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REVIEW ON SYNTHESIS SCHEMES OF FIRST LINE DRUGS OF ANTITUBERCULAR DRUGS

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Abstract*:* Tuberculosis (TB) is an infectious disease caused by a variety of mycobacterium strains, the most prevalent of which being Mycobacterium tuberculosis. *M. tuberculosis, M. africanum, M. bovis*, and the Bacillus Calmette-Guérin strain, *M. microti, M. canettii, M. caprae, M. pinnipedii, and M. mungi* are all members of the M. tuberculosis complex. Other than M. tuberculosis complex, other species (*M. avium* complex, *M. gordonae*, *M. kansasii*, *M. simiae, M. chelonae, M. fortuitum*, etc.) do not cause tuberculosis in humans. TB mainly affects the lungs but can also affect other regions of the body. For many years, it was thought to be a poverty disease due to its rarity in developed countries. The present review focus on some synthesis schemes of first line drugs of antitubercular drugs**.**

Key words: Antitubercular**,** Synthesis Schemes, Review

Introduction: Tuberculosis (TB) is one of the leading health problems in developing as well as developed countries. It is an airborne transferable disease caused by the bacterium Mycobacterium tuberculosis (MTB) and that predominantly affects the lungs. The best estimate in 2018 is that, including 251000 people with HIV, total 1.5 million death from TB. Furthermore, 10 million new cases found worldwide, mostly in developing countries [1]. The most familiar symptoms of active TB infection are depicted in. In 1940, the first anti-TB drug (Promin) was administered to a sample of guinea pig, but it was never given to humans. For the treatment of MTB, streptomycin was developed as the first effective drugs in the year 1944 [2].

The currently recommended treatment for new cases of drug-susceptible TB is a 6-month regimen of four first-line drugs such as isoniazid, rifampicin, ethambutol and pyrazinamide . Treatment success rates of at least 85% for new cases of drug susceptible TB are regularly reported to WHO by its 194 Member States. Treatment for Rifampicin -resistant TB (RR-TB), Multidrug-resistant TB (MDR-TB) and Extensively drug resistant TB (XDR-TB) requires longer period of time (up to 2 years) with more expensive and toxic medicines. Until early 2016, the treatment regimens recommended by WHO typically lasted for 20 months, and cost about US$ 2000-5000 per person. New TB drugs have begun to emerge from the pipeline, and combination regimens that include new compounds are being tested in clinical trials [3].

In the last few decades, heterocyclic chemistry gains numerous attentions due to their diverse application in the field of synthetic organic chemistry as well as biological and pharmaceutical industry . For the discovery of new drug candidates, heterocyclic compounds play crucial role as they can enlarge the existing drug-like chemical space and helps in designing new drug molecules. Presence of heterocycles in drugs can enhance the solubility, lipophilicity, polarity and H-bonding capacity which results in the optimization of absorption, distribution, metabolism, excretion and toxicity (ADME/Tox) properties of drug candidates . The heterocyclic compound mainly contains nitrogen, oxygen and sulphur as important heteroatom. Among these

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heterocyclic compounds nitrogen containing heterocycles have been used in different industrial fields and also find in therapeutic applications [4].

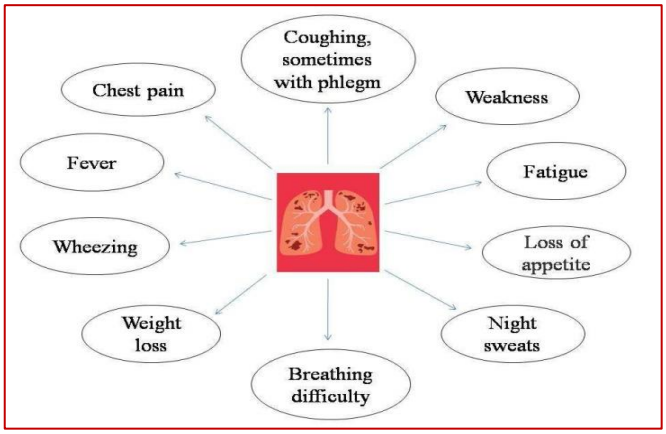


Figure 1: Common symptoms of active TB infection

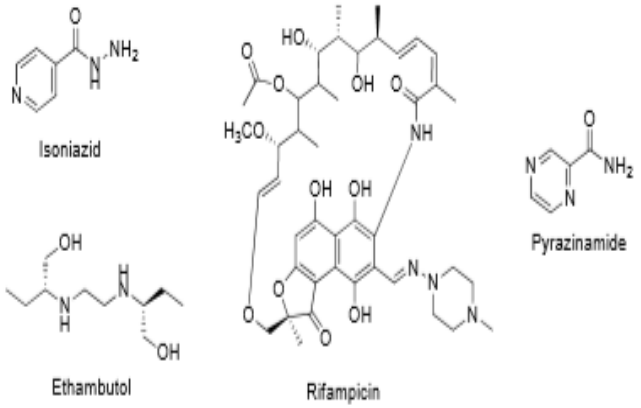


Figure 2: Structures of first-line anti-TB drugs

There is a large number of nitrogen containing heterocyclic compounds found in a plethora of medicinal applications. Among them quinazoline was found to be an important N-containing heterocycle having chemical formula C8H6N2 and contains a benzene ring and a pyrimidine ring in its structure [5].

In quinazoline, the reactivity of pyrimidine ring is greatly affected by the presence of benzene nucleus. Structure activity relationship studies revealed that the presence of halogens as substituent at position 6 and 8, amine and substituted amine at position 4, substituted aromatic ring at position 3 and methyl, amine or thiol at position 2 of the quinazoline molecules can enhance their antimicrobial activity [6].

Quinazoline and its derivatives possess broad range of biological, medicinal and pharmacological activities such as anti-tumor, antibiotic, anti-tubercular, anti-defibrillatory, anti-pyretic, analgesic, anti-hypertonic, diuretic, anti-histamine, anti-depressant and vasodilating agents [7].

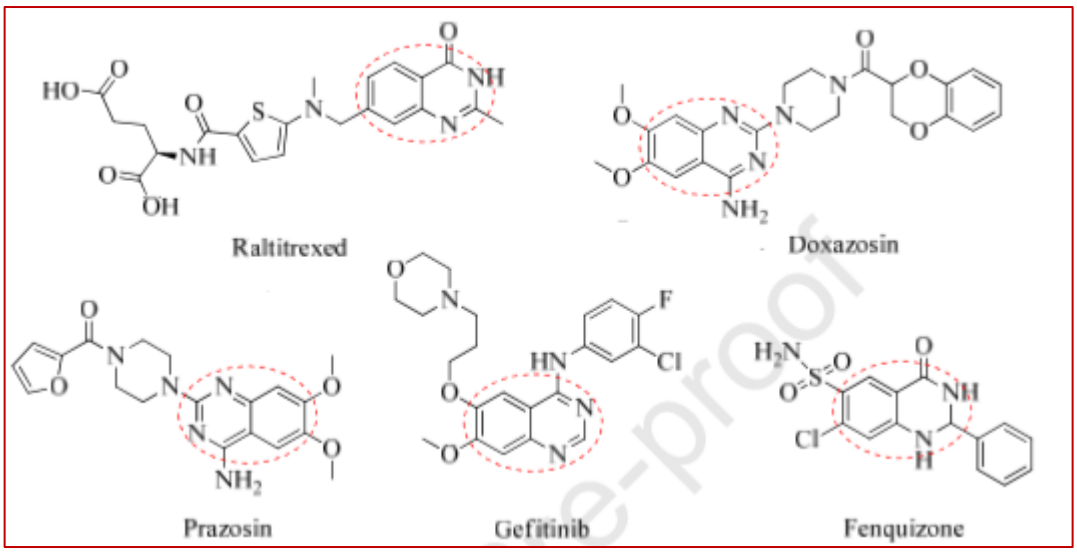


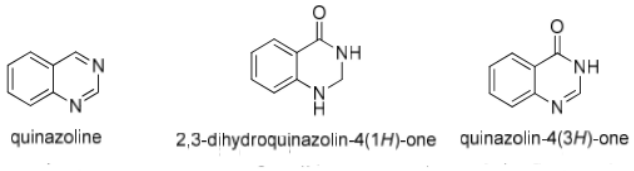
Figure 3: Drug molecules having quinazoline moiety

From the synthetic point of view, the first quinazoline compound was obtained as early as in 1869 from anthranilic acid and cyanogens and since then, a proliferation of research activities have been done on this particular field. A large number of classical methods for

the synthesis of quinazolines have been reported by many research groups [8].

Among those, the most common one for quinazoline synthesis is based on the Niementowski reaction by the fusion of anthranilic acid analogues with amides at 130-150 °C via an o-amidobenzamide intermediate . But in this method, the yields are low and impurities also formed which is difficult to remove by column chromatography or recrystallization. Two other important methods for the synthesis of quinazolines are:- (1) the condensation of anthranilamide (2-aminobenzamide) derivatives with carbonyl compounds and (2) one-pot three component reaction of isatoic anhydride, aldehydes and amines [9]. Efforts are underway on the development of even milder, straightforward, novel and ecofriendly approach towards the synthesis of this important heterocycles and their novel derivatives.

Important derivatives of quinazoline:



The 5000 year old Ayurveda particularly recommends the use of 'Vasaka' or Malabar nut, scientific name Justicia adhatoda Linn./ Adhatoda vasica Nees as a potent remedy for Phthisis. The WHO manual "The Use of Traditional Medicine in Primary Health Care" also includes Justicia Adhatoda. This plant is chiefly constituted of pyrroquinazoline alkaloidsvasicine (concentration- 1.3%), vasicol, vasicinone, peganine along with other minor constituents . Both natural derivatives of vasicine, viz., vasicinone, vasicine acetate and 2-acetyl benzylamine and its semi-synthetic derivatives bromhexine and ambroxol were found to inhibit the growth of M. tuberculosis with MIC values of 64-6 µg/mL [10]. Since the above derivatives of quinazoline were applied in the treatment of tuberculosis, researchers attempted to synthesize different types of novel quinazoline derivatives and tested against M. tuberculosis.

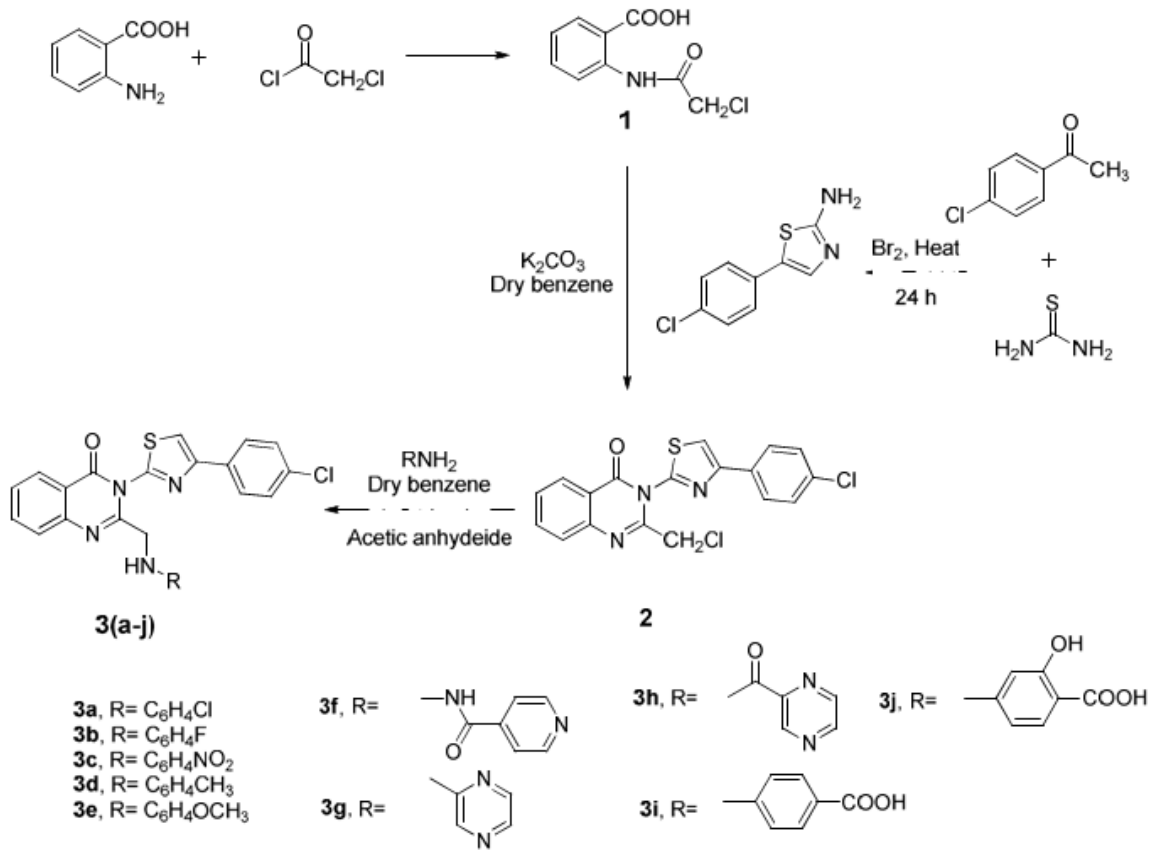
In pursuit of searching new anti-TB agents, a number of novel quinazoline containing molecules have already been synthesized and some of them showed promising anti-TB activity. The present review provides an overview of the recent advances made towards the development of anti-TB agents containing quinazoline motifs.

Quinazoline derivatives with anti-TB activity: In 2000, J. Kunes et al. [11] prepared a set of novel 4-alkylthioquinazoline derivatives (Scheme 1) and the structure of these compounds was confirmed by FT-IR, ^{1}H, ^{13}C NMR and MS analysis. After confirmation of the structures, the compounds were tested for their in vitro anti-TB activity against the strains of M. tuberculosis CNCTC TBC 1:47 and found that all the synthesized compounds gave good to excellent activity with MIC value ranges from 500-63 µM. For the compounds containing an un-branched alkyl chain, the activity of the compounds depends upon the length of the chain. The maximum activity was found in the compounds containing four-carbon residue. Further, increasing the length of the alkyl chain in the molecules, the activity of the compounds goes down. Similarly, molecules containing branched alkyl chain also showed good anti-tubercular activity. Branching on the α-carbon of the alkyl chain showed better activity in comparison with branching on the ß-carbon. When an unsaturated alkyl group is attached with the sulphur atom of the quinazoline ring the antiTB activity decreases. The compounds containing benzylthio and 2-phenylethylthio groups showed very good anti-TB activity among the series. The compound containing 2- phenylethylthio group was the second most active compound of this set of derivatives. Among these compounds, 4-butylthioquinazoline was the most active compound with MIC 63 µM. This series of novel molecules was the 1st quinazoline derivatives which were found to have anti-TB activity.

4-alkylthioquinazoline derivatives with their synthesis

In 2006, Shashikant et al. [12]synthesized a series of N-3[4-(4-chlorophenyl thiazole2-yl)-2-aminomethyl] quinazoline-4(3H)-one analogues (Scheme 2) and the structure of the novel compounds were confirmed by various spectroscopic analysis such as FT-IR and 1H NMR spectra. The compounds were screened for their in vitro anti-TB activity using $H_{37}RV$ strain on Lowenstain-Jensen egg medium (L J Medium). All the synthesized compounds showed moderate to excellent anti-TB activity with MIC ranges 100-10 µM. Compounds 3f, 3h and 3j showed maximum anti-TB activity at the concentration of 10 µg /mL among these compounds. The compounds 3c, 3d and 3g showed moderate activity while 3a, 3b and 3e did not show significant activity. On the other hand, the compound 3i did not show any anti-TB activity up to the concentration of 100 µg /mL. Highest anti-TB activity of 3f, 3h and 3j were due to the

presence of isoniazid, pyrazinamide and para-amino salicylic acid respectively along with the quinazolinone moiety.



N-3[4-(4-chlorophenyl thiazole-2-yl)-2-aminomethyl] quinazoline-4(3H)-one analogues with their synthesis

S. Rajasekaran's group [13]synthesized a series of novel 2-phenyl-3-substituted quinazolin-4(3H)-one derivatives shown in Scheme 3 and their structures were confirmed by various spectroscopic analysis such as FT-IR, ^{1}H NMR, Mass spectra and Elemental analysis. For all the synthesized compounds, in vitro anti-TB activity was performed against M. tuberculosis by agar dilution method with the use of Middlebrook 7H-9 broth and standard strain of M. tuberculosis $H_{37}R_v$. Out of the seven compounds (4a-g), six compounds showed moderate to high activity with the MIC ranges from 100-25 µg/mL.

The compound 4b showed very less activity at the concentration of 100 µg/mL. The compounds 4c, 4d and 4f showed moderate to low activity at the concentrations of 100 and 50 µg /mL respectively. The most active compounds in this series were 4e and 4g which showed excellent activity at 100 µg/mL, moderate activity at 50 µg/mL and less activity at 25 µg/mL concentrations respectively. The compounds 4e and 4g showed similar activity to the standard compounds streptomycin and pyrazinamide used in this study. Journal Pre-proof Scheme 3: Structure of 2-phenyl-3-substituted quinazolin-4(3H)-ones with their synthesis .

Dodiya et al., in 2010 [14]synthesized a series of novel derivatives of 4-aryl-5,5- dimethyl-7-(2´-piperidin-1´-yl-ethyl)-2-hydroxy-3,4,5,6-tetrahydroquinazoline (3a-i) and all of them were screened for their anti-TB activity (Scheme 4). The primary anti-TB screening of the synthesized derivatives was conducted at concentration 6.25 µg/mL against M. tuberculosis $H_{37}R_v$ (ATCC 27294) in BACTEC 12B medium using a broth micro dilution assay, the Microplate Almar Blue Assay. From the primary screening it was found that all the investigated compounds showed 6.25 µg/mL. Since all the compounds showed moderate anti-TB activity with MIC >6.25 µg/mL .

4-aryl-5,5-dimethyl-7-(2´-piperidin-1´-yl-ethyl)-2-hydroxy-3,4,5,6- tetrahydroquinazolines with their synthesis

In 2013,Srivastav et al. [15]synthesized a series of novel 2-trichloromethyl-4- substituted quinazoline analogues and screened for their in vitro anti-TB activity against bacterial strain of M. tuberculosis $H_{37}R_v$ ATCC (American Type Culture Collection) by Alamar Blue assay method (MABA). All the tested compounds (4a-4j) displayed moderate to good anti-TB activity with MIC ranges from 50-6.25 µg/mL. Among them the compounds 4a and 4f exhibited excellent activity with MIC 6.25 µg/mL which is equipotent with the reference pyrazinamide and streptomycin employed in this study. The compounds 4e and 4h also showed significant activity with MIC 12.5 µg/mL. All the other tested compounds except 4c (MIC 50 µg/mL) showed moderate anti-TB activity with MIC 25 µg/mL.

2-trichloromethyl-4-substituted quinazoline analogues with their synthesis

Further, a close examination of all the active compounds showed that the presence of N-methyl piprazine (4a) and 4-diethanolamine (4f) counterpart at 4th position of the 2- trilchlorometyl quinazoline framework exhibited excellent activity in comparison with the other derivatives. Substitution on the 4th position of 2-trichloromethyl quinazoline moiety and genetic/biochemical background of bacterial strain M. tuberculosis $H_{37}R_v$ ATCC may be the main factors of different MIC values associated with the active compounds.

The anti tubercular activity mainly depends on the substitutions at the phenyl ring of the pyrazole-quinazolinone nucleus. The compounds containing ortho directing substitutions such as chloro, methyl, and methoxy in basic skeleton showed highest activity

2-(substituted-phenyl)-3-(((3-(pyridin-4-yl)-1-(p-tolyl)-1H-pyrazol-4-yl) methylene) amino)-quinazolin-4(3H)-ones with synthetic route

Various substituted 5,6-dihydro-8-methoxybenzo[h]quinazolin-2-amine derivatives (4a-d, 5a-c and 6a-c) were synthesized by H. K. Maurya et al. [16] and evaluated for their anti-TB activity against M. tuberculosis H37Rv strain using micro plate alamar blue assay. At first the authors tested the anti-TB activity of the starting precursor benzo[h]quinazoline (3) and found that the compound was inactive up to concentration 200 µg/mL. After that, the newly synthesized 10 novel compounds were screened for their antiTB activity and found that all the compounds showed moderate to good activity with MIC ranges 200-50 µg/mL. Among all the compounds, 4a and 5a exhibited highest anti-TB activity with MIC 50 µg/mL.

The compound 4c also showed good activity with MIC 100 µg/mL and all other compounds were anti-TB active with MIC value of 200 µg/mL. Structure-activity relationship (SAR) revealed that compounds 4a and 5a with piperidine ring and propanoate chain as substituent respectively had better activity as compared to other related derivatives. using non cancerous hepatic monocytes (THP-1) cells. Cytotoxicity concentration (CC50) values of 4a, 4c and 5a were found to be 200 µg/mL, confirmed that the active compounds were non-toxic to the healthy cells.

4-(substituted)-5,6-dihydro-8-methoxybenzo[h]quinazolin-2-amines with synthetic route

A novel series of cationic fullerene-quinazolinone hybrids having substituted quinazoline in the side chain was synthesized and characterized by different spectroscopic analyses by Patel's research group [17]. The authors have chosen fullerene due to its wide application in the field of biological and medicinal chemistry. All the quinazolinone compounds (1a-1f, 2a-2f and 3a-3f) were screened for their in vitro anti-TB activity against M. tuberculosis $H_{37}R_v$ using the LJ minimal inhibitory concentration method (MIC). From the results it was observed that incorporation of fullerene enhanced the activity of the compounds to a great extent. Initially the compounds (1a-1f) showed anti-TB activity with MIC 200 µg/mL, but attachment of fullerene spheroid with the quinazolinone compounds enhanced the activity with MIC ranges of 25-1.562 µg/mL. To have good anti-TB activity, a compound passes through the mycobacterium cell wall which has higher concentration of lipids.

The presence of fullerene in the molecules can make easy passes of the hybrids through the waxy cell, rupture it and facilitate the entry of quinazolinone into the cytoplasm. The quinazolinone molecule then easily causes cell death by inhibiting cell metabolism. Hence, fullerene-quinazolinone analogues showed excellent activity in comparison of fullerene free quinazolinone analogues (1a-1f). Moreover, presence of lipophilic substituent and the positive charges near the fulleropyrrolidine backbone plays an important role in increasing anti-TB potency.

Among all the synthesized compounds, 3f showed highest activity compared to standard drugs used in this

study. The fullerene cage gives proper exterior geometry and hydrophobic character for interaction with the target and on the other hand quinazolinone moiety plays an important role in establishing H-bonding with the active site which was confirmed from the structure analysis of HGPRT enzyme and its binding mode by computational study.

Cationic fullerene-quinazolinone hybrids with synthetic route

A novel series of ethyl 5-(4-substituted phenyl)-3-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazoline-2-carboxylate (3a-3j) derivatives were synthesized by Selvam's group [55]. The designed molecules Journal Pre-proof were tested for their first and second level of anti-TB activity against MTB H37Rv strain (ATCC 25618) by Resazurin assay using isoniazid as a standard drug for comparison. Among the ten derivatives tested against MTB H37Rv strain, 3g, 3i, 3f, 3h, 3j, 3d, 3e and 3b showed anti-TB activity at concentrations 10 and 1 µg/mL. Further the active compounds were used for 2nd level of testing and found that all the active compounds in the 1st level of investigation were also active at 1.25 and 0.625 µg/mL concentrations. Among the active compounds, 3g, 3f and 3h showed superior activity which had similar anti-TB potency as that of standard drug isoniazid.

Ethyl 5-(4-substituted phenyl)-3-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazoline-2-carboxylate derivatives with their synthesis

In 2014, Reddy *et al.* [18]synthesized a series of new analogues of isoniazid incorporated 2-styry l quinazolinone and the structures of these compounds were established by various physical and spectral data. The anti-TB screening was carried out against INH sensitive strain H37Rv and MDR strain DKU 156 by broth dilution assay using isoniazid as standard drug. All the newly synthesized derivatives showed moderate to excellent anti-TB activity against both H37Rv and MDR DKU 156 strains with MIC ranges 0.625-10 and 0.3125-10 µg/mL respectively.

Among all the tested derivatives, derivative 3j containing indole moiety showed excellent activity with MIC 0.625 and 0.3125 µg/mL against H37Rv and DKU 156 respectively. This compound showed better activity than the standard drug isoniazid which had activity with MIC 0.625 and 10 µg/mL against H37Rv and DKU 156 respectively. Compounds 3f, 3g, and 3h showed slightly lower activity with MIC values 1.25, 2.5 and 2.5 µg/mL against H37Rv and 0.625 µg/mL against and DKU 156. Compounds 3d and 3e showed activity with MIC 2.5 and 5 µg/mL against $H_{37}R_v$ and 1.25 µg/mL against DKU 156 while 3a and 3b showed moderate activity with MIC 5 and 10 µg/mL against $H_{37}R_V$ and 2.5 and 5 µg/mL against DKU 156. The least active compounds among the series were 3c and 3i which had MIC values >10 µg/mL against both $H_{37}R_v$ and MDR DKU 156 strains.

Isoniazid incorporated 2-styrylquinazolinone derivatives with their synthesis

Patel *et al.* [19]developed a method for the synthesis of some novel quinazoline analogues based on urea or thiourea. All the synthesized compounds were well characterized and further tested for their in vitro anti-TB activity against M. tuberculosis $H_{37}R_v$ using L J MIC method. The compounds having halogen as substituent showed promising activity with MIC 50-12.5 µg/mL. All the other compounds also showed moderate activity with MIC ranges of 250-62.5 µg/mL. Among the series, compound 4j showed highest activity in terms of MIC value of 12.5 µg/mL. From the biological results we can say that presence of thiourea linkage is responsible for moderate to good activity of the synthesized compounds.

Urea/thiourea-based quinazoline derivatives with their synthesis: Lu *et al.* [20]synthesized a series of benzoate derivatives of quinazolinone using anthranilic acid as an easily available starting material . All the synthesized analogues were fully characterized by melting point determination, ^{1}H, ^{13}C NMR, FT-IR, elemental analysis or ESI-MS. All the compounds were tried for crystallization but only one compound could be successfully recrystallized and characterized by single crystal X-ray diffraction and found that the whole molecule adopts a twisted shape with the quinazolinone and the two phenyl rings in different planes. After successful characterization, synthesized compounds were evaluated for their anti-MTB analysis and found that seven compounds showed activity with MIC ranges of 50-2.5 µM. Among the series, compound 4h showed highest anti-MTB activity with MIC 2.5 µM. Simultaneously, the synthesized benzoate derivatives of quinazolinone were subjected to MTB-acetohydroxyacid synthase (AHAS) inhibition assay and found that most of them showed some inhibition against MTB-AHAS at the concentration of 100 µM. Among them 4h, 4m, 4p, 4w and 4x showed significant inhibitory activity with IC50 values of 6.50, 9.68, 12.08, 8.74 and 9.57 µM respectively.

Conclusion: Overall, the recent decade has seen the most promising developments in tuberculosis therapy

since the 1960s, but these breakthroughs have yet to have an impact on the stubbornly high worldwide burden of the disease. Long-term investment, political commitment, and scientific endeavour will be critical to ensuring that progress is maintained and that the benefits of recent advancements reach the most vulnerable.

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