 2 h under observation. Then, medium with MTT was sucked out and crystals of formazan were dissolved in DMSO. Cell viability was assessed spectrophotometrically by the amount of formazan produced. Absorbance was measured at 570 nm with 650 nm reference wavelength [33].

5.5. References

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