Chapter VI

6-chloro, 6,7-dichloro and 2-methyl-3-(((1-(substitutedphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide derivatives as anti-tubercular agents

Chapter 6

6-chloro, 6,7-dichloro and 2-methyl-3-(((1-(substitutedphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide derivatives as anti-tubercular agents

6.1. Introduction

Quinoxaline derivatives are a class of compounds that show very exciting biological properties and the importance in these compounds is growing within the field of medicinal chemistry [1]. Over the last three decades, many mono- and di-N-oxides and 2-oxo derivatives of this heterocyclic system have appeared on the scene and their biological activities have been reported. Oxidation of both nitrogens of the pyrazine ring to obtain quinoxaline-1,4-di-*N*-oxide dramatically increases the diversity of biological properties [2]. The quinoxaline 1,4-di-*N*-oxides were known as potent antibacterial agents since the 1940s. Quinoxaline-1,4-di-*N*-oxide derivatives even improve the biological results shown by their reduced analogues and are endowed with antiviral, anticancer, antibacterial and antiprotozoal activities [3]. Sainza *et al.,* reported quinoxaline l,4-di-*N*-oxide derivatives with different substituents in 2, 3, 6 and 7 positions gave in order to obtain new hypoxia selective agents. Some of these products gave good results as antituberculosis agents [4]. Different 7-chloro-3-(*para* substituted) phenylaminoquinoxaline-2-carbonitrile 1,4-di-*N*-oxides have shown to possess MTB growth inhibition value of 99% [5]. 6,7-dichloro-2-ethoxycarbonyl-3-methylquinoxaline 1,4-di-*N*-oxide and 3-acetamide-6,7-dichloroquinoxaline-2-carbonitrile 1,4-di-*N*-oxide derivatives produced growth inhibition values of 100% [4, 6]. Jsco *et al.,* reported 2-acetyl and 2-benzoyl-6(7)-substituted quinoxaline 1,4-di-*N*-oxide derivatives with MTB MIC ranging from 3.3 to 62.5 μM against MTB H37Rv. Same groups reported twenty nine new 6 (7)-substituted quinoxaline-2-carboxylate 1,4-dioxides with better activity MTB MIC ranging from 0.10 to >6.25 μg/mL [7]. Torres *et al.,* reported 1,4-di-*N*-oxide-quinoxaline-2-ylmethylene isonicotinic acid hydrazide with MTB IC_{50} ranging from 0.58 to 90.84 μM against MTB H37Rv [8]. Twenty seven 2-acetylquinoxaline 1,4-di-*N*-oxide and seven 2-benzoylquinoxaline 1,4-di-*N*-oxide derivatives

showed MTB IC_{50} ranging from 0.20 to 99.91 µg/mL against MTB H37Rv [9]. Pan *et al.*, synthesized thirty one compounds of quinoxaline 1,4-di-*N*-oxides variously substituted at C-2 position and evaluated their antimycobacterial activity with MTB MIC ranging from 0.39 to 50 µg/mL [10]. Quinoxaline *N*-oxide based anti-TB agents are depicted in **figure 6.1**.

Recently some select analogues were found to be active against a panel of single-drug-resistant strains of MTB and in the TAACF macrophage model [9]. Two derivatives, compounds **C** and **D** were successful *in vivo* in a murine model of low dose aerosol infection. Moreover, these two compounds also showed activity against non-replicating (NRP) bacteria. If the bactericidal activity and activity on NRP bacteria *in vitro* translate to *in vivo* conditions, quinoxaline 1,4-di-*N*-oxides may lead to reduced therapy, since the presence of NRP bacteria is assumed to be major cause responsible for the prolonged nature of antitubercular therapy [11].

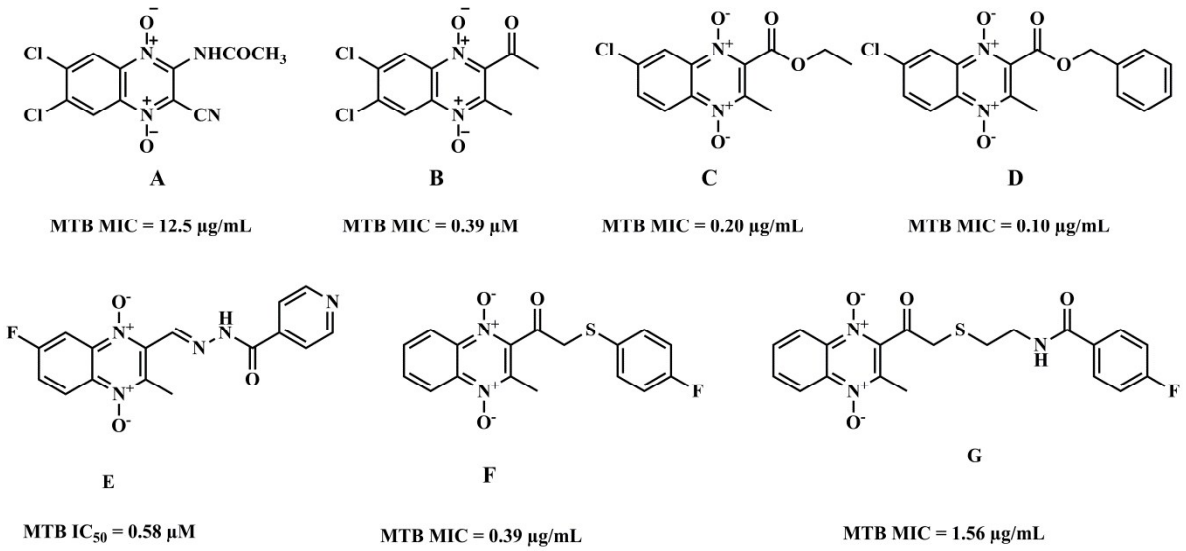


Figure 6.1: Some of the *N*-oxide based anti-tubercular agents

1,2,3-triazole and its derivatives have attracted continued interest in the medicinal chemistry field owing to their varied biological activities such as anti-bacterial, antiviral, antifungal, anti-allergic, anti-HIV, anticonvulsant, anti-inflammatory and β-lactamase inhibition properties [12]. It is quite evident that the favorable properties of 1,2,3-triazole ring *viz.*, moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions are

responsible for their enhanced biological activities [13, 14]. Triazole derivatives have also been shown to possess strong inhibitory activities *in vitro* and *in vivo* against MTB. These inhibit bacteria by blocking the biosynthesis of certain bacterial lipids. 1,2,3-triazole at all positions with varied substituents has produced potent anti-TB activity. Till date many triazole anti-TB agents were published here depicted in **Figure 6.2** some triazole anti-TB agents [15].

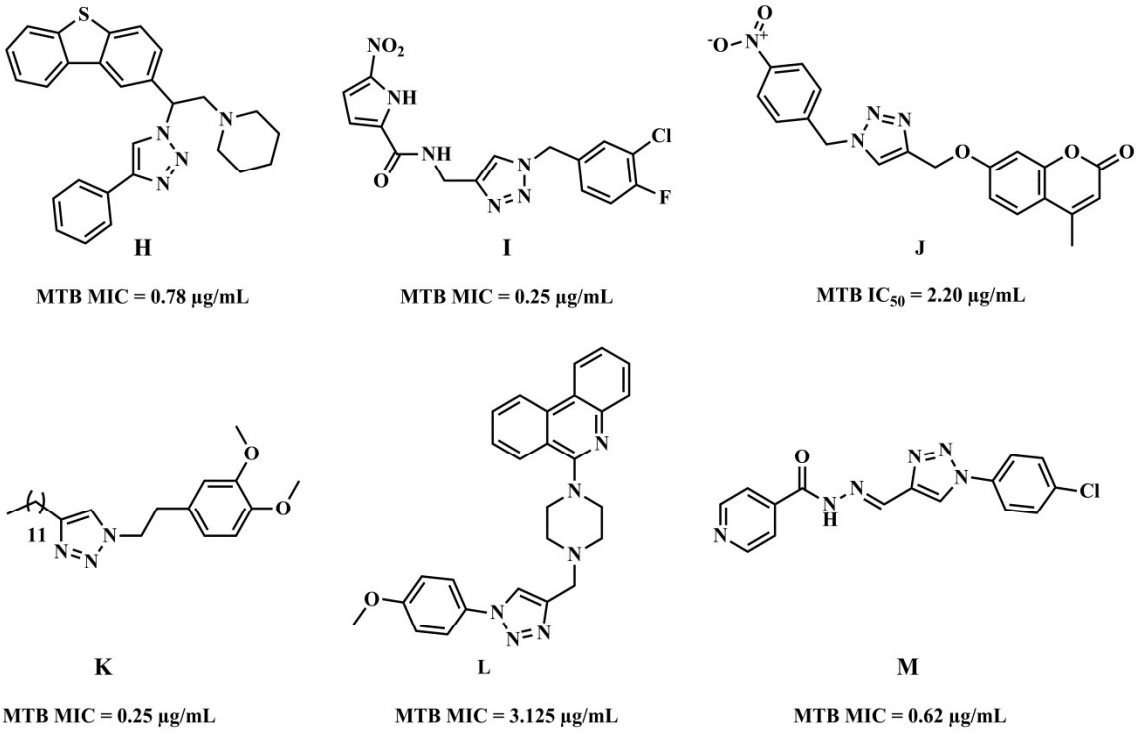


Figure 6.2: Some of the triazole based anti-tubercular agents

Quinoxaline 1,4-di-*N*-oxide and 1,2,3-triazoles moieties are kwit in a single molecular scaffold and antitubercular activity was studied. It has been established that more efficacious antimicrobial compounds can be designed by joining two or more biologically active heterocyclic systems together in a single molecular framework. Based on this strategy we designed and synthesized the target compounds [14].

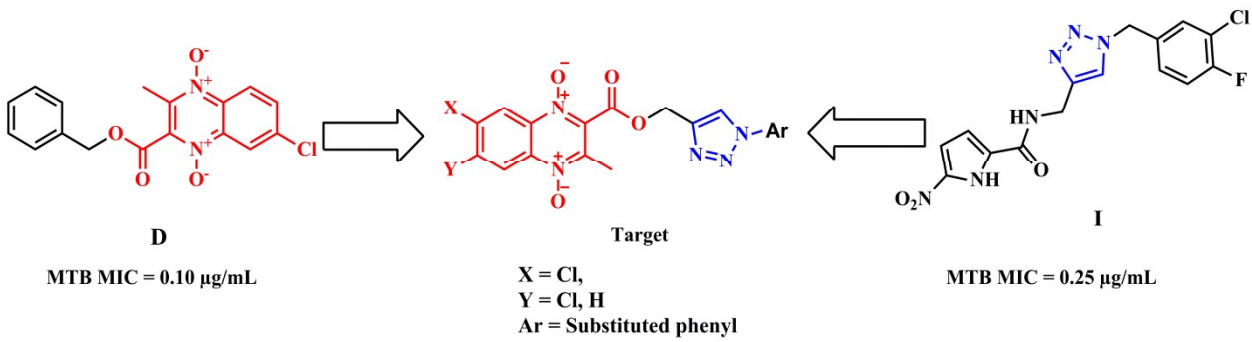
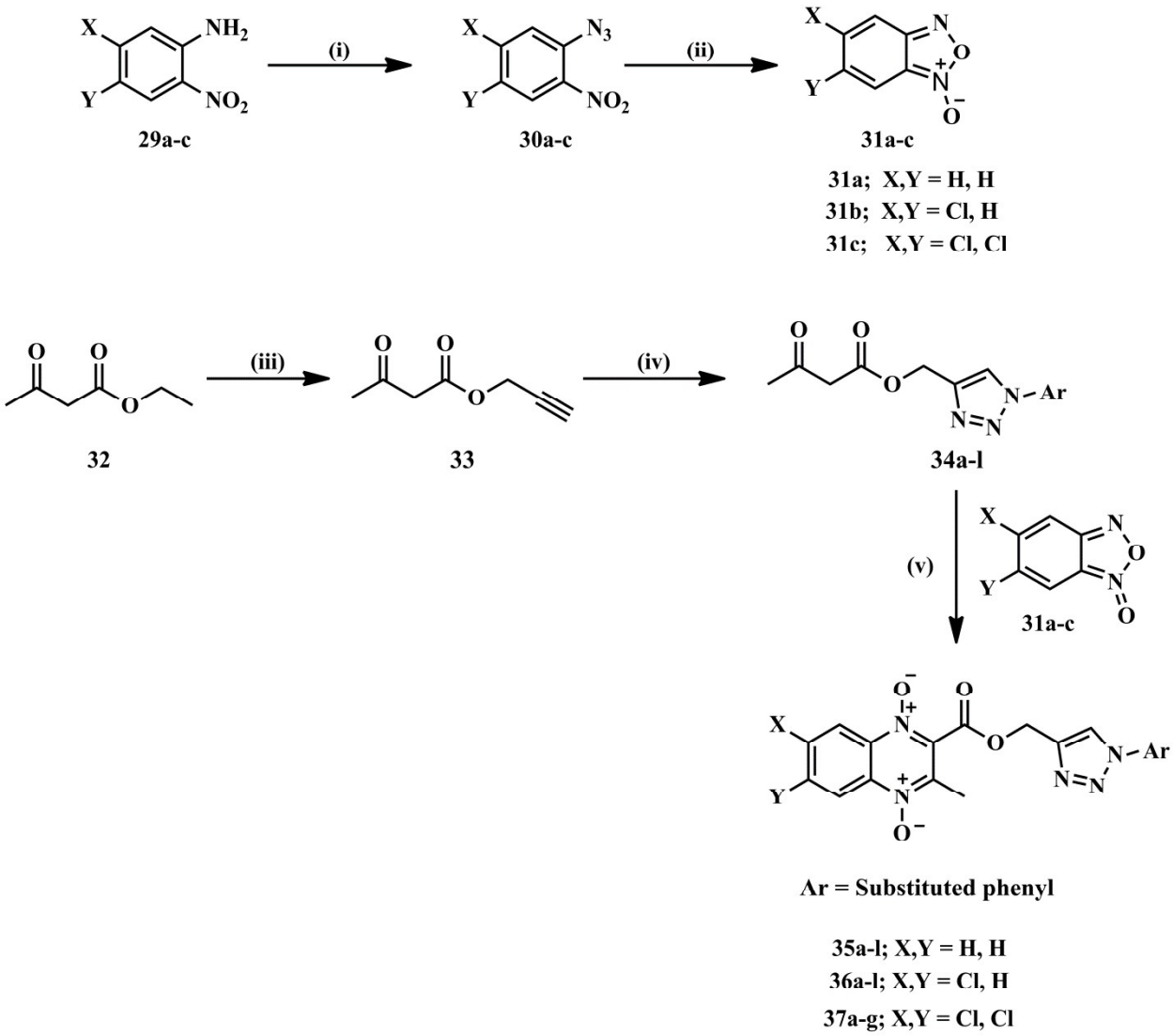


Figure 6.3: Design strategy of the title compounds.

6.2. Results and Discussion

6.2.1. Chemistry

The designed molecules were synthesized in five steps (**Scheme 6.1**). Initially we prepared *N*-oxide intermediate (**31a-c**) *via* azides compound (**30a-c**). Ethyl acetoacetate was treated with proprgyl alcohol in toluene at 110 °C to get transesterified compound **33**. The free acetylene group of **33** was converted to various 1*H*-1,2,3-triazoles (**34a-l**) using different aromatic azides *via* click chemistry method [16]. Compound **34** on reacting with various *N*-Oxide intermediates (**31a-c**) in the presence of triethylamine formed quinoxaline 1,4-dioxide (**35a-l, 36a-l** & **37a-g**). The purity of synthesized compounds was checked by LC-MS and elemental analyses. Structures of the compounds were confirmed by spectral data. In ^{1}H NMR and ^{13}C NMR, the signals of the respective protons and carbons were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The results of elemental analysis were within ± 0.05 of the theoretical values.



Scheme 6.1: Synthetic protocol of titled compounds.

Reagents and conditions: (i) $NaNO_2$ (1.50 eq), NaN_3 (1.50 eq), 6N HCl (8 wt/v), 0 °C, 2 h. (ii) toluene (30 wt/v), 110 °C, 24 h. (iii) Propargyl alcohol (10.0 eq), toluene, 24 h. (iv) Substituted phenyl azides, $CuSO_4.5H_2O$ (10 mol %), Sodium ascorbate (10 mol %), H_2O:^{t}BuOH (1:2), rt, 16 h. (v) *N*-oxide intermediate (31a-c) (1.2 eq), Triethylamine, rt, 16 h.

6.2.2. In-vitro MTB screening

All the synthesized compounds were tested for their capacity to inhibit the growth of MTB. In assay three different *M. tuberculosis* strains were used. One of them was reference strain *M. tuberculosis H37Rv ATTC 25618* and the others were 'wild' strains isolated from tuberculosis patients [17, 18]. MTB strain *spec. 210* was resistant to *p*-aminosalicylic acid (PAS), INH, ETB

and RMP and another (*Spec. 192*) fully sensitive to the administrated tuberculostatics [18]. In this study three different strains were used for screening as we wanted to know the kind of activity synthesized compounds showed against the reference strain as well as against the strains isolated from TB patients. In this study the influence of the compound on the growth of mycobacteria at a certain concentration: 3.1, 6.2, 12.5, 25, 50 and 100 µg/mL were evaluated INH was used as reference drug. The *in vitro* antimycobacterial results of title compounds are arranged in **Table 6.1** as MIC (µM) and the activity ranged from 30.35- >252 µM.

Table 6.1: Result of Antimycobacterial screening of title compounds

Entry	X	Y	Ar	MIC in µM (µg/mL) against MTB *H37Rv*	MIC in µM (µg/mL) against MTB *Spec. 192*	MIC in µM (µg/mL) against MTB *Spec. 210*
35a	H	H	phenyl	132.50 (50)	132.50 (50)	132.50 (50)
35b	H	H	4-Ethylphenyl	123.33 (50)	123.33 (50)	123.33 (50)
35c	H	H	4-Fluorophenyl	>252.94 (>100)	>252.94 (>100)	>252.94 (>100)
35d	H	H	4-Chlorophenyl	>242.84 (>100)	>242.84 (>100)	>242.84 (>100)
35e	H	H	4-Bromophenyl	109.59 (50)	109.59 (50)	109.59 (50)
35f	H	H	4-Nitrophenyl	>236.77 (>100)	>236.77 (>100)	>236.77 (>100)
35g	H	H	2- Fluorophenyl	126.47 (50)	126.47 (50)	126.47 (50)
35h	H	H	2-Chlorophenyl	60.71 (25)	60.71 (25)	60.71 (25)
35i	H	H	2-Nitrophenyl	59.19 (25)	59.19 (25)	59.19 (25)
35j	H	H	3-Nitrophenyl	59.19 (25)	59.19 (25)	59.19 (25)
35k	H	H	3-Trifluoromethyl pheny	224.54 (100)	224.54 (100)	112.27 (50)
35l	H	H	3,5-dichlorophenyl	97.06 (50)	97.06 (50)	194.12 (100)
36a	Cl	H	phenyl	30.35 (12.5)	30.35 (12.5)	30.35 (12.5)
36b	Cl	H	4-Ethylphenyl	56.83 (25)	56.83 (25)	56.83 (25)
36c	Cl	H	4-Fluorophenyl	58.16 (25)	58.16 (25)	58.16 (25)

Entry	X	Y	Ar	MIC in µM (µg/mL) against MTB *H37Rv*	MIC in µM (µg/mL) against MTB *Spec. 192*	MIC in µM (µg/mL) against MTB *Spec. 210*
36d	Cl	H	4-Chlorophenyl	56.02 (25)	56.02 (25)	56.02 (25)
36e	Cl	H	4-Bromophenyl	50.94 (25)	50.94 (25)	>203.76 (>100)
36f	Cl	H	4-Nitrophenyl	54.72 (25)	54.72 (25)	54.72 (25)
36g	Cl	H	2-Fluorophenyl	58.16 (25)	58.16 (25)	58.16 (25)
36h	Cl	H	2-Chlorophenyl	56.02 (25)	56.02 (25)	56.02 (25)
36i	Cl	H	2-Nitrophenyl	54.72 (25)	54.72 (25)	109.44 (50)
36j	Cl	H	3-Nitrophenyl	109.45 (50)	109.45 (50)	109.45 (50)
36k	Cl	H	3-Trifluoromethyl phenyl	104.21 (50)	104.21 (50)	104.21 (50)
36l	Cl	H	3,5-dichlorophenyl	52.00 (25)	52.00 (25)	52.00 (25)
37a	Cl	Cl	phenyl	112.04 (50)	112.04 (50)	112.04 (50)
37b	Cl	Cl	4-Fluorophenyl	53.85 (25)	53.85 (25)	53.85 (25)
37c	Cl	Cl	4-Chlorophenyl	52.00 (25)	52.00 (25)	52.00 (25)
37d	Cl	Cl	4-Bromophenyl	47.60 (25)	47.60 (25)	47.60 (25)
37e	Cl	Cl	2-Fluorophenyl	107.70 (50)	107.70 (50)	107.70 (50)
37f	Cl	Cl	2-Chlorophenyl	104.01 (50)	104.01 (50)	104.01 (50)
37g	Cl	Cl	3,5-dichlorophenyl	97.06 (50)	97.06 (50)	97.06 (50)
INH	-	-	-	<22.59 (<3.1)	<22.59 (<3.1)	91.15 (12.5)

Among the thirty one compounds screened , eight compounds (**36a, 36e, 36f, 36i, 36l, 37b, 37c** and **37d**) showed activity against MTB with MIC <55.00 µM. Two compounds (**36a** & **37d**) inhibited MTB with MIC <50.00 µM. Compound **36a** (6-chloro-2-methyl-3-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide) was found to be the most active compound with MTB MIC 30.35 µM.

SAR of compound 35a-l

SAR is explained based on activity of compound **35a**. Structural changes at *ortho*, *meta* & *para* positions alter the activity. Compound **35a** was inhibiting growth of MTB H37Rv strain at 132.50 μM. In this series, introduction of electron donation ethyl group at the 4th position activity remained unaltered. Presence of electron withdrawing **F** and **Cl** on the phenyl ring at para position resulted in decease in activity by the two folds (**35c**, MIC >252.94 μM; **35d,** MIC >242.84 μM) but the presence of bromo (**35e**) at the *para* position resulted in increase in activity by one fold with MIC 109.59 μM. Presence of electron withdrawing nitro group at *para* position decreased activity by two folds (**35f**, >236.77) but nitro at the *ortho* and *meta* position activity increased by two folds (**35i,** MIC 59.19 μM; **35j,** MIC 59.19 μM). With introduction of fluoro group at *ortho* position activity remained unchanged compared with compound **35a** but the presence of chloro (**35h**) at *ortho* position enhanced the activity by two folds with MIC 60.71 μM. Presence of two **Cl** (**35l**) at 3rd and 5th position resulted increase in activity by one fold with MIC 97.06 μM. Introduction of withdrawing CF_3 group (**35k**) at *meta* position activity decreased by two folds with MIC 224.54 μM.

SAR of compound 36a-l

SAR is explained based on activity of compound **36a**. Compound **36a** was inhibiting growth of MTB H37Rv strain at 30.35 μM. With the presence of electron donating ethyl group at *para* position activity fell by two folds with MIC 56.83 μM. Introduction of electron withdrawing groups like *viz.,* **F, Cl** & **Br** at *artho, meta* and *para* position with mono or disubstituted resulted in decrease in activity by two folds. Presence of electron withdrawing nitro group at *para* position (**36f**) decreased in activity two folds with MIC 54.72 μM but the introduction nitro group at *meta* position (**36j**) activity decreased by four folds with MIC 109.45 μM. Introduction of electro withdrawing CF_3 group (**36k**) at meta position activity decreased by four folds with MIC 104.21 μM. All these results show that the insertion of a halogen moiety will increases the anti-tubercular activity.

SAR of compound 37a-g

In this series, two **Cl** groups were introduced on the quinoxaline 1,4-dioxide frame but activity did not improve. SAR explained based on activity of compound **37a** (MIC 112.04 μM).

With introduction of electron withdrawing halogens like *viz.,* **F, Cl** & **Br** at the *para* position on the phenyl, activity increased by two folds (**37b,** MIC 53.85 µM; **37c,** MIC 52.00 µM & **37d,** MIC 47.60 µM) but presence of **F** & **Cl** at the *ortho* position activity remained unchanged (**37e,** MIC 107.70 µM; **37f,** MIC 104.01 µM). Introduction of chlorine at the 3rd and 5th position resulted in retention of activity.

Over all, we notice that 6-chloro-3-(((1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide derivatives (**36a-l**) exhibited better anti-TB activity followed by 2-(((1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide derivative (**35a-l**) and 6,7-dichloro-2-(((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide derivatives (**37a-g**).

6.2.3. In vitro cytotoxicity studies

Compounds with MTB MIC < 12.5 µg/mL were subjected to cytotoxicity studies against HEK 293 cell line. Cytotoxicity assay of **36a, 36e, 36f, 36i, 36l, 37b, 37c** & **37d** was determined. Cell viability was measured by in vitro MTT assay [19]. Cells were exposed to compounds for 24 hours at three concentrations 50 µM, 25 µM and 10 µM (n=2). Data represent mean values of measurements ± s.d. (**Figure 6.4**). Data clearly indicate the active compounds **36e, 36f, 36i, 36l & 37d** were not toxic at even 50 µM. However, the compounds **36a** and **37c** were moderately toxic.

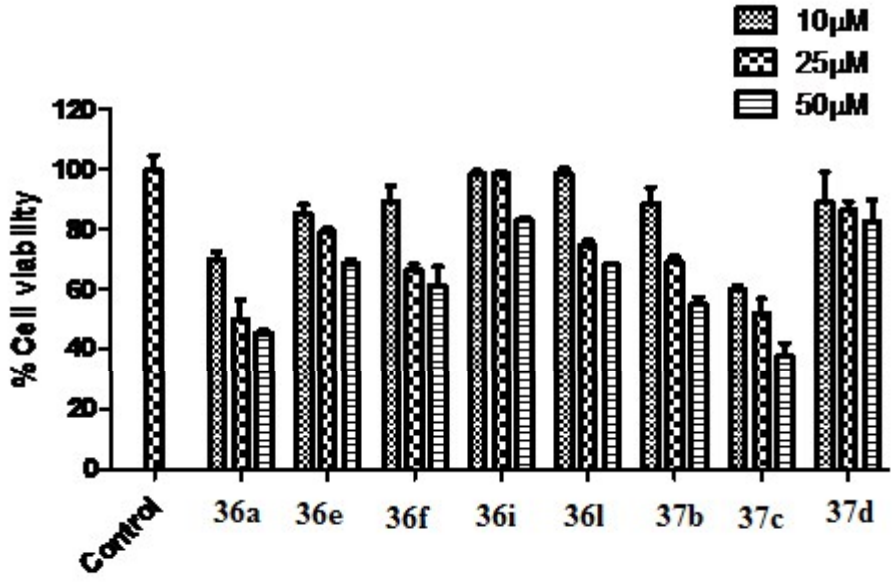


Figure 6.4: Cytotoxicity assay of **36a, 36e, 36f, 36i, 36l, 37b, 37c** & **37d** on HEK-293 cells.

6.3. Conclusion

In this chapter, quinoxaline 1,4-dioxide analogues synthesized with three different series; 2-methyl-3-(((substituted pheny)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide derivatives, 6-chloro-3-(((1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide derivatives and 6,7-dichloro-2-(((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide derivatives by the molecular hybridization approach using reported 1,4-dioxides anti-TB agents and substituted 1*H*-1,2,3-triazol antitubercular agents. Amongst the synthesized compounds, 6-chloro-3-(((1-(substitutedphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide derivatives showed good ant-TB results. One of the compound **36a** showed excellent MTB activity with MIC 30.35 μM. Further, the most active compounds (**36e, 36f, 36i, 36l** & **37d**) did not exhibit cytotoxicity against HEK 293 cell line for the most active compounds at 50 μM while **36a** and **37c** were moderately toxic.

6.4. Experimental

6.4.1. Materials and methods

Chemicals and solvents were procured from commercial source. The solvents and reagents were of LR grade and if necessary purified before use. 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 NMR and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz respectively using a Bruker AV 400 spectrometer (Bruker CO., Switzerland) in $CDCl_3$ and DMSO-d_6 solution with tetramethylsilane as the internal standard and chemical shift values (δ) were given in ppm. Melting points were determined on an electro thermal melting point apparatus (Stuart-SMP30) in open capillary tubes and are uncorrected. Elemental analyses were performed by Elementar Analysensysteme GmbH vario MICRO cube CHN Analyzer. Mass spectra (ESI-MS) were recorded on Schimadzu MS/ESI mass spectrometer. Purity of all tested compounds were determined by LC-MS/MS on Schimadzu and was greater than 95%.

6.4.2. Chemistry

***Representative procedure for the synthesis of compound* (30a-c)**

A stirred solution of compound (**29**) (1.0 equiv.) in 6N HCl was cooled to 0 °C. The reaction mixture was stirred for 5 minutes and $NaNO_2$ (1.50 equiv.) in water at 0 °C was slowly added and stirred for 5 minutes. This was followed by addition of NaN_3 (1.50 equiv.) in water at 0 °C it was stirred for 2 h at 0 °C. Once completion of the reaction, as indicated by TLC, the reaction was quenched with cold water and extracted with ethyl acetate. The organic layers were collected, washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was obtained as yellow solid (**30a-c**) yields (70-85%).

***Representative procedure for the synthesis of compound* (31a-c)**

A stirred solution of compound (**30a-c**) in toluene was heated at 110 °C for 24 h under argon. After completion of the reaction, as indicated by TLC, the reaction was concentrated *in vacuo*. The resultant crude product was purified by column chromatography [ethyl acetate / hexane (5 - 10%)] to get the compound **31a-c** (75-85%) as yellow solid.

***Representative procedure for the synthesis of compound* (33)**

To solution of compound **32** (1.0 equiv) in toluene propargyl alcohol (5.0 equiv.) was added. The solution was heated at 110 °C for 12 h then another 5.0 equivalence of propargyl alcohol was added and continued for another 12 h at 110 °C. Once completion of the reaction, as indicated by TLC, the toluene was removed *in vacuo*. The crude product was purified by column chromatography [ethyl acetate / hexane (30 - 40%)] to get the compound **33** (79-90%) as yellow oil.

***Representative procedure for the synthesis of compound* (34a-l)**

A solution of compound **33** (1.0 equiv.) is reacted with substituted phenyl azides (1.2 equiv.) in the presence of sodium ascorbate (0.01 equiv.), $CuSO_4.5H_2O$ (0.02 equiv.) and *t*-BuOH: H_2O (2:1), at rt for 16 h. Once completion of the reaction, as indicated by TLC, the reaction was quenched with cold water and extracted with DCM. The DCM layers were collected, washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The

resultant crude product was purified by column chromatography [ethyl acetate / hexane (30 - 40%)] to yield (35-65%) the title compounds **34a-l**.

***Representative procedure for the synthesis of compound* (35a-l, 36a-l & 37a-h)**

To stirred suspension of an appropriate compound **31a-c** (1.0 equiv.) compound **34a-l** (1.2 equiv.) in triethylamine is added and stirred 16 hours at room temperature under nitrogen. Once completion of the reaction, as indicated by TLC, the triethylamine was removed under vacuum distillation. The remaining reaction mixture was dissolved in ethyl acetate and washed with water. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to give crude product. The resultant crude product was purified by column chromatography [ethyl acetate / hexane (30 - 40%)] to get compound (**35a-l, 36a-l** & **37a-h***)*. Yield ranging from 45 to 85%.

***2-methyl-3-(((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (35a)**

Yellow solid (47%); m.p. 188-189 °C; IR (KBr) υ_{max} / cm^{-1} 3017, 2895, 1663, 1339, 1020, 960. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 – 8.62 (m, 1H), 8.60 – 8.56 (m, 1H), 8.32 (s, 1H), 7.95 – 7.83 (m, 2H), 7.81 – 7.75 (m, 2H), 7.60 – 7.53 (m, 2H), 7.53 – 7.45 (m, 1H), 5.77 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.34, 143.10, 139.01, 138.18, 137.85, 136.14, 135.28, 133.06, 132.22, 129.73, 129.42, 122.03, 121.99, 121.04, 119.04, 60.71, 14.68. EI-MS *m/z* 378.12 $(M+H)^+$; Anal. calcd for $C_{19}H_{15}N_5O_4$: (%) C, 60.48; H, 4.01; N, 18.56; Found: C, 60.49; H, 4.03; N, 18.58.

***2-(((1-(4-ethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (35b)**

Pale yellow solid (63%); m.p. 134-135 °C; IR (KBr) υ_{max} / cm^{-1} 3012, 2890, 1670, 1340, 1060, 975. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 – 8.60 (m, 1H), 8.57 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.25 (s, 1H), 7.87 (dddd, *J* = 18.2, 8.5, 7.0, 1.5 Hz, 2H), 7.69 – 7.62 (m, 2H), 7.40 – 7.33 (m, 2H), 5.75 (s, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.90, 145.28, 142.09, 138.93, 138.14, 136.79, 134.88, 134.83, 133.32, 132.21, 129.63, 123.98, 120.72, 120.14, 120.13, 60.17, 28.15, 15.91, 14.54. EI-MS *m/z* 405.15

$(M+H)^+$; Anal. calcd for $C_{21}H_{19}N_5O_4$: (%) C, 62.23; H, 4.72; N, 17.27; Found: C, 62.24; H, 4.73; N, 17.28.

***2-(((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (35c)**

Yellow solid (44%); m.p. 220-221 °C; (KBr) υ_{max} / cm^{-1} 3025, 2897, 1675, 1412, 1369, 1127, 1022. 972, ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 – 8.61 (m, 1H), 8.61 – 8.55 (m, 1H), 8.29 (s, 1H), 7.90 (dddd, J = 18.4, 8.4, 7.0, 1.5 Hz, 2H), 7.81 – 7.72 (m, 2H), 7.29 (d, J = 1.9 Hz, 1H), 7.27 – 7.24 (m, 1H), 5.77 (s, 2H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.89, 142.25, 138.94, 138.15, 136.80, 134.87, 133.34, 132.23, 124.35, 123.18, 123.09, 120.15, 117.41, 117.18, 60.10, 14.55. EI-MS *m/z* 396.10 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}FN_5O_4$: (%) C, 57.72; H, 3.57; N, 17.71; Found: C, 57.73; H, 3.58; N, 17.72.

***2-(((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4 dioxide* (35d)**

Off white solid (57%); m.p. 221-222 °C; (KBr) υ_{max} / cm^{-1} 3075, 2867, 1675, 1412, 1369, 1020, 987, 765. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 – 8.62 (m, 2H), 8.31 (s, 1H), 7.99 – 7.86 (m, 2H), 7.70 – 7.26 (m, 4H), 5.76 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.99, 144.25, 138.14, 138.75, 136.80, 134.87, 134.34, 133.34, 132.73, 125.55, 123.78, 123.19, 121.19, 117.55, 117.28, 60.10, 14.59. EI-MS *m/z* 412.21 $(M+H)^+$ Anal. calcd for $C_{19}H_{14}ClN_5O_4$: (%) C, 50.02; H, 3.09; N, 15.35; Found: C, 50.03; H, 3.10; N, 15.36.

***2-(((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (35e)**

Off white solid (49%); m.p. 204-205 °C; (KBr) υ_{max} / cm^{-1} 3092, 2867, 1685, 1412, 1373, 1024, 962, 653. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 – 8.60 (m, 2H), 8.33 (s, 1H), 7.92 – 7.87 (m, 2H), 7.70 – 7.28 (m, 4H), 5.77 (s, 2H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.85, 142.51, 139.03, 138.07, 136.84, 135.78, 134.97, 133.03, 132.77, 131.62, 122.81, 122.12, 122.05, 120.31, 120.26, 60.27, 14.43. EI-MS *m/z* 457.21 $(M+H)^{+2}$; 455.02 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}BrN_5O_4$: (%) C, 50.02; H, 3.09; N, 15.35; Found: C, 50.03; H, 3.10; N, 15.36.

***2-methyl-3-(((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (35f)**

Yellow solid (51%); m.p. 220-221 °C; (KBr) υ_{max} / cm^{-1} 3035, 2877, 1695, 1510, 1273, 1031, 987. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 – 8.61 (m, 1H), 8.57 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.23 (dddd, *J* = 18.3, 8.5, 7.1, 1.6 Hz, 2H), 8.09 (s, 1H), 7.69 – 7.62 (m, 2H), 7.40 – 7.33 (m, 2H), 5.78 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.97, 144.72, 142.87, 138.10, 138.74, 136.86, 135.12, 134.73, 134.15, 132.60, 130.96, 129.10, 129.49, 128.09, 127.11, 126.09, 119.89, 60.39, 14.56. EI-MS *m/z* 423.11 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}N_6O_6$: (%) C, 54.03; H, 3.34; N, 19.90; Found: C, 54.04; H, 3.36; N, 19.91.

***2-(((1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (35g)**

Pale yellow solid (63%); m.p. 148-150 °C; (KBr) υ_{max} / cm^{-1} 3082, 2897, 1697, 1412, 1373, 1027, 972, 697. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 – 8.52 (m, 2H), 8.37 (d, *J* = 2.7 Hz, 1H), 8.01 – 7.80 (m, 3H), 7.47 (tdd, *J* = 8.2, 4.9, 1.8 Hz, 1H), 7.40 – 7.27 (m, 2H), 5.77 (s, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.76, 154.65, 152.15, 141.81, 139.06, 137.97, 136.81, 134.96, 132.72, 131.55, 130.63, 130.55, 125.49, 125.41, 125.35, 125.31, 125.04, 124.94, 120.31, 120.16, 117.20, 117.00, 60.14, 14.37. EI-MS *m/z* 396.10 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}FN_5O_4$: (%) C, 57.73; H, 3.57; N, 17.72; Found: C, 57.74; H, 3.58; N, 17.73.

***2-(((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (35h)**

Off white solid (54%); m.p. 181-182 °C; (KBr) υ_{max} / cm^{-1} 3076, 2893, 1691, 1421, 1363, 1025, 966, 653. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 – 8.65 (m, 2H), 8.39 (d, *J* = 2.5 Hz, 1H), 8.11 – 7.90 (m, 3H), 7.40 (tdd, *J* = 8.4, 4.7, 1.8 Hz, 1H), 7.36 – 7.26 (m, 2H), 5.76 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.86, 154.65, 150.15, 142.80, 138.16, 137.17, 136.31, 134.96, 132.72, 131.55, 130.63, 130.55, 125.49, 125.41, 125.35, 125.31, 125.44, 124.48, 120.14, 120.61, 117.11, 117.21, 60.44, 14.57. EI-MS *m/z* 412.07 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}ClN_5O_4$: (%) C, 55.42; H, 3.43; N, 17.02; Found: C, 55.74; H, 3.44; N, 17.03.

***2-methyl-3-(((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (35i)**

Yellow solid (48%); m.p. 197-198 °C; (KBr) υ_{max} / cm^{-1} 3096, 2913, 1693, 1427, 1363, 1033, 986. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 – 8.57 (m, 2H), 8.39 (d, *J* = 2.5 Hz, 1H), 8.11 – 7.94 (m, 3H), 7.57 (tdd, *J* = 8.4, 4.8, 1.6 Hz, 1H), 7.42 – 7.29 (m, 2H), 5.76 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.87, 144.52, 141.87, 139.00, 138.14, 136.76, 135.02, 134.83, 133.25, 132.20, 131.96, 129.80, 129.40, 128.29, 127.37, 126.09, 119.87, 59.91, 14.46. EI-MS *m/z* 423.11 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}N_6O_6$: (%) C, 54.03; H, 3.34; N, 19.90; Found: C, 54.04; H, 3.36; N, 19.91.

***2-methyl-3-(((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline1,4-dioxide* (35j)**

Yellow solid (65%); m.p. 186-187 °C; (KBr) υ_{max} / cm^{-1} 3032, 2943, 1695, 1424, 1360, 1023, 976. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 – 8.57 (m, 2H), 8.41 (d, *J* = 2.7 Hz, 1H), 8.32 (s, 1H), 8.14 – 7.93 (m, 2H), 7.57 (tdd, *J* = 8.6, 4.8, 1.8 Hz, 1H), 7.40 – 7.26 (m, 2H), 5.75 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.77, 143.52, 140.97, 139.10, 138.24, 136.86, 135.12, 133.83, 133.27, 132.27, 131.96, 129.80, 129.40, 128.29, 127.37, 126.09, 119.87, 60.21, 14.49. EI-MS *m/z* 423.11 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}N_6O_6$: (%) C, 54.03; H, 3.34; N, 19.90; Found: C, 54.04; H, 3.36; N, 19.91.

***2-methyl-3-(((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl) quinoxaline 1,4-dioxide* (35k)**

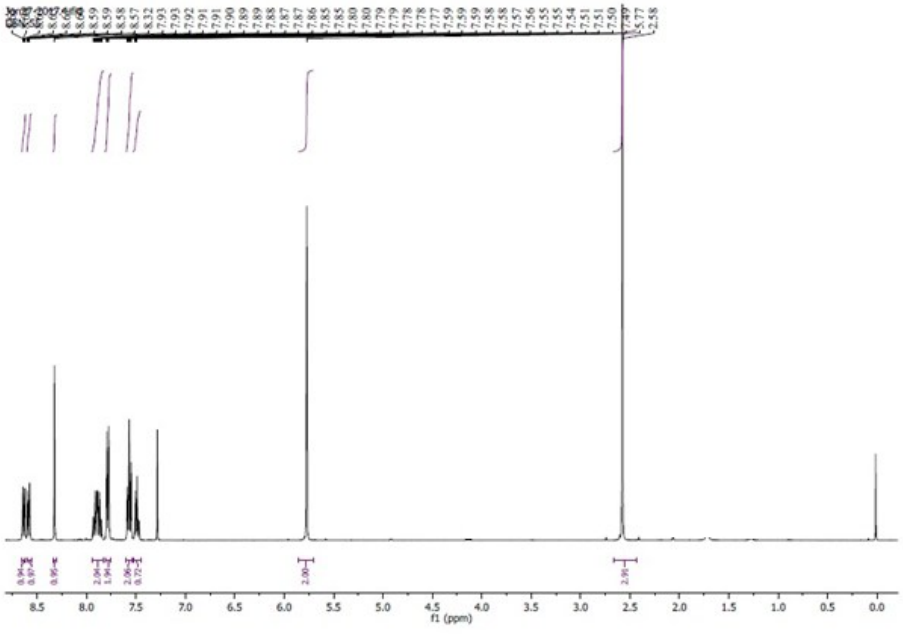
Pale yellow (40%); m.p. 193-194 °C; (KBr) υ_{max} / cm^{-1} 3042, 2963, 1689, 1420, 1361,1150, 1029, 973. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 – 8.62 (m, 2H), 8.44 (s, 1H), 8.19 (t, *J* = 1.9 Hz, 1H), 8.04 – 7.99 (m, 3H), 7.87 (dt, *J* = 7.4, 2.1 Hz, 1H), 7.60 (m, 1H), 5.77 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.49, 142.58, 139.29, 138.78, 137.13, 136.61, 135.59, 133.63, 132.71, 132.38, 130.69, 127.32, 125.76, 123.64, 122.27, 121.92, 119.72, 117.60, 60.27, 14.41. EI-MS *m/z* 446.11 $(M+H)^+$; Anal. calcd for $C_{20}H_{14}F_3N_5O_4$: (%) C, 53.95; H, 3.17; N, 15.73; Found: C, 53.96; H, 3.19; N, 15.74.

***2-(((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (35l)**

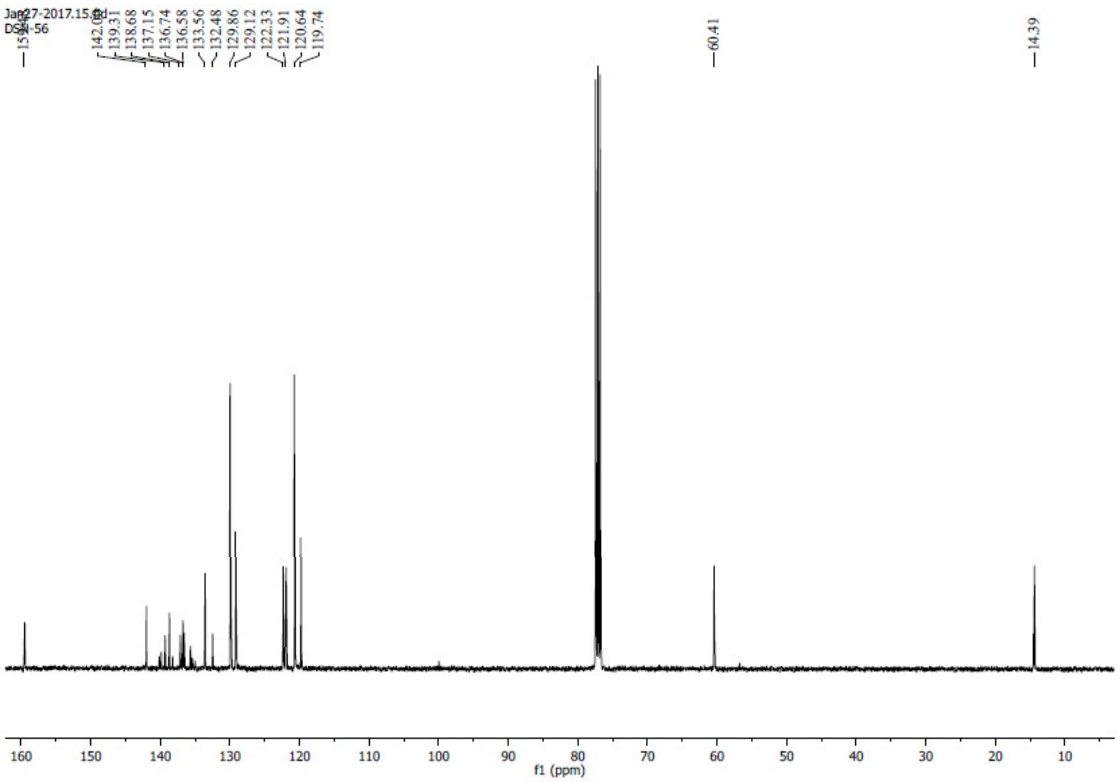
Pale yellow solid (52%); m.p. 205-206 °C; (KBr) υ_{max} / cm^{-1} 3076, 2893, 1691, 1421, 1363, 1025, 966, 653. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.63 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.60 – 8.55 (m, 1H), 8.34 (s, 1H), 7.88 (dddd, *J* = 21.2, 8.4, 7.0, 1.5 Hz, 2H), 7.74 (d, *J* = 1.8 Hz, 2H), 7.50 – 7.42 (m, 1H), 5.75 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 159.58, 142.74, 138.46, 137.79, 137.17, 137.03, 136.92, 136.54, 135.05, 134.64, 132.17, 129.55, 123.17, 121.82, 119.25, 60.49, 14.52. EI-MS *m/z* 445.04 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}Cl_2N_5O_4$: (%) C, 51.15; H, 2.94; N, 15.80; Found: C, 51.16; H, 2.95; N, 15.81.

***6-chloro-2-methyl-3-(((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (36a)**

Off white solid (61%); m.p. 193-194 °C; (KBr) υ_{max} / cm^{-1} 3066, 2893, 1701, 1383, 1043, 966, 715. ^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 8.66 – 8.44 (m, 2H), 8.30 (d, *J* = 3.4 Hz, 1H), 7.79 (dd, *J* = 17.5, 8.4 Hz, 3H), 7.52 (dt, *J* = 32.0, 7.4 Hz, 3H), 5.75 (s, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 159.48, 142.00, 139.31, 138.68, 137.15, 136.74, 136.58, 133.56, 132.48, 129.86, 129.12, 122.33, 121.91, 120.64, 119.74, 60.41, 14.39. EI-MS *m/z* 411.08 $(M+H)^+$; Anal. calcd for $C_{19}H_{14}ClN_5O_4$: (%) C, 55.42; H, 3.44; N, 17.01; Found: C, 55.43; H, 3.45; N, 17.02.



^{1}H NMR spectrum (400 MHz, Chloroform-*d*)) of compound **36a**



^{13}C NMR spectrum (101 MHz, Chloroform-*d*)) of compound **36a**

***6-chloro-3-(((1-(4-ethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide* (36b)**

Yellow solid (49%); m.p. 207-208 °C; (KBr) υ_{max} / cm^{-1} 3096, 2893, 1694, 1383, 1049, 986, 727. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 – 8.48 (m, 2H), 8.23 (d, *J* = 4.1 Hz, 1H), 7.81 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.41 – 7.33 (m, 2H), 5.76 (s, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 158.23, 143.10, 139.33, 138.45, 137.56, 136.64, 136.18, 134.88, 132.18, 129.76, 128.22, 122.33, 121.22, 120.34, 119.55, 60.34, 28.25, 15.87, 14.59. EI-MS *m/z* 439.11 $(M+H)^+$; Anal. calcd for $C_{21}H_{18}ClN_5O_4$: (%) C, 57.34; H, 4.13; N, 15.92; Found: C, 57.35; H, 4.14; N, 15.93.

***6-chloro-3-(((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide* (36c)**

Pale yellow solid (65%); m.p. 208-209 °C; (KBr) υ_{max} / cm^{-1} 3096, 2951, 1667, 1401, 1039, 976, 707. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.64 – 8.46 (m, 2H), 8.25 (d, *J* = 4.3 Hz, 1H), 7.81 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.25 (d, *J* = 1.3 Hz, 2H), 5.75 (s, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.79, 143.25, 138.84, 138.35, 136.78, 135.07, 134.87, 133.76, 132.03, 124.87, 123.65, 123.19, 121.15, 117.43, 117.28, 60.21, 14.56. EI-MS *m/z* 430.06 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}ClFN_5O_4$: (%) C, 53.11; H, 3.05; N, 16.30; Found: C, 53.12; H, 3.06; N, 16.31.

***6-chloro-3-(((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide* (36d)**

Off white solid (55%); m.p. 222-223 °C; (KBr) υ_{max} / cm^{-1} 3084, 2981, 1677, 1411, 1022, 944, 737. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.69 – 8.48 (m, 2H), 8.33 (d, *J* = 4.1 Hz, 1H), 7.78 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.49 – 7.36 (m, 2H), 5.74 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.73, 144.12, 139.73, 139.45, 137.56, 136.94, 135.18, 134.78, 134.76, 132.28, 129.66, 128.72, 122.33, 121.22, 119.95, 60.34, 14.59. EI-MS *m/z* 436.04 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}Cl_2N_5O_4$: (%) C, 51.15; H, 2.94; N, 15.69; Found: C, 51.16; H, 2.96; N, 15.70.

***3-(((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-6-chloro-2-methylquinoxaline 1,4-dioxide* (36e)**

Pale yellow solid (59%); m.p. 222-223 °C; (KBr) υ_{max} / cm^{-1} 3079, 2971, 1687, 1421, 1036, 976, 798, 707. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.70 – 8.56 (m, 2H), 8.39 (d, *J* = 4.4 Hz, 1H), 7.79 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.28 (d, *J* = 1.3 Hz, 2H), 5.78 (s, 2H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.79, 143.25, 138.84, 138.35, 136.78, 135.07, 134.87, 133.76, 132.03, 124.87, 123.65, 123.19, 121.15, 117.43, 117.28, 60.21, 14.56. EI-MS *m/z* 490.98 $(M+H)^{+2}$; 488.96 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}BrClN_5O_4$: (%) C, 46.51; H, 2.68; N, 14.28; Found: C, 46.53; H, 2.69; N, 14.29.

***6-chloro-2-methyl-3-(((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (36f)**

Yellow solid (65%); m.p. 220-221 °C; (KBr) υ_{max} / cm^{-1} 3089, 2982, 1690, 1411, 1026, 954, 757. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.66 – 8.46 (m, 2H), 8.30 (d, *J* = 4.1 Hz, 1H), 7.79 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.50 – 7.39 (m, 2H), 5.78 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.83, 144.92, 139.73, 139.45, 138.96, 136.94, 135.08, 134.78, 134.16, 133.78, 129.96, 128.82, 122.33, 121.22, 119.95, 60.74, 14.61. EI-MS *m/z* 457.08 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}ClN_6O_6$: (%) C, 49.96; H, 2.88; N, 18.41; Found: C, 49.97; H, 2.89; N, 18.42.

***6-chloro-3-(((1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide* (36g)**

Off white solid (46%); m.p. 195-196 °C; (KBr) υ_{max} / cm^{-1} 3078, 2972, 1693, 1421, 1145, 1026, 974, 787. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 – 8.47 (m, 2H), 8.36 (t, *J* = 2.3 Hz, 1H), 7.97 (td, *J* = 7.8, 1.7 Hz, 1H), 7.80 (ddd, *J* = 14.7, 9.2, 2.2 Hz, 1H), 7.49 (tdd, *J* = 8.1, 4.9, 1.7 Hz, 1H), 7.41 – 7.28 (m, 2H), 5.77 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.64, 155.58, 153.09, 141.73, 139.42, 137.42, 137.02, 135.48, 133.54, 132.01, 127.40, 126.50, 126.07, 124.96, 122.58, 119.32, 117.54, 60.12, 14.48. EI-MS *m/z* 430.06 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}ClFN_5O_4$: (%) C, 53.11; H, 3.05; N, 16.30; Found: C, 53.12; H, 3.06; N, 16.31.

***6-chloro-3-(((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide* (36h)**

Pale yellow solid (67%); m.p. 176-177 °C; (KBr) υ_{max} / cm^{-1} 3079, 2979, 1697, 1434, 1026, 973, 776. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 – 8.47 (m, 2H), 8.36 (t, *J* = 2.3 Hz, 1H), 7.97 (td, *J* = 7.8, 1.7 Hz, 1H), 7.80 (ddd, *J* = 14.7, 9.2, 2.2 Hz, 1H), 7.49 (tdd, *J* = 8.1, 4.9, 1.7 Hz, 1H), 7.41 – 7.28 (m, 2H), 5.77 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.70, 153.58, 150.09, 142.73, 139.02, 137.42, 137.12, 135.48, 133.54, 132.01, 127.40, 126.92, 126.77, 125.16, 122.78, 119.52, 117.64, 60.52, 14.68. EI-MS *m/z* 436.04 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}Cl_2N_5O_4$: (%) C, 51.15; H, 2.94; N, 15.69; Found: C, 51.16; H, 2.96; N, 15.70.

6-chloro-2-methyl-3-(((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide (36i)

Yellow solid (64%); m.p. 165-166 °C; (KBr) υ_{max} / cm^{-1} 3067, 2989, 1695, 1414, 1026, 975, 766. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 – 8.49 (m, 2H), 8.33 (t, *J* = 2.4 Hz, 1H), 7.95 (td, *J* =

7.9, 1.8 Hz, 1H), 7.81 (ddd, *J* = 14.7, 9.2, 2.2 Hz, 1H), 7.50 (tdd, *J* = 8.1, 4.9, 1.6 Hz, 1H), 7.43 – 7.26 (m, 2H), 5.78 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.71, 150.58, 148.19, 142.73, 139.11, 137.32, 137.02, 135.54, 134.44, 132.11, 127.66, 126.92, 126.87, 125.06, 122.78, 119.59, 117.64, 60.58, 14.58. EI-MS *m/z* 457.08 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}ClN_6O_6$: (%) C, 49.96; H, 2.88; N, 18.41; Found: C, 49.97; H, 2.89; N, 18.42.

***6-chloro-2-methyl-3-(((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (36j)**

Yellow solid (62%); m.p. 205-206 °C; (KBr) υ_{max} / cm^{-1} 3097, 2988, 1685, 1422, 1031, 961, 771. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 – 8.42 (m, 2H), 8.30 (t, *J* = 2.4 Hz, 1H), 7.92 (td, *J* = 7.9, 1.8 Hz, 1H), 7.79 (ddd, *J* = 14.6, 9.3, 2.2 Hz, 1H), 7.44 – 7.25 (m, 3H), 5.77 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.71, 151.59, 148.19, 142.73, 139.21, 137.42, 137.52, 136.57, 134.44, 132.11, 127.68, 126.22, 126.07, 125.16, 123.78, 119.79, 117.64, 60.58, 14.68. EI-MS *m/z* 457.08 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}ClN_6O_6$: (%) C, 49.96; H, 2.88; N, 18.41; Found: C, 49.97; H, 2.89; N, 18.42.

***6-chloro-2-methyl-3-(((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (36k)**

Pale yellow solid (66%); m.p. 160-161 °C; (KBr) υ_{max} / cm^{-1} 3095, 2887, 1688, 1420, 1132, 1039, 971, 772. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 – 8.52 (m, 2H), 8.42 (s, 1H), 8.09 (t, *J* = 1.9 Hz, 1H), 8.01 (dt, *J* = 7.4, 2.0 Hz, 1H), 5.77 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.49, 142.58, 139.29, 138.78, 137.13, 136.61, 135.59, 133.63, 132.71, 132.38, 130.69, 127.32, 125.76, 123.64, 122.27, 121.92, 119.72, 117.60, 60.27, 14.41. EI-MS *m/z* 480.06 $(M+H)^+$; Anal. calcd for $C_{20}H_{13}ClF_3N_5O_4$: (%) C, 50.08; H, 2.74; N, 14.61; Found: C, 50.09; H, 2.75; N, 14.62.

***6-chloro-3-(((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-2-methylquinoxaline 1,4-dioxide* (36l)**

Off white solid (55%); m.p. 197-198 °C; (KBr) υ_{max} / cm^{-1} 3079, 2891, 1691, 1420, 1364, 1029, 969, 663. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.66 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.60 – 8.55 (m, 1H), 8.42 (s, 1H), 7.88 (m, 2H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.50 (s, 1H), 5.78 (s, 2H), 2.56 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.48, 142.64, 139.26, 138.79, 137.97, 137.13, 136.62, 136.41, 135.55, 133.64, 132.57, 129.05, 122.17, 121.92, 119.73, 119.05, 60.19, 14.42. EI-MS *m/z* 480.01 $(M+H)^+$; Anal. calcd for $C_{19}H_{12}Cl_3N_5O_4$: (%) C, 47.48; H, 2.52; N, 14.58; Found: C, 47.49; H, 2.54; N, 14.59.

***6,7-dichloro-2-methyl-3-(((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)quinoxaline 1,4-dioxide* (37a)**

Off white solid (66%); m.p. 219-220 °C; (KBr) υ_{max} / cm^{-1} 3076, 2899, 1698, 1422, 1374, 1049, 989, 653. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 8.64 (s, 1H), 8.33 (s, 1H), 7.79 – 7.71 (m, 3H), 7.28 (d, *J* = 4.8 Hz, 2H), 5.78 (s, 2H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.89, 166.77, 148.73, 134.66, 133.71, 131.76, 129.87, 129.65, 128.53, 127.02, 126.65, 124.34, 123.15, 123.06, 119.38, 60.29, 14.59. EI-MS *m/z* 446.04 $(M+H)^+$; Anal. calcd for $C_{19}H_{13}Cl_2N_5O_4$: (%) C, 51.14; H, 2.95; N, 15.69; Found: C, 51.15; H, 2.96 N, 15.71.

***6,7-dichloro-2-(((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (37b)**

Off white solid (64%); m.p. 223-224 °C; (KBr) υ_{max} / cm^{-1} 3091, 2889, 1697, 1432, 1374, 1165, 1040, 980, 673. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 8.68 (s, 1H), 8.26 (s, 1H), 7.81 – 7.70 (m, 2H), 7.29 (d, *J* = 4.9 Hz, 2H), 5.76 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.99, 167.78, 146.53, 134.94, 132.11, 131.66, 129.30, 129.12, 127.83, 127.12, 126.61, 124.34, 123.15, 123.06, 121.88, 117.38, 117.15, 60.22, 14.59. EI-MS *m/z* 464.04 $(M+H)^+$; Anal. calcd for $C_{19}H_{12}Cl_2FN_5O_4$: (%) C, 49.16; H, 2.62; N, 15.09; Found: C, 49.17; H, 2.63 N, 15.11.

***6,7-dichloro-2-(((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (37c)**

Pale yellow solid (63%); m.p. 213-214 °C; (KBr) υ_{max} / cm^{-1} 3089, 2980, 1687, 1401, 1042, 964, 750. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 8.66 (s, 1H), 8.28 (s, 1H), 8.30 (d, *J* = 4.1 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.39 – 7.32 (m, 2H), 5.76 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.73, 143.12, 139.93, 139.75, 137.66, 136.14, 135.88, 134.78, 133.76, 132.83,

129.09, 128.92, 122.83, 121.42, 119.87, 60.44, 14.61. EI-MS *m/z* 480.01 $(M+H)^+$; Anal. calcd for $C_{19}H_{12}Cl_3N_5O_4$: (%) C, 47.47; H, 2.52; N, 14.58; Found: C, 47.49; H, 2.53 N, 14.59.

***2-(((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-6,7-dichloro-3-methylquinoxaline 1,4-dioxide* (37d)**

Off white solid (54%); m.p. 214-215 °C; (KBr) υ_{max} / cm^{-1} 3099, 2983, 1688, 1451, 1046, 984, 779, 675. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 8.68 (s, 1H), 8.29 (s, 1H), 8.31 (d, J = 4.1 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.41 – 7.36 (m, 2H), 5.78 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.79, 143.82, 139.90, 139.55, 138.86, 137.74, 135.18, 134.78, 133.76, 132.83, 129.19, 128.02, 122.83, 121.22, 119.87, 60.54, 14.68. EI-MS *m/z* 524.96 $(M+H)^{+2}$; 522.94 $(M+H)^+$; Anal. calcd for $C_{19}H_{12}BrCl_2N_5O_4$: (%) C, 43.46; H, 2.32; N, 13.34; Found: C, 43.47; H, 2.33 N, 13.35.

***6,7-dichloro-2-(((1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (37e)**

Off white solid (61%); m.p. 219-220 °C; (KBr) υ_{max} / cm^{-1} 3079, 2893, 1697, 1443, 1165, 1046, 980, 769, 675. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 8.68 (s, 1H), 8.36 (d, J = 2.7 Hz, 1H), 7.99 (td, J = 7.7, 1.7 Hz, 1H), 7.50 (tdd, J = 7.8, 4.9, 1.8 Hz, 1H), 7.43 – 7.28 (m, 2H), 5.78 (s, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.50, 141.69, 139.28, 137.42, 136.73, 136.20, 135.64, 132.57, 132.07, 131.99, 127.37, 126.51, 126.09, 121.90, 121.83, 117.74, 117.55, 60.19, 14.55. EI-MS *m/z* 464.04 $(M+H)^+$; Anal. calcd for $C_{19}H_{12}Cl_2FN_5O_4$: (%) C, 49.16; H, 2.62; N, 15.09; Found: C, 49.17; H, 2.63 N, 15.11.

***6,7-dichloro-2-(((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (37f)**

Yellow solid (62%); m.p. 182-183 °C; (KBr) υ_{max} / cm^{-1} 3091, 2890, 1682, 1433, 1046, 984, 763, 675. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 8.66 (s, 1H), 8.38 (d, J = 2.8 Hz, 1H), 7.98 (m, 1H), 7.55 (tdd, J = 7.6, 4.9, 1.8 Hz, 1H), 7.43 – 7.29 (m, 2H), 5.78 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.50, 144.69, 139.78, 138.02, 136.83, 136.44, 135.04, 132.77, 132.17, 131.09, 128.37, 126.50, 125.19, 121.90, 121.03, 117.84, 117.55, 60.59, 14.69.

EI-MS *m/z* 480.01 $(M+H)^+$; Anal. calcd for $C_{19}H_{12}Cl_3N_5O_4$: (%) C, 47.47; H, 2.52; N, 14.58; Found: C, 47.49; H, 2.53 N, 14.59.

***6,7-dichloro-2-(((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)carbonyl)-3-methylquinoxaline 1,4-dioxide* (37g)**

Pale yellow solid (55%); m.p. 214-215 °C; (KBr) υ_{max} / cm^{-1} 3090, 2899, 1695, 1421, 1374, 1039, 968, 683. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.64 (s, 1H), 8.40 (s, 1H), 7.86 (m, 2H), 7.70 (d, *J* = 1.8 Hz, 1H), 5.75 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.88, 142.64, 139.76, 138.99, 137.97, 136.93, 136.52, 136.01, 135.55, 134.04, 132.07, 129.05, 123.67, 121.92, 118.93, 119.15, 60.39, 14.59. EI-MS *m/z* 512.98 $(M+H)^+$; Anal. calcd for $C_{19}H_{11}Cl_4N_5O_4$: (%) C, 44.31; H, 2.15; N, 13.61; Found: C, 44.32; H, 2.16 N, 13.62.

6.4.3. Biological activity

6.4.3.1. In vitro MTB screening

The antimycobacterial activities of the compounds **35a-l, 36a-l & 37a-g** were evaluated against MTB *H37Rv* strain and two "wild" strains extracted from tuberculosis patients: one strain is *Spec. 210* resistant to PAS, INH, ETB and RMP and the other strain is *Spec. 192* fully sensitive to the administrated anti-TB agents. *In vitro* anti-TB activity is performed by a classical test-tube method of successive dilution in Youmans' modification of the Proskauer and Beck liquid medium containing 10% of bovine serum [18]. Bacterial respites were prepared from 14 days old cultures of gradually growing strains. Solutions of compounds in DMSO were tested. Stock solutions contained 10 mg of compounds in 1 mL. Dilutions (in geometric progression) were prepared in Youmans' medium [18]. The medium is without compounds and containing INH as reference drug was used for comparison. Incubation was performed at 37 °C. The MIC values were determined as MIC inhibiting the growth of tested TB strains in relation to the probe with no tested compound. The influence of the compound on the growth of bacteria at concentrations of 3.12, 6.25, 12.5, 25, 50 and 100 μg/mL was evaluated.

6.4.3.2. In vitro cytotoxicity screening

The human embryonic kidney cells (HEK-293) were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Himedia Laboratories Pvt. Ltd., Mumbai, India), supplemented with 10%

heat inactivated fetal bovine serum (Himedia Laboratories Pvt. Ltd., Mumbai, India) and 1 % of Antibiotic solution (10000 U Penicillin and 10 mg Streptomycin per ml, Himedia Laboratories Pvt. Ltd., Mumbai, India). Cells were cultured at 37 °C in humidified atmosphere with 5% CO_2. Stock solutions of compounds was prepared in DMSO at a concentration of 50 μM and stored.

Cytotoxicity screening of the synthesized compounds was determined using MTT assay [19]. 7.5×10^3 cells were seeded in 96 well plates and incubated overnight. Cells were treated with synthesized compounds at three concentrations (50μM, 25 μM & 10 μM) in duplicates and incubated for 24 hrs. 50 μL of 5 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Himedia Laboratories Pvt. Ltd., Mumbai, India) was added and incubated for 4 hours. 150 μL of DMSO was added to dissolve formazan crystals and evaluated spectrophotometrically at 570 nm and 650 nm using Spectramax M4 (Molecular Devices, USA).

6.5. References

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