Recent Progress on Pyrazole Scaffold-Based Antimycobacterial Agents

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New and reemerging infectious diseases will continue to pose serious global health threats well into the 21st century and according to the World Health Organization report, these are still the leading cause of death among humans worldwide. Among infectious diseases, tuberculosis claims approximately 2 million deaths per year worldwide. Also, agents that reduce the duration and complexity of the current therapy would have a major impact on the overall cure rate. Due to the development of resistance to conventional antibiotics there is a need for new therapeutic strategies to combat Mycobacterium tuberculosis. Subsequently, there is an urgent need for the development of new drug candidates with newer targets and alternative mechanism of action. In this perspective, pyrazole, one of the most important classes of heterocycles, has been the topic of research for thousands of researchers all over the world because of its wide spectrum of biological activities. To pave the way for future research, there is a need to collect the latest information in this promising area. In the present review, we have collated published reports on the pyrazole core to provide an insight so that its full therapeutic potential can be utilized for the treatment of tuberculosis. In this article, the possible structure–activity relationship of pyrazole analogs for designing better antituberculosis (anti-TB) agents has been discussed and is also helpful for new thoughts in the quest for rational designs of more active and less toxic pyrazole-based anti-TB drugs.

Keywords: Anti-tubercular / Medicinal chemistry / Mycobacterium tuberculosis / Pyrazole / Synthesis / Tubercle bacillus

Received: December 9, 2014; Revised: February 14, 2015; Accepted: February 17, 2015
DOI 10.1002/ardp.201400452

Introduction

Human tuberculosis (TB) is caused by infection with members of the Mycobacterium tuberculosis complex, which includes M. tuberculosis (Mtbc), M. africanum, M. caprae, M. caprae, and M. microti. Mtb also known as the white plague was identified by Robert Koch in 1882 [3]. Highly complex interactions of Mtbc with the human host have been studied intensively ever since. Despite these efforts, many critical gaps in our knowledge remain, precluding successful control of the TB pandemic [4, 5]. TB...
usually attacks the lungs but can also spread through air. Many people become symptom-free carriers of the TB bacteria. Although common and deadly in the third world, TB was almost non-existent in the developed world, but has been making a recent resurgence. Certain drug-resistant strains are emerging and people with immune suppression such as acquired immunodeficiency syndrome (AIDS). Most infections in humans result in an asymptomatic, latent infection and about 1 in 10 latent infections eventually progresses to active disease. New infections caused by Mycobacterium tuberculosis (MTB) are registered to occur at a rate of about one per second [6].

TB has been one of the deadliest diseases over the past few decades affecting nearly one-third of the world’s population [7] with new infection occurring at 1% of population each year [8]. According to World Health Organization (WHO), in 2011 there were 8.7 million new cases of TB (13% co-infected with human immunodeficiency virus [HIV]) and 1.4 million people died from TB including 1 million HIV negative people [9]. It is estimated that 1.7 million people died in 2009 due to TB only [9], while new 9.4 million cases of TB were identified in the same year, of which the majority were in Asia and Africa. It is thought that the rates of new TB infections and deaths per capita have probably been falling globally for several years now. However, the total number of new TB cases is still slowly rising due to population growth and poor health. Between 1990 and 2005, TB incidence in Africa accounted for an estimated 78% of TB cases among HIV-positive people worldwide. The largest number of TB cases occurs in Asia, which in 2009 accounted for an estimated 56% of the global total. However the estimated incidence per capita in sub-Saharan Africa is around twice that of South-East Asia. The countries of Eastern Europe are also facing a serious epidemic; there were over 150000 new cases in Russia alone in 2009. TB is not only a problem in low- and middle-income countries. For example, there were 11545 new cases reported in the USA in 2009. In the UK, TB has been dubbed the disease that has never gone away, with 9040 new cases of TB reported in the UK in 2009 [10]. Although the UK’s national rate is very low in comparison with most of the world, London has become one of the world’s TB hotspots. In parts of London, TB rates are ten times higher than national rate and some countries of the former Soviet Union. About 10% of people with TB in London are likely to be co-infected with HIV [11].

Of the people who died of TB worldwide in 2008, it is estimated that 400000 were infected with HIV. TB is the leading cause of death among HIV-infected people in Africa. When someone is infected with TB, the likelihood of them becoming sick with the disease is increased many times if they are also HIV positive. The different cultures of the TB and HIV communities raise many challenges in achieving an effective and productive partnership. TB services are geared toward chronic-care services with simple and standardized technical procedures, while HIV/AIDS services are clinically oriented and tend to be more individual-patient-oriented [12]. Therefore, people with latent TB are increasingly becoming infected with HIV, and many more are developing active TB because HIV is weakening their immune system. People who are co-infected with both HIV and latent TB have an up to 800 times greater risk of developing active TB disease and becoming infectious compared to people not infected with HIV [12].

It has been established that nitrogen-containing heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications. Among nitrogen heterocyclic compounds, pyrazoles (1) and its derivatives are significant because of their wide spectrum of biological activities and their presence in naturally occurring compounds. They are widely used as core motifs for a large number of compounds for various applications such as catalysis, agro-chemicals, building blocks of other compounds, and in medicine.

Pyrazoles which belong to the family of azoles were first described by Knorr in 1833 [13]. They may be considered to have been derived from pyrrole by substitution of its 2-carbon by nitrogen atom, i.e., they are aromatic dinitrogen heterocyclic compounds. In pyrazoles, with one basic nitrogen and neutral nitrogen, the aromatic nature arises from the four π electrons and the unshared pair of electrons on the –NH nitrogen. Care should be taken in specifying which nitrogen is basic, since in unsymmetrical derivatives resonance prevents one from isolating a specific compound (1). 1H-Pyrazole (1) and its derivatives normally do not occur in nature probably due to difficulty in constructing a N–N bond by living organisms. The dihydro pyrazoles are called pyrazoline and three of them are possible depending on the position of the double bond. These are 4,5-dihydro-3H-pyrazole (2), 4,5-dihydro-1H-pyrazole (3), and 2,3-dihydro-1H-pyrazole (4) [14] (Fig. 1).

Pyrazoles and their derivatives have attracted much attention due to their diverse application in agrochemical, pharmaceutical, and chemical industries [15]. They possess a wide range of bioactivities [15, 16], including antiviral [17], anti-inflammatory [18], anticonvulsant [19], anticancer [20], insecticidal [21], antibacterial [22], antifungal [23, 24], antispasmodic [25], analgesic [26], antihyperglycemic [27], hypoglycemic [28], antineoplastic [29], antidepressive [30], antipyretic [31] activities, CNS regulants [32], and selective enzyme inhibitory activities [33]. It has been found that these compounds have hypoglycemic activity, and are also known as inhibitors and deactivators of liver alcohol dehydrogenase and oxido-reductases [34]. It has been shown in vitro that some of the pyrazole derivatives have appreciable antihypertensive activity [35]. These compounds also exhibit properties such as...
cannabinoid human cannabinoid (hCB1) and hCB2 receptor, inhibitors of p38 kinase, CB1 receptor antagonists [36, 37]. It has also been found that, various substituted pyrazoles are used as chelating and extracting reagents for many metal ions [38]. Moreover, these derivatives are used as starting material for the construction of condensed heterocyclic systems and represent an interesting template for combinatorial chemistry [38, 39].

To list a few pyrazole derivatives that are already booming in the market, some of them are as follows: celecoxib (5, COX-2 selective non-steroidal anti-inflammatory drug (NSAID)), antipyrine/phenazone (6, analgesic, NSAID and an antipyretic drug), analgin/metamizole (7, analgesic, antispasmodic (spasm reliever) and antipyretic), allopurinol/zyloprim (8, hyperuricemia and xanthine oxidase inhibitor), phenylbutazone (9, analgesic, NSAID and an antipyretic drug), oxyphenbutazone (10, NSAID) [1], pirazole (11, NSAID) [40], pyrazofurin (12, adenosine kinase) [41], ramifenazone (13, analgesic, antipyretic and anti-inflammatory agent) [42], indisteron (14) [43], apixaban (15, anticoagulant), fipronil (16, insecticide), rimonabant (17, anorectic antiobesity drug) [44] and many more are already in market (Fig. 2).

Therefore, the synthesis of pyrazole and its derivatives has received an increasing attention to synthetic organic chemists and biologists. Some reviews on involvement of pyrazole nucleus as different biological agents are available in the literature [45], but no review was published on pyrazole nucleus as anti-tubercular agents. A large amount of effort has been invested in the past decade to develop pyrazole-based compounds as modulator of antituberculosis (anti-TB), which is active on different clinically approved therapeutic targets showing excellent therapeutic potency. It is still a challenge for the pharmaceutical chemist to develop more effective and less toxic agents to treat signs and symptoms of TB disorders. By looking into the importance of this therapeutic area we decided to collect the published anti-TB data on pyrazole derivatives along with structure–activity relationship (SAR) and some opinion on different approaches to help the medicinal chemists in designing future generation potent yet safer anti-TB agents.

Common symptoms include:
- coughing that lasts longer than 2 weeks with green, yellow, or bloody sputum,
- weight loss,
- fatigue,
- fever,
- night sweats,
- chills,
- chest pain,
- shortness of breath,
- loss of appetite.

The occurrence of additional symptoms depends on where the disease has spread beyond the chest and lungs. For example, if TB spreads to the lymph nodes, it can cause swollen glands at the sides of the neck or under the arms. When TB spreads to the bones and joints, it can cause pain and swelling of the knee or hip. Genitourinary TB can cause pain in the flank with frequent urination, pain or discomfort during urination, and blood in the urine [48].

**Diagnosing tuberculosis**

TB can be diagnosed by three major methods:
- skin test,
- chest X-ray,
- sputum culture test.

A tuberculin skin test allows a doctor to check your immune response to the TB bacteria. It is a test that is used for detecting infection with the TB bacteria. It is given to people who have been exposed to patients with active, contagious TB or to those in whom reactivation of TB is suspected. Skin testing involves an injection in the forearm 2 or 3 days later, a physician will “read” the test. If it is positive, indicated by a hard and swollen region at the site of injection, this means that your body has been infected by the TB bacteria. It does not necessarily mean that you have active TB – the TB may be inactive. Chest X-rays can also be performed, and sputum samples can be analyzed in the lab. In these cases, the results are used to rule out or confirm active TB. Your doctor may also suggest other tests to confirm a diagnosis or to check for TB in other parts of your body. Sputum is a thick fluid produced in the lungs and in the airways leading to the lungs. For the sputum culture test, sputum of the person is taken and cultured in a suitable medium. If there is no bacterial growth, the culture is negative. After 2–3 weeks, a colony of bacteria can be seen if the person is infected with *M. tuberculosis* [49].

**Main tuberculosis drugs in clinical use**

Anti-TB drugs are classified into five groups based on evidence of efficacy, potency, drug class, and experience of use [50]. All first-line anti-TB drug names have a standard three-letter
and/or a single-letter abbreviation. The first-line anti-TB drugs are ethambutol (EMB/E) [51, 52], isoniazid (INH/H) [53, 54], pyrazinamide (PZA/Z) [55–58], rifampicin (RIF/R) [59–61], and streptomycin (STM/S) [62, 63] given for 6 months (Fig. 3).

Second-line drugs (SLDs) are those that are less effective than the first-line or have some side effects. The unavailability of a drug in many developing countries also makes it SLD. If the treatment fails as a result of bacterial drug resistance, or intolerance to one or more drugs, SLDs are used. The SLDs are only used to treat disease that is resistant to first-line therapy (i.e., for extensively drug-resistant tuberculosis (XDR-TB) or multidrug-resistant tuberculosis (MDR-TB)) [64]. Further, the SLDs are divided into six classes; these are (i) aminoglycosides (amikacin/AMK, kanamycin/KM), (ii) polypeptides (capreomycin, viomycin, enviromycin), (iii) fluoroquinolones (ciprofloxacin/CIP, moxifloxacin/MXF, levofloxacin), (iv) thioamides (prothionamide, ethionamide), (v) cycloserine, and (vi) terizidone and p-aminosalicylic acid/PAS/P (Fig. 4).

The third-line drugs are either not very efficient or their effectiveness is not yet established. This includes rifabutin,
Figure 3. First-line anti-TB drugs.

Figure 4. Second-line anti-TB drugs.
macrolides: e.g., clarithromycin (CLR); linezolid (LZD); thioacetazone (T); thioridazine; arginine; vitamin D; bedaquiline (Fig. 5). Rifabutin is effective, but is not included on the WHO list because for most developing countries, it is impractically expensive [65].

WHO-recommended directly observed treatment short course (DOTS) anti-TB therapy involves the administration of four drugs: INH, RIF, PZA, and EMB or SM. Treatment with these so-called first-line drugs is carried out initially over 2 months, leading to the destruction of bacteria in all growth stages, after which treatment continues with RIF and INH alone for 4 months, where any residual dormant bacilli are eliminated by RIF and any remaining Rf-resistant mutants are killed by INH [66, 67].

Pyrazole and its derivatives: Structural requirements for anti-TB activity

From collected published data, it is found that pyrazole nucleus substituted at all position with varied substituents has produced potent anti-TB activity. The 1st position of pyrazole may be unsubstituted or substituents may vary from aryl groups. Among them, pyrazole with 2-Cl, 3-Cl, 4-Cl, 4-CH$_3$, and 2-Cl-5-SO$_2$ at phenyl substituents showed excellent anti-TB activity. Similarly, 2nd position may be substituted with phenyl substituents with fluorine, trifluoro, and nitro, showed good activity. The 3 or 4-position of the nucleus may be substituents are more because of the conjugation and substituents may range. At the 3rd position of pyrazole with functional groups like halogen, methyl, methoxy, and nitro substituents in phenyl ring enhances the anti-TB activity. Also at the 4th position presence of 1-(p-methoxyphenyl)-2-propenone, 4-hydrophenyl-2-aminopyrimidine, p-chlorobenzoxyl, piperidine, or methyl piperidine showed excellent activity. Finally, 5th position with –CF$_3$, napthyl ring, phenyl ring with –Cl, –CH$_3$ of pyrazole shows good anti-TB activity (Fig. 6).

Pyrazole derivatives for treatment of tuberculosis

Yadlapalli and co-workers reported synthesis of diarylpyrazole ligated dihydropyrimidines (DHPs) derivatives by utilizing Biginelli reaction and evaluated for their in vitro anti-TB activity against $M_{tb}$ H$_{37}$Rv using microplate alamarBlue assay (MABA). Compounds 18a, b, with a minimal inhibitory concentration (MIC) value of 0.125 and 0.25 μg/mL respectively, were shown most potent in the series. SAR studies revealed, compounds with chlorine (–Cl) were more potent 18a, b, when compared to compounds with other substituents like H [68]. Fluoro substituted pyrazolylpyrazoline derivatives
were synthesized under microwave irradiation and anti-TB activity was screened at 250 µg/mL against Mtb H37Rv strain by using Löwenstein–Jensen (L–J) medium. Compounds 19a–d possess excellent activity (i.e., 90, 91, 96, and 94% at 250 µg/mL) against Mtb H37Rv. SAR study reveals, the presence of electron withdrawing group (4-F, 4-Br) at R1 position and –CF3 group at meta position of aryloxy ring illustrated anti-TB activity. The presence of bromo group at R1 position and fluoro group at ortho, meta, and para positions of aryloxy ring showed enhanced anti-TB activity [69] (Fig. 7).

Benzoxazole-based pyrazoline derivatives were synthesized by Rana et al., and evaluated for in vitro anti-TB studies against Mtb H37Rv and MDR-TB strains. Some of the compounds displayed potent activity (MIC = 0.625–25 µg/mL) and few compounds were found better than standard INH against MDR-TB (MIC = 3.25 µg/mL). Compounds 20b and 21 were found potent as good as INH against Mtb H37Rv, while 20a was found more potent than INH against MDR-TB strain [70].

Horrocks and co-workers described the synthesis of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives and tested for anti-TB activity against Mtb H37Rv strain. The introduction of electron-withdrawing groups like pyridine (22a), nitro (22b), or chloro (22c) group in the phenyl ring resulted in very good antimycobacterial activity, while the electron-releasing groups like hydroxyl, methoxy, or amino showed poor activity. SAR study reveals, the electron-withdrawing groups in the phenyl ring are important for antimycobacterial activity [71] (Fig. 8).

Pathak and co-workers investigated pyrazole bearing 2-azetidinones and 4-thiazolidinones derivatives as anti-TB agents. Best activity against Mtb H37Rv was observed for the 2-OH substituted azetidinone derivative (23), which is slightly less potent than the standard drug RIF, followed by the 3,4-(OCH3)2 substituted hydrazone derivative (24); the 2- and 4-OH substituted thiazolidinone derivatives 25a,b showed better anti-TB activity. SAR study reveals, the substituents like...
–OH, –Cl, –OCH₃ enhance the anti-TB activity [72]. A series of 4-substituted pyrazoles have performed and tested for in vitro antimycobacterial activity against Mtb H₃₇Rv. Substitution of 1-(p-methoxyphenyl)-2-propen-1-one at the 4th position of the pyrazole ring produced the most active molecule (26) with a IC₅₀ of 0.47 µM. Of compound 27 with a 4-hydroxyphenyl-2-aminopyrimidine at 4th position of the pyrazole ring, concentrations of 0.88 and 0.47 µM are required for 90 and 50% inhibition, respectively [73] (Fig. 9).

Manikannan and co-workers performed synthesis of isomeric pyrazoles derivatives and antimycobacterial activity has been screened for their in vitro activity against Mtb H₃₇Rv. Compounds with a p-nitrophenylthio ring (28a and 29) in the pyrazole ring showed excellent anti-TB activity and also all the aryl ring carrying p-chloro group (28b) or when the substituents are p-chlorophenylthio and cyclohexylthio groups (28c). SAR study reveals, p-chlorobenzoyl moiety at the C₄ of the pyrazole ring has found remarkable antimycobacterial activity in some of the pyrazole compounds [74]. Recently, Monga et al., have investigated pyrazoline inhibit the strong anti-TB activity against Mtb H₃₇Rv. Pyrazoline derivative substituted with electron-donating methoxy groups at the

Figure 8. Structures of the compounds 20–22.

Figure 9. Structures of the compounds 23–27.
meta/para position of the phenyl rings (30) displayed highest activity against \textit{Mtb} with MIC value of 12.5 \(\mu\)g/mL. Compound possessing naphthyl ring attached to C-5 of the pyrazoline ring (31) showed better anti-TB activity, having MIC value of 62.5 \(\mu\)g/mL (Fig. 10) [75].

Aragade and co-workers studied a series of pyrazole derivatives containing INH and coumarin moieties, evaluated anti-TB activity against \textit{Mtb H37Rv} using Resazurin MIC assay. Compound 32 containing a 4-fluoro group at C-3 phenyl ring of pyrazole nucleus has showed promising antimycobacterial agent. From SAR, the presence of electron withdrawing groups such as –F, –Cl, and –NO2 on the phenyl ring of pyrazole moiety at C-3 position may be attributed for enhanced antimycobacterial activity. The presence of 4-fluoro group compound displayed relatively higher inhibitory activity [76]. Chovatia and co-workers performed the synthesis of diphenyl-4,5-dihydro-(1H)-pyrazole derivatives and screened for activity against \textit{Mtb H37Rv} at a concentration of 6.25 \(\mu\)g/mL in BACTEC 12B medium using the ALAMAR radiometric and results were compared with the standard drug RIF. Compound with methoxy (33) and methyl (34) group in the phenyl ring attached to pyrazole, showed 86% inhibition at 6.25 \(\mu\)g/mL (Fig. 11) [77].

Amino-4,5-dihydro-1H-pyrazolylmethanethione derivatives were also reported as anti-TB agents by Ali et al. Compounds were tested for their antimycobacterial activity \textit{in vitro} against \textit{Mtb H37Rv} and INH resistant \textit{Mtb (INHR-Mtb)} using BACTEC method and results were compared with INH. Among the synthesized compounds, 35 was found most active agent against \textit{Mtb H37Rv} and INHR-Mtb with MIC of 0.43 \(\mu\)M. When compared to INH, compound 35 was found 1.62- and 26.41-fold more active against \textit{Mtb} and INHR-Mtb, respectively. Compounds with chloro substituted phenyl group showed higher anti-TB activity [78]. Namrata and co-workers identified benzyloxy phenyl butenyl azoles as anti-TB agents. The compounds possess potent anti-TB activities with MIC comparable to the standard drugs. Especially, compound 36 exhibited significant anti-TB activity with MIC value as low as 0.61 \(\mu\)g/mL, comparable to many standard drugs. SAR study reveals, substituent on the 4-benzyloxy ring did not display any significant change on the anti-TB activity. Compounds with imidazole and benzimidazole moieties showed promising anti-TB activity with MIC values from 1.56 to 12.5 \(\mu\)g/mL (Fig. 12) [79].

Trivedi and co-workers carried out synthesis of pyrazolo[3,4-d]pyrimidine derivatives and assessed antimycobacterial activities against \textit{Mtb} using MABA. Compounds 37a-d exhibited best results (1.2 \(\mu\)g/mL) when compared with first-line drugs such as INH and RIF. SAR study reveals, the presence of 2-
chloro-, 3-chloro-, 4-methyl-, and 2-chloro-5-sulfonyl substituents markedly enhances anti-TB activity [80]. In continuation of their work, author synthesized DHP bearing 1H-pyrazole ring substituted at C-4 position as anti-TB agents. Compound 38 was found most active compound in vitro with MIC of 0.02 mg/mL against Mtb and was more potent than INH. SAR study reveals, compounds with carbethoxy substituents at C-3 and C-5 position of DHP ring exhibited higher antimycobacterial activity than the compounds with acetyl substituents at C-3 and C-5 position [81]. Same author reported, pyrazole ring bearing 4-DHP derivatives were prepared and screened for their in vitro antimycobacterial activity at 6.25 mg/mL against Mtb H37Rv strain. Compound 39 with 4-nitro group at the 3-aryl substituent on pyrazole nucleus along with carbomethoxy group at C-3 and C-5 position of DHP ring was the most potent, while compounds 40a,b with 4-fluoro and 4-bromo groups, respectively, at the 3-aryl substituent on pyrazole nucleus along with carboxethoxy group at C-3 and C-5 position of DHP ring were the most potent. SAR reveals, DHP derivatives bearing alkyl ester group at C-3 and C-5 position along with electron-withdrawing groups at the 4th position of 3-aryl substituents on pyrazole nucleus have exhibited comparatively higher antimycobacterial activity probably due to their higher lipophilicity (Fig. 13) [82].

A series of 3H-indeno[1,2-c]pyrazole-2-carboxamide analogues were reported and evaluated for in vitro antimycobacterial activity against Mtb and INH-Mtb. The compounds 41a,b were found active against Mtb at a MIC of 0.78 µM comparable to that of INH. The compounds 41a,b were found to be active against INH-Mtb at a MIC of 0.78 and 3.12 µM, respectively. When compared with INH, the compound 41a was 16-fold more active while compound 41b was 4-fold more active against INH-Mtb. SAR study reveals, 3-substituted compounds with electron withdrawing groups such as 4-fluorophenyl, 4-pyridyl produced more inhibitory and 2-chlorophenyl produced moderate inhibitory activity while the electron releasing groups such as 4-methoxyphenyl, 3,4-dimethoxyphenyl showed less inhibitory activity. The 4-fluoro substitution on N-aryl group showed maximum inhibitory activity as compared to 4-bromo and 3-chloro-4-fluoro substitution [83]. In continuation of their work on anti-TB drugs, authors reported 3H-indeno[1,2-c]pyrazole-2-carbothioamide analogues inhibit activity against Mtb and INH-Mtb. Compound 42 was found to be active against Mtb and
INH-Mtb at a MIC of 3.12 and 6.25 µM, respectively. When compared with INH the compound 42 was fourfold less active than INH against Mtb and twofold more active than INH against INHR-Mtb. From SAR concluded same as above, 3-substituted compounds with electron withdrawing groups such as 4-fluorophenyl produced more inhibitory activity than 2-chlorophenyl and 2-pyridyl substitution [84]. In another article, same author reported synthesis pyrazole-2-carboxamide analogues as anti-TB agents. Compound 43 was active against Mtb and MDR-TB at a MIC of 0.83 and 3.32 µM, respectively. When compared with INH, the compound 43 was less potent against Mtb, while 13.6-fold more active against MDR-TB. SAR study reveals, 4-chlorophenyl substitution on N-aryl group showed maximum inhibitory activity than 4-nitrophenyl substitution or when there was no substitution (Fig. 14) [85].

Castagnolo and co-workers developed novel rigid pyrazoline derivatives and evaluated as inhibitors of Mtb. The presence of a chlorine atom on the N1-phenyl ring caused an improvement in the activity with respect to non-halogenated and compound bearing N-Me-piperazine (44a) and morpholine moieties (44b) proved to be very active with MIC 4 µg/mL. SAR study reveals, the presence of piperidine or Me-piperidine moieties showed detrimental for the activity [86]. Pyrazoline derivatized carbazole derivatives were reported as anti-TB agents by Taj et al. Compounds with electron donating groups 45a-c have exhibited excellent inhibition with MIC less than 5 µg/mL. The anti-TB activity is attributed to the presence of electron donating atoms/groups viz., –Cl, –OH, and –OCH3 through mesomeric effect appended to the pyrazoline moiety (Fig. 15) [87].

Gunasekaran and co-workers performed the synthesis of 2-aryl-1H-3-pyrazolone derivatives by one-pot, four-component sequential reactions using p-toluenesulfonic acid in water. The synthesized compounds were tested for in vitro antimycobacterial activity against Mtb. The compound 46 displayed the maximum potency with a MIC of 1.6 µM against Mtb, being 2.94 and 4.75 times more active than CIP and EMB, respectively. SAR study reveals, aryl ring at C-11 bearing electron withdrawing groups such as halogens and nitro show greater activity than that with electron-releasing groups, viz.

![Figure 13. Structures of the compounds 37-40.](image)

![Figure 14. Structures of the compounds 41-43.](image)
methoxy, methyl, and isopropyl [88]. A series of isonicotinoyl-3-(pyridin-2-yl)-pyrazole derivatives reported for evaluating their antimycobacterial activity toward a strain of \( \text{Mtb} \ H_3Rv \) and a strain of \( \text{Mtb} \ H_4 \). Compounds 47a-e showed good anti-TB activity at 8 \( \mu \text{g/mL} \) against \( \text{Mtb} \ H_3Rv \) and a strain of \( \text{Mtb} \ H_4 \) strains. The inhibition of INH release through a possible stabilizing effect of a hydrogen bond between the hydroxyl group in the ortho position on the 3-aryl residue and the nitrogen atom at the 2-position in the pyrazoline cycle of these compounds (Fig. 16) [89].

Silva and co-workers performed the synthesis of isonicotinoyl-4,5-dihydropyrazole derivatives and tested in vitro anti-TB activity against INH-susceptible \( \text{Mtb} \ H_3Rv \), INHR-\( \text{Mtb} \) isolates and non-tuberculous mycobacteria. Among the synthesized compounds 48a,b exhibited antimycobacterial activity in the same range as INH for the susceptible \( \text{H}_2Rv \) strain and higher activity than \( \text{INH} \) against resistant strains such as RGH101, RGH102, and RGH103. Compound 48c is not the most active against \( \text{Mtb} \ H_3Rv \), it is the only compound having activity against all the tested INH-R \( \text{Mtb} \). SAR study reveals, compounds with trifluoromethyl-substituted pyrazolines (48a and 48c) were more active than their analogs trichloromethyl-substituted pyrazolines [90]. Chobe et al., disclosed the synthesis of pyran-2,3-c]-pyrazole derivatives and compounds were investigated against \( \text{Mycobacterium smegmatis} \), \( \text{Mycobacterium phlei} \), and \( \text{Mtb} \) species. The activity may centered and enhanced on the presence of naphthaleno moiety containing dihalo group, i.e., chloro and fluoro as well as the methoxy group in these compounds. The strain \( \text{Mtb} \) was observed to be resistant toward compound 49 (MIC, 100 \( \mu \text{g/mL} \), was found to be effective growth inhibitors of this strain. The presence of hydroxyl, dihalo, and methoxy group shows moderate activity and these compounds might have relevance in imparting the growth inhibition (GI) activity against \( \text{Mtb} \) (Fig. 17) [91].

A series of 3-amino- pyrazole derivatives were synthesized and screened for \( \text{Mtb} \ H_3Rv \) inhibition assay. Compound 50 shows (MIC < 1 \( \mu \text{g/mL} \), IC_{50} = 0.004 mg/mL), 51 (MIC = 0. 4 \( \mu \text{g/mL} \)), 52 (MIC < 1 \( \mu \text{g/mL} \)), and 53 (MIC = 0. 4 \( \mu \text{g/mL} \)) excellent anti-TB activity [92–96]. Pandit and Dodiya reported pyrazole-quinazolinone hybrid analogs as anti-TB agents. Compounds containing ortho directing substitutions of chloro, methyl, and methoxy in basic skeleton led to increase in anti-TB activity. Compounds 54a-e exhibited excellent anti-TB activity with percentage inhibition of 96, 90, 94, 93, and 92, respectively at a MIC value of 6.25 \( \mu \text{g/mL} \). SAR study reveals, compounds containing electron-releasing groups, such as –CH_3 and –OCH_3 groups at ortho position and electron negative group –Cl at ortho and para positions led to increase in activity, while electron negative group at meta position led to increased activity owing to bulky group, ring strain increased and made compound less stable and active [97].

Khanage and co-workers described the synthesis of pyrazole Figure 16. Structures of the compounds 46 and 47.

Figure 15. Structures of the compounds 44 and 45.

Figure 17. Structures of the compounds 48 and 49.
derivatives containing 1,2,4-triazole derivatives evaluated for in vitro anti-TB and Mtb H37Rv (ATCC27294) in BACTEC 12B medium using a broth micro-dilution assay. 4-Chloro, 3-nitro, 4-methoxy, and 2-chloro substituted compounds were found to be antimycobacterial agents at MIC value of 6.25 μg/mL (Fig. 18) [98].

Conclusion and future aspects

Due to the unusual structure and chemical composition of the mycobacterial cell wall, effective TB treatment is difficult, which makes many antibiotics ineffective and hinders the entry of drugs. With approximately 33% of infection, tuberculosis is still the second most imperative infectious disease worldwide. Although pyrazoles are rarely found in natural products, numerous pyrazole derivatives display a broad spectrum of pharmaceutical and agrochemical activities, and they have also been successfully applied in other fields. This has given rise to search for molecules acting on a novel target or a multi-targeted combination therapy. With the increase in the number of new compounds screened against mycobacteria, the opportunity exists to develop a novel drug for the cure and complete eradication of TB. This review is an attempt to address the vistas of anti-TB potential of strategically placed pyrazole scaffold in medicinal chemistry and drug development. Information provided in this manuscript can be found useful for further investigations on this scaffold in order to harness its optimum anti-TB potential. To further optimize the full potential of pyrazole compounds, the SAR-based study will likely continue to play an important role. It is highly likely that optimized pyrazole compounds with excellent potency and little side effects will continue to be created. Some of these pyrazole compounds will undoubtedly be used as first and second-line anti-TB therapeutic agents in the near future. Further investment in developing fundamental genetic systems and more accurate models of human disease would significantly facilitate TB drug discovery efforts in the long term, in particular enabling robust validation of novel targets.

The authors acknowledge Jain University, Bangalore for the financial support and R.S.K. thanks Fundação para a Ciência e Tecnologia (FCT) for financial support with the project “the Postdoctoral Fellowships SFRH/BPD/75490/2010.” The author K.C. is thankful to Erasmus NAMASTE consortium grant (unique number: NAMASTE_20130125) for the award of postdoctoral fellowship.

The authors have declared no conflict of interest.

References

Pyrazole-Based Antimycobacterial Agents


