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Review

Role of Triazoles in the Field of Tuberculosis Treatment: Synthetic Approaches and Biological Investigation

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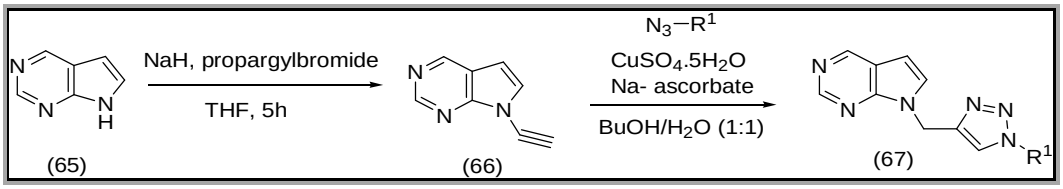
ABSTRACT

Tuberculosis, a major public health and socioeconomic problem in most of the developing countries is a chronic disease caused by different species of mycobacteria. According to WHO 10 million people fell ill with tuberculosis and 1.5 million people died from the disease in 2020 worldwide. TB is the 13th leading cause of death and second leading infectious killer after COVID 19. Though it is a treatable epidemic disease but results one of the most public health concern worldwide. To design and investigate a new therapeutic agent is one of the most difficult tasks for the medicinal chemists. Synthesis of heterocyclic systems consisting high nitrogen has been rising over the past decade owing to their usefulness in different applications such as propellants, explosives, pyrotechnics, and especially chemotherapy. In recent years, considerable attention has been received by the chemistry of triazoles and their fused heterocyclic derivatives. Due to synthetic and effective biological importance triazole derivatives are regarded as a new class of effective anti –TB candidates who show promising in vitro and in vivo anti-TB activities. This review article outlines the advances in application of incorporating 1, 2, 3 - triazole in dealing with the escalating problems of microbial resistance, and will explore the triazole scaffolds for the rational design of potent drug candidates having better efficacy, improved selectivity and minimal toxicity so that these hybrids can effectively be explored as potential leads to fight against this deadly disease Mycobacterium tuberculosis (M.tb).

Graphical Abstract:



Synthesis of 7-((1-phenyl, aryl, heteroaryl-1H-1,2,3-triazol-4-yl)methyl)-7H-pyrrolo [2,3-d] pyrimidines.

Keywords: Tuberculosis, therapeutic agent, heterocyclic systems, triazole derivatives, structure activity relationship.

INTRODUCTION

Tuberculosis is a tenacious disease that is progressively becoming harder and more expensive to treat as strains that display drug resistance to the standard treatment regimen becomes increasingly prevalent around the world. As per Global TB Report 2020 10 million people fell ill with tuberculosis and 1.5 million people died from the disease in 2020 worldwide [**1**]. The major concern arises when tuberculosis is co-infected with HIV infection [**2-4**]. TB is the 13th leading cause of death and second leading infectious killer after COVID-19. Though it is a treatable epidemic disease but results one of the most public health concern worldwide. It is a communicable disease, which mainly attacks lungs but can also affect other parts of the body. The classic form of tuberculosis is most often caused by three species of mycobacteria: *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium africanum*. It has two general states: latent infection and active infection [**5**]. Active tuberculosis is an infection in which tuberculosis bacteria rapidly multiply and invade different organs of the body as they are in active condition. A person who is suffering from active pulmonary tuberculosis disease has a strong possibility to spread his infection to others by airborne transmission of infectious particles or droplets through coughing, sneezing into the air. During latent tuberculosis, many people receive the infection of tuberculosis but may not get infected with it immediately. Although this type of infection can live in the body without making the people sick. In most cases, the body is able to fight against it if they have strong immune system and will stop them from growing therefore, in such cases TB bacteria remain inactive for a lifetime. However, in people having weak immune system, the bacteria become active, multiply and result in TB disease. As mycobacterium tuberculosis can persist in slow growing as well as fast growing stages which makes treatment challenging. A serious problem in the treatment of tuberculosis is its high infectivity, which is why the anti-tuberculosis nature of the action of triazole derivatives is an important search direction. As it turns out, the triazole derivatives have specific anti -tuberculosis activity [**6**]. Almost all of the antibiotics that can be used to treat TB work when the bacteria are actively dividing. In the intensive phase of TB treatment, the antibiotics mainly kill rapidly growing bacteria, which causes rapid sputum conversion and eradication of clinical symptoms. Treatment is essential in order to kill the slow growing strains. The standard regimen recommended by WHO for the treatment of drug sensitive and drug resistant TB have some drawbacks as the current first line treatment for TB are based on the administration of a combination of INH (isonazid), RIF (rifamicin), PZA (pyrazinamide), EMB (ethambutol) for the first two months, followed by prolonged treatment with INH and RIF for a further 4-7 months. Isoniazid and rifampicin have been the first line anti-TB agents widely used for the treatment of especially pulmonary TB, however their efficacy has been reported to diminish due to hepatotoxicity, CNS toxicity or multi-organ toxicity. With a view of prevention of damage to live in patients treated with these anti-TB drugs, co-administration of hepatoprotective agents have been found as safe and efficacious. MDR TB occurs when a *Mycobacterium tuberculosis* strain is resistant to isoniazid and rifampin, two of the most powerful first-line drugs. To cure MDR TB, healthcare providers must turn to a combination of second-line drugs and may have more side effects, the treatment may last much longer, and the cost may be up to 100 times more than first-line therapy. MDR TB strains can also grow resistant to second-line drugs, further complicating treatment.

Bedaquiline (1), delamanid (2) and pretominid (3) are new drugs approved (Figure 1) however, the first two drugs, bedaquiline and delamanid have been reported for major side effects including, hepatotoxicity and CNS toxicity, respectively along with cardiac dysrhythm. Many other new chemical entities such as adamantyl amine derivative (SQ109) (4), and imidazopyridine amide (Q203), etc. are under clinical trial to evaluate their safety and efficacy. The available treatment for MDR (multidrug resistant TB) is lengthy (9-24 months), complicated and poorly tolerated. These drugs have limited data on efficacy and long term safety.

Tuberculosis drugs target various aspects of *Mycobacterium tuberculosis* biology, including inhibition of cell wall synthesis, protein synthesis, or nucleic acid synthesis. For some drugs, the mechanisms of action have not been fully identified. Some common strategies could be adopted to

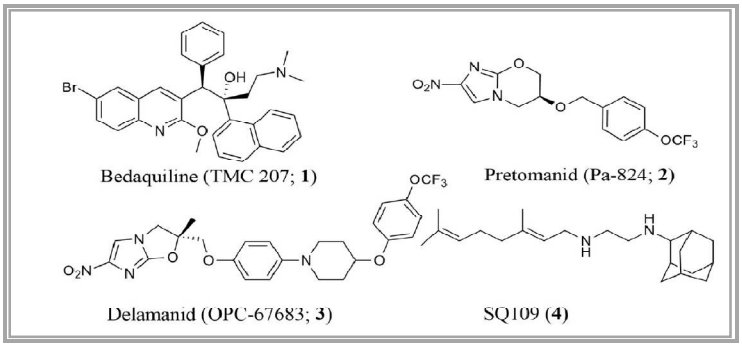


Figure 1. Structure of new TB drugs.

achieve the desired results-structural modifications of identified drug molecule, molecular hybridization, click chemistry, computer aided drug design. Among them, the molecular hybridization of preclinical or clinically validated molecules is one of the most effective tools to design a novel, safe and fast acting drug. The method involves the combination of two or different active pharmacophoric moieties to produce a new compound with improved affinity and efficacy when compared to the parent compound against various diseases [**7, 8**]. To design and investigate a new therapeutic agent is one of the most difficult tasks for the medicinal chemists. Synthesis of heterocyclic systems consisting high nitrogen has been rising over the past decade owing to their usefulness in different applications such as propellants, explosives, pyrotechnics, and especially chemotherapy. In recent years, considerable attention has been received by the chemistry of triazoles and their fused heterocyclic derivatives because of their synthetic and effective biological importance [**9**]. While working in the field of drug development [**10-20**] we believe that the review to highlight the recent development on 1,2,3 –triazole, 1,2,4 –triazole analogues and their hybrids as antitubercular agents with structure – activity relationship will be highly useful. The present review describes the recent synthetic strategies and anti-tubercular activity of 1,2,3 –triazole, 1,2,4 –triazole analogues and their hybrids.

Pharmacological activities of triazole derivative: Triazoles including 1, 2 ,3 – triazoles and 1,2,4– triazoles are one of the most important class of nitrogen containing heterocycles exhibiting various biological activities showing promising *in vitro* and *in vivo* anti – TB activities and might be able to prevent the drug resistance to some extent [**21**]. Triazoles have gained tremendous applications in the vast variety of field like material science, polymer chemistry and pharmaceutical chemistry. The 1,2,4-triazole core has been incorporated into a wide variety of therapeutically important compounds available in clinical therapy, such as antibacterial, antifungal (Itraconazole, 5) [**22, 23**], anxiolytic (Alprazolam, 6) [**24**], antitumoral (Letrozoles, 7) antidepressant (Trazadone, 8), antiviral (Ribavirin, 9), anti-HIV agent (TSAO, 10), antibiotic (Cefatrizine, 11), anti-bacterial agent (Tazobactum, 12), anticancer agent (CAI, 13), anti –tb agent in clinical evalutions (1-A09, 14), antioxidant, antimicrobial, anticancer, anti-inflamatory and anti-neurodegenerative (8-HQ derivative, 15) (Figure 2).

1, 2, 3 –Triazole hybrids effective as antitubercular agents: 1. Sudeep K. Mandal, *et al.* in 2010, synthesized substituted 1,2,4-(triazole-3yl)benzene-1,2,3-triols [**25**] for screening against *M.tb,* H37Rv using Microplate Alamar Blue Assay (Scheme 1). Among the synthesized compounds (Table 1, 21a-21e) only one namely, 5-(4-(substituted benzylideneamino)-5-(phenylamino)-4H-1,2,4-triazol-3-yl) benzene-1,2,3-triol showed significant antitubercular activity. 3,4,5-trihydroxy benzohydrazide (18) was prepared by using propylgallate (16) and hydrazine hydride (17) in ethanol refluxed for 6 h and the mixture of 3,4,5-trihydroxybenzohydrazide (18) was formed and to this mixture, phenyl isothiocynate was added in ethanol refluxed for 2 h and compound 2-[(3,4,5-tri hydroxyphenyl)carbonyl]- N-hydrazine ethyl carbothiomide (19) was formed and to this compound ,again hydrazine hydrate in ethanol refluxed for 2 h yielded 5-(4-amino-5-(phenylamino)-4H-1,2,4-

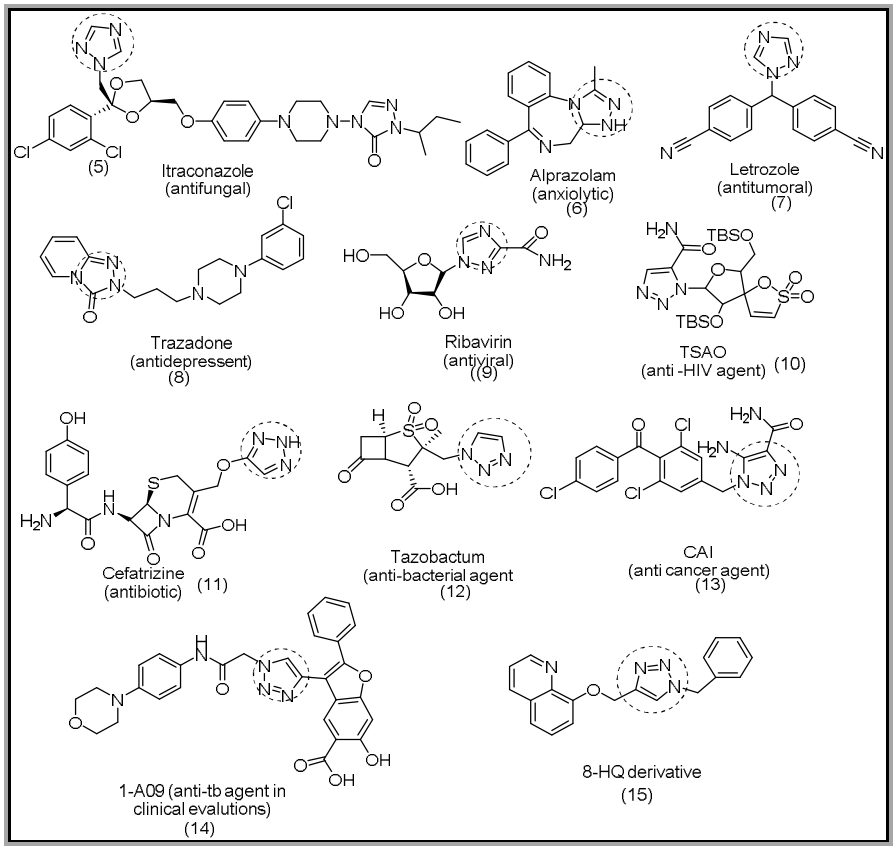
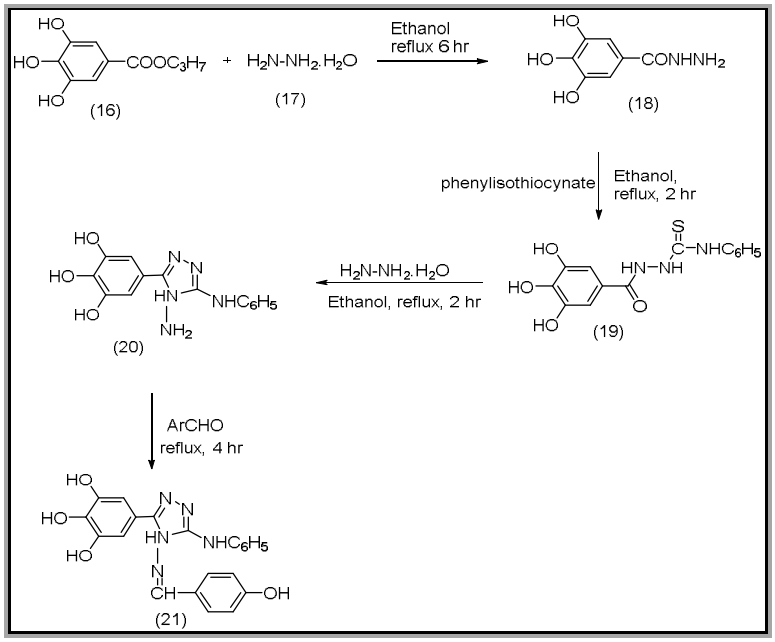


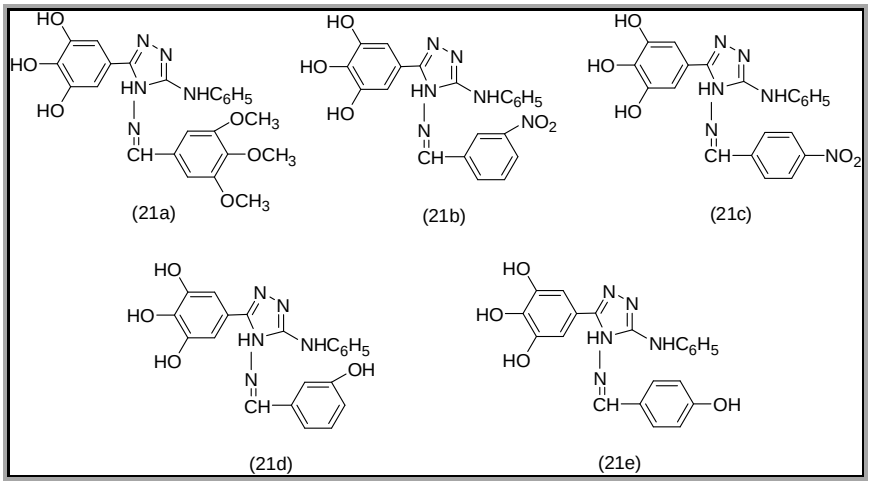
Figure 2. Drugs containing 1,2,3 – triazole core used for the treatment of various diseases.

trizol-3yl)benzene-1,2,3-triol (20). To a solution of 5-(4-amino-5-(phenylamino)-4H-1,2,4-trizol-3yl)benzene-1,2,3-triol (20) in absolute ethanol the appropriate aromatic aldehydes was added and refluxed for 4 h and compound 5-(4-(subsrtituted benzylideneamino)-5-phenylamino-4H-1,2,4-trizole-3yl)benzene-1,2,3-triol (21) was formed.

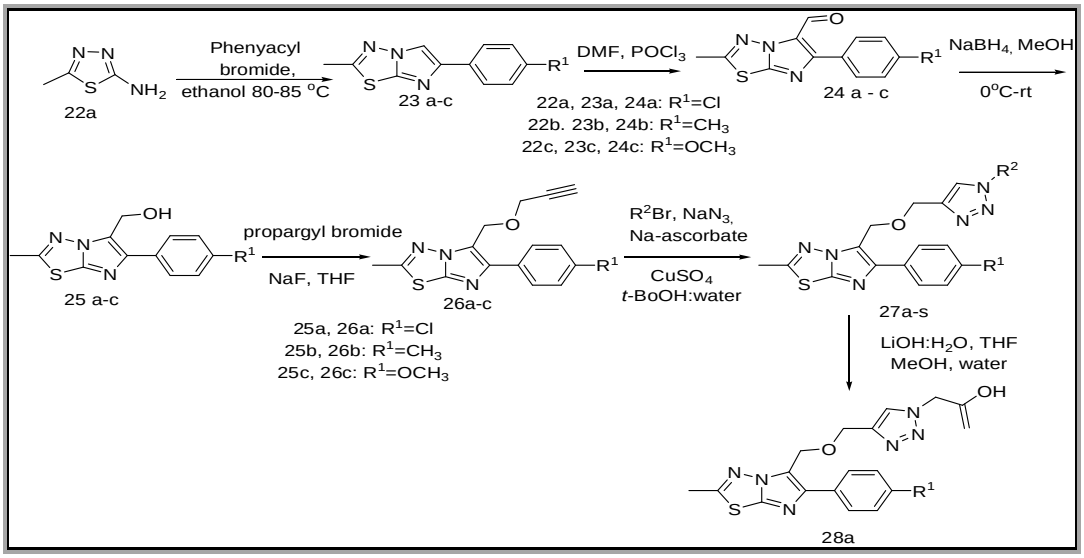


Scheme 1. Synthesis of 1,2,4-(triazole-3yl)benzene – 1,2,3-triols.

Table 1. structure of the various compounds (21a-21e) synthesized.

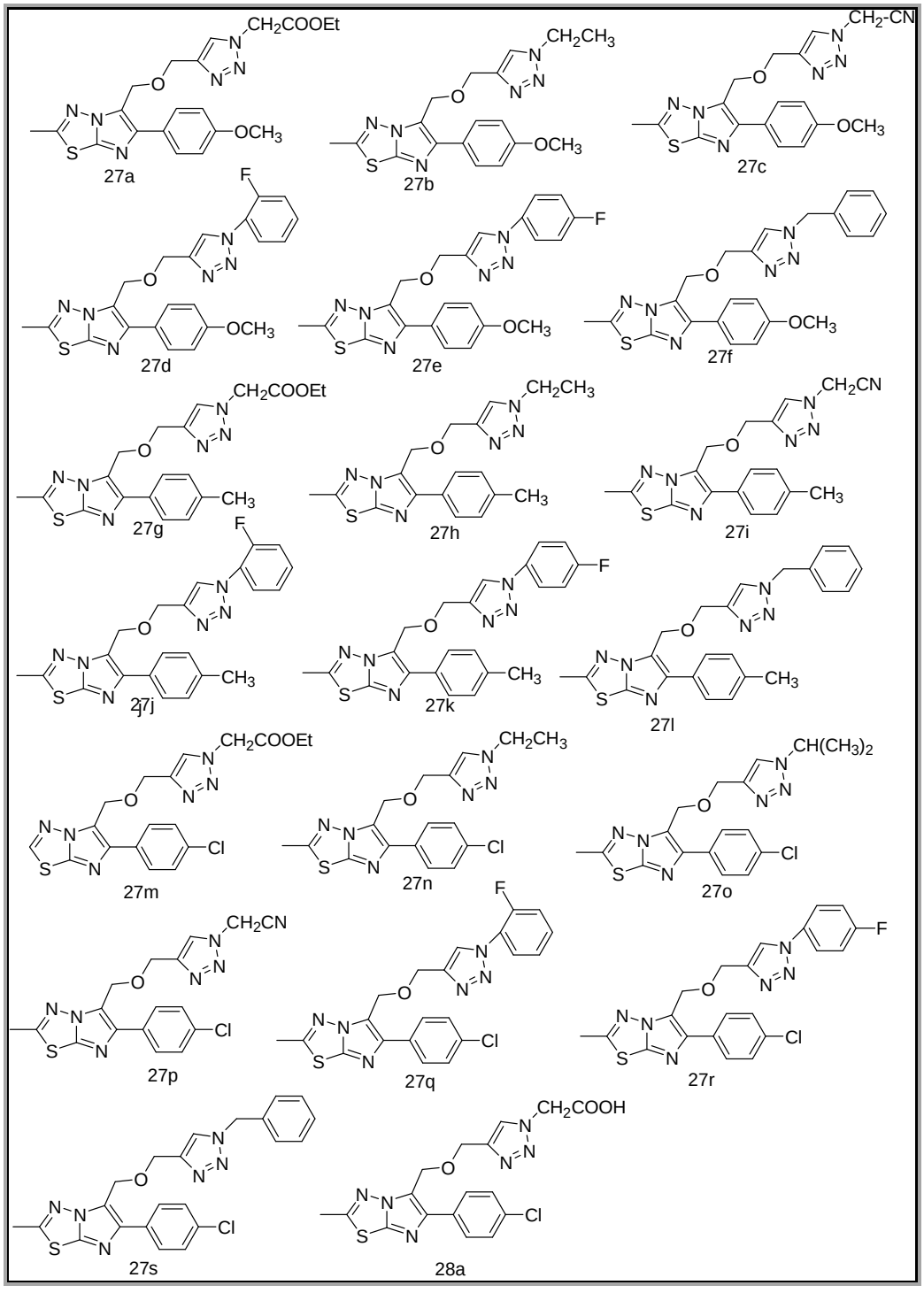


2. J. Ramprasad *et al* in 2015 [**26**] synthesized and designed a novel series of triazole- imidazole [2,1–b] [1,3,4] thiadiazole hybrids against *mycobacterium tuberculosis* H37RV by molecular hybridization approach using click chemistry (Scheme 2). Screening revealed that compounds 27f and 27n showed significant activity against the growth of *M.tb* with MIC: 3.125 µg mL^{-1} and 22p showed moderate activity with MIC: 6.25 µg mL^{-1} (Table 2). The presence of chloro substituent on the imidazole [2,– b] [1,3,4] thiadiazole ring and ethyl benzyl or cyanomethylene groups on the 1,2,3 – triazole ring enhanced the inhibition activity of the molecule. The 6-aryl-2-methylimidazo [2,1-b][1,3,4] thiadiazoles (23a-c) were synthesized by treating thiadiazole (22a) with corresponding phenyacyl bromide derivatives. These compounds were then subjected to Vilsmeier Haack formylation reaction to yield 6-aryl-2-methylimidazo [2,1-b][1,3,4] thiadiazoles-5-carboxaldehydes (24a-c). The intermediate 6-aryl-2-methylimidazo[2,1-b][1,3,4]thiadiazoles-5-carboxaldehydes (24a-c) was then subjected to $NaBH_4$ as reducing agent to yield 6-aryl-2-methylimidazo[2,1-b][1,3,4]thiadiazoles-5-yl methanol (25a-c). Intermediates (25a-c) were then treated with propargyl bromide in the presence of sodium hydride to yield 6-aryl-2-methyl-5-((prop-2-ynyloxy) methyl) imidazo [2,1,b] [1,3,4] thiadiazoles (26a-c). Finally the target compound (27a-s) was synthesized by click reactions in which alkyne intermediates (26a-c) was treated with different substituted alkyl bromides in presence of sodium azides, ester group in 27m was hydrolyzed using LiOH to get the target compound 28a.



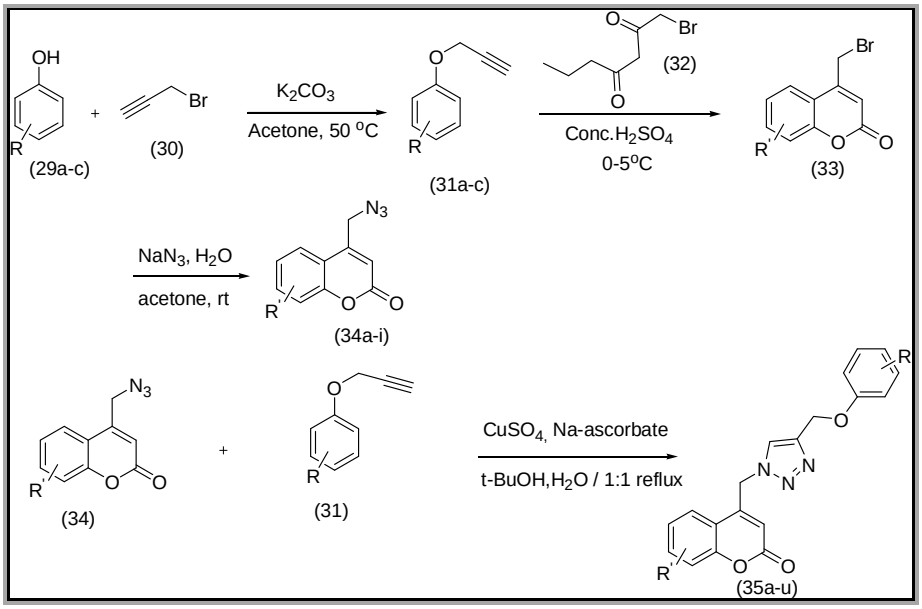
Scheme 2. Synthesis of 1,2,3-triazole-imidazo[2,1-b][1,3,4]thiadiazol hybrid compounds.

Table 2. Library of the compounds (27a-s, 28a) synthesized using scheme 2.



3. A. Ashish *et al.* (2015) synthesized a series of mono and bis –triazole –coumarin hybrids against *M.tb* H37Rv using CuAAC (Cu (I) catalysed azide–alkyne cycloaddition reaction under click chemistry conditions (Scheme 3; Table 3) [27]. Antitubercular screening showed moderate activity for mono aryloxy compounds 36 a –u with MIC: 50 -100 µg mL^{-1} and bis aryloxy linked coumarinyl triazoles were more effective with MICs between 0.2- 12.5 µg m L^{-1}. Molecular docking studies against InhA –D1448G mutant in complex with NADH, showed better hydrogen bonding with the presence of two triazole rings. Substituted phenols (29) was subjected to propargyl bromide (30) in

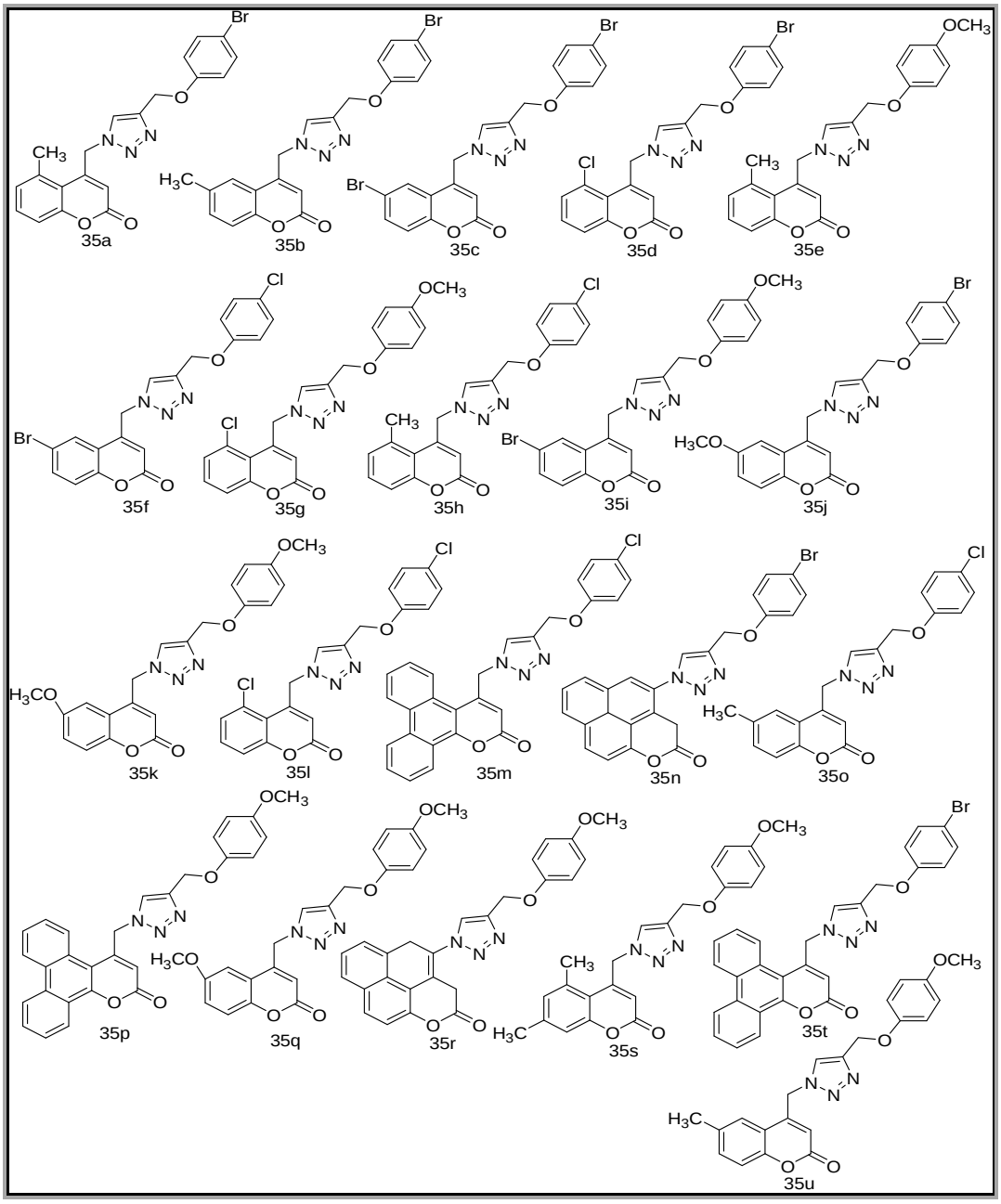
dry acetone and K_2CO_3 propargylbromide formed substituted 1- (prop-2-ynyloxy)benzene (31). The compound (31) was then treated with ethyl 4-bromoacetoacetate (32) in presence of H_2SO_4 to yield 4-(bromomethyl)-2-H-chomen-2-one (33), and to this sodium azide in water was added to obtain 4-(azidomethyl)-2-H-chomen-2-one (34a-i). The compounds (34a-i) were added to substituted 1-(prop-2-ynyloxy)benzene (31) in presence of C_4SO_4, Na-ascorbate, *t*-BuOH:H_2O(1:1) on reflux to obtain compound mono aryloxy linked coumarinyl triazoles (35a-u). Bis aryloxy linked coumarinyl triazoles (40a-f) were synthesized using substituted phenols and propargyl bromide in presence of acetone and K_2CO_3 (Scheme 4, Table 4). The obtain 1,4-bis-(prop-2-ynyloxy)benzene (38) was reacted with the azide (39) in presence of C_4SO_4, Na-ascorbate, *t*-BuOH:H_2O (1:1) on reflux to obtain compound (40a-f).

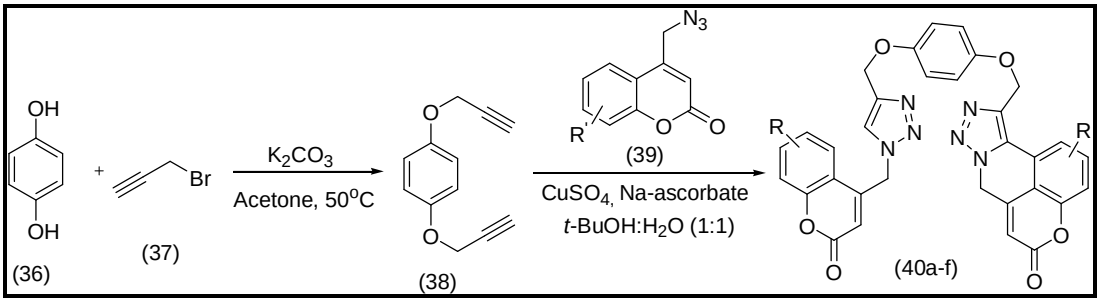


Scheme 3. Synthesis of a series of mono and bis –triazole–coumarin hybrids against *M.tb* H37Rv using CuAAC (Cu (I) catalysed azide–alkyne cycloaddition reaction under click chemistry conditions.

4. N. Nayak *et al.* (2015) synthesized a novel series of pyrazole – based 1,2,3- triazole derivatives using a multi-step synthetic route in which a substituted 1,2,3 – triazole ring was constructed in the final step through click chemistry protocol (Scheme 5, Table 5) [**28**]. Screening of molecules against MTB H37Rv strain revealed that the derivative with 4 – chlorophenyl substitution on the pyrazole ring and a cyclohexyl moiety on the 1,2,3 –triazole ring showed best activity with MIC of 3.13 µg mL^{-1} as compared to their 4 – methoxyphenyl and 4-bromophenyl substituent analogues. The anti – TB activity is enhanced with the electron withdrawing substituents on 1, 2, 3- triazole ring. Cytotoxicity study revealed that the active antitubercular compounds are nontoxic and have high selectivity index. The intermediate 5(4- aryl)-1-phenyl - 3 - ((prop-2-ynyloxy) methyl)-1H- pyazoles (45) was prepared by the claisen condensation of 4-substituted acetophenones (41) with diethyl acetate in the presence of sodium ethoxide in ethanol yielded sodium salt of αγ-diketoesters (42). The 5- aryl)-1-phenyl-1H- pyazole-3-carboxylic acids (43) was prepared by the conventional cyclization reaction between (42) and aryl hydrazines in the presence of acetic acid. Compound (42) was then reduced to corresponding alcohols (44) by using $LiAlH_4$. The propargylated scaffolds (45) was obtained by treating compound (44) with propargyl bromide in presence of sodium hydride (NaH) in tetrahydrofuran (THF).The targeted regioselective 1,4-substituted 1,2,3-triazole derivatives (46) was synthesized by treating the propargylated scaffolds (45) with alkyl bromides or benzyl bromides in presence of a catalytic amount of copper sulphate pentahydrate and sodium ascorbate in a 2:1 mixture of polyethylene glycol -400 (PEG-400) and water.

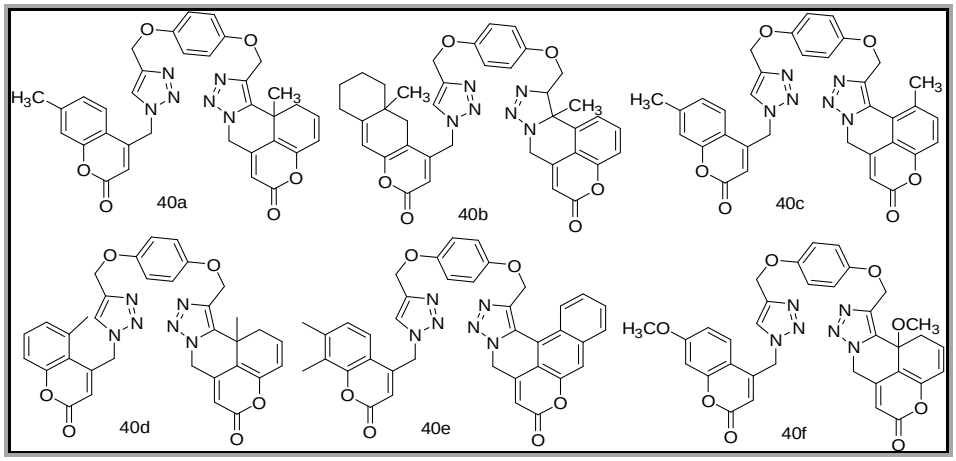
Table 3. Library of the mono and bis –triazole-coumarin hybrids synthesized.

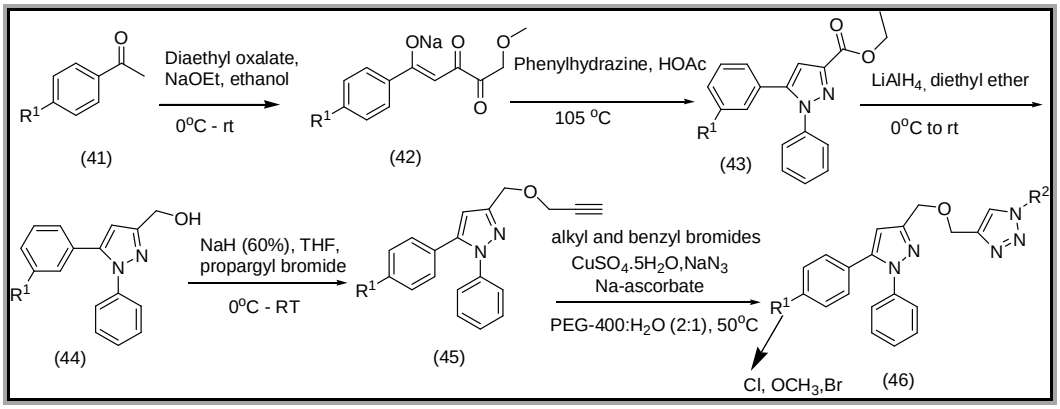




Scheme 4. Synthesis of bis aryloxy linked coumarinyl triazoles.

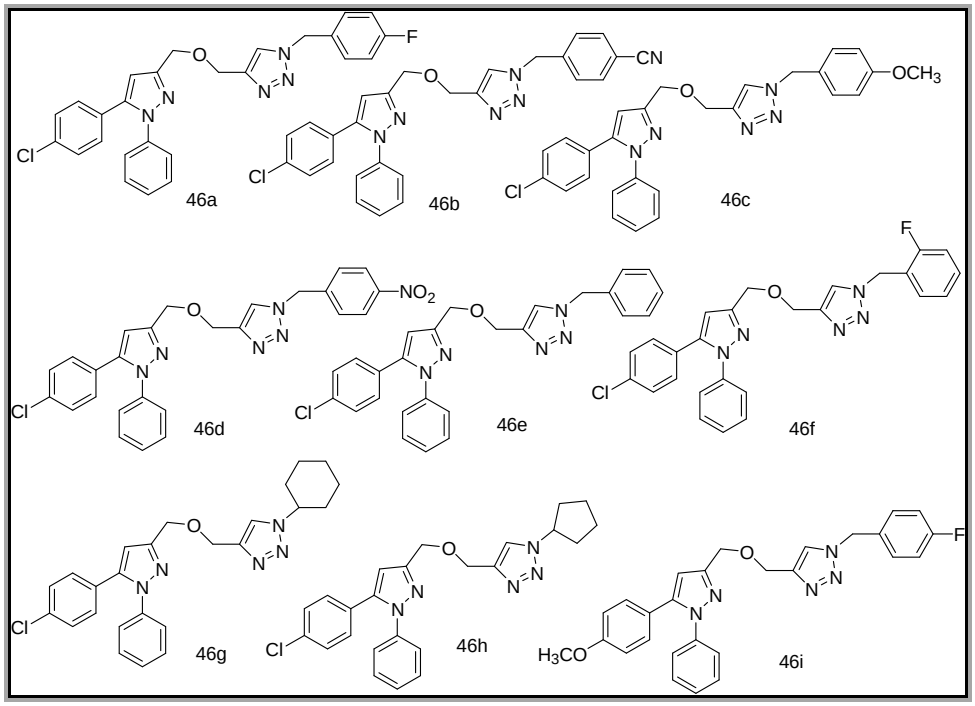
Table 4. Library of the bis aryloxy linked coumarinyl triazoles synthesized.





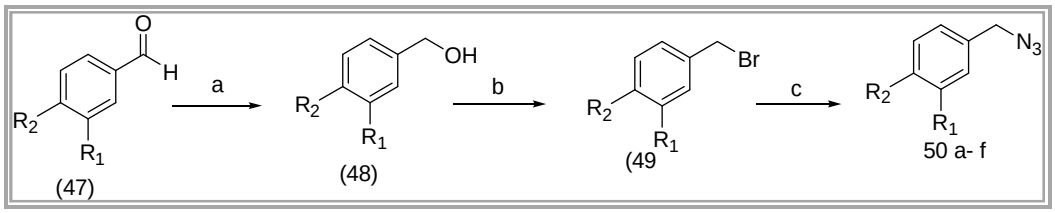
Scheme 5. Synthetic strategy used for the synthesis of pyrazole -1,2,3 – triazole hybrids.

Table 5. Library of the compounds synthesized



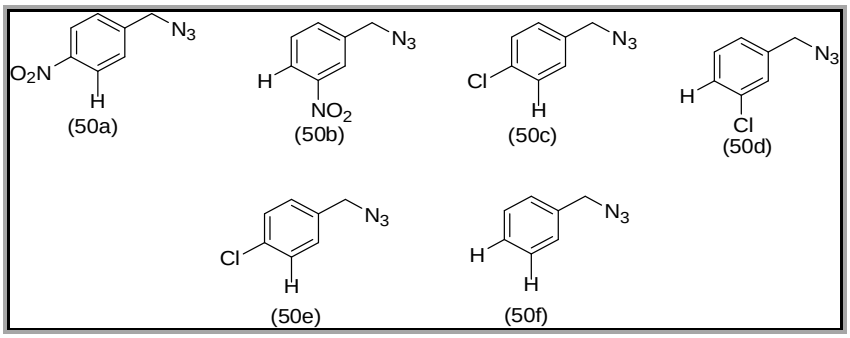
5. M. H. Shaikh *et al*. in 2016 synthesized novel triazole based coumarin derivatives through click chemistry (Scheme 6, 7) and were evaluated for their antitubercular activity in vitro against *M.tb* H37Ra [**29**] among the compounds only 56f exhibited interesting and most promising antitubercular activity with (MIC =1.80 µg mL^{-1}). The biological activity showed that some synthesized coumarin triazoles displayed better antitubercular, antioxidant antibacterial, anti-fungal efficacy when compared with reference drugs. Molecular docking revealed that the synthesized triazoles derivatives showed high affinity towards the active site of the $DprE_1$ enzyme and provides a strong plate - form for new structure based design efforts.

Benzalazide (50a-f; Table 6) was prepared by the fusion of benzyl azides viz $NaBH_4$ reduction, bromination and nucleophilic substitution reaction of sodium azide. The synthesis of 7-hydroxy-4-methyl comarin (53a) has been achieved via Pechman condensation between resorcinol and ethylacetonate in the presence of acid. The compound (53a and 53b) undergoes propargylation in presence of K_2CO_3 and N,N-dimethylformide (DMF) to yield 4-methyl-7(prop-2-yn-1-yloxy)-2H-chomen-2-one (54a) and 4-(prop-2-yn-1-yloxy)-2H-chomen-2-one (54b). Finally benzylazides (50a-f) and coumarin based alkynes (54a and 54b) were subjected to 1,3-dipolar cycloaddition reaction in the presence of $Cu(Ac)_2$ in *t*-BuOH:H_2O (3:1) at room temperature for 16-22 h to obtain the corresponding 1,4-disubstituted-1,2,3-triazole based coumarin derivatives (55a-f and 55g-k; Table 7).

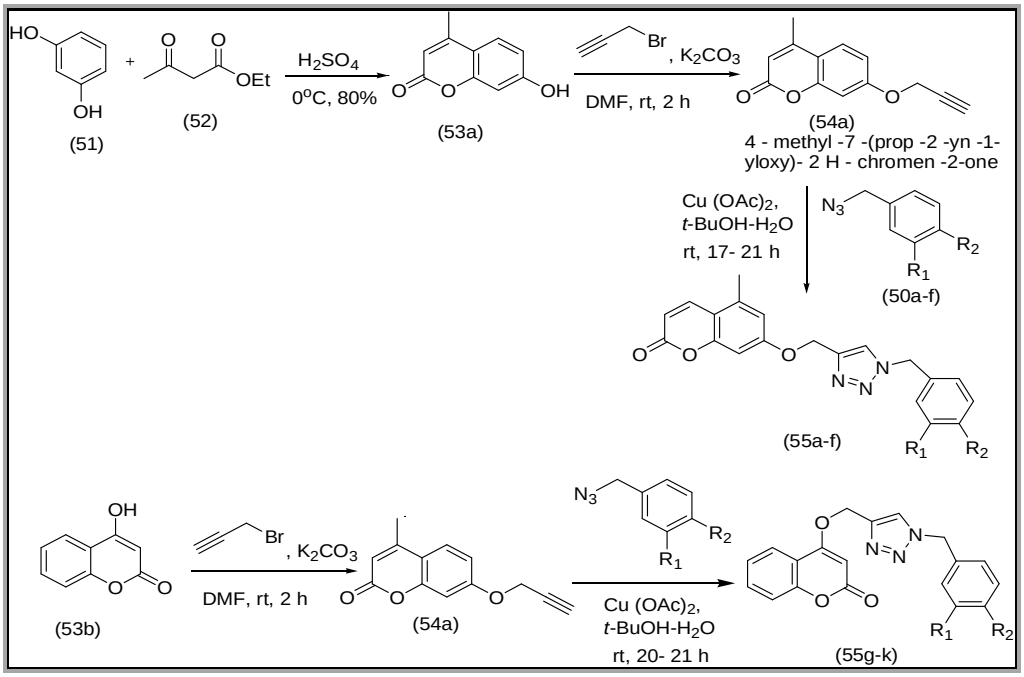


Scheme 6. Synthesis of benzyl azides, reagents and conditions: a) $NaBH_4$, methanol, 0°C to rt, 2h; b) PBr_3, CH_2Cl_2, 0°C, 0.5 h; c) NaN_3, acetone / water (3:1), rt , 24 h.

Table 6. Library of the triazoles synthesized for preparation of triazoles.

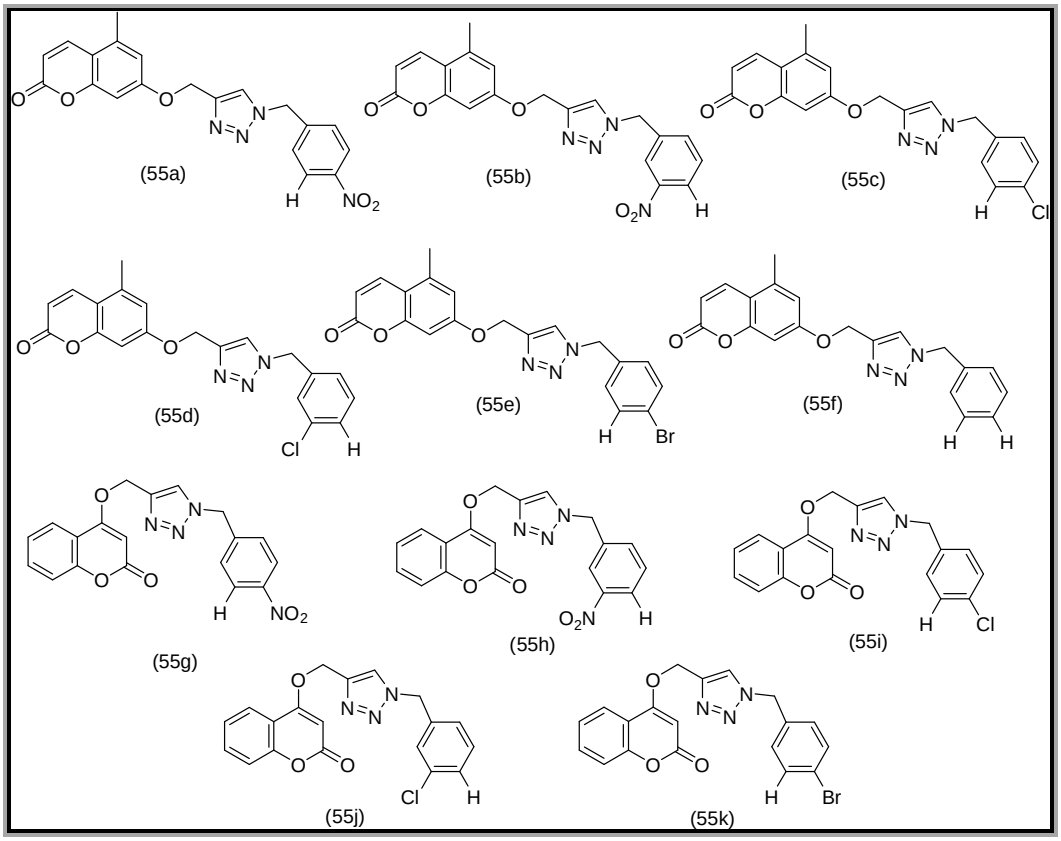


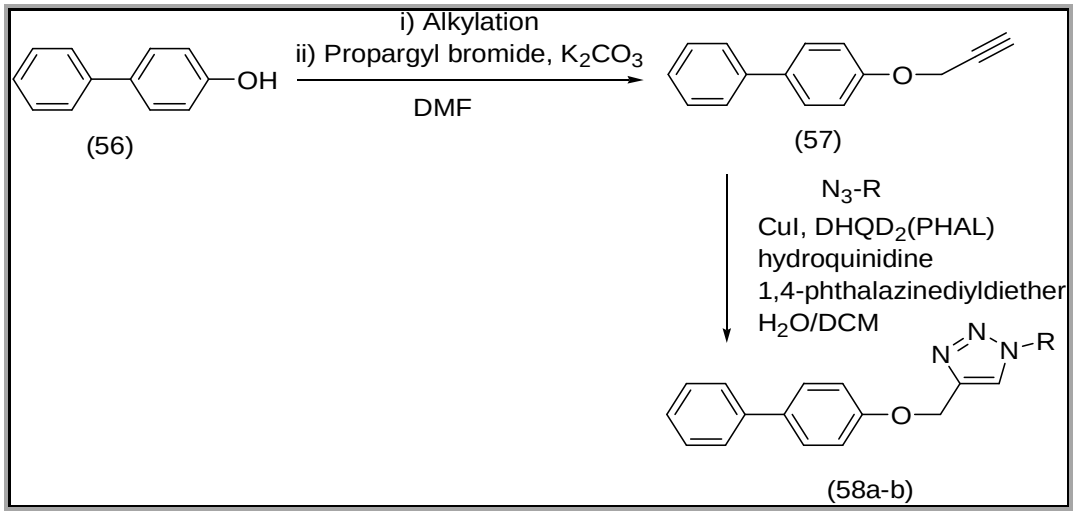
6. A. Aziz Ali *et al.*, in 2017 synthesized and investigated seventeen new 1,2,3-triazole derivatives [**30**] against *M.tb* H37Ra (ATCC 25177 strain) (Scheme 8). Among them only 58a and 58b substituted with the fluoro group at second position of phenyl ring of the triazole derivatives demonstrated higher anti-mycobacterial activity with MIC value of 0.7 µg mL^{-1} as compared with the first line anti-tubercular drug, ethambutol (MIC 2.00 µg mL^{-1}). However, compound 58b with the ester group also showed significant activity with an MIC value of 1.56 µg mL^{-1} (Table 8). The starting alkyne (57) by using commercially available 4-phenylphenol (56) by simple alkylation with propargylbromide in presence of potassium carbonate as a base in N,N-dimethylformamide (DMF). The 1,2,3-triazole derivatives was accomplished through Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition reaction between (57) and appropriate azide in presence of Cu(I) as catalyst and DHQD (PHAL as ligand in H_2O/DCM for 0.5-2 h afforded compound (58a-b) 1,4-disubstituted-1,2,3-triazoles.



Scheme 7. Synthesis of 4 – Methyl – 7 – (prop – 2 –yn – 1 – yloxy)- 2 H – chromen – 2 –one and 1,4 – disubstituted -1,2,3 – triazole – based coumarin derivatives (55 a – k).

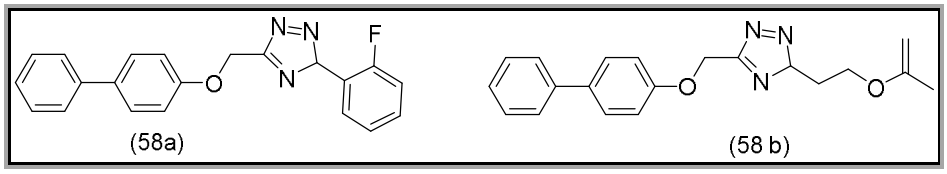
Table 7. Library of the coumarin derivatives synthesized for investigation as anti-Tb agents.





Scheme 8. Synthesis of 1,4-disubstituted -1,2,3-triazoles.

Table 8. Structure of the 1,4-disubstituted -1,2,3-triazoles synthesized.



7. S. Zhang *et al.* (2017) while considering azoles as the most important class of nitrogen containing heterocycles possessing anti –bacterial, anti – malarial, anti – fungal, anti – HIV, anti – inflammatory and anti –TB properties investigating the compounds for anti-TB activity (Table 9). PA- 824 (59) displayed excellent *in vitro* and *in vivo* activity against both replicating and non – replicating cultures of *M.tb* including MDR –TB [**31, 32**] and showed great potency in phase II clinical trial for treatment of TB infection patients. Meanwhile a recently approved drug delamanid (OPC67683) (60) is recommended against MDR –TB [**33**]. Therefore hybridization of the pharmacophore of two compounds with 1,2,3 –triazole prone to give promising agents against MDR-TB. Two series (6S) – 2 nitroimidazo [2,1- b] [1,3] oxazines (61) and (62) bearing 1,2, 3 – triazole side chains having great liphophilicity was evaluated against replicating *M.tb* by MABA and LORA assay methods. SAR revealed that hybrid (62) was more potent than (61) and lipophilicity of the hybrid was positively correlated with the activity, having MIC_{90}: 0.03 µM and 1.6 µM (LORA) which was more active than the reference PA-824 (MIC: 0.5 -2.6 µM). Among two hybrids (61d) was selected for *in vivo* evaluation in a mouse model of acute TB infection but the efficiency was inferior to PA – 824.

Pyrimidine (nucleosides) containing1,2,3–triazoles (63; Figure 3): Pyrimidine salvaging pathway is vital for all bacterial cells and enzymes involved in this pathway are different from those present in humans, thus could act as attractive targets and have important role in the mycobacterial latent state. Based upon above features of pyrimidine Alexandrova *et al.* [**34**] synthesized six pyrimidine nucleoside derivatives bearing alkyltriazolidomethyl substituents at C-5 position of the nucleobase were evaluated as potential anti –TB agents. Although hybrids showed low toxicity in VERO A549 and jurkat cell lines and effectively inhibited the growth of *MTB* H37Rv (MIC_{99}: 10-40 µg mL^{-1}) and clinical MDR-TB MS-115 which was resistant to five first-line anti-TB drugs and suggesting these derivatives may have a novel mechanism and could be used to treat both drug-susceptible and MDR-TB infected patients. The SAR revealed that hybrids with -OH at C-4 position of the nucleobase were more potent than corresponding $-NH_2$ analogues against both strains, indicating further modification on this position may lead to more active candidates.

Table 9. Azoles investigated for anti-TB activity

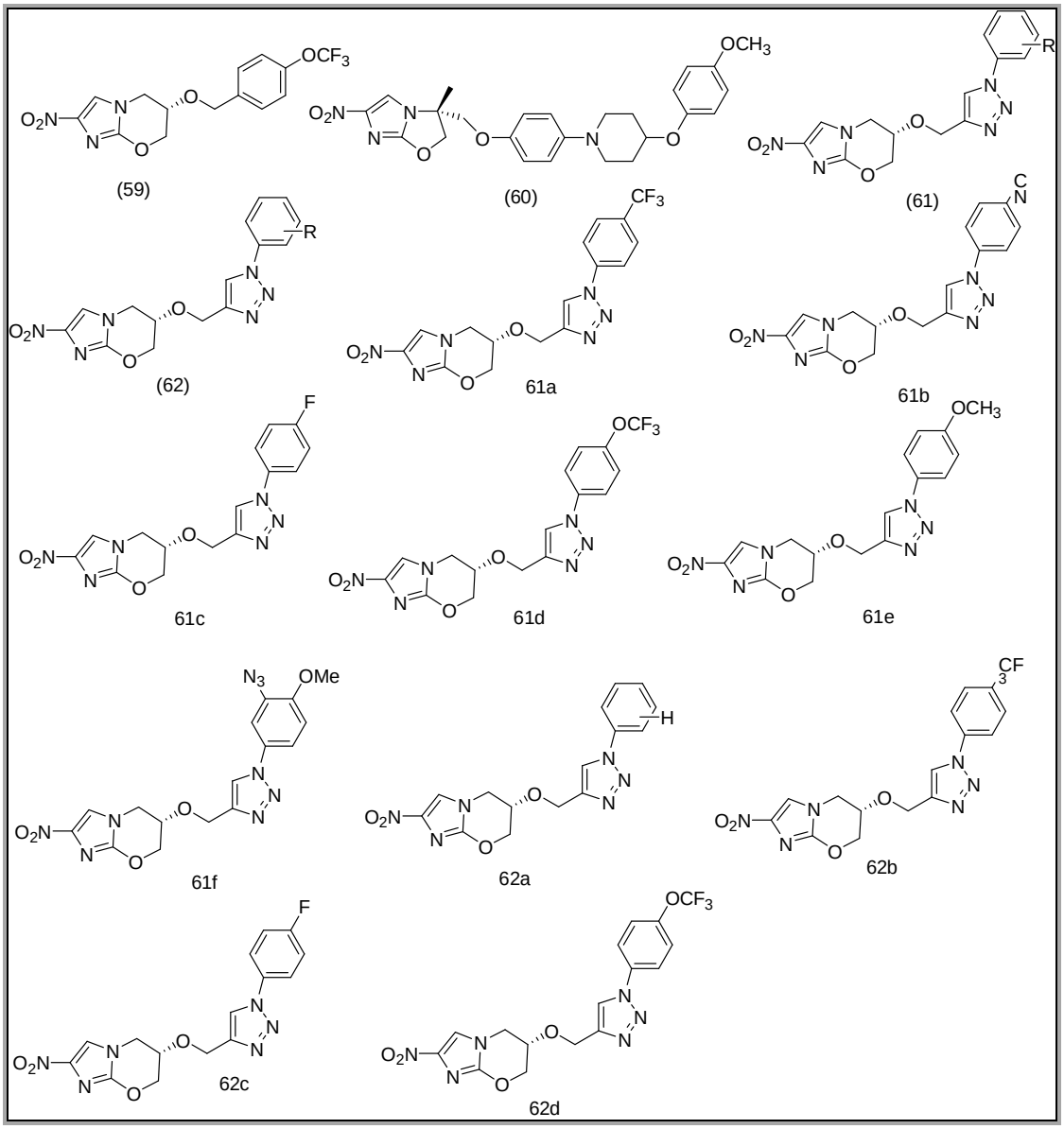
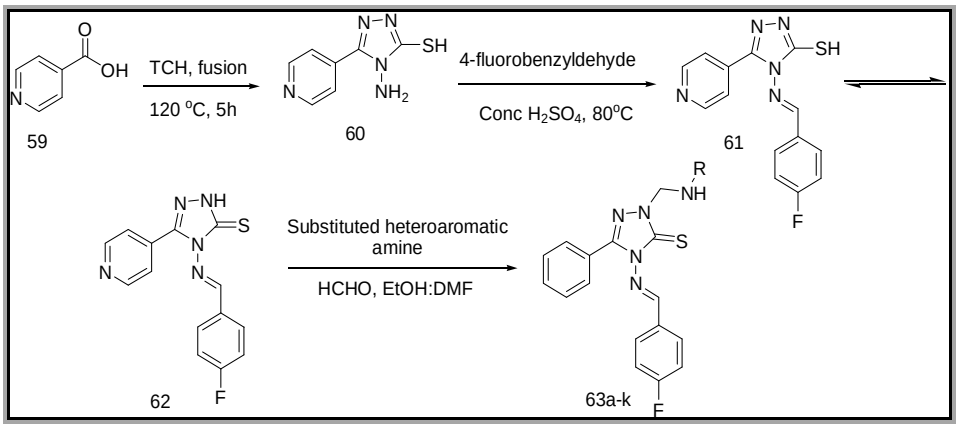


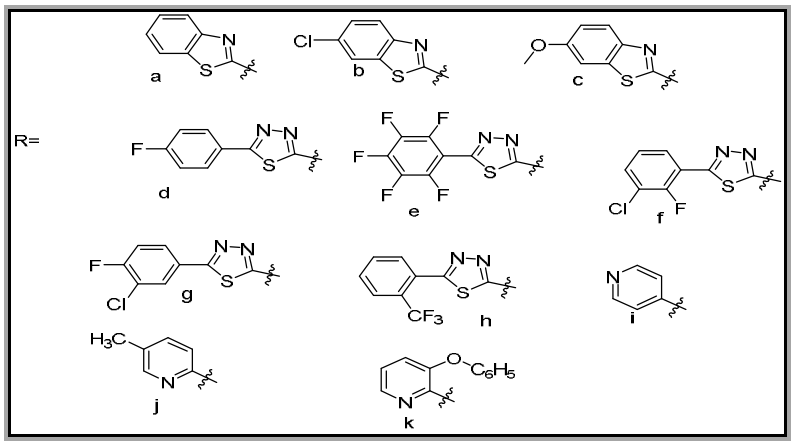
Figure 3. Strutctures of pyrimidine 1,2,3 -triazole hybrids

8. V. M. Patel *et al.* in 2018 [35] synthesized novel analogous series of triazoles by the introduction of N-Mannich reaction using conventional as well as microwave synthetic route (Scheme 9**,** Table 10). Screening showed that the synthesized compounds were effective against *in vitro* antimicrobial, antitubercular and antiprotozoal activity. The compound (64b) displayed excellent potency against *M.Tb* (MIC: 6.25 µM) in the primary screening. The computational studies revealed that the mannich derivatives (64b) showed high affinity towards the active site of enzyme which provides a strong platform for new structure based design.

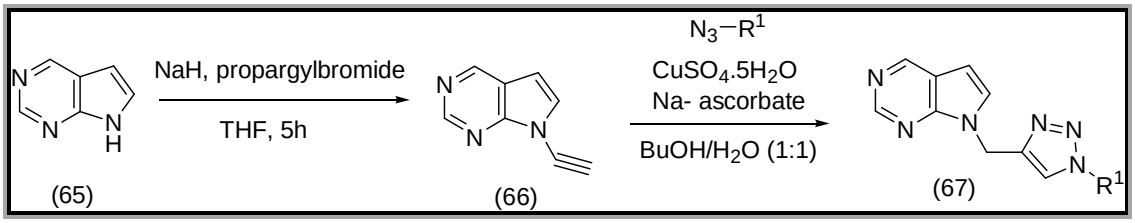


Scheme 9. Synthesis of novel triazoles by the introduction of N-Mannich reaction using conventional as well as microwave synthetic route.

Table 10. Library of the compounds 63a-63k synthesized

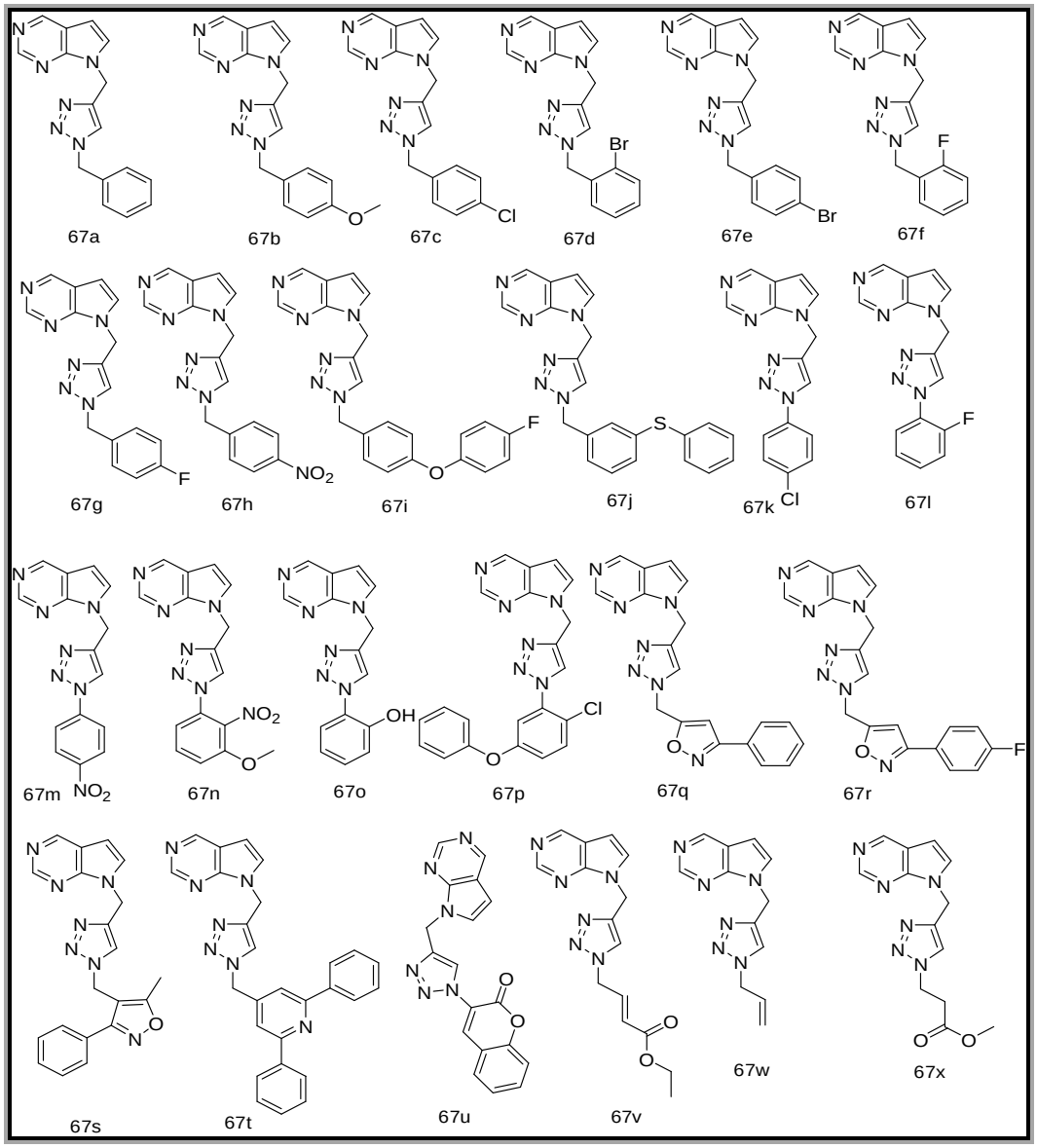


10. In view of the complexity of the disease and limited available treatment options a need to identify and develop new drugs for the treatment of TB was felt. It was found that some naturally occurring pyrrolo [2,3-d] pyrimidine antibiotics have significant activity against *M.tb* [**36-40**]. To search for novel scaffold K.S. Raju, *et al*. in 2019 synthesized a series of 1H–pyrrolo [2,3-d]pyrimidine-1,2,3-triazole derivatives by intramolecular 1,3 dipolar cycloaddition reaction between easily affordable azides and alkynes in presence of $CuSO_4.5H_2O$ and sodium ascorbate (Scheme 10, Table 11). In this scheme treatment of 7H-prrolo[2,3,d]pyrimidine(deazapurine) (65) with NaH and propargylbromide led to the formation of N-propargylated compound (66) and then compound (66) was subjected to copper-catalyzed azide-alkyne cycloaddition conditions to yield 7-((1-phenyl,aryl,heteroaryl-1H-1,2,3-triazol-4-yl)methyl)-7h-pyrrolo[2,3-d]pyrimidines. Screening revealed that the compound 1H–pyrrolo [2,3-d] pyrimidine -1,2,3-triazole showed prominent antituberculosis activity against *M.tb* with an MIC value of 0.78 µg mL^{-1}. The range of MIC values was found to be highly significant in



Scheme 10. Synthesis of 7-((1-phenyl, aryl, heteroaryl-1H-1,2,3-triazol-4-yl)methyl)-7H-pyrrolo [2,3-d] pyrimidines.

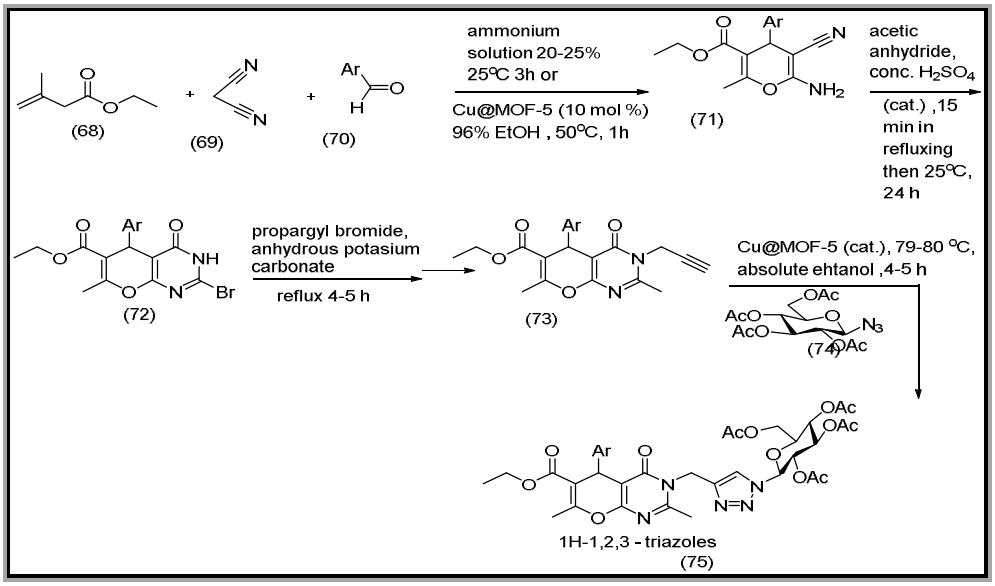
Table 11. Series of 1H–pyrrolo [2,3-d]pyrimidine-1,2,3-triazole derivatives synthesized by intramolecular 1,3 dipolar cycloaddition reaction between easily affordable azides and alkynes



comparison to standard antitubercular drugs, ciprofloxacin and ethambutol. Few more compounds showed moderate activity with MIC value of 3.2 µg mL^{-1}. The docking results reveal that there is a similar binding interaction of co –crystallized ligand at the active site of the *M.tb*, DprE1. Structure activity relationship also showed that triazole ring increases the antibacterial activity if substituted with heteroaryl compounds containing highly electronegative atoms depicting their efficacy as potential antitubercular drugs.

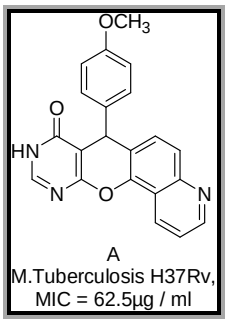
11. Due to the broad range of pharmacological activities, synthesis of pyranopyrimidine derivatives has gained lot of interest in medicinal chemistry. The pyrano [2,3-d] pyrimidine tethered 1,2 ,3-triazole moiety was expected to exhibit the higher pharmaceutical activity. Kamdar, *et al.*, [41] showed that compound (A) fused with quinoline ring had anti-tubercular activity against *M.tb* with MIC value of 62.5 µg mL^{-1} (Table 12). N. D. Thanh *et al.* in 2019 synthesized novel series of 4H-pyrano [2,3-d] pyrimidine bearing $_{D}$-glucose moiety tethered with 1,2,3-triazole derivatives through an easy and convenient synthetic protocol [**42**]. About 24 analogues were accomplished in four step sequence using click chemistry but among them only six 1H -1,2,3 triazoles 75g,75t,75u,75v,75x and

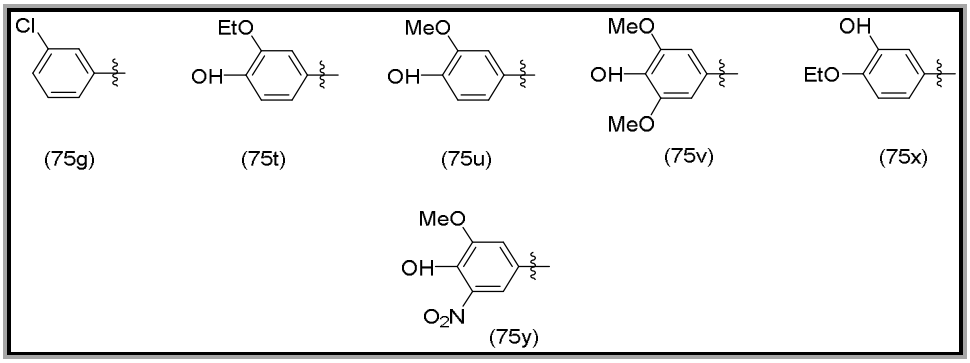
75y displayed inhibitory activity against *M.tb* protein, tyrosine phosphatase with IC_{50} ranging from 1.56-9.52µM. Cross- docking studies revealed that compound 75y is the most potent and effective against *M.tb* protein, tyrosine phosphatase with IC_{50} of 1.56 µM. The ethyl 4H-pyran-3-carboxylates (71) was prepared by three component reactions between ethyl acetoacetate (68), malononitrile (69) and substituted benzyldehyde (70) in presence of catalyst (ammonium hydroxide or Cu@MoF). The compound (71) was reacted with acetic anhydride to obtain the compound (72) 4H-pyrano[2,3,d] pyrimidnes (Scheme 11; Table 12). The compound (72) was subjected to propargylation in dry acetone in presence of K_2CO_3 to form the N-propargylated derivative (73). Click chemistry of compound (73) derivative of compound (72) with 2,3,4,6-tetra-o-acetyl-beta-D-gluopyranosylazide (74) afforded the corresponding 1H-1,2,3-triazoles.



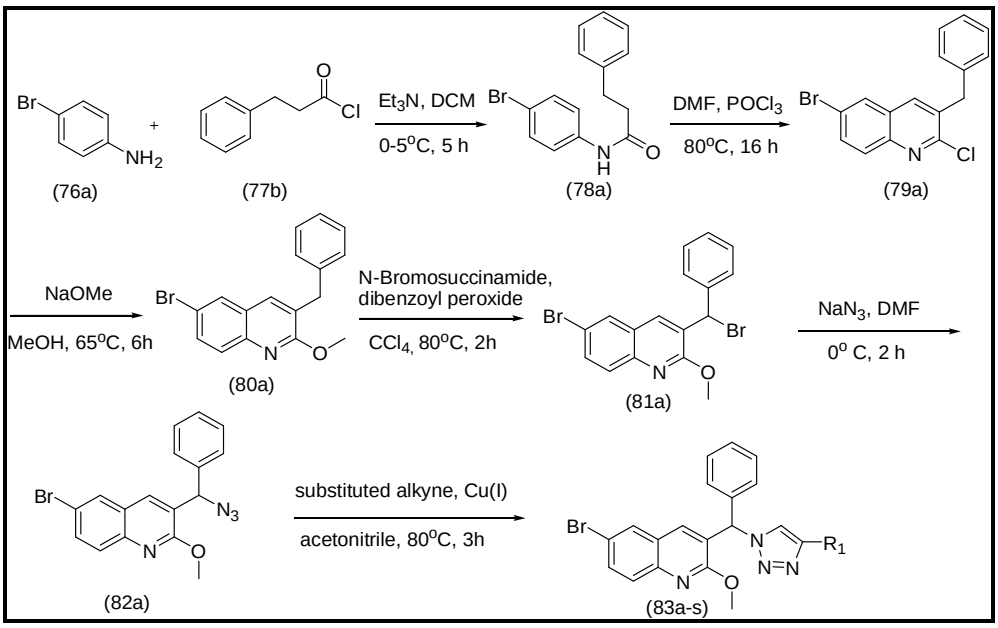
Scheme 11. Synthesis of 1H – 1,2,3 – triazoles.

Table 12. Compound (A) fused with quinoline ring investigated for anti-tubercular activity against *M.tb.*



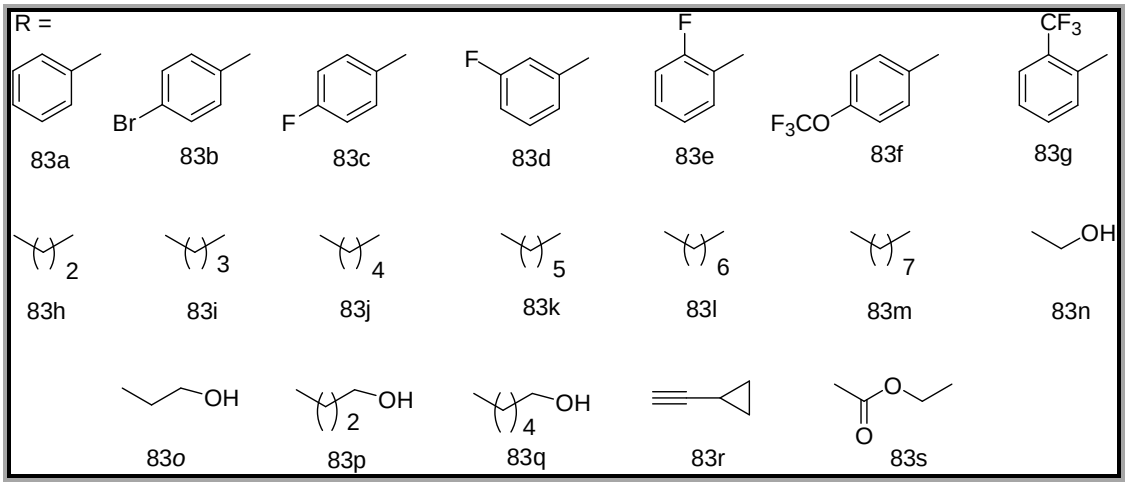


12. J. Ramprasad *et al* (2019) [**43**] designed new quinoline – triazole hybrid analogs by using structural modification of bedaquiline antitubercular drug against *mycobacterium bovis*. Interestingly two compounds showed (83d-83m) significant inhibition with mic of 31.5 and 34.8 µM. SAR study revealed that the presence of 3- fluoro phenyl and n- octyl groups on 1,2,3-triazole ring emerged showed most potent activity. The target quinoline-triazole analogues (83a-s) was synthesized as shown in (Scheme 12, Table 13) N-(4- bromophenyl)-3- phenyl prompanamide (78a) was synthesized by the reaction of 4-bromo-aniline(76a) and triethylamine in DCM at 0^oC-RT for 5hrs.Compound (78a) was subjected to Vilsmier-Haack formylation reaction followed by cyclisation of to give 3-benzyl-6- bromo -2-chloroquinoline (79a). Compound (79a) was further treated with NaOMe to yield compound (80a) which on bromination with NBS, CCl_4 and catalytic amount ofdibenzoyl peroxide a converted to 6-bromo -3-(bromo(phenyl)methyl)-2-methoxyquinoline (81a) and was converted into substituted azide (82a) in presence of sodium azide, DMF. The target compounds quinoline-triazole derivatives (83a-s) was synthesized by the reaction between substituted alkynes and substituted azides (82a) in acetonitrile under reflux conditions.

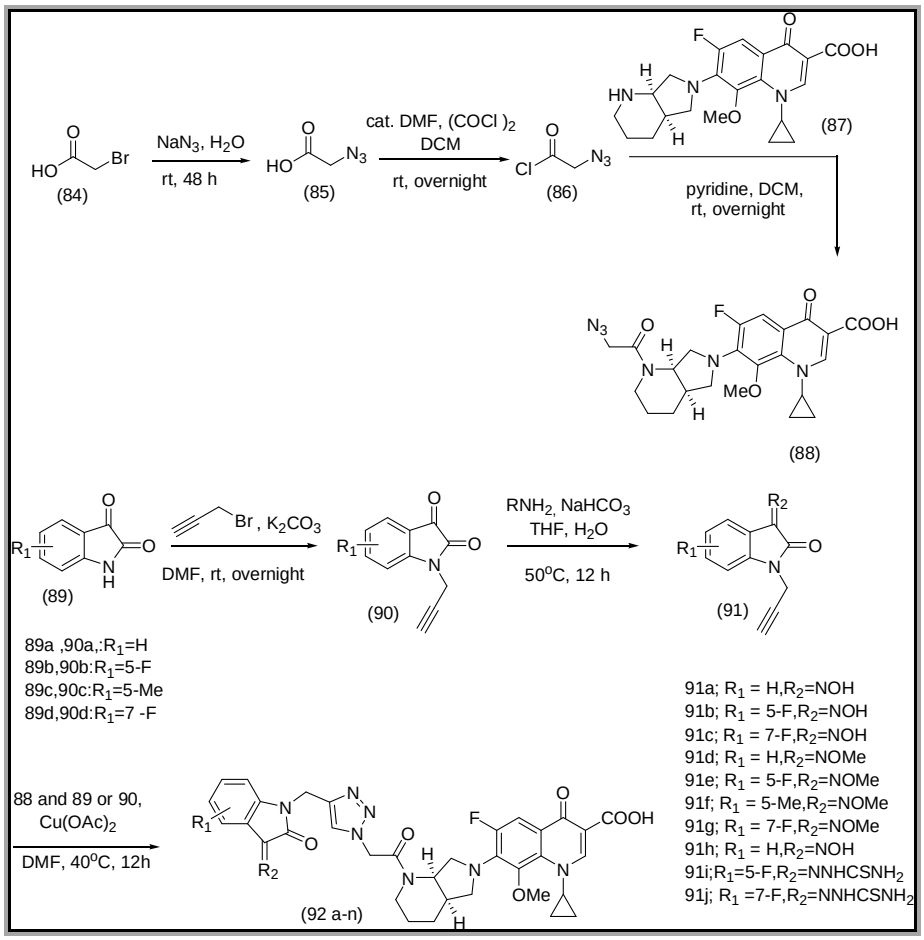


Scheme 12. Synthesis of quinoline triazole analogs.

Table 13. Library of the quinoline triazole analogs synthesized for evaluation against *mycobacterium bovis.*

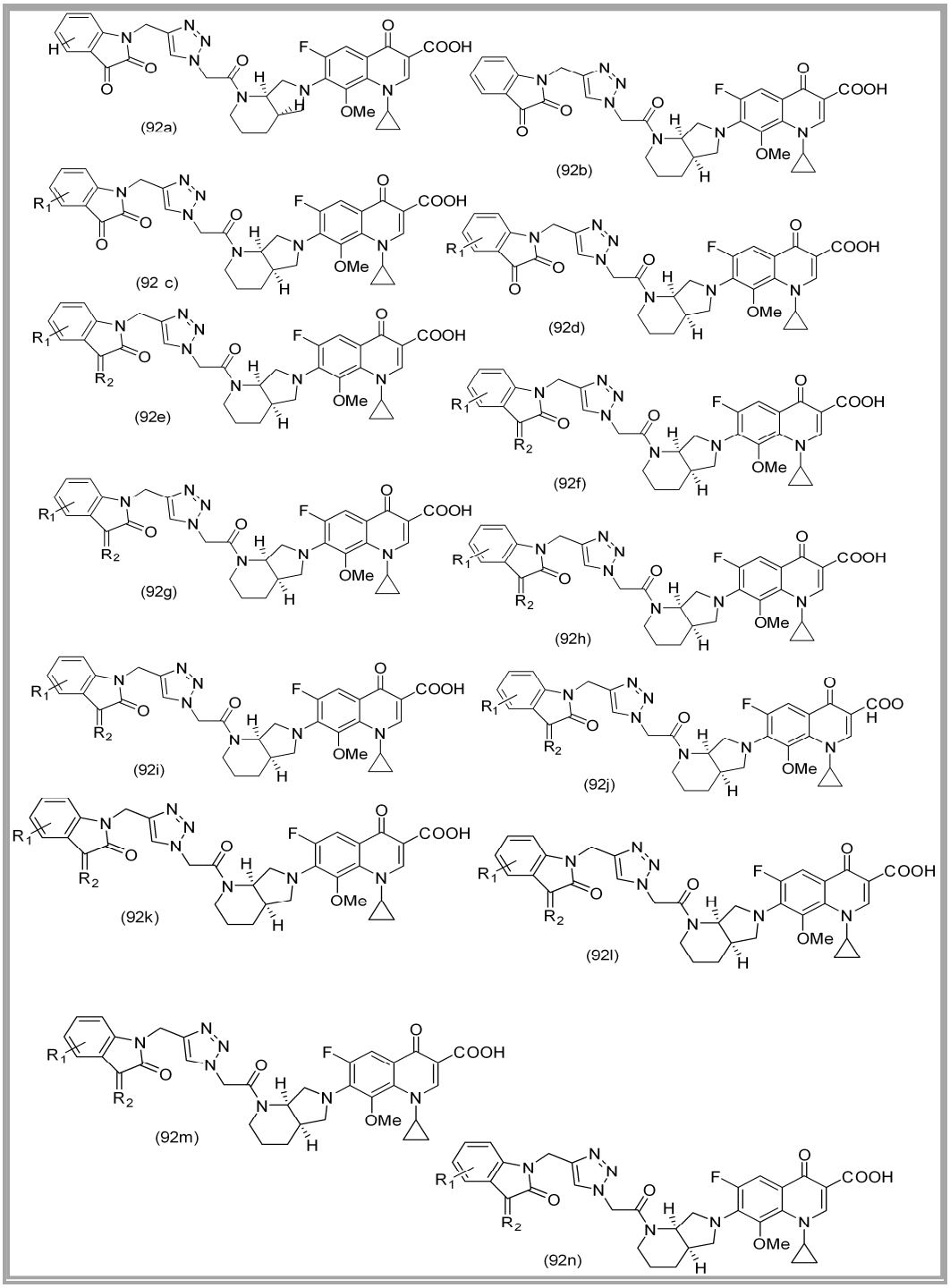


13. F. Gao *et al.* (2019) synthesized 14 moxifloxacin –acetyl -1,2,3 -1H- triazole – methylene –isatin for their in vitro anti mycobacterial activity against both drug susceptible *M.tb* H37Rv, rifampicin resistant and multidrug resistant mycobacterium tuberculosis strains [**44**]. Among them only (92h) and (92I) showed excellent activity with MIC :0.12 – 0.5 µg mL^{-1}. Cytotoxicity towards VERO cells as well as inhibitory activity against *M.tb* DNA gyrase of the hybrids could act as a platform for further investigation. Structure activity relationship and structure – cytotoxicity relationship revealed that the substituents on the C_3 _C_5 and C_7 position of isatin enhances the activity and may help for identification of new chemical entities as potent anti TB agents. The synthetic pathway for the desired moxifloxicin-acetyl-1,2,3-1H-triazole-methylene-isatin hybrids (92a-n) was prepared by using 2-Bromoacetic acid (84) to yield 2-azidoacedic acid (85) in presence of sodium azide in H_2O. Compound (85) was treated with oxalyl chloride in presence of catalytic amount of DMF in DCM to yield 2-azidoacetyl chloride (86) acylation reaction between moxifloxicin and compound (86) with pyridine as base in DCM provided 2-azidoacetyl chloride moxifloxicin (88). Isatin (89) undergoes propargylation in presence of K_2CO_3 in DMF gives N-propargylisatin intermediate (90) and isatin intermediate (91) was prepared by the condensation of (90) compound with the requested amine hydrochlorides in presence of $NaHCO_3$ in a mixture of THF and H_2O yielded isatin intermediate (91). Finally cyclization of (88) with (89) or (90) with copper acetate as a catalyst generated the desired compound (92; Scheme 13, Table 14).



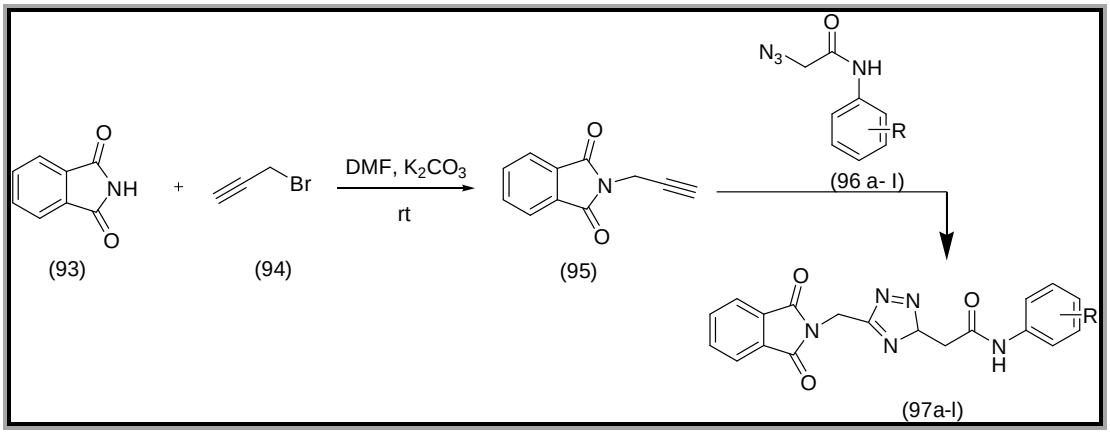
Scheme 13. Synthesis of moxifloxacin –acetyl -1,2,3 -1H- triazole – methylene –isatin for their in vitro anti mycobacterial activity against both drug susceptible *Mtb* H37Rv, rifampicin resistant and multidrug resistant mycobacterium tuberculosis strains.

Table 14. Library of the compounds synthesized.



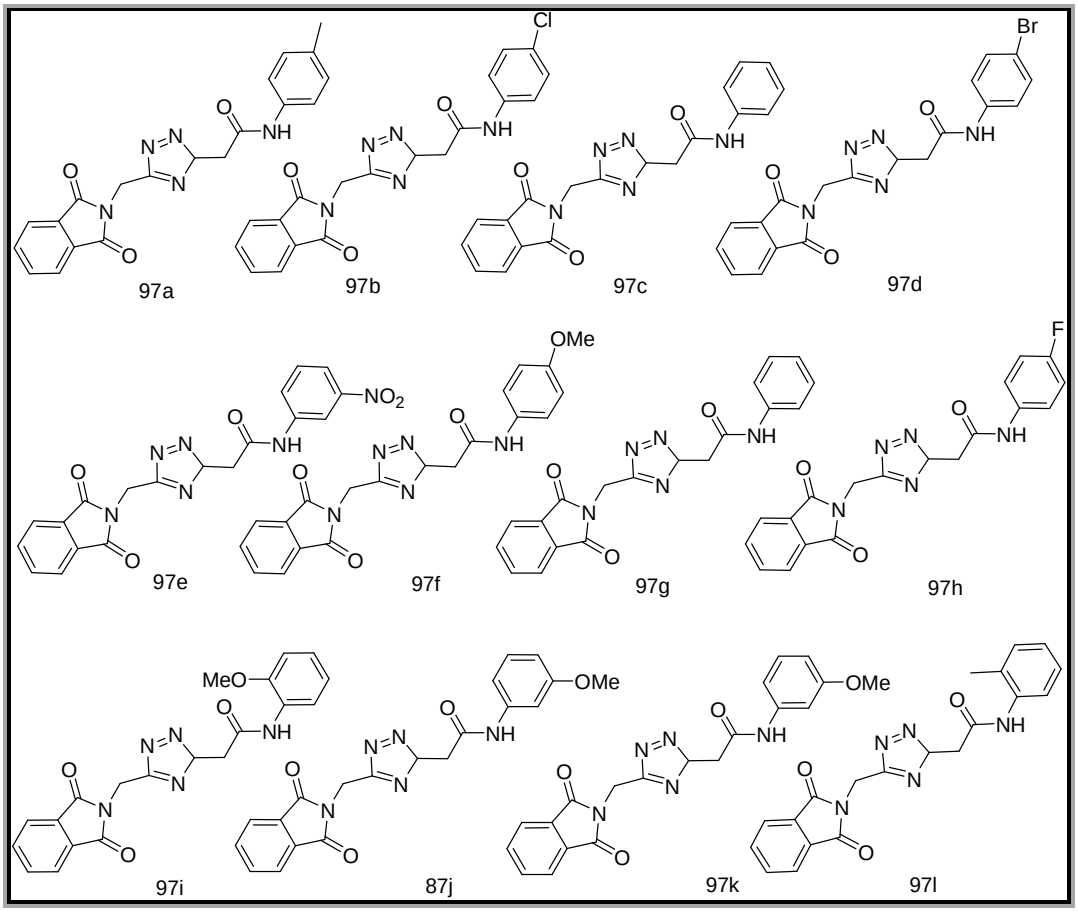
14.P. S. Phatak *et al.* (2019) synthesized a series of newly substituted dioxoisoindolininylmethyl – triazolyl–N–phenylacetamide derivatives (97 a-l) through click chemistry by 1,3–dipolar cyclo addition of the alkyne and substituted phenyl acetamide [**45**]. The synthesized compounds were evaluated for their antituberculosis activity against *M.tb* H37Rv. Among the synthesized 1, 2, 3-triazoles the compounds (97d, 97e, 97g, 97I) have showed very effective antitubercular activity against *M.tb* with MIC:12.5µg mL^{-1}. Molecular docking study indicates that all the molecules are binding to the enoyl reductase of the *M.tb.* The reaction of phthalimide (93) and propargyl bromide (94) in presence of K_2CO_3 in DMF to yield 2-(prop-2-ynyl)isoindoline -1,3-dione (95; Scheme 14,

Table 15). Further the reaction of compound (95) and freshly prepared substituted N-phenyl acetamides (96a-i) in presence of $CuSO_4.5H_2O$ and sodium ascorbate in PEG-400 yielded substituted 2-(4-((1,3-dioxoisoindolin -2 yl)methyl-1H-1,2,3-triazole-1-yl)-N-phenylacetamide (97a-i).



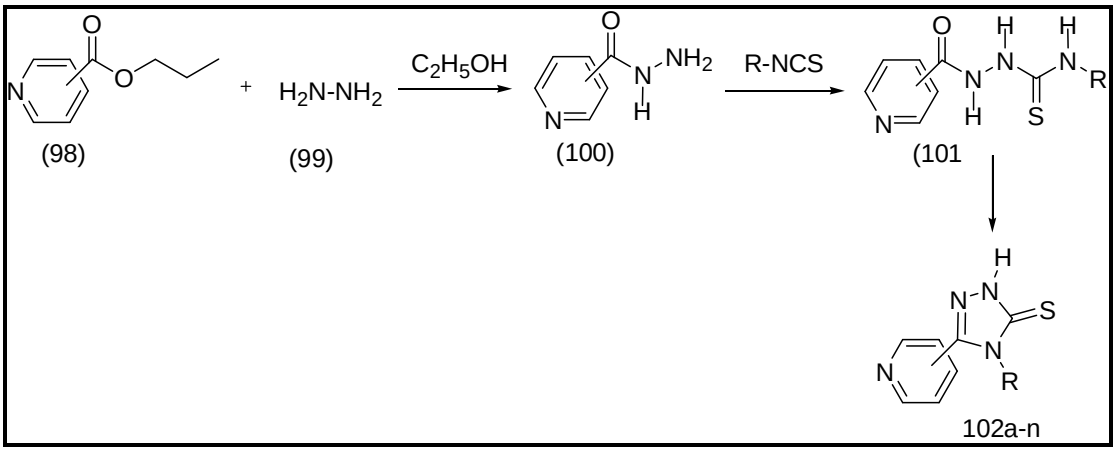
Scheme 14. Synthesis of substituted 2-(4-((1,3-dioxoisoindolin -2 yl)methyl -1H-1,2,3 –triazole -1-yl)- N –phenylacetamide.

Table 15. Library of substituted 2-(4-((1,3-dioxoisoindolin -2 yl)methyl -1H-1,2,3 –triazole -1-yl)- N –phenylacetamide synthesized



15. Z. Karczmarzyk *et al*. in 2020 synthesized a series of 1,2,4-triazole derivatives for investigating as antituberculosis substances/agents [**46**]. The synthesized 1,2,4 triazole derivatives were obtained through cyclization reaction of appropriate thiosemicarbazide derivatives in alkaline medium (Scheme

15, Table 16). The molecular docking study showed that the synthesized 1,2,4-triazoles bind to the active site of the P450CYP21 enzyme as was observed in case of compound 102 which showed noticeable activity against *M.tb H37Ra*.



Scheme 15. Synthesis of 1,2,3-triazole derivatives.

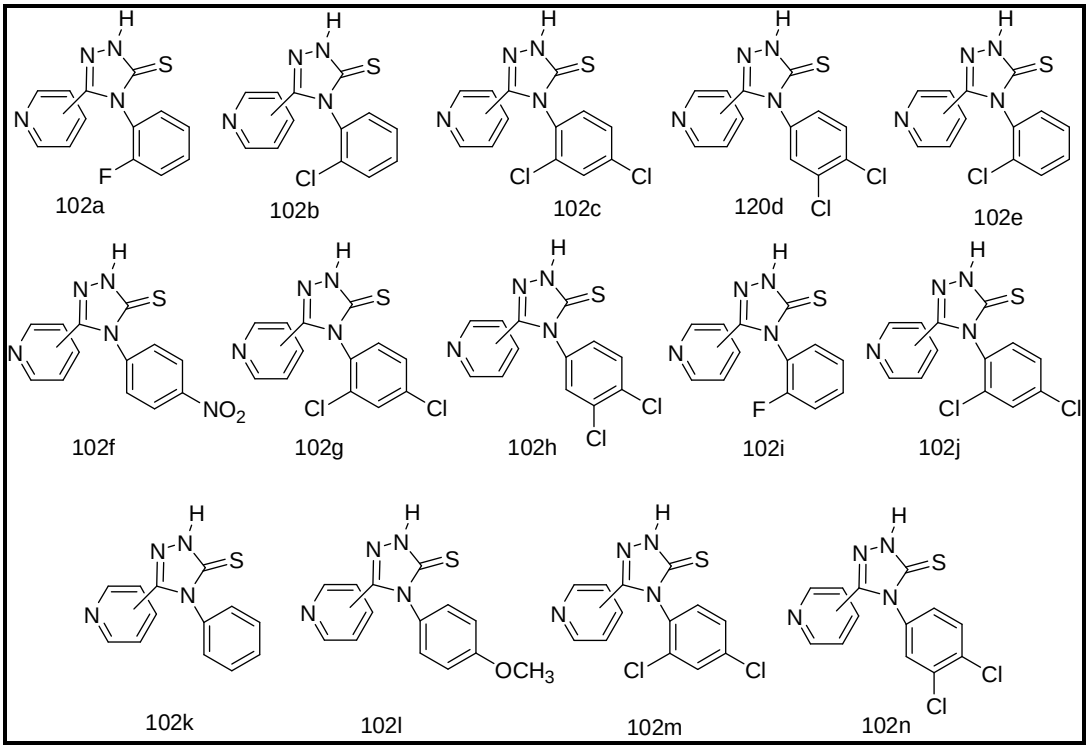
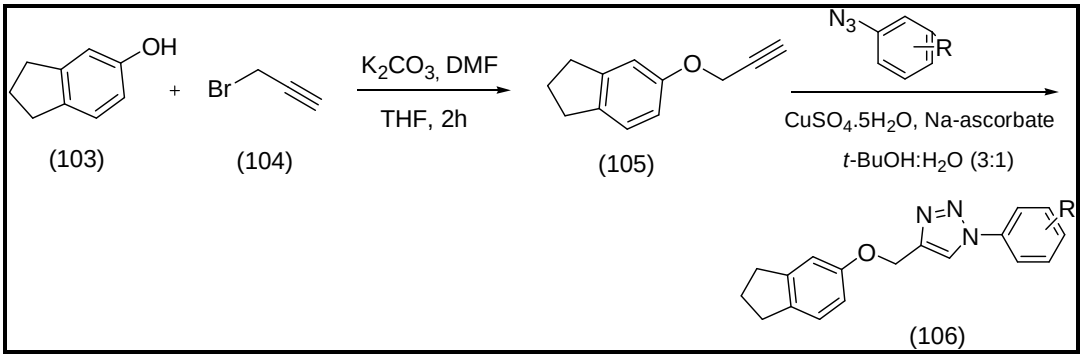


Table 16. Library of 1,2,3-triazole derivatives synthesized.

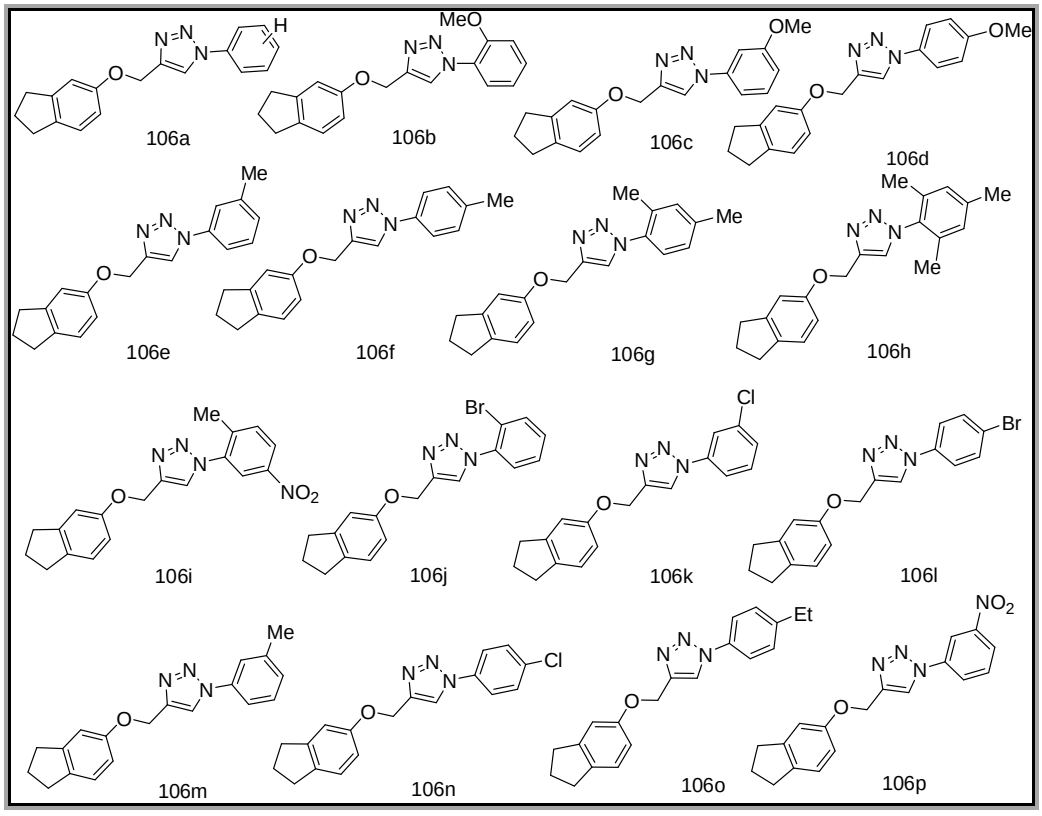
16. P.S. Phatak *et al*. in 2020 synthesized a series of 32 indanole-1,2,3-triazole derivatives [**47**] through click chemistry (Scheme 16). The reaction sequence followed for the synthesis of compound 2-(4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives (108a-p) was synthesized by propargylation of 5-indanol (103) in presence of potassium carbonate in DMF at room temperature yielding 5-(prop-2-ynyloxy)-2,3-dihydro-1H-indene (105). To compound (105) freshly prepared substituted phenyl azides was used in presence of copper acetate and sodium ascorbate to obtain 4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1-phenyl-1H-1,2,3-triazole derivatives (106 a-p) .Similarly the click reaction of compound (105) and freshly prepared substituted 2-azido-N-

phenylacetamide (107) afforded 2-(4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives (108a-p). The compounds were evaluated against *M.tb H37Ra*and cytotoxic effects against HEK 297 (Human Embryonic Kidney) cells. Among them only compound (108g) has been identified as an excellent antitubercular agent and have equivalent activity to the standard drug, ciprofloxine having MIC value 1.56 µg mL^{-1}.



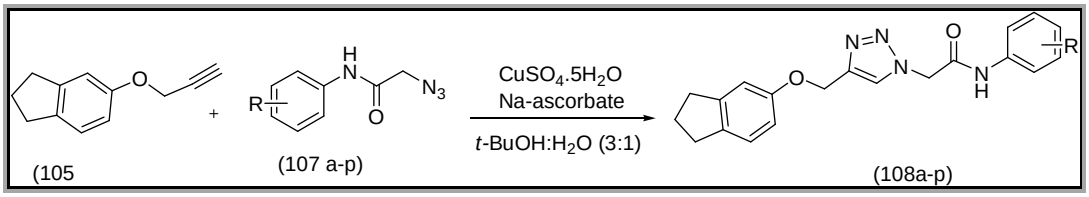
Scheme 16. Synthesis of 5-(prop-2-ynyloxy)-2,3-dihydro-1H-indene, 4-((2,3-dihydro-1H-inden-5-yloxy)methyl) -1-phenyl-1H-1,2,3-triazole derivatives (106a-p), 2-(4-((2,3-dihydro-1H-inden-5-yloxy)methyl) -1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives (108a-p).

Table 17. Library of 5-(prop-2-ynyloxy)-2,3-dihydro-1H-indene, 4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1-phenyl-1H-1,2,3-triazole derivatives (106a-p), 2-(4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives synthesized.



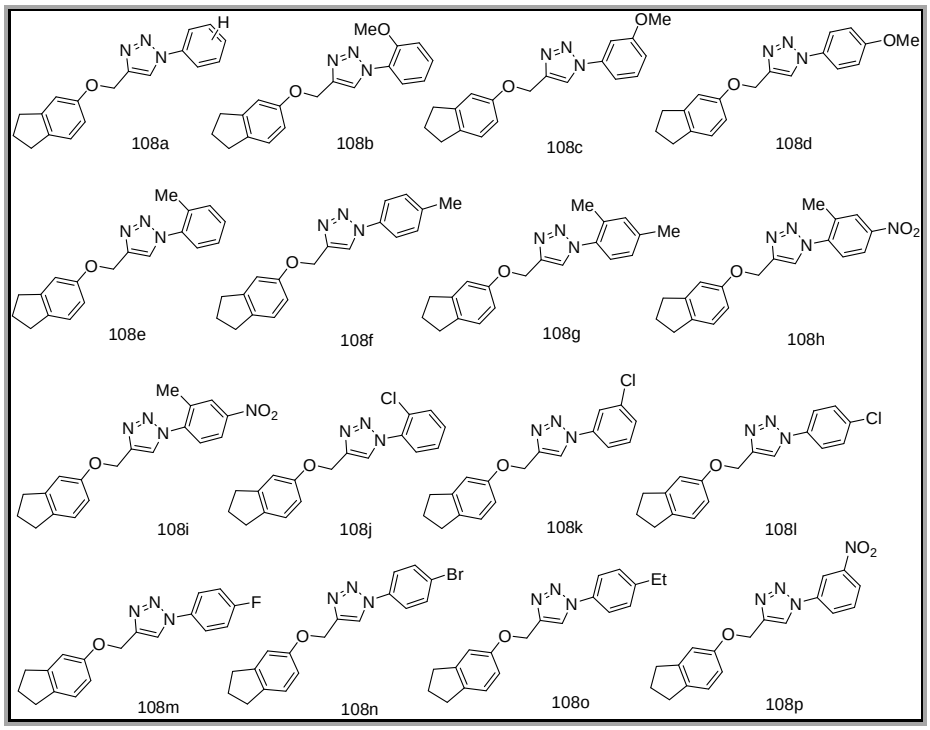
17. Isoniazid used as most effective first line anti –TB drug combined with rifampisin, ethambutol and prazamide to treat infection for more than 60 years but unfortunetley it has several adverse effects particularly psycharitric,allergic reactions, etc. To overcome the drug resistence and adverse effects, P. S. Patil *et al.* in 2020 synthesized a series of novel isoniazid embedded 1,4–disubstituted 1,2 ,3

triazole analogues which were evaluated for their *in vitro* antitubercular and antimicrobial activities [**48**]. As 1,2 ,3 triazole derivatives inhibit the growth of bacteria by blocking cell wall biosynthesis inhibition which is most alternative strategy for developing effective anti -TB agents. Therefore both isoniazid and triazole entities conjugate covently into one single molecule and may offer a new lead with potential antitubercular activity [**49-60**]. Among the screened compound six showed potent antitubercular activities against *Mtb H27Rv* strain with MIC (0.78 µg mL^{-1}, whereas other three compounds antitubercular activities with MIC (1.56- 3.125µg mL^{-1}. Molecular docking against mycobacteial InhA enzyme has been performed to gain plausible mechanism of action which could pave the way for our endeavor to identify potent antitubercular condition and further optimization of these molecules may lead to potent antitubercular agent. For the synthesis of alkyne (111), firstly 2-hydroxy-5-nitrobenzaldehyde (109) undergoes propargylation in presence of potassium carbonate in DMF at room temperature to obtain aldehyde (110; Scheme 17, Table 18). The condensation of compound (110) and isonicotinohydrazide was carried out in diisopropyl ethylammonium acetate (DIPEAC) to obtain alkyne (111). The click reaction of alkyne (111) and substituted azidobenzenes (112a-p) in presence of $CuSO_4.5H_2O$ and sodium ascorbate was performed to furnish corresponding triazole derivatives (113a-p).

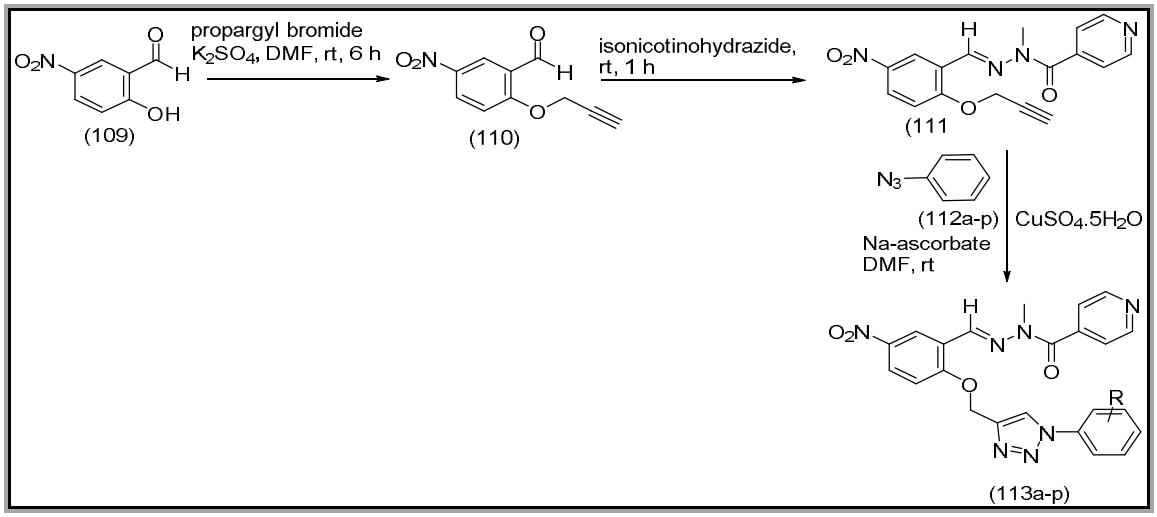


Scheme 17. Synthesis of 5-(prop-2-ynyloxy)-2,3-dihydro-1H-indene, 4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1-phenyl-1H-1,2,3-triazole derivatives (106a-p), 2-(4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives (108a-p).

Table 18. Series of 5-(prop-2-ynyloxy)-2,3-dihydro-1H-indene, 4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1-phenyl-1H-1,2,3-triazole derivatives (106a-p), 2-(4-((2,3-dihydro-1H-inden-5-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives (108a-p) synthesized.



18. Isoniazid used as most effective first line anti–TB drug combined with rifampisin, ethambutol and prazamide to treat infection for more than 60 years but unfortunately it has several adverse effects particularly psycharitric, allergic reactions, etc. To overcome the drug resistance and adverse effects P.S. Patil *et al.*, in 2020 synthesized a series of novel isoniazid embedded 1, 4 – disubstituted 1,2 ,3 triazole analogues which were evaluated for their *in vitro* antitubercular and antimicrobial activities [**48**]. As 1,2 ,3 triazole derivatives inhibit the growth of bacteria by blocking cell wall biosynthesis inhibition which is most alternative strategy for developing effective anti - TB agents. Therefore both isoniazid and triazole entities conjugate covalently into one single molecule and may offer a new lead with potential antitubercular activity [**49-60**]. Among the screened compound six showed potent antitubercular activities against *M.tb H27Rv* strain with MIC (0.78 µg mL^{-1}, whereas other three compounds antitubercular activities with MIC (1.56- 3.125µg mL^{-1}. Molecular docking against mycobacteial InhA enzyme has been performed to gain plausible mechanism of action which could pave the way for our endeavour to identify potent antitubercular condition and further optimization of these molecules may lead to potent antitubercular agent. For the synthesis of alkyne (111), firstly 2-hydroxy-5-nitrobenzaldehyde (109) undergoes propargylation in presence of potassium carbonate in DMF at room temperature to obtain aldehyde (110; Scheme 18, Table 19). The condensation of compound (110) and isonicotinohydrazide was carried out in diisopropylethylammonium acetate (DIPEAC) to obtain alkyne (111). The click reaction of alkyne (111) and substituted azidobenzenes (112a-p) in presence of $CuSO_4.5H_2O$ and sodium ascorbate was performed to furnish corresponding triazole derivatives (113a-p)

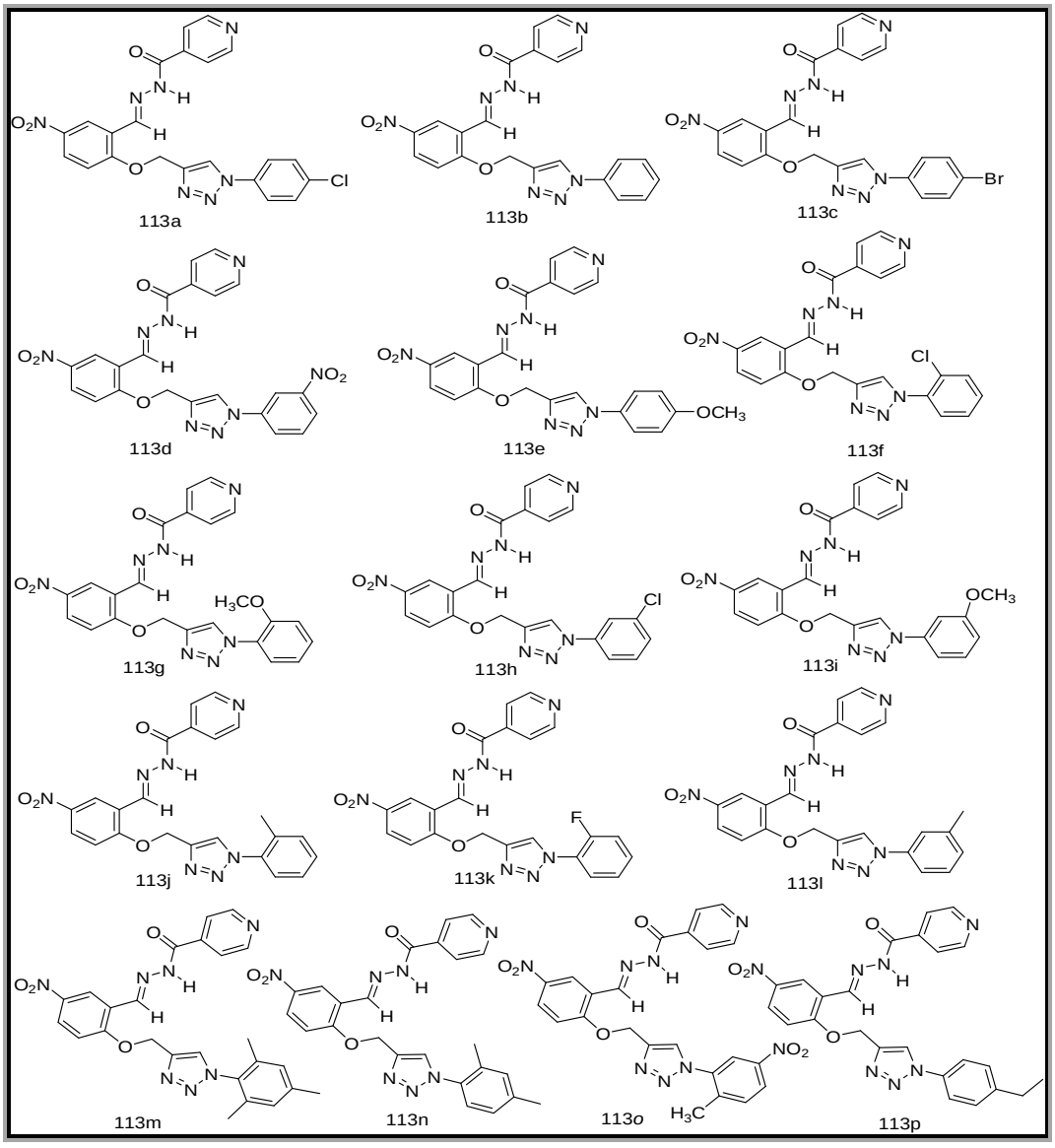


Scheme 18. Synthesis of triazole derivatives for evaluation against *mycobacterium tuberculosis.*

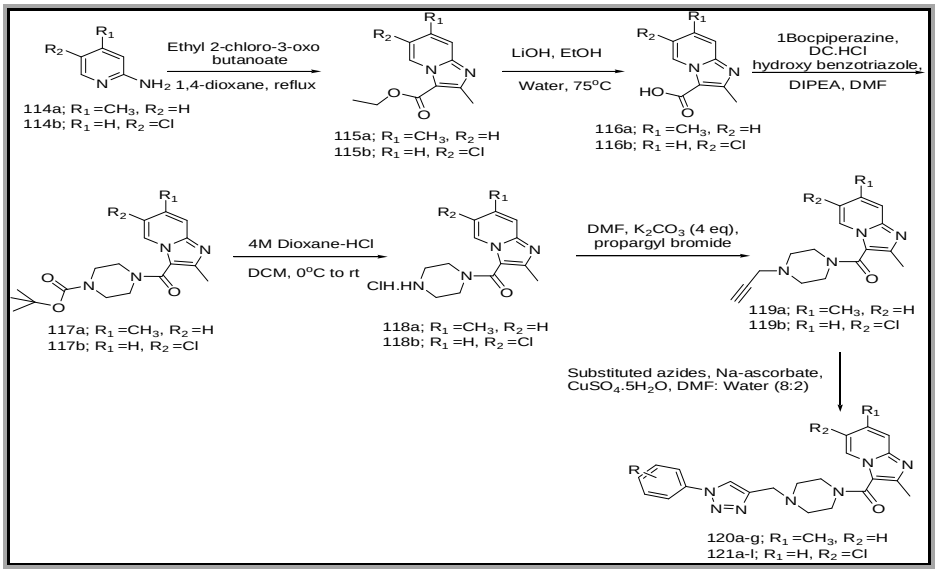
19. Imiadazoles offer great impact in drug development as imiadazo is a core structure in several drugs which include Zolpidem which is an approved drug for insomnia and also exhibits antitubercular activity with MIC of 10 µM against *M.tb* H37Rv strain [**61**]. Moraski *et al.* Identified the modified structure of Zolpiden derivatives which showed most potent anti TB activity with MIC value of 0.004 µM [**62**]. A. Nandikolla *et al.* in 2021 synthesized twenty eight novel 1,2,3 – triazole analogues of imidazo–[1,2,a] – pyridine -3-carboxamide [**63**] for investigation against *M.tb H37Rv* strains in replicating and non – replicating forms of the bacteria. Among the screened analogues, compound (123b) (((2 ,7 - dimethylimidazo - [1,2 - a] - pyridine - 3yl) (4 - (2 -(4 -nonyl-1H - 1,2, 3 -triazol - 1- yl) - ethyl - piperazin - 1 - yl) methanone was found to be most active compound with *in vitro* MIC value of 13.74 and 24.63 µg mL^{-1} in MABA and LORA methods. 4 -Methyl pyridine-2-amine (114a) and 5-chloropyridin-2-amine (114b) on treatment with ethyl 2-chloro-3-oxobutanoate in DME under reflux for 24 h (i) yielded ethyl-2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (115a) and ethyl-6-chloro-2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (115b) respectively. Further reaction of ethyl ester with LiOH in ethanol and water at 70 °C for 12 h afforded substituted

carboxylic acids (116a–b). The acids 116a and 116b on coupling with 1-Boc-piperazine using EDC·HCl, HOBt, and DIPEA in DMF yielded 117a and 117b, respectively. The key intermediate 118a and 118b were prepared by BOC deprotection of 117a and 117b using 4 M dioxane–HCl at 0°C to rt for 4 h. First, they performed the S_N2 reaction, involving the reaction

Table 19. Series of triazole derivatives synthesized for evaluation against *mycobacterium tuberculosis.*

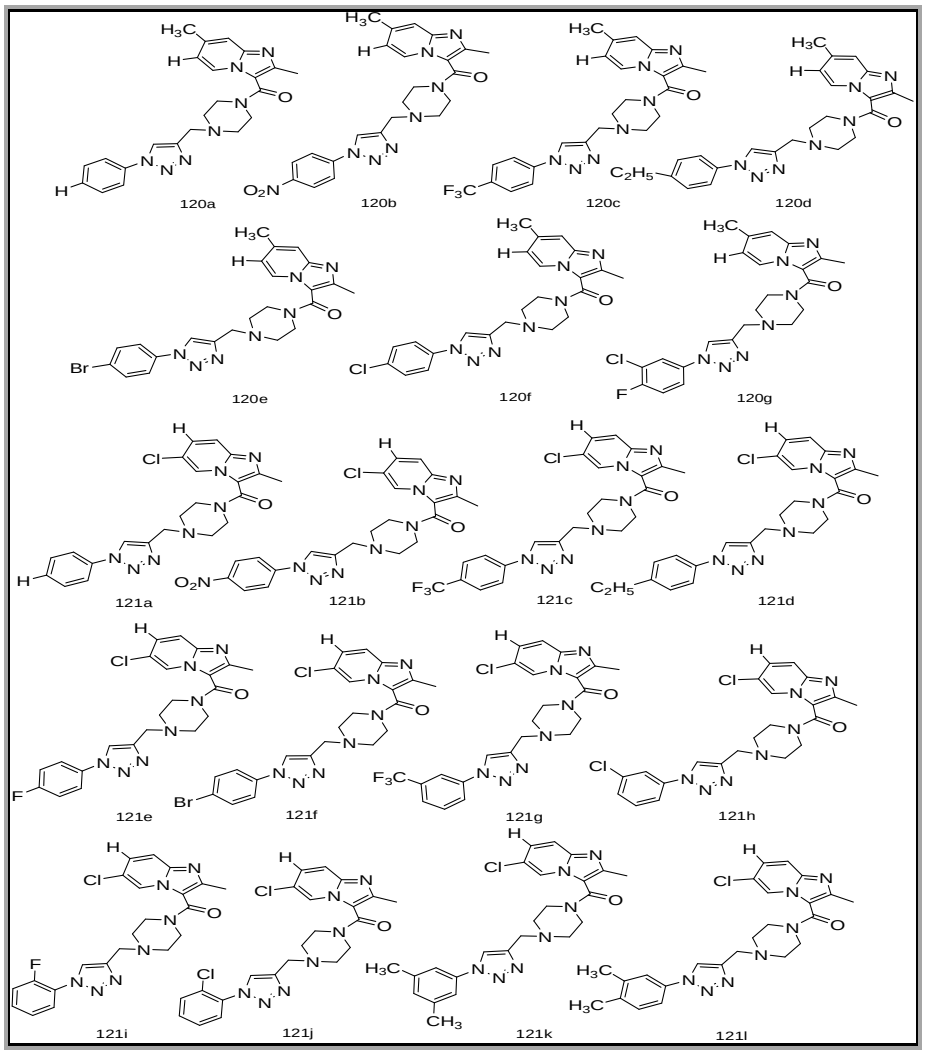


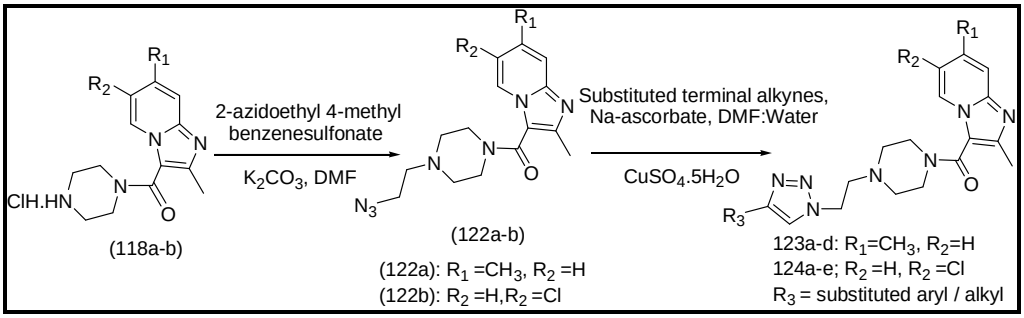
of 118a and 118b with propargyl bromide, potassium carbonate, and a catalytic amount of potassium iodide in acetone and water at 50°C for 24 h yielding 119a and 119b. Further, 119a and 119b on the treatment with various substituted azides using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in DMF and water for 12 h afforded the title compounds 120a–j and 121a–p. compounds 10a–d and 11a–e in two steps (Scheme 19, Table 20). Compounds 118a and 118b on treatment with 2-azidoethyl 4-methylbenzene sulfonate using K_2CO_3 and a catalytic amount of KI in acetone and water at 50 °C for 24 h (vii) yielded 122a and 122b. Finally, 122a and 122b on treatment with various substituted acetylenes using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in DMF and water at rt to 55 °C for 12 h afforded the compounds 123a–d and 124a–e. (2 ,7 - dimethylimidazo - [1,2 - a] - pyridine-3 yl) (4 - (2 -(4 - nonyl- 1 H-1 ,2, 3 -triazol - 1- yl) - ethyl - piperazin - 1 - yl) methanone



Scheme 19. Preparation of (2 ,7 – dimethylimidazo – [1,2 – a] – pyridine – 3 yl) (4 – ((1 – (substituted phenyl) – 1 H – 1 ,2, 3 –triazol – 4 – yl) – methyl – piperazin – 1 – yl) methanone .

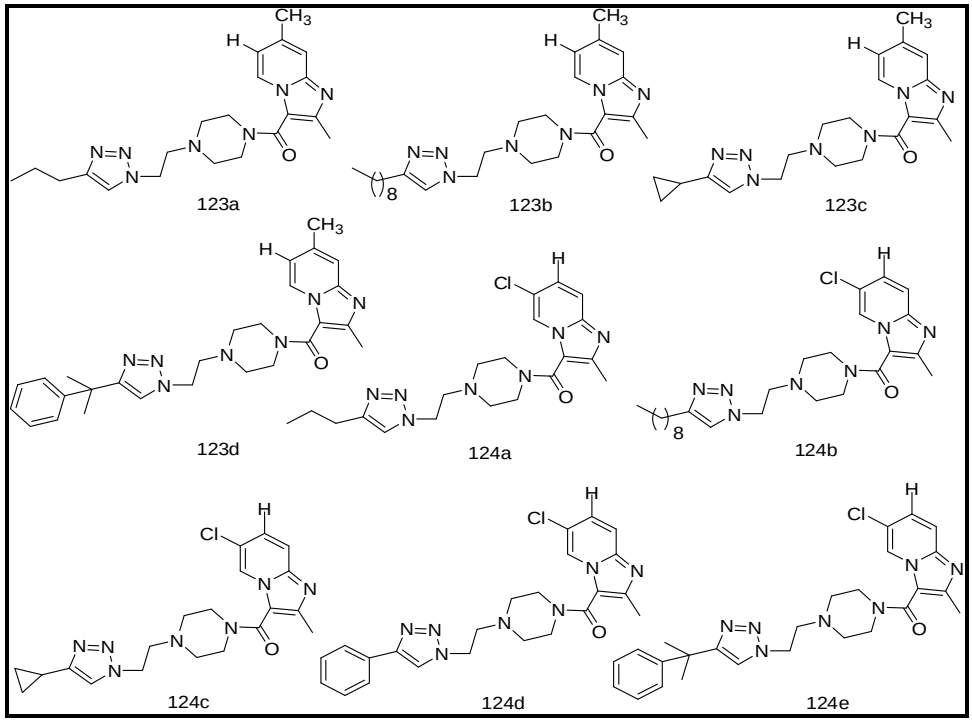
Table 20. Library of (2 ,7 – dimethylimidazo – [1,2 – a] – pyridine – 3 yl) (4 – ((1 – (substituted phenyl) – 1 H – 1 ,2, 3 –triazol – 4 – yl) – methyl – piperazin – 1 – yl) methanone synthesized.





Scheme 20. Synthesis of (((2 ,7 - dimethylimidazo - [1,2 - a] - pyridine - 3 yl) (4 - (2 -(4 - nonyl - 1 H - 1 ,2, 3 -triazol - 1- yl) - ethyl - piperazin - 1 - yl) methanone.

Table 21. Library of (((2 ,7 - dimethylimidazo - [1,2 - a] - pyridine - 3 yl) (4 - (2 -(4 - nonyl - 1 H - 1 ,2, 3 -triazol - 1- yl) - ethyl - piperazin - 1 - yl) methanone (123 a- d) (124 a-e) synthesized.



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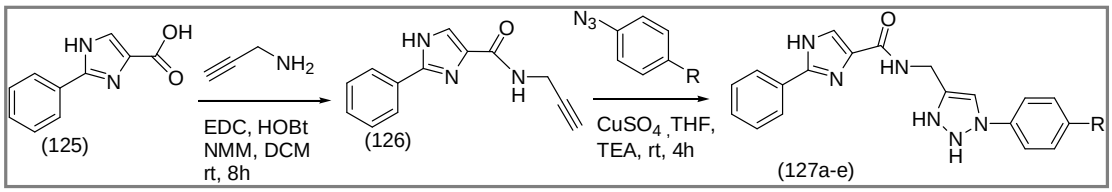
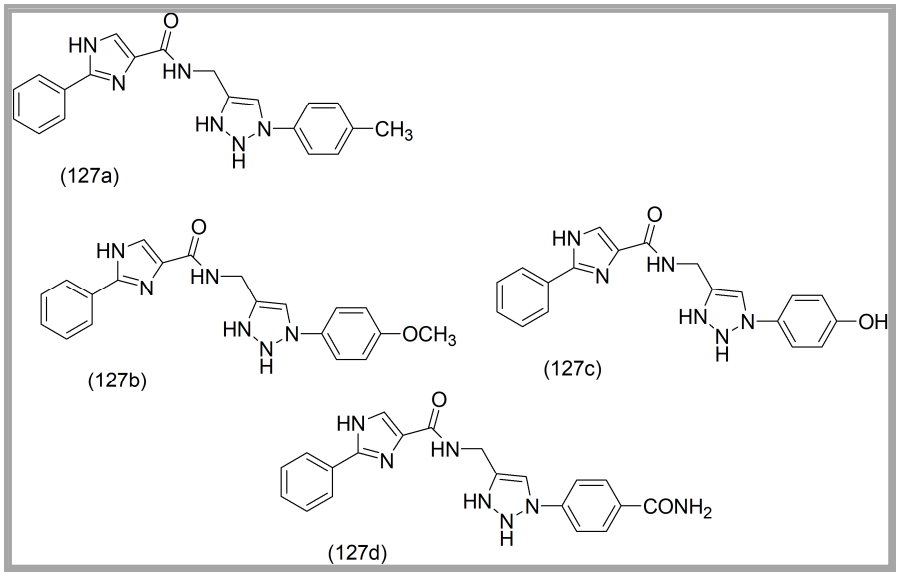
20. Due to intolerance and noncompliance of patients of TB, development of novel mechanism of action for the treatment of TB. Triazole heterocycles are an important part of a broad range of drug candidates of high importance as well as a variety of ring structure that use this heterocyclic core [**64-67**], while as imidazoles are also important for their frame work and thus are active therapeutic agent [**68-70**]. Click chemistry played a vital role in synthesizing libraries of wide number of molecular frames that are biologically active; the importance of click reactions is clearly demonstrated [**71-74**]. Therefore C.B. Pradeep Kumar *et al.* (2021) synthesized or reported 1,2,3 – triazole based imidazole derivatives by CuAAC reaction (Cu(I) –catalyzed cycloaddition of alkyne and azide against *M.tb* H37RV strain and cytotoxic activity against mammalian vero cell line (Scheme 21, Table 22). Screening revealed that compounds 127d and 127e displayed potent in vitro antitubercular activity with (MIC 2.03 µM and 1.47µM and may serve as a lead for further optimization. A cytotoxicity result showed that they have lower toxicity has been found in the synthesized compounds. The two step reaction sequence shown in scheme 22 would streamline the synthesis of imidazole based triazole derivatives. 2-phenyl-1H- imidazole-4-carboxylic acid (125) was coupling with propargylamine in presence of EDC, HOBt and N-methylmorphioline in DCM to furnish alkyne derivative (126). So the

reaction between alkyne and azides has been studied to obtain novel based 1,2,3-triazole based imidazole derivatives (127a-e).



Scheme 21. Synthesis of 1,2,3 – triazole based imidazoles.

Table 22. Library of Synthesis of 1,2,3 – triazole based imidazoles synthesized for screening as anti-tubercular agents.



21. B. Sharma *et al*. (2022) synthesized hybrid compound 128 having isoniazid core which showed effective antimycobacterial activity against *M.tb* mc^2 6230 strains [75] with MIC of 0.36-0.78 µg mL^{-1} (Figure 4). The compound also showed reduced cytotoxicity against Vero cells as compared to hybrids having semicarbazones/thiosemicarbazones or pyrazine 2 -carbohydrzine unit (MIC: 2-200 µg mL^{-1}. Substitution at C-5 with polar electron – donating groups are identified as most active compound of the series. However, further optimization is required to target INH- resistant strains of tuberculosis

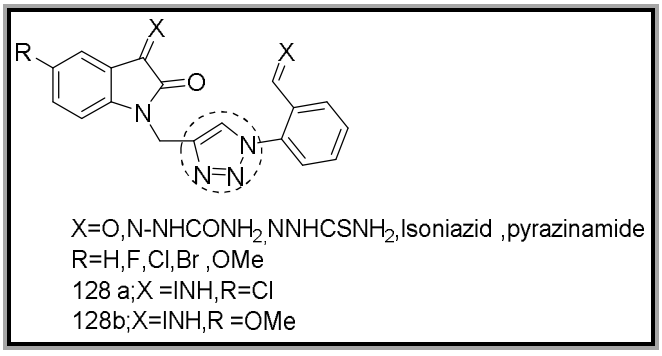
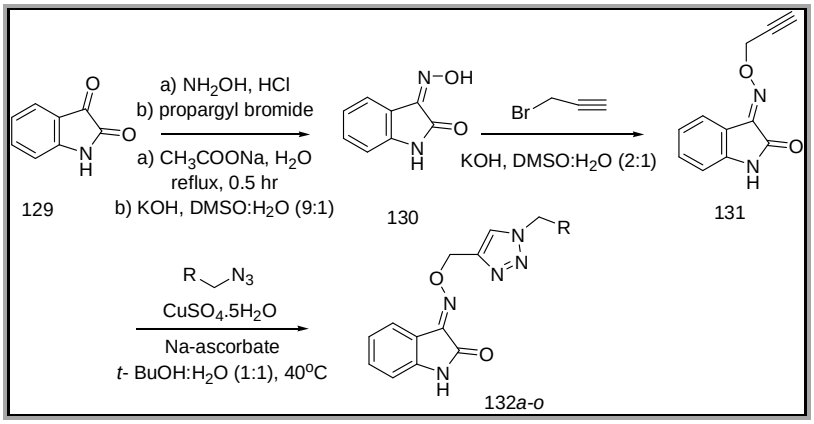


Figure 4. Hbrid compound 128 having isoniazid core which shows effective antimycobacterial activity against *M.tb.*

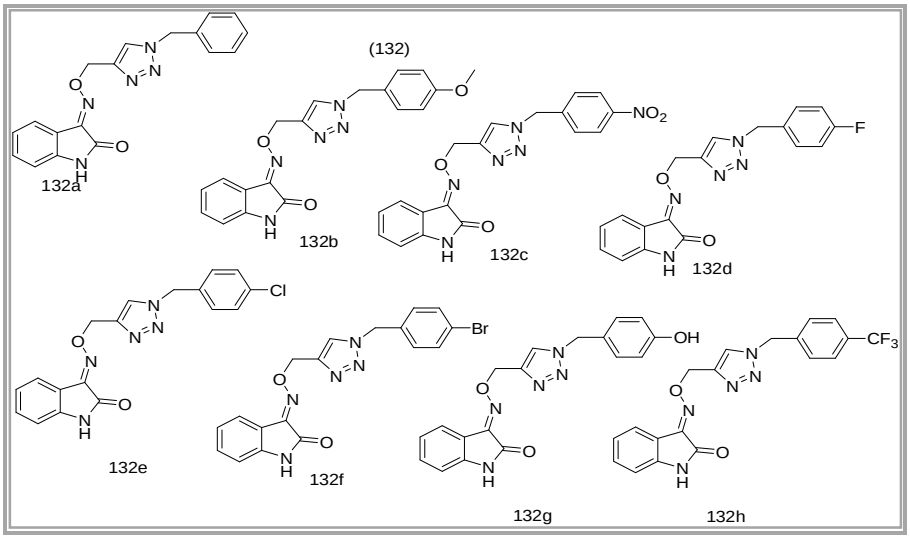
22. Isatin (indole 1 H-2,3-dinone) is a renowned natural product which is found as a metabolite of adrenaline in humans [76]. Isatin and its derivatives possess a unique set of chemical and structural

features that make them particularly attractive biological pharmacophore, for antimicrobial, antitumoral, antiviral, anticonvulent, anti–HIV, and anti–TB agents [**66**]. In recent years isatin derivatives have gained overwhelming response as promising hybrids [**77**] and showed promising *in vitro* anti–TB activity with MIC 0.0125 µg mL^{-1} against *M.tb* and MDR–TB [**78**]. Biological importance of triazole and oxime ether moiety of isatin containing derivatives [**80-82**] and the promising anti–TB activity of isatin compounds has also been reported. Sampath *et al.* synthesized a series of fifteen novel isatin oxime ether – tethered aryl 1 –H -1,2,3 – triazole hybrids by employing Cu (I) catalysed azide – alkyne [3+2] cycloaddition (CuAAC) between isatin oxime O- propargyl ether and aryl azides (Scheme 22, Table 23). These compounds were screened for their *in vitro* anti – TB activity against *M.tb* H37Rv (ATCC 2799999294 strain) [83]. Among these compounds only eight compounds showed good activity with MIC [0.78-6.25 µg mL^{-1}] in comparison with the standard drugs. Isatin oxime O-propargyl ether (130) required for the synthesis of isatin oxime ether aryl 1H-1,2,3-triazole hybrids was synthesized by converting isatin (129) into isatin oxime with subsequent O-propargylation using potassium hydroxide in DMSO:H_2O and then compound (130) was treated with azide in presence of $CuSO_2.5H_2O$ and sodium ascorbate in *t*-BuOH/H_2O (1:1) as solvent.



Scheme 22. Synthesis of isatin oxime ether – tethered aryl 1 –H -1,2,3 – triazole hybrids by employing Cu (I) catalysed azide – alkyne [3+2] cycloaddition for *in vitro* anti –TB activity screening against *M.tb* H37Rv.

Table 23. Series of isatin oxime ether – tethered aryl 1 –H -1,2,3 – triazole hybrids synthesized by employing Cu (I) catalysed azide – alkyne [3+2] cycloaddition for *in vitro* anti –TB activity screening against *M.tb* H37Rv.



CONCLUSION

To overcome the problems and drawbacks associated with currently available TB treatment, there is dire need to develop novel tuberculosis therapeutic strategies. Keeping this in mind researchers are looking for a novel approach from conventional mono-targeted drug discovery to multi-targeted drug discovery strategies. Therefore, the search for new therapeutic agents that could pave a novel target or multi-targeted combination therapy to reduce the regimen time. As observed from the above literature review the triazoles are reported important for different pharmacological activities. Due to this unique moiety it is responsible for various biological activities such as inhibition of the growth of mycobacterium by blocking lipid biosynthesis, cell wall biosynthesis inhibition or alternative mechanism and thus displayed significant antitubercular activities. The importance of triazole moiety can be magnified by the molecular hybridization of the triazole skelton with some other pharmaceutically active frameworks such as isatin, quinoline, isoniazid, etc may provide a vital role for the development of noval and effective anti-TB agents having better efficacy, minimal toxicity as compared to the parent compound. This review prevents a 8-year compressive details of triazole analogues having potential *in vitro* and *in vivo* anti TB activity. To conclude this review we hope it will be very fruitful for the medicinal chemists to design and develop novel anti TB drugs with enhanced efficacy and minimal toxicity.

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