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THIAZOLE DERIVATIVES CONTAINING COMPOUNDS AS CURATIVE AGENTS FOR TUBERCULOSIS: A REVIEW

Prashant P. Mogle[a], Priya D. Gavhane[b] and Bhaskar S. Dawane[c,*]

[a]Organic Research laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded- 431606 (MS) India
[b]Organic Research laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded- 431606 (MS) India
[c]Organic Research laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded- 431606 (MS) India
Email-bhaskardawane@rediffmail.com

ABSTRACT: Tuberculosis disease is the second main cause of deaths worldwide & become more dangerous because of increasing resistance towards novel anti-tubercular agents. In the last few decades, the number of development & research acomplished for the synthesis and biological studies of novel anti-tubercular agents. Among heterocycles, thiazole is a versatile building block useful in the field of medicinal chemistry. Recently these compounds used for lead generation of future anti-tubercular agents having high effectiveness, potent anti-tubercular activity & possessing less toxicity.

In this review, our focal point is to investigate the recent developments in the synthesis of thiazole derivatives & evaluate their biological importance in anti-tubercular drug discovery. This review accessible for researchers which involves the rational designing of more potent anti-tubercular drugs containing thiazole moiety.

KEYWORDS: Thiazole moiety, anti-tubercular agents.

INTRODUCTION

Tuberculosis (TB) is a widespread infectious airborne disease[i] , day by day the infection goes on increasing because of poverty and health problem. It is one of the top 10 causes of death globally and a leading cause of death by a single infectious agent (ranking above HIV/AIDS).[ii] Tuberculosis caused by mycobacterium tuberculosis (MTB), among the other species like M. microti, M. capre, M. africanum & M. bovis[iii] According to a recent global tubercular report 2019 by WHO, 10.0 million fell ill with tuberculosis. In India new cases rose from 1.2 million to 2.0 million in between the year of 2013-2018.[ii]

Tuberculosis mainly affects on lungs, then it is called pulmonary tuberculosis, when it affects other organs labelled as extra pulmonary.[iv] Studies of the biological mechanism of Mycobacterium tuberculosis show that it is an intracellular pathogen that grows & reproduces in the host macrophages. The primary response of macrophages for this infection is the

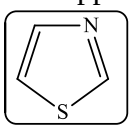
production of reactive oxygen & nitrogen intermediates, which are highly toxic and their interaction changes the normal cell functioning [v]. Generally, these intermediates produced in the lung cells but are neutralized by antioxidants present in the body. But in diseased condition overproduction of reactive intermediates does not neutralized by antioxidants.[vi]

To control the tuberculosis various approach put forward by a researchers in last few decades [vii]. Tuberculosis has incarnated itself in other deadly forms like multidrug resistance (MDR-TB) defined as resistance towards the first-line anti-TB drug likes Rifampicin & Isoniazid, more advance extensively drug-resistant (XDR) defined as MDR strain plus supplementary resistance at least one fluoroquinoline & one-second line injectable drug (amikacin, capreomycin & kenanmycin) used in TB treatment [viii].

Primitive control blueprint for tuberculosis is antibiotic therapy, but due to long-range treatment (Max. six months), less efficacy with toxicity and produce health issues are the hardship observed in TB patients using drugs.[ix] The causative agent M. tuberculosis nowadays resistant to all first and second-line anti-TB drugs which results into urgent requirement for the development of novel pharmacophore to treat MDR-TB & XDR-TB. In this connection, some remarkable therapeutic moieties under pipeline e.g. maxifloxacin, linezolid, gatifolxacin, and sutezolid have been recycled in clinical trials for the treatment of tuberculosis[x].

Tuberculosis is a globally infected disease which remains a problem for high distress & fatality rate other than different infectious diseases[xi]. The benefit of antibiotic drugs for the treatment of tuberculosis remains the backbone in controlling program[xii], however long duration of treatment i.e. up to the 24 weeks possessing toxicity with low efficacy and producing health issues in TB patients, by using these drugs are the main barriers to become biologically less potent.[xiii] Modern investigation shows that thiazole ring clubbed or hybridized with other pharmaceutically active heterocycles, the novel pharmacophore formed have intensified properties against mycobacterium tuberculosis viz. pyridyl,[xiv] hydrazolyl,[xv] thiosemicarbazonyl,[xvi] piperidinyl,[xvii] & pyrazinyl.[xviii] The worldwide researcher are involved in the discovery of new scaffolds which having the ability to decrease resistant property of various strains of mycobacterium tuberculosis. The sum of heterocycles is involved in the discovery of novel pharmaceutical moiety, among them, some thiazole bearing derivatives showed promising anti-tubercular activity.

Medicinal chemistry involves in the development & designing of new drugs and evaluates their biological importance for various diseases, it is present on the shoulder of studies of heterocyclic compounds.[xix] Heterocyclic compounds earned from natural source or synthetic mode show superb biological & pharmacological activity. Most of the heterocyclic compounds with a five or six-membered ring containing nitrogen, oxygen, sulfur atom are of great interest. From several heterocyclics, Thiazole a unique heterocycle, having both nitrogen & sulfur atom as part of an aromatic five-membered ring, these heterocycles also called 1, 3 azoles. The development in the study of thiazole begins with chemically synthesized thiazole in laboratory by Hantzsch in 1887[xx], in 1889 Popp confirmed its structure. (**Fig.1**)



Thiazole

Fig.1. Structure of Thiazole

Thiazole itself is not found in nature, but the thiazole ring is present in many natural products such as alkaloids, metabolites, cyclopeptides & penicillin (first antibiotic).[xxi] It is a versatile biologically important moiety, essential component present in many synthetic medicinally relevant compounds, Niridazole,[xxii] Ruvaconazole,[xxiii] Nitazoxanide,[xxiv] Thiamethoxam,[xxv]

Vorelexin,[xxvi] Dasatinib,[xxvii] Ritonavir[xxviii] and Nizatidine[xxvix] are some examples of thiazole containing commercially available drugs.(**Fig.2**)

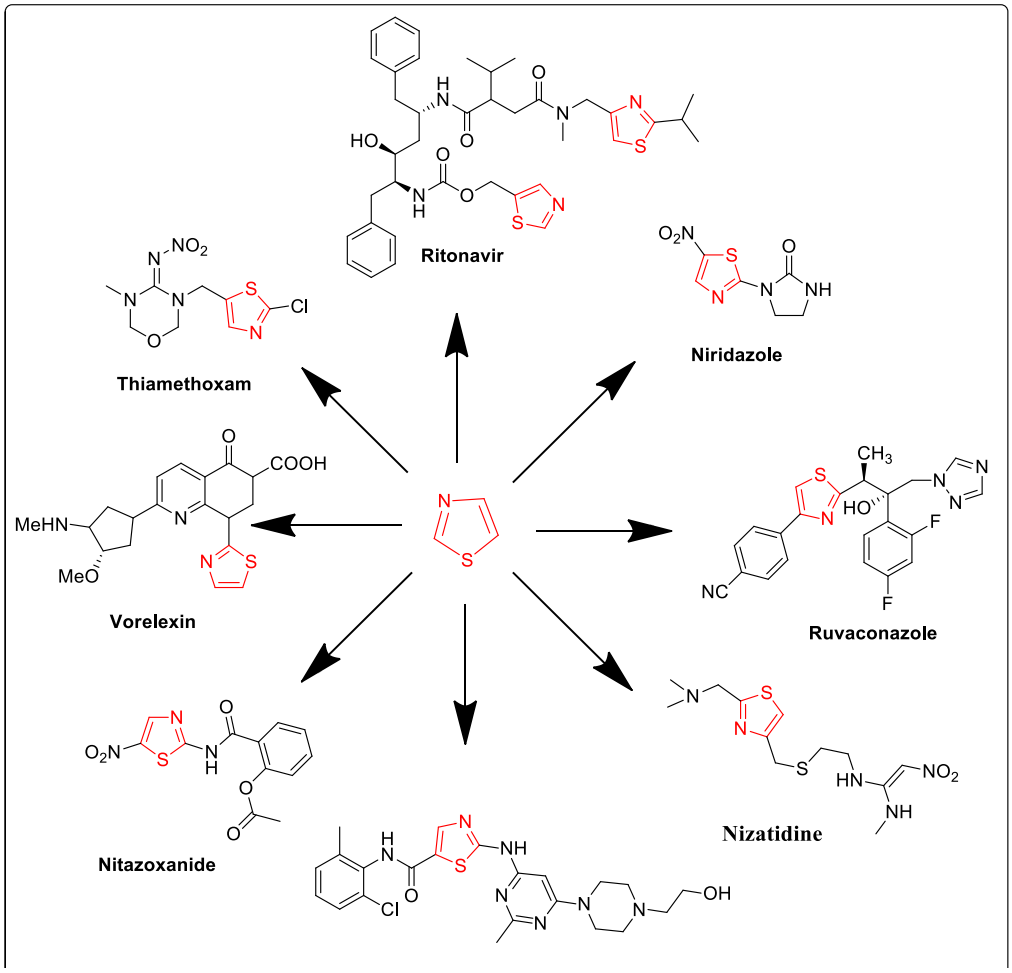


Fig.2 Commercially available drugs contain thiazole ring**.**

Thiazole possesses a crucial role in drug discovery because of its derivative that show a broad spectrum of biological activities such as anti-HIV,[xxx] antibacterial,[xxxi] antimycobacterial,[xxxii] antifungal,[xxxiii] antiviral,[xxxiv] anti-cancer[xxxv] which have tremendously fascinated the attention of research community. Recent studies show that thiazole derivatives and hybrid molecule (one or more biologically significant nucleus combine) extensively useful as anti-mycobacterial agents.

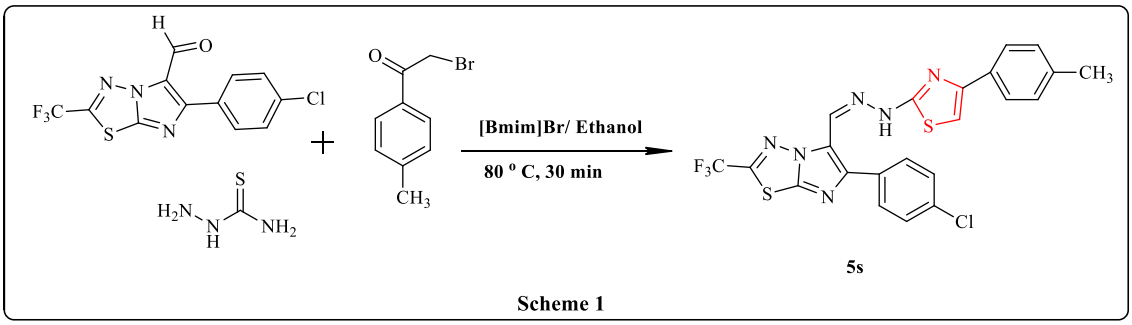
LITERATURE REVIEW

Our main attempt for this review is to search recently developed, designed and synthesized some thiazole containing compounds by various researchers for being more potent, less producing toxicity towards mycobacterium tuberculosis.

Anti-tubercular activity shown by various thiazole derivatives:

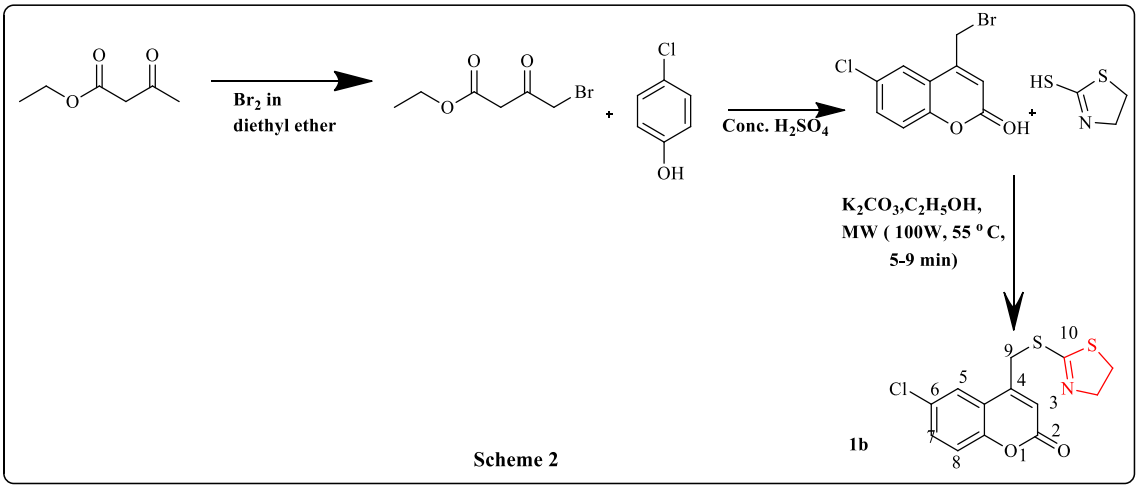
J. Ramprasad & Co-researchers synthesized 1-((6-phenylimidazo [2,1b] [1, 3, 4] Thiadiazyl-5-yl) methylene) 2-(4-phenylthiazol-2yl) hydrazine derivatives from multicomponent reaction by using an ionic liquid (1-butyl-3-methyl imidazolium bromide ([Bmim] Br). The compound **5s** was screened for their in vitro anti-tuberculosis activity against Mycobacterium tuberculosis. The derivatives containing trifluoromethyl & p-chlorophenyl substituted at position 2 & 6

respectively on imidazo-thiadiazol ring [ITD], is the most active molecule having MIC value 6.03 μM.[xxxvi] [Scheme 1]



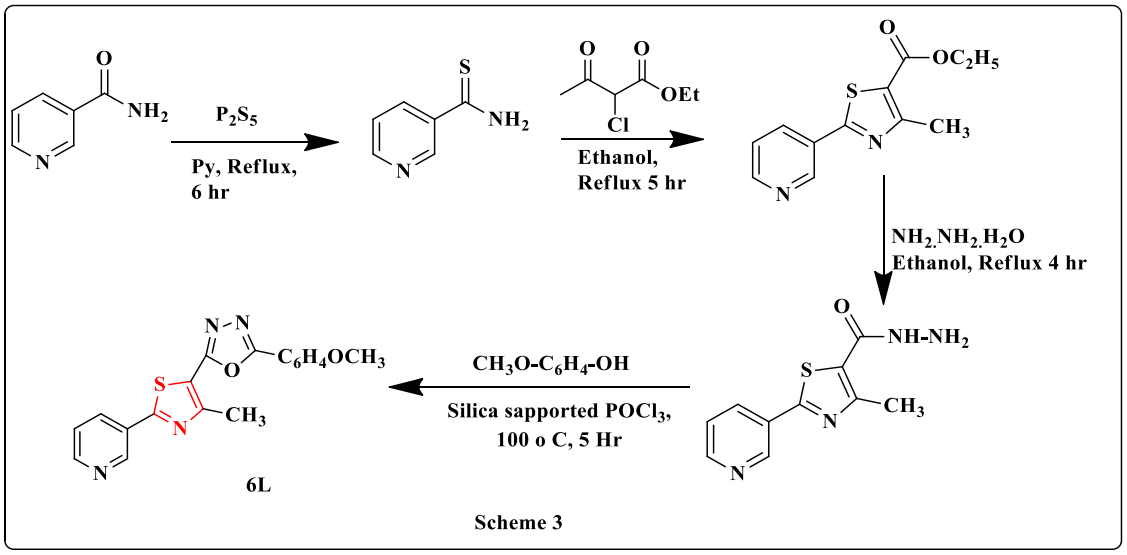
Scheme 1

The most important greener approach for the synthesis of 4-[4, 5-dihydro-1, 3-thiazol-2-ylthiol) methyl] substituted -2H-chromen-2-one investigated by K. M. Hosamani et al. The series of analogues were screened for their potential in vitro anti-tuberculosis. The chloro substituted derivatives **1b** observed most active/ml in vitro against Mtb H37 strain (ATCC-27294) and it possesses a low level of cytotoxicity against Vero cells.[xxxvii] [Scheme 2]



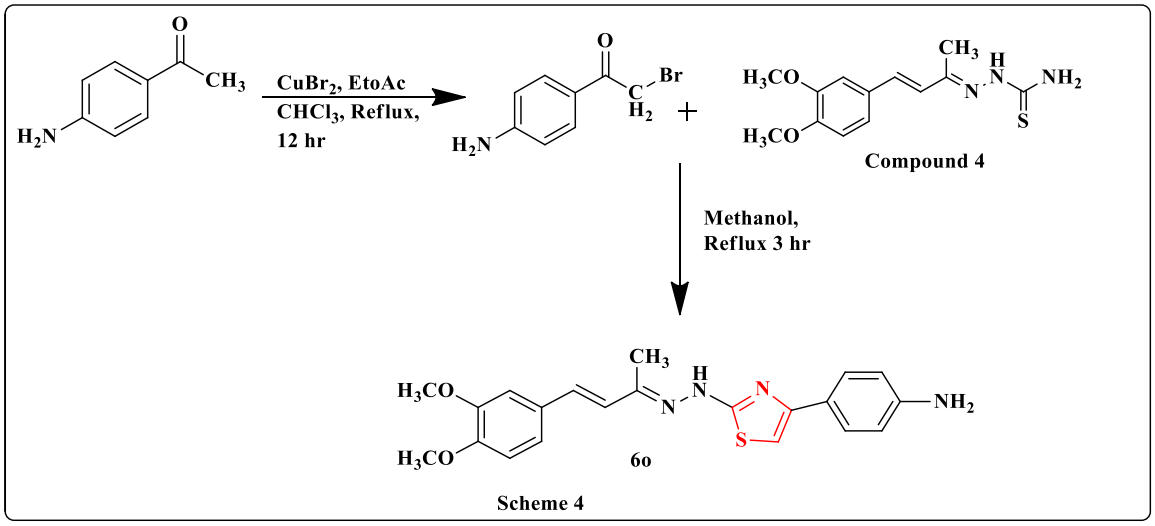
Scheme 2

S.T. Dhumal & co-workers synthesized the hybrid molecule by 1, 3, 4- oxadiazole clubbed with thiazole having pyridyl moiety. The new 2-pyridinyl substituted thiazolyl-5-aryl-1, 3, 4-oxadiazoles have displayed significant anti-tuberculosis against M. bavis BCG. Molecular docking studies show the binding confirmation of these compounds in the active site of potential target mycobacterial enoyl reductase (InhA) enzymes.[xxxviii] [Scheme 3]



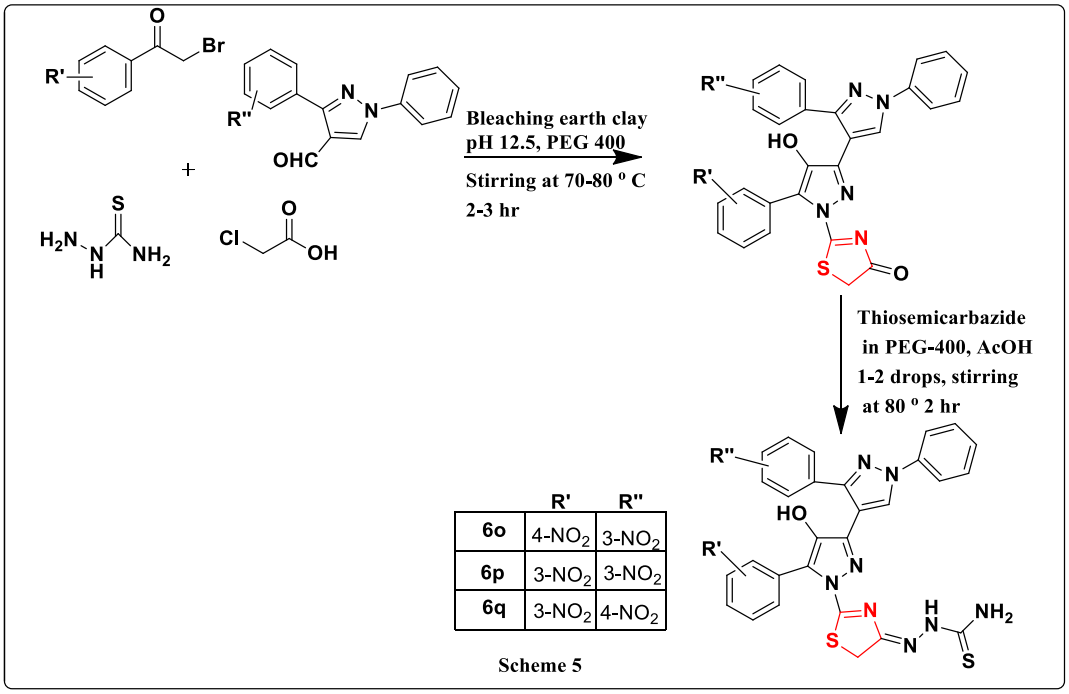
Scheme 3

Hampanavar et al.[xxxix] designed & synthesized a series of styryl hydrazine thiazoles hybridised with dehydrozingerone (DZG) by molecular hybridisation. 2-(2- ((2E, 3E)-4-(3, 4-dimethoxy phenyl) but-3-ene-2-ylidene) hydrazinyl)-4-(substituted phenyl) thiazoles compound evaluate in vitro against M. tuberculosis H37 Rv strain and exhibit significant activity MIC value is 1.5 μM. [Scheme 4]



Scheme 4

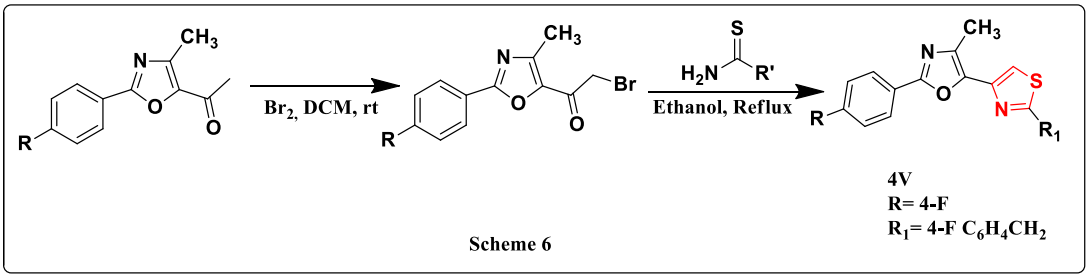
Mogle P. P & co-researchers, synthesized & developed a new class of anti-tubercular agent. Bipyrazol-yl-thiazol-ylidene-hydrazinecarbothioamides derivatives were synthesized by combining three biologically active moieties such as hydrazinecarbothioamides- thiazol-pyrazole and in all derivatives, the compound **6o**, **6p** & **6q** shown remarkable biological activity in vitro against Mycobacterium tubercle (MTCC 300). All derivatives show minimum toxicity in haemolysis method. [xl] [Scheme 5]



	R'	R''
6o	4-NO_2	3-NO_2
6p	3-NO_2	3-NO_2
6q	3-NO_2	4-NO_2

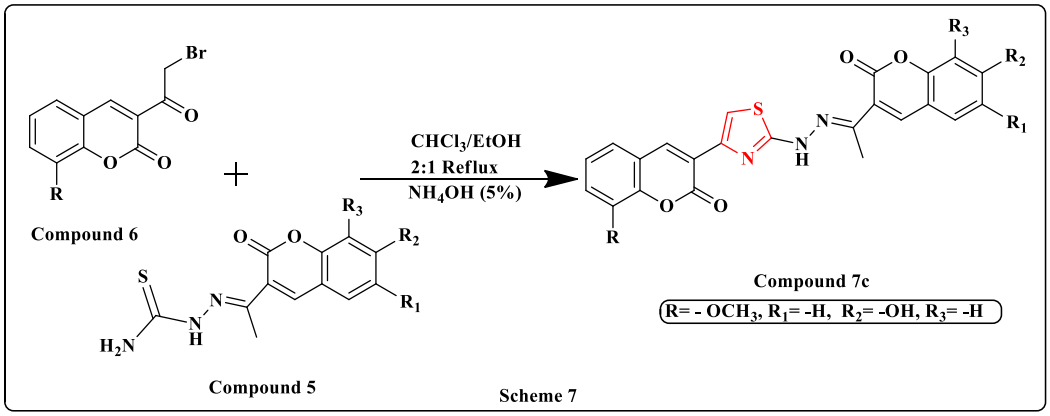
Scheme 5

Abhale Y. K. and co-workers synthesized novel thiazole derivatives i.e. 4-methyl -2-aryl-5(2-aryl/ benzyl thiazol-4yl) oxazole have been evaluated for their anti-tubercular activity. Among them compound **4v** show prominent results versus MTB H37 Ra strain & M. Bavis BCG correlate with stranded drug Rifampicin. The structure activity relationship reported that substitution of hydrogen atom in ring A by fluorine and in ring B by Br, Cl, F & -CH_3 consequently affects on anti-tubercular activity.[xli] [Scheme 6]



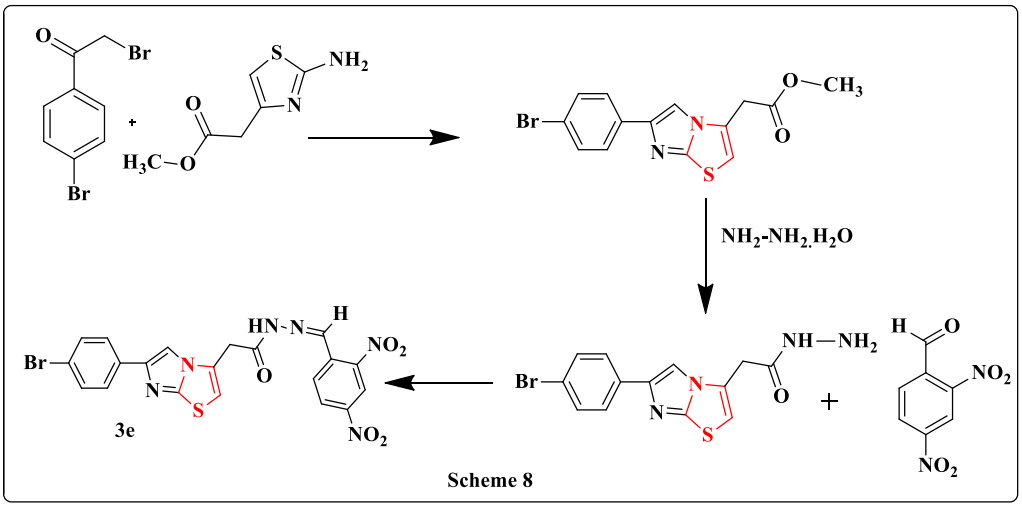
Scheme 6

Yusufzail & co-workers developed a new class for anti-TB agent i.e. thiazolyl coumarin derivatives, all derivatives were screened for antibacterial activity versus different gram (+) & gram (-) bacteria and in vitro for tuberculosis versus MTB H 37 Rv ATCC 25618 strain. Among the derivatives the compound **7c** show highest anti-TB activity/mL.[xlii] [Scheme 7]



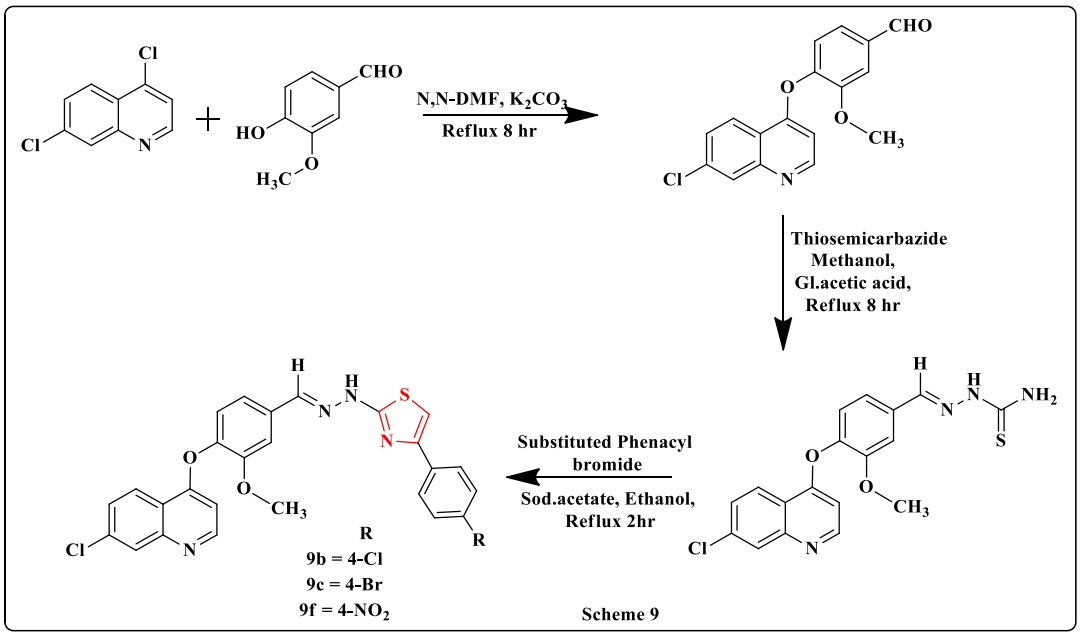
Scheme 7

Gazeldemirci et al. synthesized new N'- (arylidine) -2- [6-(4-bromophenyl) imidazo [2, 1b] thiazol-3-yl] acetohydrazides. The all derivatives were screened in vitro for anti-TB drug against M. tuberculosis H37 Rv strain, by applying the BACTEC-460 radiometric system. Among them **3e** derivatives was found to show prominent results versus MTB with MIC value is 6.25 μg/mL.[xliii] [Scheme 8]



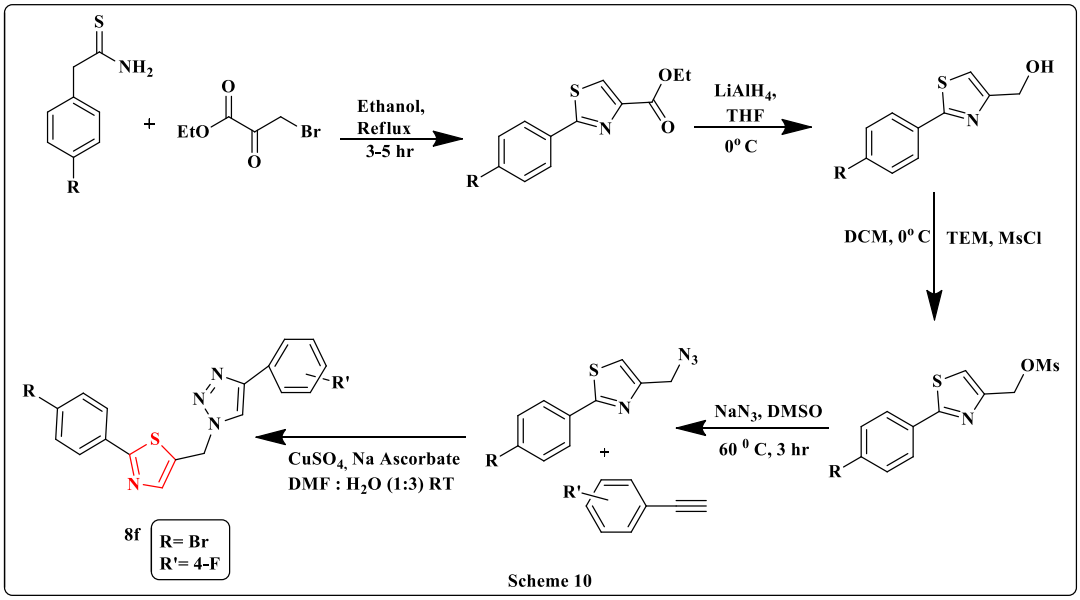
Scheme 8

Salve et al. intelligently synthesized a new analogues of 7-chloro-4-phenoxy quinolone bearing pyrazole, imidazole, thiazole-4-one, 4-aryl thiazole substituents and screened them for their anti-TB activity. Among them derivatives **9b**, **9c** & **9f** displayed moderate anti-TB activity versus MTB H37 Rv (ATCC27294) in vitro using the MABA method.[xliv] [Scheme 9]



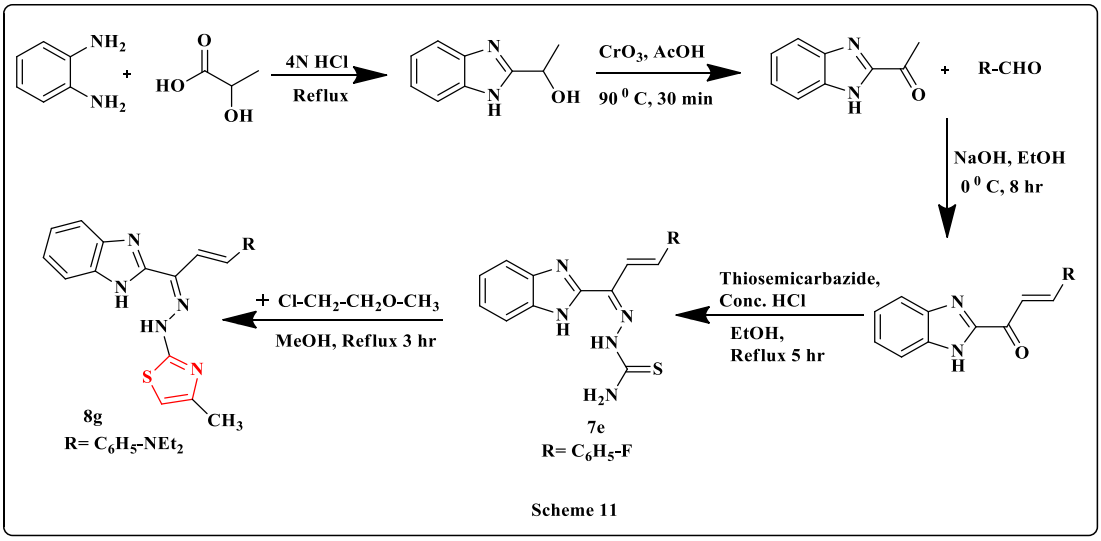
Scheme 9

Shinde et al. synthesized a new compound of 2-aryl-4-((4-aryl-1H-1, 2, 3 triazol-1yl) methyl) thiazole. These compounds screened for preliminary anti-TB against MTB H37 Ra (ATCC 25177) and M. Bavis (BCG, ATCC 35743).[xlv] [Scheme 10]



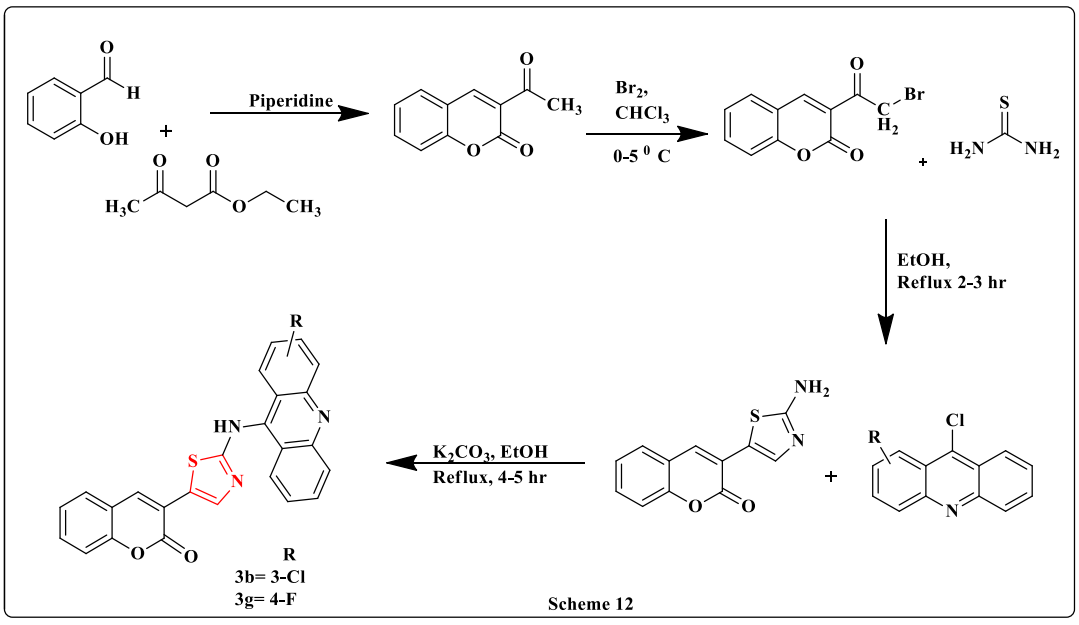
Scheme 10

Surineni & co-researchers, designed and synthesized a novel series of substituted benzmidazolallylidenehydrazinyl methyl thiazole derivatives via multicomponent reaction system. From the target compounds 7e & 8g derivatives show prominent biological activity against H37 Ra strain of mycobacterium tuberculosis, both having MIC values is 2.5 μg/mL.[xlvi] [Scheme 11]



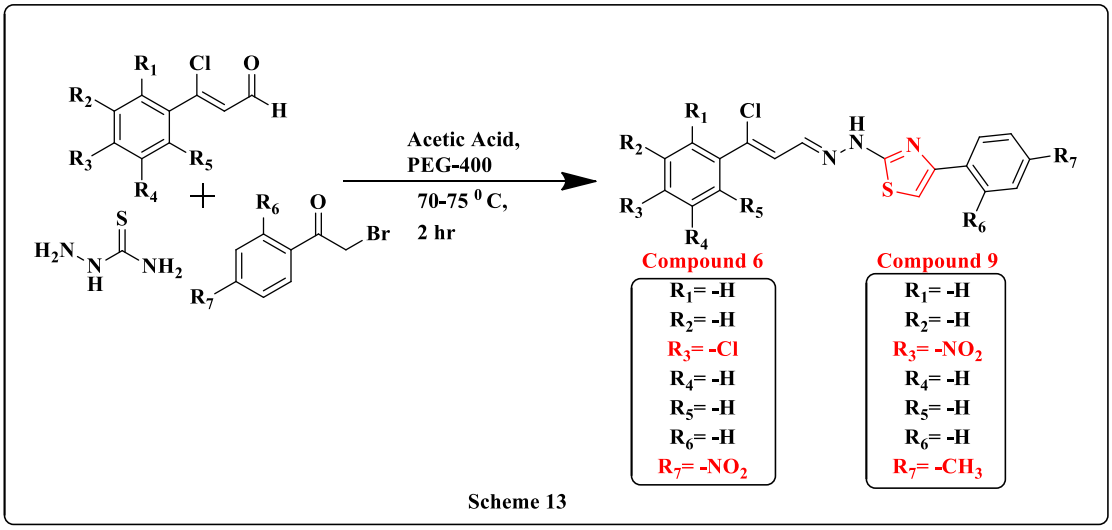
Scheme 11

To find new anti-TB agents, Mane S.G et al. synthesized novel acridin-(9-yl-amino) thiazo-5-yl) -2H- chromene-2-one derivatives. The compound **3b** & **3g** exhibit excellent anti-TB activity with MIC value 0.78 mg/mL and 1.56 mg/mL respectively. Their molecular docking studies carried out on InhA complex. All compounds show good interaction with M. tuberculosis. SAR studies of these compounds revealed that more electronegative substitution at C_1, C_2& C_3 position of acridine ring has shown the outstanding anti-TB activity.[xlvii] [Scheme 12]



Scheme 12

Hublikar. M et al. discovered and designed the novel anti-TB agent by simple, green approach & MCR system to synthesize a series of (E)-2-(2-allylidenehydrazinyl) thiazole derivative. In vitro inhibition potential was measured for different derivatives by the micro plate almar blue assay method, among them compound **6** shows excellent activity against MTB H37 Rv strain with MIC value is 6.5 μg/mL. They were also studying the dual-action properties of the compounds (antioxidant & NO radical scavenging activity), among them compound **9** exhibits promising results.[xlviii] [Scheme 13]



Scheme 13

CONCLUSION:

In the present review article, we shortly described the various synthetic routes of synthesis of thiazole containing compounds that have been useful in drug designing program towards the development of new anti-tubercular agents in the last five years.

We conclude that this review will be helpful for researchers involved in the synthesis of thiazole derivatives as anti-tubercular agents.

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