Chapter IV

Design, synthesis of 9*H*-fluorenone based 1,2,3-triazole analogues as *Mycobacterium tuberculosis* InhA inhibitors

Chapter 4

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4.1. Introduction

Fluorenones contain a planar skeleton with fused aromatic rings and only one carbonyl prochiral center; these are normally used as photo-catalysts in organic synthesis. The fluorenone scaffold is widespread both in natural products and in industrial by-products. Over the last few years its derivatives have generated interest because of their use in various fields ranging from drugs to materials science. The fluorenone scaffold is found in natural biologically active (Kinamycins, Nakiterpiosin, Gracilamine, Dendroflorin, Gramniphenols D & E, and caulophine) and semisynthetic compounds [1, 2]. The representative fluorenone containing natural products are shown in **Figure 4.1**.

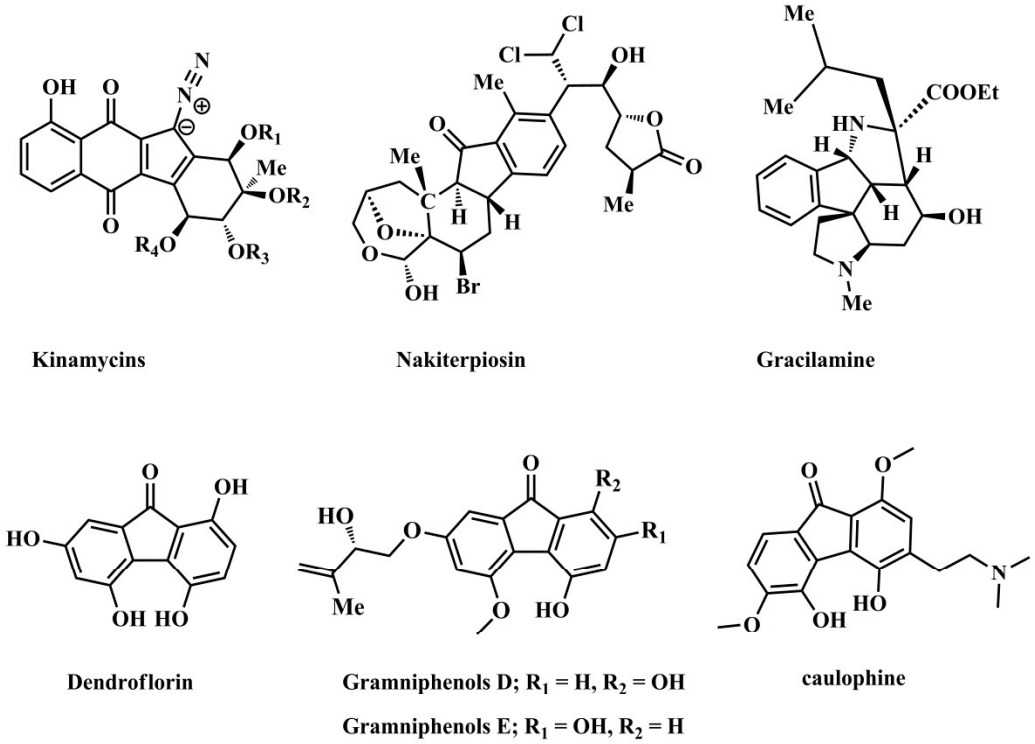


Figure 4.1: Fluorenone containing natural products and semi synthetic compounds.

Dendroflorin containing fluorenone scaffold has antioxidant properties. Tilorone and 9-Fluorenylmethyl Polyglycosides are used for different viral diseases [3] and 2,7-disubstituted amidofluorenones[4], show anticancer properties. 9-Fluorenone-2-carboxylic acid is tubulin binders\ [2], 9-fluorenone carboxyhydroxyesters and amides are immunomodulators and anti-herpes simplex virus-2 agents [5]. 9-Hydroxyazafluorenes are thrombin inhibitors [6].

The fatty acid synthase arrangement of *Mycobacterium tuberculosis* contains unique signature fatty acid, the mycolic acid, which is a central constituent of the mycobacterial cell wall. Mycolic acid biosynthesis is carried out by several successive enzymatic cycles equivalent to two related but different Fatty Acid Synthase (FAS) systems, FAS I and II [7]. FAS II system is present in bacteria but is absent in humans. InhA protein (ENR, EC number: 1.3.1.9) is a key enzyme of FAS II and shows a NADH-dependent enoyl-ACP reductase activity. It has already been validated as the primary molecular target of the frontline anti-tubercular drug isoniazid [8]. It is a prodrug which upon activation by KatG, the mycobacterial catalase-peroxidase, forms adduct with NADH called NAD-INH [9]. The X-ray structure of the complex InhA isonicotinoyl moiety of this adducts shows that it occupies a hydrophobic pocket. Different research groups validated this cavity as a suitable site to increase inhibitors potency. Several approaches exist towards the design of new inhibitors for InhA [10].

Tilorone and doxorubicin inhibit primase DnaG from *B. anthracis* and MTB at the low micromolar range of IC_{50}. Based on this Choi *et al.,* modified fluorenone scaffold to various derivatives of C2 symmetry compounds that are similar to tilorone. They added different chain lengths and terminal groups and synthesized 9-fluorenone alkyl amines which exhibited antibacterial properties [1]. Genz-10850 (also called GEQ) (**A**) has been identified as a very promising inhibitor of InhA, after *in vitro* screening of a library of five million compounds [11]. Later, He *et al.,* synthesized a series of GEQ derivatives with InhA inhibitory activities ranging from 0.09 to 2.04 μM [12]. Amongst these, (4-(9*H*-fluoren-9-yl)piperazin-1-yl)(phenyl)methanone (**B**) was the most active compound with IC_{50} 0.09 μM. Unfortunately these molecules have poor *in vitro* activity against MTB (MIC ≥ 125 μM) because of their low absorptivity [12]. Matviiuk *et al.* reported 3-(9*H*-fluoren-9-yl)pyrrolidine-2,5-dione derivatives

with InhA inhibition at 50 µM ranging from 8 to ≥ 95% and they exhibited MIC in the range from 2 to ≥ 16 µg/mL against MTB H37Rv. Among these, **C** was the most active with InhA inhibition ≥ 95% at 50 µM. It also exhibited MTB MIC 19.6 µM against MTB H37Rv. Same group reported 3-heteryl substituted pyrrolidine-2,5-diones derivatives with InhA inhibition at 50 µM ranging from 9 to 56% and its exhibited MTB MIC ranged from 2.5 to 40 µg/mL. Amongst these, 1-benzyl-3-[4-(9*H*-fluoren-9-yl)-1-piperazinyl]-2,5-pyrrolidinedione (**D**) was the most active with the InhA inhibition of 56% at 50 µM and MTB MIC 2.5 µg/mL against MTB H37Rv [13]. Chollet *et al.,* incorporated modifications in GEQ skeleton; piperazine was replaced with piperidine and other modifications include replacement of amide with sulfonyl, phosphonyl and phosphinamide groups. They also introduced 2- and 3-alkyl-substituted fluorenone derivatives as inhibitors of InhA with IC_{50} 102 to 2690 nM and these derivatives exhibited MTB MIC ranging from 11 to 88.2 µM against MTB H37Rv. Among these series, (4-(3-(hexyloxy)-9*H*-fluoren-9-yl)piperazin-1-yl)(phenyl) methanone (**E**) bearing an additional hexyloxy chain on the fluorenone moiety demonstrated enhanced activity against InhA enzyme (IC_{50} up to 102 nM) as well as MTB growth (MIC 11 µM) [14]. Described InhA active compounds are depicted in **Figure 4.2**.

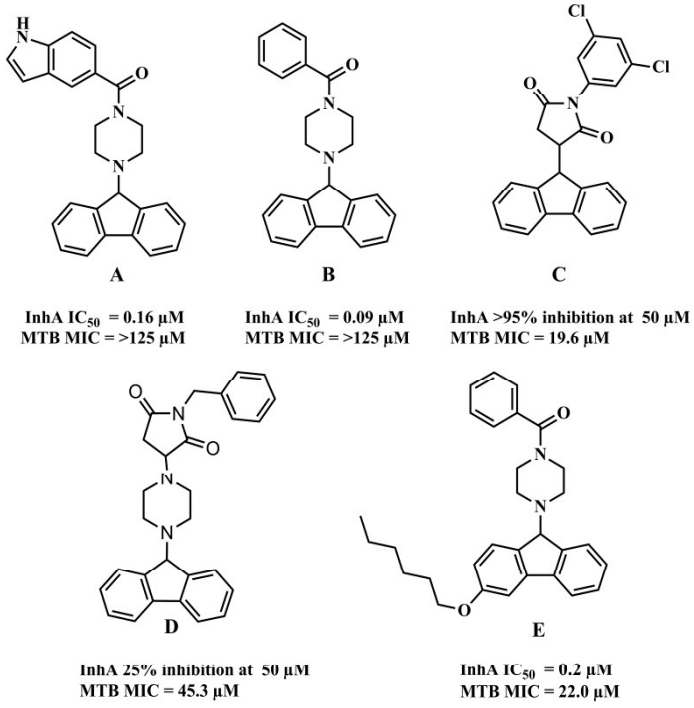


Figure 4.2: InhA inhibitors.

Additionally, 1,2,3-triazole and its derivatives have attracted continued interest in the medicinal field owing to their varied biological activities such as anti-fungal [15], anti-bacterial [16], anti-allergic [17], anti-HIV, antiviral [18], anti-inflammatory, anesthetic [19], anti-cancer [20] and β -lactamase inhibition properties [21]. It is quite obvious that the favourable properties of 1,2,3-triazole ring similar to moderate dipole character, hydrogen bonding capability, and π stacking interactions, rigidity and stability under *in vivo* conditions are responsible for their easy binding with the biological targets and also improve their solubility in biological systems[22].

Kumar and co-workers reported the synthesis of triazole-isoniazid conjugates (**F**) and their *in vitro* evaluation as possible anti-TB agents against MTB H37Rv. The compounds exhibited potent activity against MTB strain with MIC values ranging from 0.195 to 1.56 μM [23]. Pullapati *et al.,* reported synthesis of novel piperidine, piperazine, morpholine and thiomorpholine appended dibenzo[*b,d*]thiophene-1,2,3-triazoles (**G**) for *in vitro* activity against MTB H37Rv with MIC ranging from 0.78 to 1.56 μg/mL and these compounds showed lower cytotoxicity [24]. Boechat *et al.,* reported (*E*)-*N*'-((1-(1-aryl)-1*H*-1,2,3-triazol-4-yl)methylene)isonicotinohydrazide derivatives (**H**) which exhibited activity with MIC values ranging from 0.62 to 1.5 μg/mL [25]. Yempala *et al.,* published dibenzo[*b,d*]furan-1,2,3-triazole conjugates (**I**) with *in vitro* activity against MTB with MIC in the range of 0.78 to 50.0 μg/mL [26]. Goverdhan *et al.,* reported novel-substituted 1,2,3-triazolylmethyl carbazoles (**J**) for *in vitro* antimycobacterial activity against MTB H37Rv with MIC values ranging from 6.25 to 50 μg/mL [27]. Menendez et *al.,* reported 1,4-disubstituted triazoles and *α*-ketotriazole derivatives (**K**) these compounds with MIC values varied from 2 to 100 μg/mL against MTB H37Rv they also exhibited InhA inhibition from 10 to 58% at 50 μM [28]. The representative triazole derivatives are given in **Figure 4.3**.

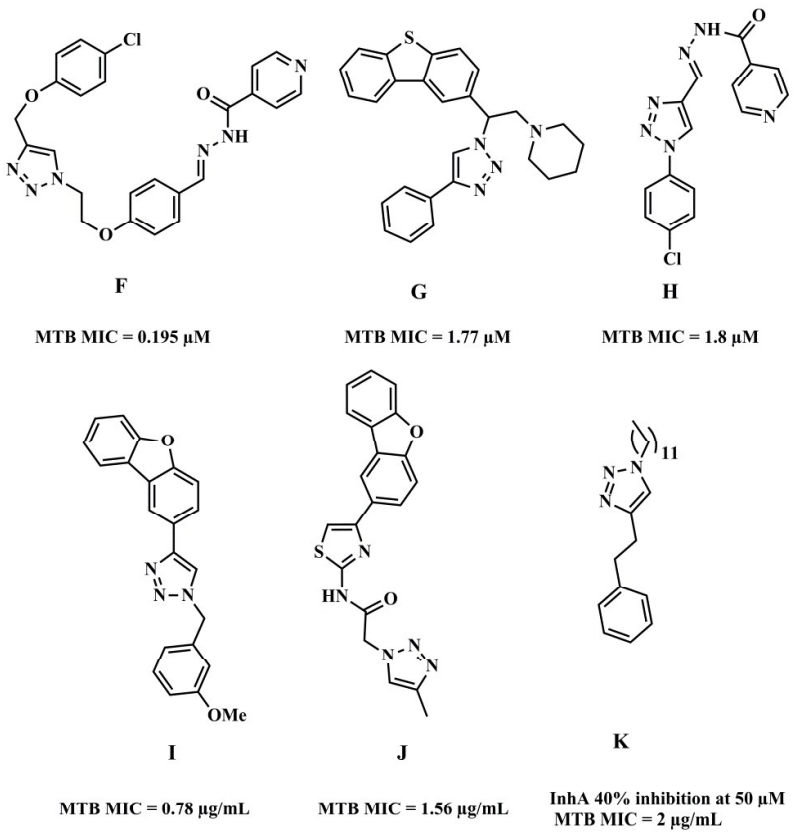


Figure 4.3: Anti-TB activity of triazole.

In our design, two key elements for InhA inhibition, i.e. the fluorenyl and the triazole moieties, were considered. The fluorenyl moiety that could act as an anchor [14] will occupy the same hydrophobic position than the long alkyl chain of the substrate. The triazole moiety could interact by hydrogen bonds with the hydroxyl group of the key residue Tyr158, essential for a good recognition. Furthermore, triazoles, synthesized in one step by "click" chemistry reaction, could bring diversity [23]. With this collective information and emphasizing on molecular hybridization approach we drew a synthetic stratagem to fit these imperative pharmacophoric groups into one distinct scaffold and synthesized *N*-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-9*H*-fluoren-9-amine, 4-(((9*H*-fluoren-9-yl)thio)methyl)-1-substituted phenyl-1H-1,2,3-triazole, and 4-(((9*H*-fluoren-9-yl)sulfonyl)methyl)-1-substituted phenyl-1*H*-1,2,3-triazole analogues (**Figure 4.4**). Of note, only aryl groups were introduced on the triazole moiety of our designed target (**Figure 4.4**) because molecules bearing alkyl groups at this position were found to be less efficient as inhibitors against InhA enzyme [14].

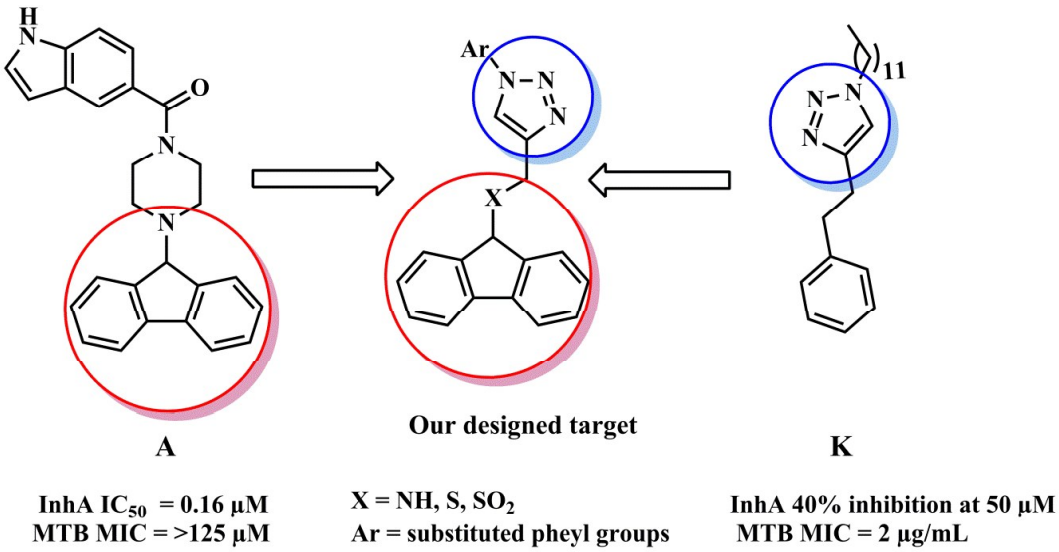
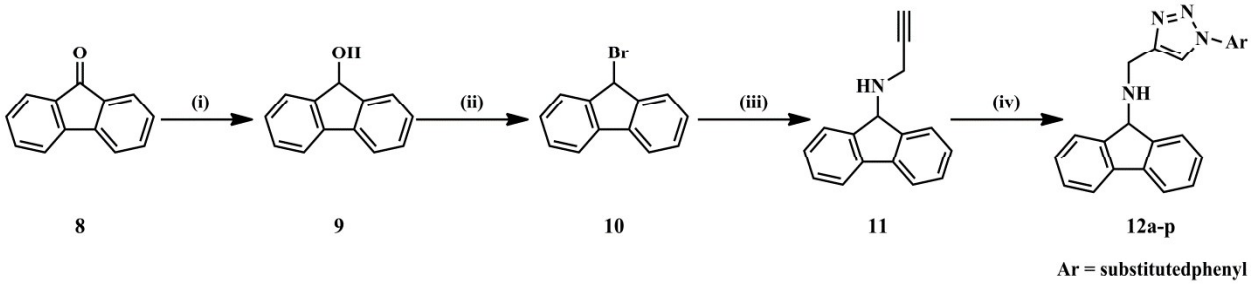


Figure 4.4: Design strategy to achieve title compounds.

4.2. Results and Discussion

4.2.1. Chemistry

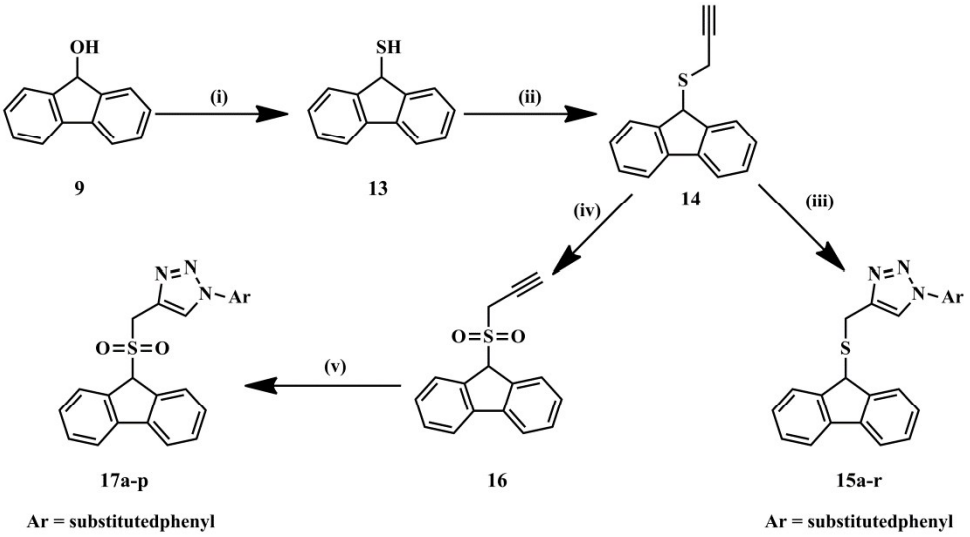
We synthesized *N*-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-9*H*-fluoren-9-amine, 4-(((9*H*-fluoren-9-yl)thio)methyl)-1-substituted phenyl-1*H*-1,2,3-triazole, and 4-(((9*H*-fluoren-9-yl)sulfonyl)methyl)-1-substituted phenyl-1*H*-1,2,3-triazole analogues as sketched in **scheme 4.1** and **scheme 4.2**.



Scheme 4.1: Synthetic protocol to achieve the compound (**12a-p**)

Reagents and conditions: (i) $NaBH_4$ (0.5 eq), MeOH, 0 ºC - rt, 4 h. (ii) PBr_3 (1.2 eq), DCM, 0 ºC - rt, 4 h. (iii) Propargyl amine (1.2 eq), K_2CO_3 (2.0 eq), ACN, rt, 16 h. (iv) Substituted phenyl azides, $CuSO_4.5H_2O$ (0.02 eq), Sodium ascorbate (0.01 eq), H_2O:^{t}BuOH (1:2), rt, 4 h.

In the **scheme 4.1** we adopted reported procedure with slight modification to prepare 9*H*-fluoren-9-ol (**9**), then the compound **9** was brominated with phosphorus tribromide to form compound (**10**) [29]. Compound **10** on reacting with propargyl amine in the presence of K_2CO_3 formed *N*-alkyl product (**11**). The free acetylene group was converted to various *N*-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-9*H*-fluoren-9-amines (**12a-p**) using different aromatic azides *via* click chemistry method [30].



Scheme 4.2: Synthetic protocol to achieve the compounds (**15a-r**) & (**17a-p**).

Reagents and conditions: (i) Lawesson's reagent (2.0 eq), toluene, 110 ºC, 16 h. (ii) Propargyl bromide (80% in toluene) (2.0 eq), TEA (3.0 eq), DCM, 16 h. (iii) Substituted aromatic azides, $CuSO_4.5H_2O$ (10 mole %), Sodium ascorbate (5 mole %), H_2O:^{t}BuOH (1:2), rt, 16 h. (iv) *meta*-Chloroperoxybenzoic acid (2.0 eq), DCM, rt, 2h. (v) Substituted aromatic azides, $CuSO_4.5H_2O$ (10 mol %), Sodium ascorbate (5 mole %), H_2O:^{t}BuOH (1:2), rt, 16 h.

In the **scheme 4.2** 9*H*-fluorene-9-thiol (**13**) was obtained from compound **9** using lawesson's reagent in toluene at 110 °C for 16 h [31]. **13** on reacting with propargyl bromide in the presence of TEA formed (9*H*-fluoren-9-yl)(prop-2-yn-1-yl)sulfane (**14**). The compound **14** was converted to various 4-(((9*H*-fluoren-9-yl)thio)methyl)-1-substituted phenyl-1*H*-1,2,3-triazoles (**15a-r**) using different aromatic azides *via* click chemistry method [30]; further compound **14** on oxidation with *meta*-chloroperbenzoic acid in the presence of DCM at room temperature formed

9-(prop-2-yn-1-ylsulfonyl)-9*H*-fluorene (**16**). Subsequently **16** was converted to various 4-(((9*H*-fluoren-9-yl) sulfonyl) methyl)-1-substituted phenyl-1*H*-1,2,3-triazole (**17a-p**) using different aromatic azides [30]. The purity of compounds synthesized 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.

4.2.2. 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 [32]. MTB strain *spec. 210* was resistant to *p*-aminosalicylic acid (PAS), INH, ETB and RMP and another *Spec. 192* was fully sensitive to the administrated tuberculostatics [33]. 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. The influence of the compound on the growth of mycobacteria at certain concentrations 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 4.1** as MIC (μM) and the activity ranged from 52.35 ->250 μM.

Table 4.1: Antimycobacterial activities of compounds **12a-p, 15a-r** & **17a-p** against MTB H37Rv, *Spec. 192* and *Spec. 210* in μM.

Entry	Ar	MIC (μg/mL) against MTB H37Rv	MIC (μg/mL) against MTB *Spec.* 192	MIC (μg/mL) against MTB *Spec.* 210
12a	Phenyl	>295.49 (>100)	>295.49 (>100)	>295.49 (>100)
12b	4-Methylphenyl	141.87 (50)	141.87 (50)	141.87 (50)
12c	4-Ethylphenyl	136.44 (50)	136.44 (50)	136.44 (50)
12d	4-Methoxyphenyl	135.71 (50)	135.71 (50)	>271.42 (>100)

Entry	Ar	MIC (µg/mL) against MTB H37Rv	MIC (µg/mL) against MTB *Spec.* 192	MIC (µg/mL) against MTB *Spec.* 210
12e	4-Fluorophenyl	280.58 (100)	280.58 (100)	>280.58 (>100)
12f	4-Chlorophenyl	268.22 (100)	268.22 (100)	268.22 (100)
12g	4-Bromophenyl	239.63 (100)	239.63 (100)	239.63 (100)
12h	4-Trifluoromethylphenyl	123.30 (50)	123.30 (50)	123.30 (50)
12i	4-Nitrophenyl	>260.82 (>100)	>260.82 (>100)	>260.82 (>100)
12j	2-Fluorophenyl	280.58 (100)	280.58 (100)	280.58 (100)
12k	2-Nitrophenyl	260.82 (>100)	>260.82 (>100)	>260.82 (>100)
12l	3,4-dimethylphenyl	>272.88 (>100)	>272.88 (>100)	>272.88 (>100)
12m	3-Chloro,4-fluorophenyl	>255.85 (>100)	>255.85 (>100)	>255.85 (>100)
12n	2,4-dichlorophenyl	>245.51 (>100)	>245.51 (>100)	>245.51 (>100)
12o	3,5-dichlorophenyl	>245.51 (>100)	>245.51 (>100)	>245.51 (>100)
12p	3,4,5-trimethoxyphenyl	58.34 (25)	58.34 (25)	58.34 (25)
15a	Phenyl	140.66 (50)	140.66 (50)	140.66 (50)
15b	4-Methylphenyl	135.32 (50)	135.32 (50)	135.32 (50)
15c	4-Ethylphenyl	260.74 (100)	260.74 (100)	>260.74 (>100)
15d	4-Methoxyphenyl	129.70 (50)	129.70 (50)	>259.41 (>100)
15e	4-Fluorophenyl	66.94 (25)	66.94 (25)	>267.77 (>100)
15f	4-Chlorophenyl	74.20 (25)	74.20 (25)	>256.80 (>100)
15g	4-Bromophenyl	57.55 (25)	57.55 (25)	115.1 (50)
15h	4-Trifluoromethylphenyl	>236.21 (>100)	>236.21 (>100)	>236.21 (>100)
15i	4-Nitrophenyl	>249.71 (>100)	>249.71 (>100)	>249.71 (>100)
15j	2-Chlorophenyl	>256.47 (>100)	>256.47 (>100)	>256.47 (>100)
15k	2-Nitrophenyl	>249.71 (>100)	>249.71 (>100)	>249.71 (>100)
15l	3,4-dimethylphenyl	>260.74 (>100)	>260.74 (>100)	>260.74 (>100)
15m	4-Fluoro, 2-nitrophenyl	>238.98 (>100)	>238.98 (>100)	>238.98 (>100)

Entry	Ar	MIC (µg/mL) against MTB H37Rv	MIC (µg/mL) against MTB *Spec.* 192	MIC (µg/mL) against MTB *Spec.* 210
15n	2,4-dichlorophenyl	>235.65 (>100)	>235.65 (>100)	>235.65 (>100)
15o	3,4-dichlorophenyl	>235.65 (>100)	>235.65 (>100)	>235.65 (>100)
15p	3,5-dichlorophenyl	117.82 (50)	117.82 (50)	>235.65 (>100)
15q	3,4,5-trimethoxyphenyl	56.11 (25)	56.11 (25)	56.11 (25)
15r	3-Chloro,4-fluorophenyl	245.61 (100)	245.61 (100)	>245.61 (>100)
17a	Phenyl	>258.09 (>100)	>258.09 (>100)	258.09 (>100)
17b	4-Methylphenyl	124.53 (50)	124.53 (50)	124.53 (50)
17c	4-Ethylphenyl	120.33 (50)	120.33 (50)	240.66 (>100)
17d	4-Methoxyphenyl	119.76 (50)	119.76 (50)	119.76 (50)
17e	4-Fluorophenyl	123.32 (50)	123.32 (50)	123.32 (50)
17f	4-Chlorophenyl	118.51 (50)	118.51 (50)	118.51 (50)
17g	4-Bromophenyl	>214.43 (>100)	>214.43 (>100)	>214.43 (>100)
17h	4-Trifluoromethylphenyl	109.78 (50)	109.78 (50)	109.78 (50)
17i	4-Nitrophenyl	>231.24 (>100)	>231.24 (>100)	>231.24 (>100)
17j	2-Nitrophenyl	>231.24 (>100)	>231.24 (>100)	>231.24 (>100)
17k	2-Chlorophenyl	237.02 (100)	237.02 (100)	237.02 (100)
17l	3,4-dimethylphenyl	120.33 (50)	120.33 (50)	120.33 (>100)
17m	4-Fluoro, 2-nitrophenyl	>222.00 (>100)	>222.00 (>100)	>222.00 (>100)
17n	2,4-dichlorophenyl	>219.13 (>100)	>219.13 (>100)	>219.13 (>100)
17o	3,4-dichlorophenyl	>219.13 (>100)	>219.13 (>100)	>219.13 (>100)
17p	3,4,5-trimethoxyphenyl	52.35 (25)	52.35 (25)	52.35 (25)
INH	-	22.59 (<3.1)	22.59 (<3.1)	91.14 (<12.5)

Among the three series of 9*H*-fluorenone analogues, totally fifty compounds were screened. Fifteen compounds (**12b, 12c, 12d, 12h, 15a, 15b, 15d, 15p, 17b, 17c, 17d, 17e, 17f, 17h,** & **17l**) showed moderate activity with MIC ranging from 141.87 to 109.78 µM. Five compounds

(**12p, 15e, 15f, 15g,** & **15q**) showed good activity with MIC 74.20 to 56.11 μM. Compound **17p** (4-(((9*H*-fluoren-9-yl)sulfonyl)methyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole) was found to be the most active compound with *in vitro* MIC 52.35 μM.

*Structure activity relationship (SAR) of N-((1-substituted phenyl-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amines derivatives (**12a-p**)*

In this series, we screened sixteen compounds against the three different strains (MTB *H37Rv*, MTB *spec. 192* & MTB *spec. 210*). We noticed that among electron withdrawing and electron donating substituents on the triazoles, electron donating group containing substituent show major impact in exhibiting anti-TB activity. SAR is explained based on activity of **12a**. Compound **12a** was inhibiting 99% growth of MTB strains at 295.49 μM. Introduction of electron donating group on the phenyl ring increased activity. Compounds **12b** (MIC 141.87 μM), **12c** (MIC 136.44 μM) and **12d** (MTB 135.71 μM) with methyl, ethyl, methoxy groups increased the activity by two folds compared to **12a**. Introduction of electron withdrawing groups *viz.,* **F, Cl, Br** and $\mathbf{NO_2}$ at either second or fourth position in phenyl resulted in either decrease in activity or the activity remained unaltered. Exception being electron withdrawing CF_3 at 4^{th} position with which the activity increased by two fold (**12h**, MIC 123.30 μM). Compound **12p** with three electron donating methoxy groups emerged to be the most active compound among these sixteen derivatives with MIC 58.34 μM exhibiting fivefold increase in activity compared to **12a**.

*SAR of sulfide derivatives (**15a-r**)*

Among the eighteen sulfide derivates SAR is explained with respect to compound **15a** (140.66 μM). Presence of electron donating groups at the 4^{th} position impacted the activity. Interestingly, presence of electron withdrawing halogens like F, Cl, Br at the 4^{th} position resulted in increase in activity by the two folds. But the presence of electron withdrawing at the ortho position decreased the activity by two folds. Among the dichloro substituted compounds, **15p** was most active with MIC 117.82 μM similar to that of **15a**. In this series, trimethoxy derivative **15q** was most active with MIC 56.11 μM.

*SAR of sulfonyl derivatives (**17a-p**)*

Eighteen compounds based on sulfonyl were synthesized and screened for MTB. SAR is explained with respect to **18a** which showed MIC 258.09 μM. Activity increased by more than two folds with electron dontaining 4-methyl, 4-ethyl and 4-methoxy (MIC 124.53, 120.33 and 119.76 μM with respectively). Among the halo derivatives, activity remained unaltered with bromo where as it increased by two folds with 4-flouro and 4-chloro with derivatives. Electron withdrawing NO_2 at 2^{nd} & 4^{th} positions did not impact the activity with electron withdrawing disubstituted derivatives activity remained with unaltered (**17m, 17n** & **17o**). Presence of electron donating dimethyl increased the activity by two folds (**17l,** MIC 120.33). Among this series, **17p** with three methoxy groups emerged to be the most active compound (MIC 52.35 μM).

Over all, we notice that sulfide derivatives exhibited better anti-TB activity followed by sulfonyl derivative and amines. Electron donating 3,4,5-trimethoxy derivates emerged to be the most active compound in all the series of compounds.

4.2.3. InhA enzyme Inhibition studies

The compounds were tested for their capacity to inhibit the reduction of the substrate double bond by NADH in the presence of InhA. The assays were performed in triplicate in the presence of the substrate analogue 2-*trans*-dodecenoyl-CoA and the percentage of InhA inhibition was determined by measuring the conversion of the NADH cofactor to its oxidized form NAD^+ by means of the decreasing of the absorbance at 340 nm [34]. The molecules were tested at 50 Mm, GEQ was used as reference and results are reported in **Table 4.2.**

15 compounds whose activities were ≤ 50 μg/mL were selected for screening the InhA activity. Among the amine derivatives (**12a-p**) the most active compound **12p** (MIC 25 μg/mL) was selected for screening; among the sulfide derivatives except **15d** all other compounds with MIC ≤ 50 μg/mL were selected. Among the sulfonyl derivatives except **17b** and **17d** remaining all other compounds with MIC ≤ 50 μg/mL were selected for screened.

Investigations on these fifteen compounds indicated that among the -NH- group containing 9*H*-fluorene derivate, **12p** exhibited only 7% inhibition. Presence of sulpur in the 9*H*-fluorene increased the InhA activity, as the results were moderate in this series of compounds. **15p** showed the maximum InhA inhibition of 31%. The series of sulfonyl (-SO_2-) compounds showed

relatively good inhibition. Compounds **17f** and **17p** were the most active with 74 and 73% inhibition.

On the whole we notice that compounds with (O=S=O) exhibited the highest InhA inhibition which is in agreement with the already reported literature [14].

Table 4.2: MTB InhA activity

S. No	Compound Code	% of inhibition at 50 μM of inhibitor
1	**12p**	7
2	**15a**	23
3	**15b**	24
4	**15e**	6
5	**15f**	< 5
6	**15g**	NI
7	**15h**	21
8	**15p**	31
9	**15q**	30
10	**17c**	27
11	**17e**	NI
12	**17f**	74
13	**17h**	27
14	**17l**	NI
15	**17p**	73
16	**GEQ**	88

NI = No inhibition

4.2.4. Docking study

All the final compounds were docked into the crystal structure of InhA protein (PDB ID: 1BVR) to know the exact binding pattern with the receptor. Validation of docking protocol revealed that, the value of RMSD obtained between experimental binding mode of co-crystallized ligand (as in X-ray) and its re-docked pose (**Figure 4.6**) was found to be 0.76, which suggested that, docking procedure could be relied on for further docking studies.

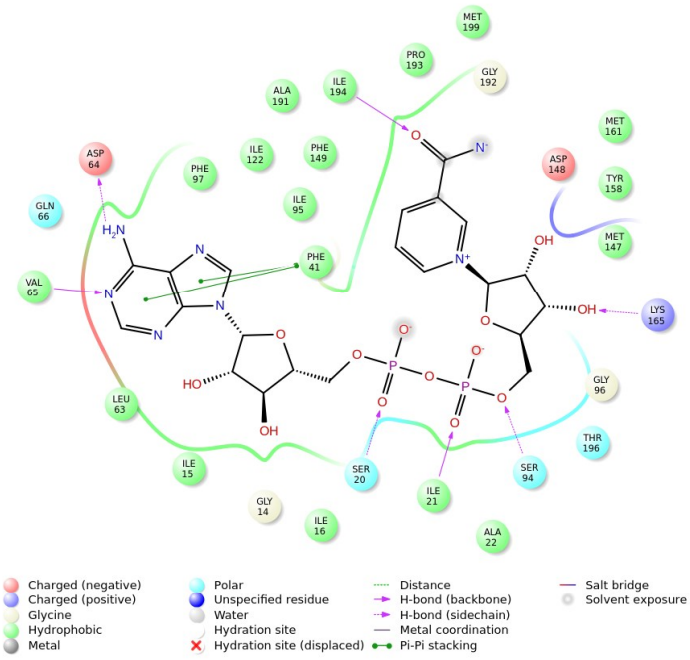


Figure 4.5: Superimposed view of co-crystallized ligand in 1BVR.

Further, in the docking studies, molecules exhibited good binding energy in the range of -5.65 to -10.36 kcal/mol and exhibited good fitness with the InhA protein. Several compounds displayed interactions with hydrophobic pockets MET103, ILE215, ALA22, ALA157, ALA198, LEU63, LEU218, PRO193, MET103, MET199, PHE41, PHE149, ILE194, ALA191, ILE95, ILE21, ILE122, VAL65, MET147, ILE95 and MET161, hydrogen bonding interaction with ILE194 amino acid residues. Ligand also exhibited π-π interactions with amino acids. Compound 4-(((9*H*-fluoren-9-yl)sulfonyl)methyl)-1-(4-chlorophenyl)-1*H*-1,2,3-triazole (**17f**) with 74% of inhibition at 50 μM showed docking score of -7.808 kcal/mol. This compound exhibits hydrophilic interaction with THR196 and SER94. The active site in the hydrophobic pocket is within the vicinity of MET103, ILE215, ALA157, LEU218, PRO193, MET199, PHE149, ILE194, ALA191, ILE21, MET147, ILE95 and MET161. **17f** showed π-π interactions with PHE149 and TYR 158. One of the ligands, 4-(((9*H*-fluoren-9-yl)sulfonyl)methyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (**17p**) with 73% of inhibition at 50 μM showed docking score of -8.298 kcal/mol. The active site in the hydrophobic pocket is within the vicinity of MET103, MET199, ALA198, ILE194, ILE21, ALA22, PHE41, VAL65, ILE122, PHE97, LE63, ILE15, ILE16 and ILE95 as well as some polar amino acid residues THR196, SER20, SER94, GLN66, THR39 and SER13 respectively. The ligand also exhibited π-π interactions with PHE41

These results correlate with the *in vitro* InhA and MTB screening. The binding pattern of **17f** and **17p** with InhA is shown in **Figures 4.6** & **4.7.**

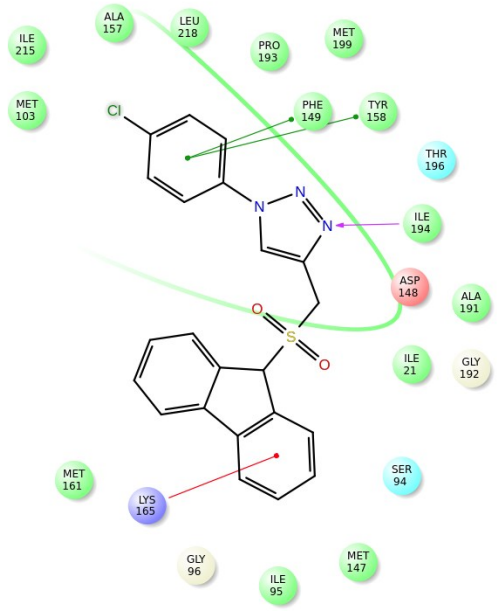


Figure 4.6: Docked pose of compound **17f** inside the 1BVR, showing two-dimensional interactive diagram.

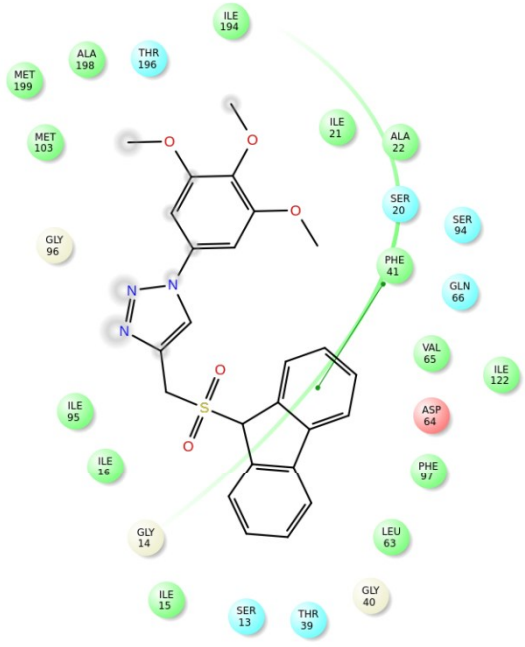


Figure 4.7: Docked pose of compound **17p** inside the 1BVR, showing two-dimensional interactive diagram.

Table 4.3: Docking scores

Compound	Docking score	XPG Score	Glide gscore	glide emodel
1bvr.pdb.1_ligand(Standard)	-6.812	-8.867	-8.867	-65.276
12a	-8.287	-8.364	-8.364	-62.465
12b	-8.215	-8.292	-8.292	-57.717
12c	-8.452	-8.472	-8.472	-59.783
12d	-8.701	-9.951	-9.951	-59.502
12e	-7.881	-7.958	-7.958	-58.549
12f	-7.376	-8.625	-8.625	-65.755
12g	-8.064	-8.141	-8.141	-62.141
12h	-8.872	-8.948	-8.948	-65.417
12i	-6.06	-6.137	-6.137	-67.008
12j	-8.639	-8.716	-8.716	-60.259
12k	-5.515	-6.764	-6.764	-70.419
12l	-8.734	-8.811	-8.811	-61.442
12m	-8.67	-8.747	-8.747	-65.104
12n	-6.763	-8.013	-8.013	-68.347
12o	-8.834	-8.91	-8.91	-70.276
12p	-8.543	-8.543	-8.543	-61.742
15a	-8.282	-8.282	-8.282	-66.587
15b	-8.265	-8.265	-8.265	-64.06
15c	-7.995	-7.995	-7.995	-63.307
15d	-6.551	-6.551	-6.551	-66.408
15e	-7.699	-7.699	-7.699	-63.197
15f	-8.54	-8.54	-8.54	-62.504
15g	-7.935	-7.935	-7.935	-66.545
15h	-9.421	-9.421	-9.421	-67.959
15i	-5.655	-5.655	-5.655	-73.157
15j	-8.1	-8.1	-8.1	-59.23
15k	-8.308	-8.308	-8.308	-56.864
15l	-8.777	-8.777	-8.777	-67.67
15m	-6.695	-6.695	-6.695	-64.54
15n	-8.205	-8.205	-8.205	-66.244
15o	-8.324	-8.324	-8.324	-71.519
15p	-9.233	-9.233	-9.233	-63.54
15q	-10.365	-10.365	-10.365	-66.401
17a	-8.572	-8.572	-8.572	-71.139

17b	-8.753	-8.753	-8.753	-69.495
17c	-8.886	-8.886	-8.886	-67.672
17d	-6.609	-6.609	-6.609	-69.43
17e	-8.203	-8.203	-8.203	-71.884
17f	-7.808	-7.808	-7.808	-66.086
17g	-8.193	-8.193	-8.193	-71.343
17h	-9.655	-9.655	-9.655	-72.269
17i	-6.274	-6.274	-6.274	-71.62
17j	-8.154	-8.154	-8.154	-71.356
17k	-7.715	-7.715	-7.715	-74.456
17l	-6.563	-6.563	-6.563	-71.969
17m	-6.416	-6.416	-6.416	-71.38
17o	-9.279	-9.279	-9.279	-78.853
17p	-8.298	-8.298	-8.298	-68.615

4.2.5. In vitro cytotoxicity studies

Compounds with MTB MIC < 25 µg/mL were subjected to cytotoxicity studies against HEK 293 cell line. Cytotoxicity assay of **12p**, **15e, 15f, 15g, 15q** & **17p** was determined. Cell viability was measured by *in vitro* MTT assay [35]. Cells were exposed to compounds for 24 hours at three concentrations 50µM, 25 µM and 10 µM (n=2). Data represent mean values of measurements ± s.d. (**Figure 4.8**). Data clearly indicate the active compounds were not toxic at even 50 µM.

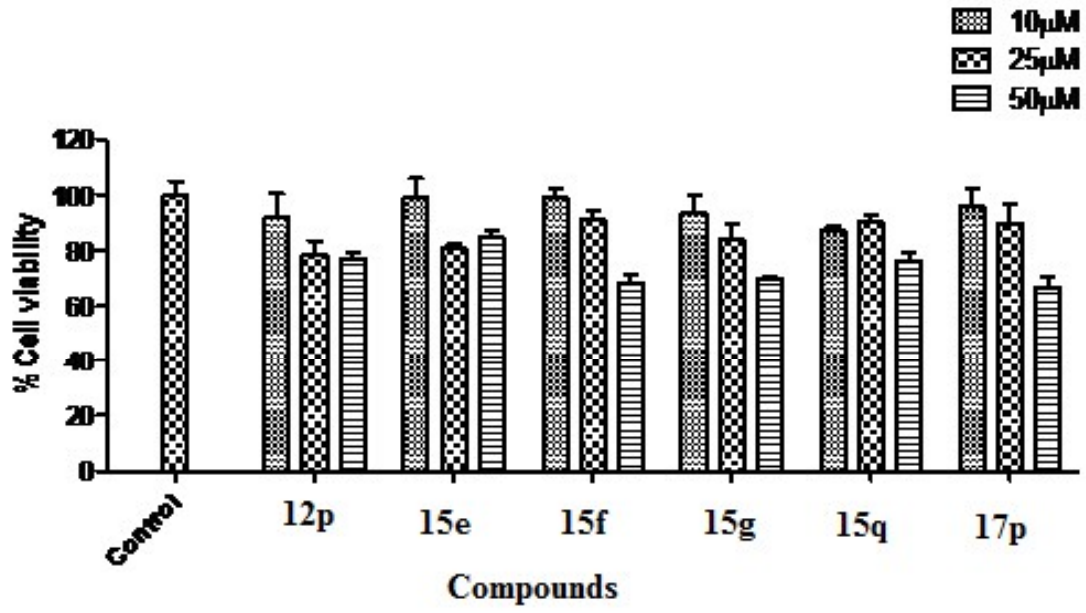


Figure 4.8: Cytotoxicity assay of **12p, 15e, 15f, 15g, 15q** & **17p** on HEK-293 cells.

4.2.6. Single Crystal X-ray Crystallographic Structure of Compound 15a

The suitable crystals of the compound **15a** for X-ray crystallographic study were grown from ethylacetate solution. The single crystal X-ray diffraction measurement of the molecule ($C_{22}H_{17}N_3S$) was done using Rigaku XtaLAB P200 diffract meter using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) on 0.2 mm x 0.15 mm x 0.1 mm pale yellow crystal. Data were collected and processed using CrysAlisPro (Rigaku Oxford Diffraction). The data were collected at a temperature of 20 ± 2 °C to a maximum 2θ value of 49.99°. Of the 10529 reflections collected, 2118 were unique (Rint = 0.0328) and equivalent reflections were merged. The diffraction data were refined and structure was solved using Olex 2 version 2.1, ShelXL software program. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The compound crystallized into a monoclinic crystal system with $P2_1/c$ space group. In a single unit cell four partially occupying molecules of crystallization are observed with Z=4. The basic crystallographic data are shown in **Table 4.4.** The molecular structure of the compound crystallization is given as an ORTEP diagram in **Figure 4.8.** Crystallographic data for the compound **15a** is deposited to the Cambridge Crystallographic Data Center and corresponding deposition number is **CCDC 1523811**.

Table 4.4: Crystal data and structure refinement for **15a**

Empirical Formula	$C_{22}H_{17}N_3S$
Formula Weight	355.44
Crystal Color, Habit	Light yellow
Crystal Dimensions	0.2 mm × 0.15 mm × 0.1 mm
Crystal System	Monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 13.509(2) A°
	b = 5.6467(8) A°
	c = 22.601(4) A°
	α = 90 A°
	β = 95.080(16) A°
	γ = 90 A°

	$\delta = 1717.3(5)\ A^{\circ 3}$
Space Group	$P2_1/c$
Z value	4
D_{calc}	$1.375 g/cm^3$
F_{000}	744.00
$\mu(MoK\alpha)$	$19.99\ cm^{-1}$
Radiation	Mo-Kα($\lambda = 0.71073\ A^{\circ}$)
Radiation monochromator	Graphite
Voltage, Current	50kV, 40mA
Temperature	19.5 °C
Maximum 2θ	49.992°
Number of measured reflections	10529°
Number of Unique reflections	2998 ($R_{int} = 0.0328$)
Number of parameters	235
Goodness-of-fit on F^2	1.071
$\Delta\rho_{max,mix}(e^-/A^{\circ 3})$	0.35, -0.28
Residuals: R1 (I>2.00σ(I))	$R_1 = 0.0346$, $wR_2 = 0.0931$
Residuals: R (All reflections)	$R_1 = 0.0388$
Residuals: wR2 (All reflections)	0.0955
Crystal refinement	Olex 2 version 2.1, ShelXL, ShelXL

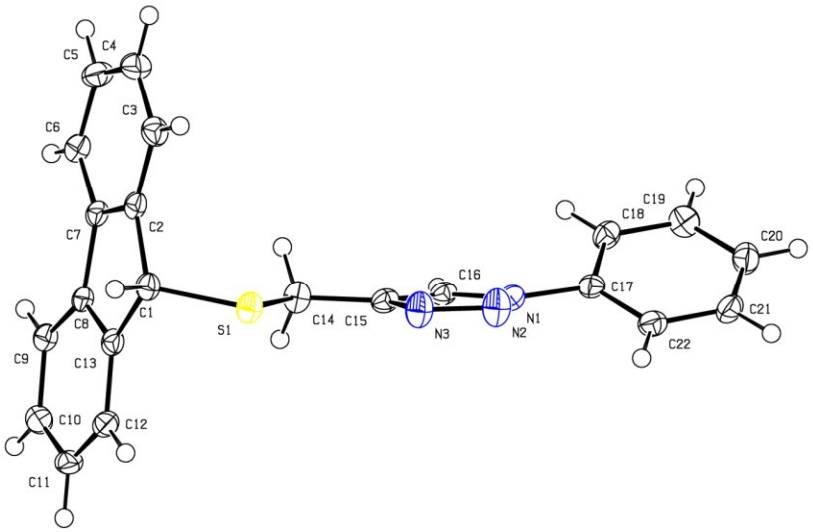


Figure 4.9: ORTEP diagram showing the X-ray crystal structure of the compound **15a**.

4.2.5.1 Single Crystal X-ray Crystallographic Structure of Compound 15r

The suitable crystals of the compound **15r** for X-ray crystallographic study were grown from ethylacetate solution. The single crystal X-ray diffraction measurement of the molecule ($C_{22}H_{15}ClFN_3S$) was done using Rigaku XtaLAB P200 diffract meter using graphite monochromated Mo-Kα radiation (λ = 1.54184 Å) on 0.7 mm x 0.05 mm x 0.05 mm pale yellow crystal. Data were collected and processed using CrysAlisPro (Rigaku Oxford Diffraction). The data were collected at a temperature of -173 ± 2 °C to a maximum 2θ value of 133.144°. Of the 7975 reflections collected, 3213 were unique (Rint = 0.0122) and equivalent reflections were merged. The diffraction data were refined and structure was solved using Olex 2 version 2.1, ShelXL software program. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The compound crystallized into a triclinic crystal system with P-1 space group. In a single unit cell four partially occupying molecules of crystallization are observed with Z=2. The basic crystallographic data are shown in **Table 4.5.** The molecular structure of the compound crystallization is given as an ORTEP diagram in **Figure 4.9.**

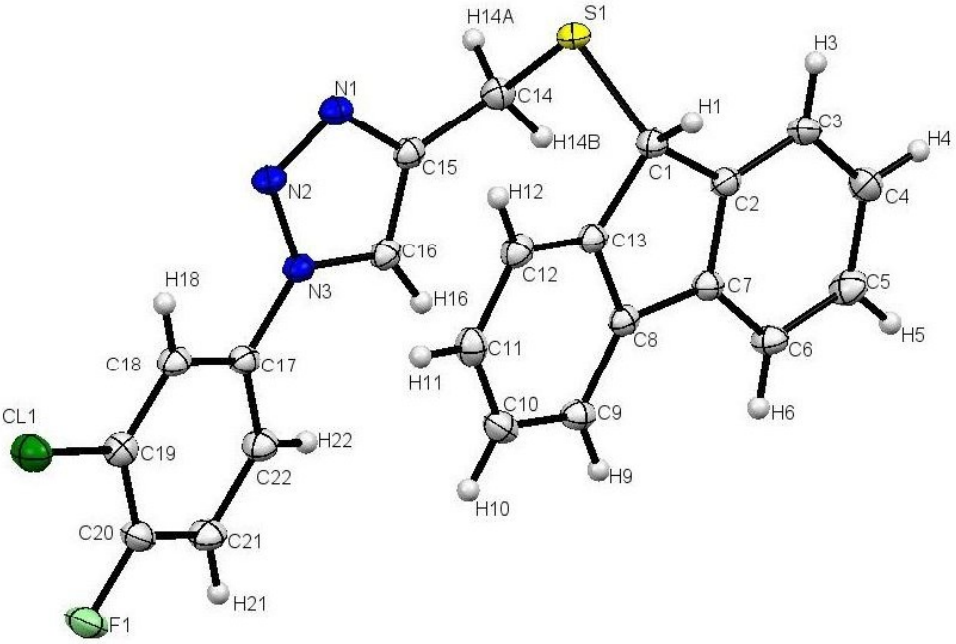


Figure 4.10: ORTEP diagram showing the X-ray crystal structure of the compound **15r**.

Table 4.5: Crystal data and structure refinement for **15r**

Empirical Formula	$C_{22}H_{15}ClFN_3S$
Formula Weight	407.88
Crystal Color, Habit	Light yellow
Crystal Dimensions	0.7 mm × 0.05 mm × 0.05 mm
Crystal System	Triclinic
Lattice Type	Primitive
Lattice Parameters	a = 6.7474(2) A°
	b = 7.4267(2) A°
	c = 18.8856(5) A°
	α = 86.538(2) A°
	β = 82.680(2) A°
	γ = 77.639(2) A°
Volume/ $A°^3$	δ = 916.37(4)
Space Group	P-1
Z value	2
D_{calc}	1.478g/cm^3
F_{000}	420.00
μ(MoKα)	31.02 cm^{-1}
Radiation	Cu-Kα(λ = 0.71073 A°)
Radiation monochromator	Graphite
Voltage, Current	50kV, 40mA
Temperature	-173 °C
Maximum 2θ	133.144°
Number of measured reflections	7975°
Number of Unique reflections	3213 (R_{int} = 0.0122)
Number of parameters	253
Goodness-of-fit on F^2	1.049
$\Delta\rho_{max,mix}$($e^-/A°^3$)	0.35, -0.28
Residuals: R1 (I>2.00σ(I))	R_1 = 0.0291, wR_2 = 0.0757
Residuals: R (All reflections)	R_1 = 0.0293

Residuals: wR2 (All reflections)	0.0759
Crystal refinement	Olex 2 version 2.1, ShelXS, ShelXL

4.3. Conclusion

In this chapter, we designed novel 9*H*-fluorenone analogues with three different series *N*-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-9*H*-fluoren-9-amine, *N*4-(((9*H*-fluoren-9-yl)thio)methyl)-1-substituted phenyl-1*H*-1,2,3-triazole & 4-(((9*H*-fluoren-9-yl) sulfonyl) methyl)-1-substituted phenyl-1*H*-1,2,3-triazole) by the molecular hybridization approach using reported MTB InhA inhibitors and substituted 1*H*-1,2,3-triazole antitubercular compounds. Fifty compounds were synthesized and characterized. One of the compounds **17p** showed good MTB activity with MIC 52.35 μM. Out of fifty compounds studied InhA activity was studied for fifteen compounds. Amongst these compounds, **17f** & **17p** showed >73% of inhibition at 50 μM. Further, the most active compounds did not exhibit cytotoxicity against HEK 293 cell line for the most active compounds at 50 μM.

4.4. Experimental Section

4.4.1. 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 spectra and ^{13}C NMR spectra were recorded at 400 MHz 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. IR spectra were recorded with an FT-IR spectrophotometer (Jasco FTIR-4200). Elemental analyses were analyzed by Elementar Analysensysteme GmbH vario MICRO cube CHNS/O Analyzer. Mass spectra (ESI-MS) were recorded on Schimadzu MS/ESI mass spectrometer. Purity of all tested compounds was greater than 95%.

4.4.2. Chemistry

***Synthesis of 9H-fluoren-9-ol* (9)**

A solution of 9*H*-fluoren-9-one (10.0 g, 55.49 mmol) in methanol was cooled to 0 ºC add sodium borohydride (1.0 g, 27.74 mmol) was slowly added at 0 ºC andallowed to reach room temperature andstirred the reaction mixture for 2 h. Once completion of the reaction, as indicated by TLC, the reaction was quenched with excess of methanol at 0 ºC. Added excess of water and stirred for 30 minutes. White solid formed was filtered and was washed with excess of water. 9H-fluoren-9-ol (**2**) was dried in oven at 60 °C for 6 h. Yield (9.5 g, 93%). ESI-MS found *m/z* 183.07 $(M+H)^+$; m.p. 153-154 ºC (reported m.p. 152-156 ºC).

***Synthesis of 9-bromo-9H-fluorene* (10)**

A solution of 9*H*-fluoren-9-ol (5.0 g, 27.43 mmol) in dichloromethane was cooled at 0 °C under the N_2. Then PBr_3 (3.12 mL, 32.92 mmol) was slowly added over 15 minutes at 0 ºC to it. The mixture was kept at 0 ºC for two hours and then saturated potassium bromide solution was slowly added under stirring until no bubble was generated. Water was added to reaction mixture and extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, and concentrated to provide a crude product which was purified by recrystalization from petroleum ether to afford pale yellow crystals yield:(6.2 g, 92%). ESI-MS found *m/z* 244.98 $(M+H)^+$; 246.98 $(M+H)^{+2}$; m.p. 104-105 ºC (reported m.p. 101-105 ºC).

***Synthesis of N-(prop-2-yn-1-yl)-9H-fluoren-9-amine* (11)**

A solution of 9-bromo-9*H*-fluorene (**10**) (5.0 g, 20.39 mmol) in ACN was cooled to 0 ºC and K_2CO_3 (5.63 g, 40.79 mmol) and propargylamine (1.56 mL, 24.47 mmol) were added and allowed to reach room temperature and stirred for 16 h. Once completion of the reaction, as indicated by TLC, the reaction was quenched with cold water and extracted with diethyl ether. The organic 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 (15 - 25%)] to get the compound **11** (4.8 g, 85%) as a brown solid. ESI-MS found *m/z* 220.11 $(M+H)^+$; 222.11 $(M+H)^{+2}$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.25 (dd, J = 7.9, 5.9

Hz, 2H), 5.03 (s, 1H), 3.31 (s, 2H), 2.61 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.55, 141.08, 128.79, 127.91, 126.78, 126.18, 83.47, 70.17, 63.16, 37.56.

***Synthesis of N-((1-substituted phenyl-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12a-p)**

A solution of *N*-(prop-2-yn-1-yl)-9*H*-fluoren-9-amine (**11**) (0.30 g, 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 room temperature for 4 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 [MeOH / DCM (1 -3%)] to yield the title compounds **12a-p**.

***Synthesis of 9H-fluorene-9-thiol* (13)**

To a solution of 9*H*-fluoren-9-ol (**9**) (5.0 g, 27.43 mmol) in toluene, Lawesson reagent (11.09 g, 27.43 mmol) was added. The reaction mixture was refluxed under N_2 atmosphere for 16 h. Once completion of the reaction, as indicated by TLC, the reaction was quenched with cold water and extracted with diethyl ether. The organic 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 (5 - 7%)] to get the 9*H*-fluorene-9-thiol (**13**) (4.0 g, 74%) as a light yellow solid. ESI-MS found *m/z* 199.06 $(M+H)^+$; m.p. 105-106 ºC (reported m.p. 103-107 ºC) .

***Synthesis of (9H-fluoren-9-yl)(prop-2-yn-1-yl)sulfane* (14)**

To a stirred solution of 9*H*-fluorene-9-thiol (4.0 g, 20.17 mmol) in dichloromethane (DCM), triethylamine (8.48 mL, 60.52 mmol) and propargyl bromide (80% in toluene) (3.0 mL, 40.34 mmol) were added. Reaction mixture was stirred at ambient temperature for 16 h. Reaction was monitored by TLC and water was added to reaction mixture once complete and was followed by extraction with ethyl acetate. Combined organic layers were collected and dried over dry sodium sulphate. Concentrated the organic layer and purified by column chromatography [ethyl acetate /

hexane (10 - 20%)]to get compound **14** (4.2 g, 87%) as light yellow solid. ESI-MS found *m/z* 237.08 $(M+H)^+$.

***Synthesis of 4-(((9H-fluoren-9-yl)thio)methyl)-1-substituted phenyl-1H-1,2,3-triazole* (15a-r)**

To a stirred solution of compound **14** (1.0 mmol) and substituted phenyl azide (1.2 mmol) in ^{t}butanol:water (1:1) (4 mL), $CuSO_4.5H_2O$ (10 mol %) (0.2 mmol) and sodium ascorbate (5 mol %) (0.2 mmol) were added and the reaction mixture was stirred at RT for 16 h. After completion of the reaction, as indicated by TLC, butanol was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x10 mL) and combined organic layers were collected and washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to get the crude product. The product was further purified by column chromatography [ethyl acetate / hexane (35 - 40%)] to afford the title compounds **15a-r**.

***Synthesis of 9-(prop-2-yn-1-ylsulfonyl)-9H-fluorene* (16)**A stirred solution of compound **14** (3.0 g, 12.69 mmol) in dichloromethane was cooled to 0 °C and *meta*-Chloroperoxybenzoic acid (8.48 mL, 25.38 mmol) was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Reaction was monitored by TLC and water was added to reaction mixture once complete and was followed by extraction with dichloromethane. Combined organic layers were collected and washed $NaHCO_3$ solutions. Concentrated the organic layer and purified by column chromatography [ethyl acetate / hexane (20 - 30%)]to get compound **9** (3.1 g, 91%) as light yellow solid. ESI-MS found *m/z* 269.07 $(M+H)^+$.

Synthesis of 4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-substituted phenyl-1H-1,2,3-triazole (17a-p)

To a stirred solution of compound **16** (1.0 mmol) and substituted phenyl azide (1.2 mmol) in ^{t}butanol:water (1:1) (4 mL), $CuSO_4.5H_2O$ (1 mol %) (0.2 mmol) and sodium ascorbate (5 mol %) (0.2 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, as indicated by TLC, butanol was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x10 mL) and combined organic layers were collected and washed with saturated brine solution, dried over anhydrous Na_2SO_4 and

concentrated *in vacuo* to get the crude product. The product was further purified by column chromatography [ethyl acetate / hexane (40 - 45%)] to afford the title compounds **17a-p**.

***N-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12a)**

Off white solid (82%); m.p. 167-168 ºC; IR (KBr) υ_{max} / cm^{-1} 3342, 3027, 2832, 1645, 1250, 990. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 3H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 (dd, *J* = 7.9, 5.9 Hz, 4H), 5.00 (s, 1H), 3.65 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.35, 142.92, 140.86, 133.10, 128.17,128.61, 127.45, 124.68, 122.28, 121.53, 119.62, 119.17, 64.21, 39.41. EI-MS *m/z* 339.15 $(M+H)^+$; Anal. calcd for $C_{22}H_{18}N_4$: (%) C, 78.08; H, 5.36; N, 16.56; Found: C, 78.09; H, 5.37; N, 16.58.

***N-((1-(p-tolyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12b)**

Off white solid (79%); m.p. 160-161 ºC; IR (KBr) υ_{max} / cm^{-1} 3348, 3029, 2842, 1650, 1590, 1260, 860. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.4 Hz, 2H), 7.62 – 7.54 (m, 3H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.16 (m, 4H), 5.00 (s, 1H), 3.64 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.84, 139.09, 134.92, 134.59, 134.36, 131.21, 130.11, 128.18, 127.18, 122.36, 120.82, 120.33, 71.05, 39.34, 21.25. EI-MS *m/z* 353.15 $(M+H)^+$; Anal. calcd for $C_{23}H_{20}N_4$: (%) C, 78.38; H, 5.72; N, 15.90; Found: C, 78.39; H, 5.73; N, 15.91.

***N-((1-(4-ethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12c)**

Off white solid (86%); m.p. 167-168 ºC; IR (KBr) υ_{max} / cm^{-1} 3340, 3032, 2847, 1651, 1590, 1260, 891. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 3H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 (dd, *J* = 7.9, 5.9 Hz, 4H), 5.00 (s, 1H), 3.65 (s, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.54, 141.15, 139.72, 138.58, 130.15, 128.73, 127.63, 125.75, 120.20, 119.82, 119.80, 64.20, 39.23, 22.46, 21.08. EI-MS *m/z* 367.15 $(M+H)^+$; Anal. calcd for $C_{24}H_{22}N_4$: (%) C, 78.66; H, 6.05; N, 15.29; Found: C, 78.67; H, 6.06; N, 15.30.

***N-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12d)**

White solid (75%); m.p. 148-149 ºC; IR (KBr) υ_{max} / cm^{-1} 3348, 3029, 2856, 1649, 1560, 1205, 1032, 864. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.16 (m, 2H), 6.96 – 6.88 (m, 2H), 5.00 (s, 1H), 3.79 (s, 3H), 3.64 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.66, 142.16, 141.06, 140.12, 129.12, 127.80, 126.35, 125.70, 122.32, 121.92, 120.83, 114.59, 75.24, 51.13, 40.20. EI-MS *m/z* 369.15 $(M+H)^+$; Anal. calcd for $C_{23}H_{20}N_4O$: (%) C, 74.98; H, 5.47; N, 15.21; Found: C, 74.99; H, 5.48; N, 15.22.

***N-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12e)**

Pale yellow solid (80%); m.p. 126-127 ºC; IR (KBr) υ_{max} / cm^{-1} 3340, 3025, 2874, 1641, 1563, 1383, 1235, 890. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65-7.54 (m, 5H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 4H), 5.02 (s, 1H), 3.61 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.59, 141.29, 140.12, 132.13, 129.88, 129.83, 129.43, 129.34, 129.01, 127.76, 125.67, 124.21, 121.55, 120.18, 65.89, 39.36. EI-MS *m/z* 357.15 $(M+H)^+$; Anal. calcd for $C_{22}H_{17}FN_4$: (%) C, 74.14; H, 4.81; N, 15.72; Found: C, 74.15; H, 4.82; N, 15.73.

***N-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12f)**

Off white solid (73%); m.p. 166-167 ºC; IR (KBr) υ_{max} / cm^{-1} 3347, 3021, 2875, 1644, 1560, 1235, 881, 653. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 7.4 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 3H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.27 (dd, *J* = 7.9, 5.8 Hz, 4H), 5.00 (s, 1H), 3.65 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.18, 134.44, 129.88, 129.83, 129.61, 129.43, 129.34, 129.01, 127.74, 125.66, 125.29, 121.55, 120.14, 65.76, 38.38. EI-MS *m/z* 373.10 $(M+H)^+$; 556.10 $(M+H)^{+2}$; Anal. calcd for $C_{22}H_{17}Cl_2N_4$: (%) C, 70.87; H, 4.60; N, 15.03; Found: C, 70.88; H, 4.61; N, 15.04.

***N-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12g)**

Pale white solid (81%); m.p. 168-169 ºC; IR (KBr) υ_{max} / cm^{-1} 3415, 3021, 2871, 1644, 1560, 1235, 876, 560. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 3H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.29 (dd, *J* = 7.9, 5.8 Hz, 4H), 5.01 (s, 1H), 3.69 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.35, 144.93, 140.84, 132.82, 128.27, 127.36, 124.98, 122.18, 121.83, 119.92, 119.67, 63.20, 39.40. EI-MS *m/z* 417.07 $(M+H)^{+2}$;

419.07 $(M+H)^+$; Anal. calcd for $C_{22}H_{17}BrN_4$: (%) C, 63.32; H, 4.11; N, 13.43; Found: C, 63.34; H, 4.12; N, 13.44.

***N-((1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12h)**

Off white solid (72%); m.p.126-128 ºC; IR (KBr) υ_{max} / cm^{-1} 3419, 3029, 2901, 1657, 1509, 1267, 1355, 876, 631, 560. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.76 – 7.69 (m, 4H), 7.67 – 7.60 (m, 3H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 2H), 5.00 (s, 1H), 3.65 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.06, 139.31, 129.65, 128.78, 127.80, 127.63, 127.03, 125.43, 125.31, 124.89, 120.62, 120.28, 120.08, 77.22, 41.25. EI-MS *m/z* 407.15 $(M+H)^+$; Anal. calcd for $C_{23}H_{17}F_3N_4$: (%) C, 67.97; H, 4.22; N, 13.79; Found: C, 67.98; H, 4.23; N, 13.80.

***N-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12i)**

Yellow solid (81%); m.p. 155-157 ºC; IR (KBr) υ_{max} / cm^{-1} 3420, 3021, 2911, 1632, 1530, 1280, 1355, 1020, 876. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.95 (m, 2H), 7.82 (d, *J* = 7.7 Hz, 2H), 7.78 (s, 1H), 7.58 – 7.49 (m, 4H), 7.35 (td, *J* = 7.6, 1.4 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.15 (s, 1H), 3.86 (s, 2H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.89, 143.73, 141.84, 139.19, 134.97, 134.36, 128.71, 128.08, 127.16, 126.26, 123.29, 120.62, 69.45, 45.42. EI-MS *m/z* 384.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{17}N_5O_2$: (%) C, 68.92; H, 4.47; N, 18.27; Found: C, 68.93; H, 4.48; N, 18.28.

***N-((1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12j)**

Pale yellow solid (71%); m.p. 123-124 ºC; IR (KBr) υ_{max} / cm^{-1} 3341, 3029, 2867, 1654, 1543, 1373, 1243, 895. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.66-7.51 (m, 5H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.8 Hz, 4H), 5.04 (s, 1H), 3.62 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.59, 141.29, 140.12, 132.13, 129.88, 129.83, 129.43, 129.34, 129.01, 127.76, 125.67, 124.21, 121.55, 120.18, 65.89, 39.36. EI-MS *m/z* 357.15 $(M+H)^+$; Anal. calcd for $C_{22}H_{17}FN_4$: (%) C, 74.14; H, 4.81; N, 15.72; Found: C, 74.15; H, 4.82; N, 15.73.

***N-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12k)**

Yellow solid (81%); m.p. 153-154 ºC; IR (KBr) υ_{max} / cm^{-1} 3422, 3029, 2921, 1641, 1523, 1275, 1351, 1032, 881. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 2.4 Hz, 1H), 7.74 (dd, *J* = 7.5, 1.1 Hz, 2H), 7.65 (dd, *J* = 7.4, 1.1 Hz, 2H), 7.61 (d, *J* = 4.7 Hz, 1H), 7.58 (s, 1H), 7.53 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.35 – 7.29 (m, 3H), 5.08 (s, 1H), 3.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.55, 144.84, 140.83, 136.05, 133.87, 132.62, 131.40, 128.31, 127.39, 124.99, 122.14, 119.95, 119.73, 119.32, 63.16, 39.26. EI-MS *m/z* 384.15 $(M+H)^+$; Anal. calcd for $C_{22}H_{17}N_5O_2$: (%) C, 68.92; H, 4.47; N, 18.27; Found: C, 68.93; H, 4.48; N, 18.28.

***N-((1-(3,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12l)**

Off white solid (77%); m.p. 106-108 ºC; IR (KBr) υ_{max} / cm^{-1} 3347, 3029, 2902, 1643, 1567, 1264, 866. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 7.4 Hz, 2H), 7.64 – 7.54 (m, 3H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.16 (m, 3H), 5.02 (s, 1H), 3.69 (s, 2H), 2.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.72, 135.89, 133.99, 132.13, 131.56, 128.94, 127.17, 125.73, 121.43, 120.33, 119.88, 119.27, 76.24, 48.21, 18.19. EI-MS *m/z* 367.18 $(M+H)^+$; Anal. calcd for $C_{24}H_{22}N_4$: (%) C, 78.66; H, 6.05; N, 15.29; Found: C, 78.67; H, 6.06; N, 15.30.

***N-((1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12m)**

White solid (86%); m.p. 153-154 ºC; IR (KBr) υ_{max} / cm^{-1} 3343, 3020, 2861, 1653, 1545, 1370, 1247, 891, 657. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (t, *J* = 8.3 Hz, 3H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.53 – 7.42 (m, 2H), 7.36 – 7.16 (m, 5H), 5.00 (s, 1H), 3.63 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7.21, 148.49, 144.90, 142.25, 140.84, 132.59, 128.28, 127.37, 126.12, 124.98, 122.97, 12071, 119.93, 116.91, 63.19, 39.31. EI-MS *m/z* 391.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}ClFN_4$: (%) C, 67.61; H, 4.13; N, 14.33; Found: C, 67.62; H, 4.14; N, 14.34.

***N-((1-(2,4-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12n)**

White solid (80%); m.p.102-103 ºC; IR (KBr) υ_{max} / cm^{-1} 3347, 3020, 2889, 1657, 1549, 1247, 885, 659. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 7.4 Hz, 2H), 7.64 – 7.54 (m, 3H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.17 (m, 3H), 5.01 (s, 1H), 3.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.76, 141.72, 135.89, 133.99, 132.13, 131.56, 128.94, 127.17, 126.65, 125.73, 121.43, 120.33, 119.88, 119.27, 76.21, 47.29. EI-MS *m/z* 407.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}ClN_4$: (%) C, 64.88; H, 3.96; N, 13.76; Found: C, 64.89; H, 3.97; N, 13.77.

***N-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12o)**

White solid (81%); m.p. 174-175 ºC; IR (KBr) υ_{max} / cm^{-1} 3337, 3021, 2879, 1649, 1549, 1247, 883, 657. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69-7.66 (m, 3H), 7.56 – 7.54 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.18 (m, 3H), 5.01 (s, 1H), 3.70 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.32, 135.79, 133.99, 132.13, 131.46, 128.74, 127.27, 126.75, 123.53, 121.43, 119.88, 119.27, 76.21, 47.29. EI-MS *m/z* 407.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}ClN_4$: (%) C, 64.88; H, 3.96; N, 13.76; Found: C, 64.89; H, 3.97; N, 13.77.

***N-((1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12p)**

White solid (81%); m.p. 117-118 ºC; IR (KBr) υ_{max} / cm^{-1} 3327, 3029, 2879, 1641, 1541, 1241, 1022, 883. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 6.8 Hz, 3H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 6.84 (s, 2H), 5.37 (s, 1H), 3.94 (s, 9H), 3.80 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.85, 141.84, 138.36, 134.94, 134.73, 132.49, 130.05, 128.13, 127.18, 122.51, 120.66, 98.32, 76.97, 61.19, 56.42, 45.17. EI-MS *m/z* 429.15 $(M+H)^+$; Anal. calcd for $C_{25}H_{24}N_4O_3$: (%) C, 70.08; H, 5.65; N, 13.08; Found: C, 70.09; H, 5.66; N, 15.09.

***N-((1-(3,4-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-9H-fluoren-9-amine* (12q)**

White solid (85%); m.p. 156-157 ºC; IR (KBr) υ_{max} / cm^{-1} 3341, 3021, 2885, 1657, 1547, 1247, 886, 650. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 7.4 Hz, 2H), 7.64 – 7.54 (m, 3H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.17 (m, 3H), 5.01 (s, 1H), 3.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.73, 135.89, 133.80, 132.63, 131.56, 128.64, 127.77, 125.83, 121.93, 121.33, 119.91, 119.18, 76.24, 49.21. EI-MS *m/z* 408.08 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}Cl_2N_4$: (%) C, 64.88; H, 3.96; N, 13.76; Found: C, 64.89; H, 3.97; N, 13.77.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-phenyl-1H-1,2,3-triazole* (15a)**

Off white solid (70%); m.p. 136-137 ºC; IR (KBr) υ_{max} / cm^{-1} 3031, 2913, 2595, 1649, 1542, 1237, 886. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (dd, *J* = 12.7, 7.5 Hz, 4H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.27 (dq, *J* = 24.0, 8.4, 7.5 Hz, 5H), 6.96 (s, 1H), 4.93 (s, 1H), 3.25 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.85, 134.98, 130.01, 129.71, 128.126, 128.27,

127.16, 126.16, 122.26, 120.61, 120.49, 119.21, 49.28, 22.35. EI-MS *m/z* 356.12 $(M+H)^+$; Anal. calcd for $C_{22}H_{17}N_3S$: (%) C, 74.34; H, 4.82; N, 11.80; Found: C, 74.35; H, 4.83; N, 11.81.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(p-tolyl)-1H-1,2,3-triazole* (15b)**

Off white solid (81%); m.p. 133-134 ºC; IR (KBr) υ_{max} / cm^{-1} 3025, 2925, 2547, 1577, 1235, 886. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 12.4, 7.5 Hz, 4H), 7.37 – 7.33 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.21 (m, 4H), 6.94 (s, 1H), 4.93 (s, 1H), 3.24 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.74, 144.19, 141.12, 138.45, 130.25, 128.43, 126.69, 125.59, 120.29, 119.85, 119.71, 49.26, 22.46, 20.12. EI-MS *m/z* 370.14 $(M+H)^+$; Anal. calcd for $C_{23}H_{29}N_3S$: (%) C, 74.77; H, 5.19; N, 11.37; Found: C, 74.78; H, 5.20; N, 11.39.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-ethylphenyl)-1H-1,2,3-triazole* (15c)**

Off white solid (72%); m.p. 136-137 ºC; IR (KBr) υ_{max} / cm^{-1} 3021, 2920, 2510, 1557, 1245, 896. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 12.5, 7.3 Hz, 4H), 7.36 – 7.33 (m, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.21 (m, 4H), 6.96 (s, 1H), 4.94 (s, 1H), 3.24 (s, 2H), 2.67 (q, *J* = 7.8 Hz, 2H), 1.21 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.54, 144.15, 140.72, 138.55, 130.05, 128.13, 127.60, 125.70, 120.20, 119.82, 119.80, 59.23, 49.20, 22.46, 21.08. EI-MS *m/z* 384.16 $(M+H)^+$; Anal. calcd for $C_{24}H_{21}N_3S$: (%) C, 75.16; H, 5.52; N, 10.96; Found: C, 75.18; H, 5.53; N, 10.97.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-methoxyphenyl)-1H-1,2,3-triazole* (15d)**

Off white solid (71%); m.p. 116-117 ºC; IR (KBr) υ_{max} / cm^{-1} 3029, 2921, 2511, 1549, 1254, 1020, 884. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.64 (dd, *J* = 12.4, 7.5 Hz, 4H), 7.38 – 7.33 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.19 (m, 4H), 6.94 (s, 1H), 4.94 (s, 1H), 3.69 (s, 3H), 3.25 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.27, 144.16, 141.26, 140.72, 128.22, 127.60, 126.35, 125.70, 122.32, 121.92, 119.83, 114.59, 54.24, 49.20, 22.56. EI-MS *m/z* 386.05 $(M+H)^+$; Anal. calcd for $C_{23}H_{29}N_3OS$: (%) C, 71.66; H, 4.97; N, 10.91; Found: C, 71.78; H, 4.98; N, 10.92.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-fluorophenyl)-1H-1,2,3-triazole* (15e)**

Off white solid (90%); m.p. 108-109 ºC; IR (KBr) υ_{max} / cm^{-1} 3026, 2921, 2517, 1549, 1322, 799. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 12.5, 7.4 Hz, 4H), 7.37 (d, *J* = 8.1 Hz, 2H),

7.29 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 4H), 6.95 (s, 1H), 4.92 (s, 1H), 3.24 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.27, 143.06, 141.26, 140.72, 128.22, 127.60, 126.71, 125.70, 122.35, 121.94, 119.73, 115.59, 49.22, 22.66. EI-MS *m/z* 374.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}FN_3S$: (%) C, 70.76; H, 4.32; N, 11.25; Found: C, 70.78; H, 4.33; N, 11.26.

4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-chlorophenyl)-1H-1,2,3-triazole **(15f)**

Off white solid (75%); m.p. 140-142 ºC; IR (KBr) υ_{max} / cm^{-1} 3028, 2921, 2519, 1545, 799, 655. ^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.66 (dd, *J* = 12.3, 7.4 Hz, 4H), 7.38 – 7.32 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.19 (m, 4H), 6.95 (s, 1H), 4.93 (s, 1H), 3.26 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 142.13, 140.75, 138.55, 134.34, 131.05, 128.16, 127.60, 125.71, 120.10, 119.80, 119.81, 49.24, 22.41. EI-MS *m/z* 390.05 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}ClN_3S$: (%) C, 67.77; H, 4.14; N, 10.78; Found: C, 67.78; H, 4.16; N, 10.79.

4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-bromophenyl)-1H-1,2,3-triazole **(15g)**

Off white solid (81%); m.p. 154-155 ºC; IR (KBr) υ_{max} / cm^{-1} 3031, 2926, 2535, 1533, 799, 585. ^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.61 (dd, *J* = 12.4, 7.5 Hz, 4H), 7.38 – 7.32 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.19 (m, 4H), 6.95 (s, 1H), 4.94 (s, 1H), 3.27 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 141.83, 140.65, 137.50, 134.44, 131.15, 128.76, 127.61, 125.81, 120.50, 119.81, 119.83, 49.25, 22.41. EI-MS *m/z* 434.05 $(M+H)^+$; 436.05 $(M+H)^{+2}$; Anal. calcd for $C_{22}H_{16}BrN_3S$: (%) C, 60.83; H, 3.71; N, 9.67; Found: C, 60.84; H, 4.72; N, 9.69.

4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole **(15h)**

Pale yellow solid (89%); m.p. 128-129 ºC; IR (KBr) υ_{max} / cm^{-1} 3034, 2921, 2530, 1532, 1334, 872. ^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.70 – 7.65 (m, 3H), 7.65 – 7.60 (m, 4H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 6.89 (s, 1H), 4.94 (s, 1H), 3.23 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 142.06, 140.73, 128.18, 127.66, 126.93, 126.91, 125.76, 124.24, 123.12, 120.16, 119.84, 119.57, 99.99, 49.24, 22.26. EI-MS *m/z* 424.10 $(M+H)^+$; Anal. calcd for $C_{23}H_{16}F_3N_3S$: (%) C, 65.24; H, 3.81; N, 9.92; Found: C, 65.25; H, 3.83; N, 9.93.

4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole **(15i)**

Yellow solid (77%); m.p. 167-168 ºC; IR (KBr) υ_{max} / cm^{-1} 3035, 2912, 2545, 1531, 872. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.94 (dd, *J* = 12.5, 7.6 Hz, 4H), 7.29 – 7.32 (m, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.12 (m, 4H), 6.95 (s, 1H), 4.94 (s, 1H), 3.27 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.83, 140.65, 137.50, 134.44, 131.15, 128.76, 127.61, 125.81, 120.50, 119.81, 119.83, 49.25, 22.41. EI-MS *m/z* 401.11 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}N_4O_2S$: (%) C, 65.98; H, 4.03; N, 13.99; Found: C, 65.99; H, 4.05; N, 14.00.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(2-chlorophenyl)-1H-1,2,3-triazole* (15j)**

Pale yellow solid (68%); m.p. 118-119 ºC; IR (KBr) υ_{max} / cm^{-1}3029, 2923, 2519, 1535, 876, 665. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 12.5, 7.5 Hz, 4H), 7.38 – 7.32 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.19 (m, 4H), 6.96 (s, 1H), 4.91 (s, 1H), 3.24 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.13, 140.75, 138.55, 134.34, 132.55, 132.23, 131.05, 128.16, 127.60, 126.34, 125.71, 120.10, 119.80, 119.89, 49.29, 22.46. EI-MS *m/z* 390.05 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}ClN_3S$: (%) C, 67.77; H, 4.14; N, 10.78; Found: C, 67.79; H, 4.15; N, 10.79.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole* (15k)**

Yellow solid (91%); m.p. 122-123 ºC; IR (KBr) υ_{max} / cm^{-1} 3032, 2919, 2541, 1535, 877. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 12.5, 7.6 Hz, 4H), 7.36 – 7.32 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.21 – 7.15 (m, 4H), 6.97 (s, 1H), 4.95 (s, 1H), 3.29 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145,12, 142.13, 140.65, 137.50, 134.44, 131.15, 129.23, 128.76, 127.87, 127.61, 125.81, 120.51, 119.89, 119.89, 49.29, 22.49. EI-MS *m/z* 401.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}N_4S$: (%) C, 65.98; H, 4.03; N, 13.99; Found: C, 75.18; H, 5.53; N, 10.97.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(3,4-dimethylphenyl)-1H-1,2,3-triazole* (15l)**

Pale yellow solid (72%); m.p. 119-120 ºC; IR (KBr) υ_{max} / cm^{-1} 3025, 2925, 2547, 1577, 1235, 886. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.62 (dd, *J* = 12.4, 7.5 Hz, 4H), 7.37 – 7.31 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.21 (m, 3H), 6.94 (s, 1H), 4.95 (s, 1H), 3.25 (s, 2H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.74, 142.19, 141.12, 138.45, 132.80, 130.25, 128.43, 126.69, 125.59, 124.21, 120.29, 119.85, 119.71, 49.26, 22.46, 20.09. EI-MS *m/z* 384.10 $(M+H)^+$; Anal. calcd for $C_{24}H_{21}N_3S$: (%) C, 75.16; H, 5.52; N, 10.96; Found: C, 75.17; H, 5.53; N, 10.97.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(4-fluoro-2-nitrophenyl)-1H-1,2,3-triazole* (15m)**

Yellow solid (78%); m.p. 146-147 ºC; IR (KBr) υ_{max} / cm^{-1} 3029, 2921, 2547, 1545, 1332, 1239, 886. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 – 7.71 (m, 2H), 7.62 (dd, *J* = 12.5, 7.4 Hz, 4H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.22 (m, 3H), 6.96 (s, 1H), 4.95 (s, 1H), 3.25 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.14, 148.15, 145.54, 144.15, 140.72, 138.55, 132.47, 130.05, 128.13, 127.60, 125.70, 123.54, 120.20, 119.82, 49.20, 22.46. EI-MS *m/z* 419.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}FN_4O_2S$: (%) C, 63.16; H, 3.61; N, 13.39; Found: C, 63.17; H, 3.62; N, 13.40.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole* (15n)**

Off white solid (69%); m.p. 152-153 ºC; IR (KBr) υ_{max} / cm^{-1} 3022, 2930, 2817, 1634, 1447, 887, 560. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 – 7.67 (m, 4H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.49 – 7.28 (m, 6H), 7.20 (d, *J* = 0.8 Hz, 1H), 5.01 (s, 1H), 3.36 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.74, 142.19, 141.12, 138.45, 135.72, 132.80, 130.25, 128.43, 126.69, 125.59, 124.21, 120.29, 119.85, 119.71, 49.26, 22.46. EI-MS *m/z* 424.04 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}Cl_2N_3S$: (%) C, 62.27; H, 3.56; N, 9.90; Found: C, 62.28; H, 3.59; N, 9.92.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(3,4-dichlorophenyl)-1H-1,2,3-triazole* (15o)**

Off white solid (64%); m.p. 147-148 ºC; IR (KBr) υ_{max} / cm^{-1} 3028, 2930, 2817, 1634, 1447, 887, 560. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 – 7.66 (m, 4H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.30 (m, 6H), 7.19 (d, *J* = 0.9 Hz, 1H), 5.04 (s, 1H), 3.36 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.10, 141.05, 135.72, 134.01, 132.89, 130.25, 128.43, 126.69, 125.59, 124.31, 123.19, 119.95, 119.73, 49.29, 22.41. EI-MS *m/z* 424.04 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}Cl_2N_3S$: (%) C, 62.27; H, 3.56; N, 9.91; Found: C, 62.28; H, 3.57; N, 9.92.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(3,5-dichlorophenyl)-1H-1,2,3-triazole* (15p)**

White solid (80%); m.p. 124-126 ºC; IR (KBr) υ_{max} / cm^{-1} 3024, 2921, 2817, 1532, 1435, 876, 573. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 – 7.66 (m, 4H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.30 (m, 6H), 7.19 (d, *J* = 0.9 Hz, 1H), 5.04 (s, 1H), 3.36 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.44, 144.14, 140.63, 138.14, 136.07, 128.31, 128.24, 127.67, 125.83, 119.90, 119.61, 118.58, 49.44, 22.29. EI-MS *m/z* 424.04 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}Cl_2N_3S$: (%) C, 62.27; H, 3.56; N, 9.91; Found: C, 62.28; H, 3.57; N, 9.92.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazole* (15q)**

Off white solid (77%); m.p. 105-107 ºC; IR (KBr) υ_{max} / cm^{-1} 3031, 2921, 2532, 1549, 1236, 1025, 874. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.67 (d, *J* = 6.8 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 6.94 (s, 1H), 6.84 (s, 2H), 4.94 (s, 1H), 3.85 (s, 9H), 3.25 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.27, 141.26, 139.56, 132.89, 128.22, 127.60, 126.35, 125.70, 122.89, 122.32, 119.83, 109.11, 56.02, 54.64, 49.29, 22.46. EI-MS *m/z* 446.20 $(M+H)^+$; Anal. calcd for $C_{25}H_{23}N_3O_3S$: (%) C, 67.41; H, 5.20; N, 9.43; Found: C, 67.42; H, 5.21; N, 9.44.

***4-(((9H-fluoren-9-yl)thio)methyl)-1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazole* (15r)**

Brown solid (86%); m.p. 113-114 ºC; IR (KBr) υ_{max} / cm^{-1} 3037, 2964, 2556, 1535, 1342, 1269, 886, 654. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 – 7.66 (m, 4H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.30 (m, 6H), 6.96 (s, 1H), 5.01 (s, 1H), 3.36 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.99, 156.49, 144.06, 140.71, 133.37, 128.20, 127.64, 125.77, 122.68, 122.40, 122.21, 119.88, 117.61, 117.38, 49.22, 22.23. EI-MS *m/z* 408.08 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}ClFN_3S$: (%) C, 64.78; H, 3.72; N, 10.30; Found: C, 64.79; H, 3.73; N, 10.31.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-phenyl-1H-1,2,3-triazole* (17a)**

Off white solid (75%); m.p. 167-168 ºC; IR (KBr) υ_{max} / cm^{-1} 3037, 2964, 2556, 1535, 1269, 1187, 1050, 886. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.96 (m, 4H), 7.80 (d, *J* = 7.7 Hz, 2H), 7.76 (s, 1H), 7.52 – 7.47 (m, 3H), 7.39 (td, *J* = 7.5, 1.4 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.37 (s, 1H), 3.83 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.85, 134.98, 130.01, 129.71, 128.126, 128.27, 127.16, 126.16, 122.26, 120.61, 120.49, 119.21, 70.08, 45.45. EI-MS *m/z* 388.11 $(M+H)^+$; Anal. calcd for $C_{22}H_{17}N_3O_2S$: (%) C, 68.20; H, 4.42; N, 10.85; Found: C, 68.21; H, 4.43; N, 10.86.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(p-tolyl)-1H-1,2,3-triazole* (17b)**

Pale yellow solid (81%); m.p. 203-205 ºC; IR (KBr) υ_{max} / cm^{-1} 3029, 2962, 2566, 1539, 1279, 1186, 1051, 881. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.97 (m, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.77 (s, 1H), 7.53 – 7.48 (m, 4H), 7.37 (td, *J* = 7.5, 1.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H),

5.35 (s, 1H), 3.86 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.84, 139.09, 134.97, 134.79, 134.36, 130.21, 130.01, 128.08, 127.16, 122.26, 120.62, 120.37, 70.00, 45.42, 21.14. EI-MS *m/z* 402.13 $(M+H)^+$; Anal. calcd for $C_{23}H_{19}N_3O_2S$: (%) C, 68.81; H, 4.77; N, 10.47; Found: C, 68.82; H, 4.78; N, 10.48.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-ethylphenyl)-1H-1,2,3-triazole* (17c)**

White solid (63%); m.p. 175-176 ºC; IR (KBr) υ_{max} / cm^{-1} 3033, 2956, 2534, 1541, 1265, 1165, 1057, 871. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.97 (m, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.77 (s, 1H), 7.53 – 7.48 (m, 4H), 7.37 (td, *J* = 7.5, 1.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.35 (s, 1H), 3.86 (s, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.37, 141.86, 134.99, 130.00, 129.03, 128.07, 127.16, 122.24, 120.60, 120.50, 70.04, 45.47, 28.46, 15.39. EI-MS *m/z* 416.15 $(M+H)^+$; Anal. calcd for $C_{24}H_{21}N_3O_2S$: (%) C, 69.17; H, 5.10; N, 10.11; Found: C, 69.18; H, 5.11; N, 10.12.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-methoxyphenyl)-1H-1,2,3-triazole* (17d)**

Off white solid (74%); m.p. 186-187 ºC; IR (KBr) υ_{max} / cm^{-1} 3030, 2951, 2533, 1544, 1264, 1162, 1051, 1020, 889. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 – 7.91 (m, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.76 (s, 1H), 7.53 – 7.46 (m, 4H), 7.38 (td, *J* = 7.5, 1.3 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.36 (s, 1H), 3.87 (s, 2H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.52, 141.85, 135.01, 134.72, 129.99, 128.06, 127.16, 126.52, 122.36, 122.11, 120.60, 114.73, 70.04, 55.63, 45.46. EI-MS *m/z* 418.12 $(M+H)^+$; Anal. calcd for $C_{23}H_{19}N_3O_3S$: (%) C, 66.17; H, 4.59; N, 10.07; Found: C, 66.18; H, 4.60; N, 10.08.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-fluorophenyl)-1H-1,2,3-triazole* (17e)**

Pale yellow solid (76%); m.p. 209-210 ºC; IR (KBr) υ_{max} / cm^{-1} 3035, 2941, 2543, 1554, 1269, 1162, 1331, 1051, 881. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.91 (m, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.77 (s, 1H), 7.53 – 7.46 (m, 4H), 7.39 (td, *J* = 7.5, 1.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.35 (s, 1H), 3.81 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.23, 141.83, 134.94, 134.38, 130.03, 129.92, 128.18, 127.16, 122.19, 121.71, 120.53, 99.98, 70.16, 45.44. EI-MS *m/z* 406.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}BrN_3O_2S$: (%) C, 65.17; H, 3.98; N, 10.36; Found: C, 65.18; H, 3.99; N, 10.37.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-chlorophenyl)-1H-1,2,3-triazole* (17f)**

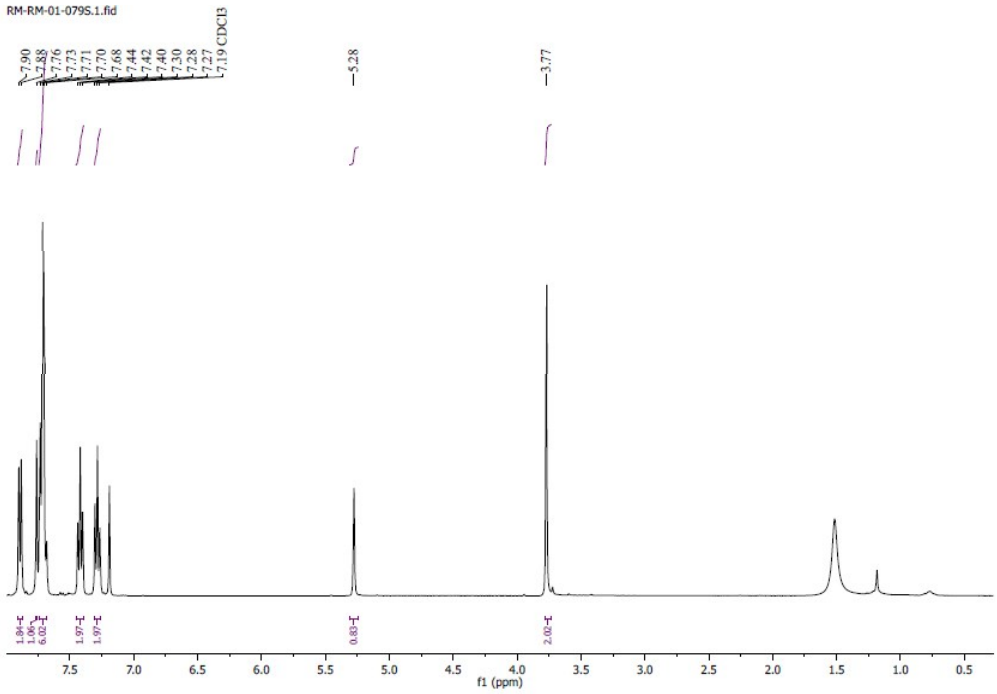
White solid (69%); m.p. 215-216 ºC; IR (KBr) υ_{max} / cm^{-1} 3031, 2942, 2547, 1557, 1269, 1162, 1331, 1051, 881, 651.^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.94 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.75 (s, 1H), 7.53 – 7.46 (m, 4H), 7.38 (td, *J* = 7.5, 1.2 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.36 (s, 1H), 3.87 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.83, 135.11, 134.95, 134.78, 130.03, 129.92, 128.08, 127.16, 122.15, 121.61, 120.63, 99.98, 70.12, 45.34. EI-MS *m/z* 422.08 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}ClN_3O_2S$: (%) C, 62.63; H, 3.82; N, 9.96; Found: C, 62.64; H, 5.53; N, 9.97.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-bromophenyl)-1H-1,2,3-triazole* (17g)**

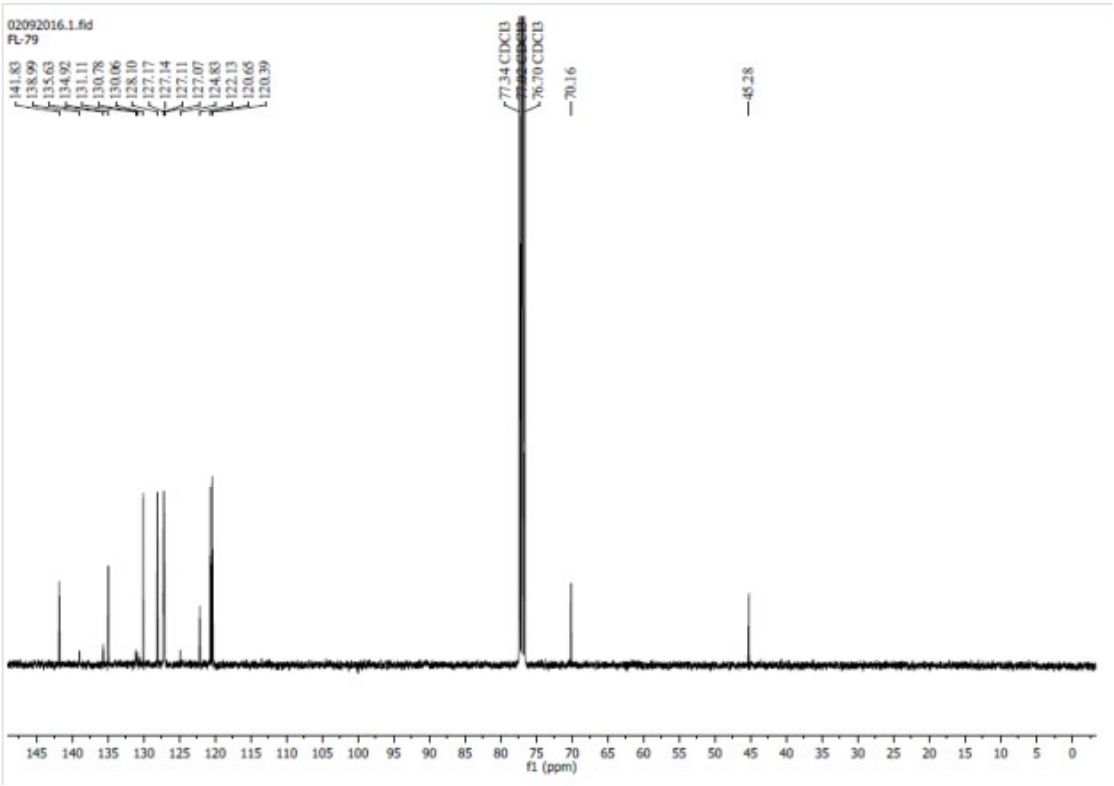
Off white solid (81%); m.p. 225-226 ºC; IR (KBr) υ_{max} / cm^{-1} 3027, 2941, 2537, 1547, 1261, 1142, 1331, 1052, 881, 543. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.95 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.75 (s, 1H), 7.53 – 7.46 (m, 4H), 7.38 (td, *J* = 7.5, 1.2 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.36 (s, 1H), 3.87 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.83, 135.11, 134.97, 131.13, 129.97, 128.18, 127.16, 123,23, 122.15, 121.61, 120.63, 99.98, 70.12, 45.34. EI-MS *m/z* 465.02 $(M+H)^+$; 467.02 $(M+H)^{+2}$; Anal. calcd for $C_{22}H_{16}BrN_3O_2S$: (%) C, 56.66; H, 3.46; N, 9.01; Found: C, 56.67; H, 3.47; N, 9.02.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole* (17h)**

Pale yellow solid (72%); mp.231-232 ºC; IR (KBr) υ_{max} / cm^{-1} 3025, 2940, 2537, 1547, 1341, 1146, 1331, 1052, 881. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 7.6 Hz, 2H), 7.76 (s, 1H), 7.72 (t, *J* = 5.7 Hz, 6H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 5.28 (s, 1H), 3.77 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.82, 138.96, 135.60, 134.89, 131.08, 130.75, 130.07, 128.11, 127.17, 124.84, 122.17, 120.66, 120.38, 70.11, 45.23. EI-MS *m/z* 456.10 $(M+H)^+$; Anal. calcd for $C_{23}H_{16}F_3N_3O_2S$: (%) C, 60.65; H, 3.54; N, 9.23; Found: C, 60.66; H, 3.55; N, 9.24.



^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **17h**



^{13}C NMR spectrum (101MHz, $CDCl_3$) of compound **17h**

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole* (17i)**

Yellow solid (91%); m.p. 246-247 ºC; IR (KBr) υ_{max} / cm^{-1} 3029, 2942, 2545, 1531, 1143, 872. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (dd, *J* = 12.5, 7.6 Hz, 4H), 7.76 (s, 1H), 7.29 – 7.32 (m, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.15 (m, 4H), 5.04 (s, 1H), 3.67 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.83, 141.65, 138.50, 135.44, 132.15, 128.76, 127.61, 125.81, 120.50, 119.81, 119.73, 71.35, 46.01. EI-MS *m/z* 433.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}N_4O_4S$: (%) C, 61.10; H, 3.73; N, 12.96; Found: C, 61.11; H, 3.74; N, 12.97.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole* (17j)**

Yellow solid (77%); m.p. 186-187 ºC; IR (KBr) υ_{max} / cm^{-1} 3042, 2939, 2542, 1535, 1149, 877. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 12.5, 7.6 Hz, 4H), 7.76 (s, 1H), 7.36 – 7.32 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.21 – 7.15 (m, 4H), 5.05 (s, 1H), 3.59 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145,17, 142.16, 140.60, 137.51, 134.42, 132.15, 129.23, 128.76, 127.85, 127.61, 125.81, 120.51, 119.89, 71.43, 46.19. EI-MS *m/z* 433.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}N_4O_4S$: (%) C, 61.10; H, 3.73; N, 12.96; Found: C, 61.11; H, 3.74; N, 12.97.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(2-chlorophenyl)-1H-1,2,3-triazole* (17k)**

Off white solid (68%); m.p. 221-222 ºC; IR (KBr) υ_{max} / cm^{-1} 3039, 2934, 2542, 1535, 1149, 876, 567. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 7.7 Hz, 2H), 7.83 – 7.78 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 2H), 5.36 (s, 1H), 3.85 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.82, 135.56, 135.28, 135.46, 134.92, 132.90, 130.05, 128.10, 127.16, 122.66, 122.11, 122.13, 121.82, 120.64, 70.08, 45.30. EI-MS *m/z* 422.08 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}ClN_3O_2S$: (%) C, 62.63; H, 3.83; N, 9.96; Found: C, 62.64; H, 3.84; N, 9.97.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(3,4-dimethylphenyl)-1H-1,2,3-triazole* (17l)**

White solid (61%); m.p. 179-180 ºC; IR (KBr) υ_{max} / cm^{-1} 3023, 2921, 2547, 1547, 1151, 886, 563. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (dd, *J* = 12.4, 7.5 Hz, 4H), 7.76 (s, 1H), 7.37 – 7.31 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.21 (m, 3H), 5.15 (s, 1H), 3.81 (s, 2H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.74, 142.19, 140.12, 138.42, 132.70, 130.21, 128.33, 126.62, 125.69, 124.20, 120.27, 119.85, 119.71, 70.45, 45.46, 20.09. EI-MS *m/z* 416.15 $(M+H)^+$;

Anal. calcd for $C_{24}H_{21}N_3O_2S$: (%) C, 69.37; H, 5.09; N, 10.11; Found: C, 69.38; H, 5.10; N, 10.12.

4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(4-fluoro-2-nitrophenyl)-1H-1,2,3-triazole **(17m)**

Yellow solid (79%); m.p. 179-180 ºC; IR (KBr) υ_{max} / cm^{-1} 3021, 2921, 2547, 1545, 1332, 1239, 1145, 887. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.75 (m, 2H), 7.73 (s, 1H), 7.62 (dd, *J* = 12.4, 7.5 Hz, 4H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.28 – 7.21 (m, 3H), 5.21 (s, 1H), 3.78 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.17, 148.35, 145.64, 144.19, 140.70, 138.57, 133.47, 131.05, 128.13, 127.61, 125.68, 123.54, 121.41, 119.82, 71.20, 46.46. EI-MS *m/z* 451.19 $(M+H)^+$; Anal. calcd for $C_{21}H_{15}FN_4O_4S$: (%) C, 58.66; H, 3.36; N, 12.44; Found: C, 58.67; H, 3.37; N, 12.45.

4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole **(17n)**

Off white solid (67%); m.p. 156-157 ºC; IR (KBr) υ_{max} / cm^{-1} 3027, 2931, 2819, 1524, 1132, 897, 562; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.81 (m, 4H), 7.76 (d, *J* = 2.1 Hz, 1H), 7.49 – 7.29 (m, 6H), 7.21 (d, *J* = 0.8 Hz, 1H), 5.27 (s, 1H), 3.66 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.84, 142.39, 141.62, 138.75, 135.77, 132.81, 130.26, 128.47, 126.69, 125.59, 124.21, 120.26, 119.81, 119.65, 77.26, 46.41. EI-MS *m/z* 456.04 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}Cl_2N_3O_2S$: (%) C, 57.90; H, 3.31; N, 9.21; Found: C, 57.91; H, 3.32; N, 9.22.

4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(3,4-dichlorophenyl)-1H-1,2,3-triazole **(17o)**

White solid (78%); m.p. 223-224 ºC; IR (KBr) υ_{max} / cm^{-1} 3026, 2931, 2817, 1534, 1136, 887, 567. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.95 (m, 4H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.51 – 7.39 (m, 6H), 7.21 (d, *J* = 0.9 Hz, 1H), 5.34 (s, 1H), 3.69 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.10, 141.05, 135.72, 134.01, 132.89, 130.25, 128.43, 126.69, 125.59, 124.31, 123.19, 119.95, 119.73, 49.29, 22.41. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.82, 136.58, 134.73, 134.11, 133.23, 131.56, 130.17, 128.81, 127.27, 122.33, 122.19, 120.76, 119.43, 76.19, 45.31. EI-MS *m/z* 456.04 $(M+H)^+$; Anal. calcd for $C_{22}H_{15}Cl_2N_3O_2S$: (%) C, 57.90; H, 3.31; N, 9.21; Found: C, 57.91; H, 3.32; N, 9.22.

4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazole **(17p)**

White solid (76%); m.p. 194-196 ºC; IR (KBr) υ_{max} / cm^{-1} 3027, 2939, 2814, 1540, 1130, 1024, 884, 569. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 7.7 Hz, 2H), 7.82 (d, *J* = 6.8 Hz, 3H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 6.84 (s, 2H), 5.37 (s, 1H), 3.94 (s, 6H), 3.90 (s, 3H), 3.84 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.85, 141.84, 138.36, 134.94, 134.73, 132.49, 130.05, 128.13, 127.18, 122.51, 120.66, 98.32, 69.97, 61.09, 56.48, 45.07. EI-MS *m/z* 478.19 $(M+H)^+$; Anal. calcd for $C_{25}H_{23}N_3O_5S$: (%) C, 62.88; H, 4.85; N, 8.80; Found: C, 62.89; H, 4.86; N, 8.81.

***4-(((9H-fluoren-9-yl)sulfonyl)methyl)-1-(3-nitrophenyl)-1H-1,2,3-triazole* (17q)**

Yellow solid (87%); m.p. 190-192 ºC; IR (KBr) υ_{max} / cm^{-1} 3039, 2939, 2540, 1536, 1147, 879. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (dd, *J* = 12.5, 7.6 Hz, 4H), 7.79 (s, 1H), 7.40 – 7.36 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.22 – 7.18 (m, 4H), 5.15 (s, 1H), 3.62 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.86, 141.81, 137.29, 135.96, 134.95, 130.98, 130.10, 128.15, 127.22, 125.88, 123.39, 122.21, 120.69, 115.26, 70.24, 45.33. EI-MS *m/z* 433.10 $(M+H)^+$; Anal. calcd for $C_{22}H_{16}N_4O_4S$: (%) C, 61.10; H, 3.73; N, 12.96; Found: C, 61.11; H, 3.74; N, 12.97.

4.4.3. Biological activity

4.4.3.1. InhA activity inhibition.

Triclosan and NADH were obtained from Sigma-Aldrich. Stock solutions of all compounds were prepared in DMSO such that the final concentration of this co-solvent was constant at 5% v/v in a final volume of 1 mL for all kinetic reactions. Kinetic assays were performed using *trans*-2-dodecenoyl-coenzyme A (DDCoA) and wild type InhA method.[34] Briefly, reactions were performed at 25 °C in an aqueous buffer (30 mM PIPES and 150 mM NaCl pH 6.8) containing additionally 250 μM cofactor (NADH), 50 μM substrate (DDCoA) and the tested compound (at 50 μM or 10 μM). Reactions were initiated by addition of InhA (100 nM final) and NADH oxidation was followed at 340 nm. The inhibitory activity of each derivative was expressed as the percentage inhibition of InhA activity (initial velocity of the reaction) with respect to the control reaction without inhibitor. Triclosan was used as a positive control. All activity assays were performed in triplicate.

4.4.3.2. In vitro MTB screening

The antimycobacterial activities of the compounds **12a-p, 15a-r** & **17a-p** 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 [32]. Bacterial respite was 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 [33]. 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.

4.4.3.3. 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 [35]. 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).

4.4.4. Docking Study

Docking studies of the title compounds (**12a-p, 15a-r** & **17a-p**) was performed using Glide 5.9 (Extra Precision) running on maestro version 9.4, in order to investigate their binding pattern with enzyme InhA [36]. Enzyme used for the docking study was retrieved from RCSB Protein Data Bank (PDB ID: 1BVR) in complex with co-crystallised ligand (NICOTINAMIDE). Protein preparation wizard of Schrödinger suite was used for preparation of selected protein. Protein was pre-processed separately by deleting the substrate co-factor as well as the crystallographically observed water molecules (water without H bonds), followed by optimization of hydrogen bonds. After assigning charge and protonation position, finally energy was minimized with root mean square deviation (RMSD) value of 0.30 Å using optimized potentials for liquid simulations-2005 (OPLS-2005) force field [37]. Finally energy minimized protein and co-crystallized ligand was used to build energy grids using the default value of protein atom scaling (1.0 Å) within a cubic box of 14 Å dimensions, centered on the centroid of the X-ray ligand pose. The structures of **12a-p, 15a-r** & **17a-p** were drawn using ChemSketch and converted to 3D structure with the help of 3D optimization tool. Using LigPrep 2.6 module, the drawn ligands were geometry optimized; partial atomic charges were computed using OPLS-2005 force field [37]. Finally, prepared ligands were docked with prepared protein using Glide 5.9 module, in extra precision mode (XP). The leading docked pose (with lowest Glide score value) found from Glide was analyzed. RMSD value was calculated between the experimental binding mode of co-crystallized ligand as in X-ray and re-docked pose to ensure accuracy and reliability of the docking procedure.

4.5. References

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