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Quinazoline as a Antitubrcular Agent: A Review

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ABSTRACT

Quinazoline analogues are effective nitrogen-containing heterocycles with substantial bioactivity that can be contained in a wide range of natural products. Tuberculosis, caused by *Mycobacterium tuberculosis* (MTB), is a severe universal health threat that mainly affects the lungs. Researchers are attempting to synthesize new quinazoline analogues that may have considerable potency against tuberculosis due to their significant bioactivity and natural occurrences.

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INTRODUCTION:

Tuberculosis (TB), which is caused by the bacteria *Mycobacterium tuberculosis*, is an infectious disease for which new medicines are still needed to improve treatment. In only one year, the WHO announced 8.8 million new cases and 1.4 million deaths due to the disease. Furthermore, billions of people have latent infections that have no clinical signs but can become active.TB therapy currently includes a two-month course of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETH), followed by another four months of INH and RIF. These medications have been in use for decades, leading to the proliferation of M. tuberculosis strains that are multidrug-resistant (MDR) and extensively drug-resistant (XDR) [1]. Tuberculosis affects the lungs in most cases, but it may also affect other parts of the body. When people with the disease cough, sneeze or spit, it spreads through the air.

1.1 *Mycobacterium Tuberculosis*:-

Under ideal conditions, M. tuberculosis grows in a doubling time of 12-24 hours. The inner portion of the cell wall is made up of mycolic acid and glycolipid, while the outer section is made up of waxy components. Peptidoglycan forms a periplasmic gap between two membranes when it is covalently connected with arabinogalactan and lipoarabinomannan. If the person with the infection coughs or sneezes small droplet nuclei that are suspended in the air for a long time, the infection is initiated by inhalation, and because of their small size, they penetrate terminal alveoli. The key component in the relationship between bacilli and host cells is mycobacterial adhesin HBHA and PE PGRS proteins. . Both Mycobacteria strains contain alkyl, hydroxy fatty acids, which have a higher molecular weight (60-90 Carbon atoms chain). Both Mycobacteria strains contain alkyl, hydroxy fatty acids, which have a higher molecular weight (60-90 Carbon atoms chain). The key characteristics of the M. tuberculosis cell wall are mycolic acid, 2-alkyl, 3-hydroxy long-chain fatty acids. Mycolic acid is produced in three forms by *Mycobacterium tuberculosis* and Mycobacterium Bovis alpha mycolate, methoxymycolate, and ketomycolate are all forms of mycolate. Chemically, mycolic acid comprises the unsaturation as well as the cyclopropane rings, indicating the presence of mycolic acid. cell wall defense bacillus mycolic acid against oxidative stress.

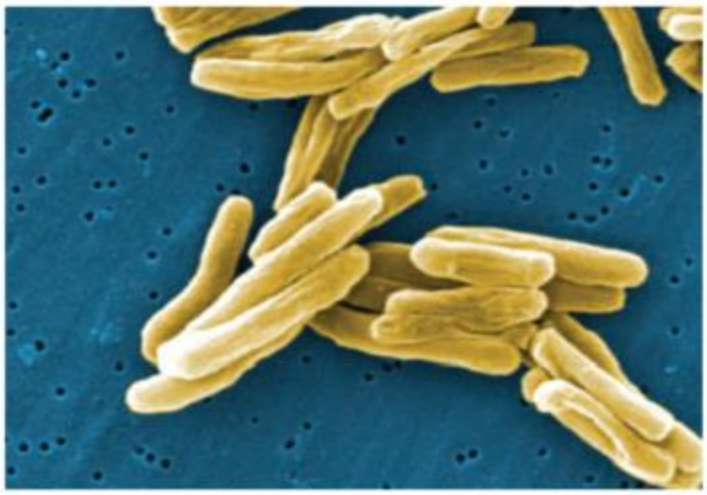


Figure No.1: ***Mycobacterium Tuberculosis***

1.2 Types of Tuberculosis:- Tuberculosis is a highly infectious and lethal disease that can spread across the body and, in some cases, cause a latent infection. In terms of clinical classification, tuberculosis is divided into two classes.

1. Pulmonary Tuberculosis:-

Primary Tuberculosis-

The Ghon complex is tuberculosis characterized by a subpleural focus of inflammation and infected lymph nodes draining the central, subpleural lesion. the infection of a person who has never been infected before; the source of bacteria is external in this case. A individual with active pulmonary tuberculosis will transmit the disease to others by coughing infectious particles into the air.

Secondary Tuberculosis (Reactivation):-

The individual has already been infected or sensitized to the disease. The bacterium is reactive and causes manifestation, with granuloma formation most often in the apex of the lungs. Since the oxygen pressure in the lungs is higher, secondary tuberculosis is more common there. QuillBot will rewrite your text for you. To begin, type or paste something into this box, then press the enter key.

2. Extrapulmonary Tuberculosis:-

Tuberculosis is infected in the body and is still spreading into deep tissue in this form. Bacillus enters the body and infects other organs. It's a rare condition that mostly affects the bones of the back, elbows, joints, knees, and brain. Extrapulmonary tuberculosis is widespread in HIV-positive people and infants.

2. Sign and Symptoms

When the disease becomes involved, pulmonary TB, or TB in the lungs, accounts for 75% of cases. Chest pain, blood in the cough, and a productive, persistent cough lasting more than three weeks are all symptoms. Fever, chills, night sweats, appetite loss, weight loss, pallor, and easy exhaustion are all typical systemic symptoms. In the remaining 25% of active cases, the infection spreads outside of the lungs, causing other forms of tuberculosis, collectively known as extrapulmonary tuberculosis. Immuno-compromised people and young children are more likely to develop this condition. The pleura in tuberculosis pleurisy, the central nervous system in meningitis, the lymphatic system in scrofula of the neck, the genitourinary system in urogenital tuberculosis, and the bones and joints in Pott's disease of the spine are all extrapulmonary infection sites. Disseminated tuberculosis, also known as miliary tuberculosis, is a particularly dangerous type [2].

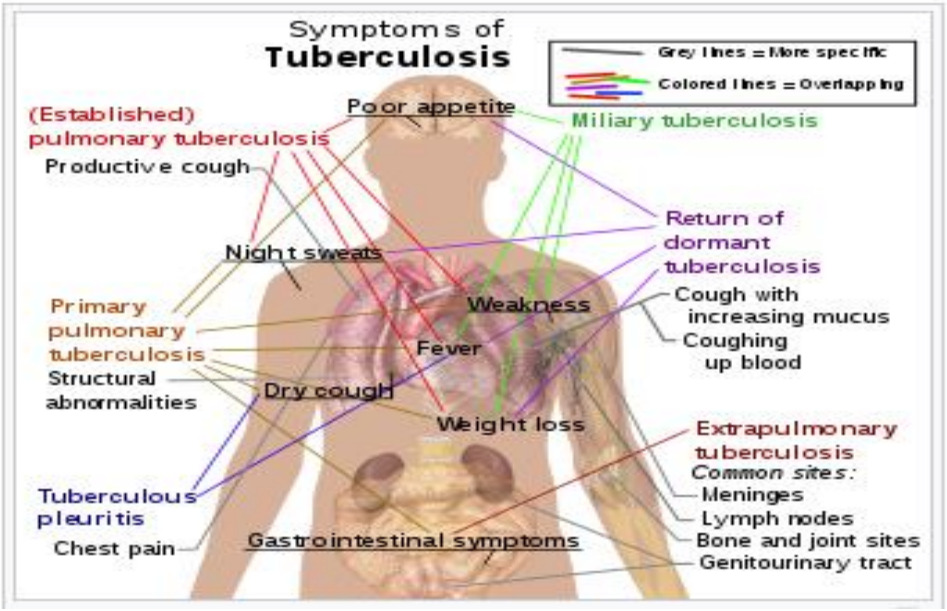


Figure No. 2: Symptoms of Tuberculosis

3. Causes OF Tuberculosis

Tuberculosis is caused by M. tuberculosis, a small aerobic non-motile bacillus. Many of this pathogen's unusual clinical features are attributed to its high lipid content. MTB is known as a Gram-positive bacterium because it has a cell wall but no phospholipid outer membrane.

M. tuberculosis is a TB-causing mycobacterium that includes *M. bovis, M. africanum, M. canetti, and M. microti* [3]. *M. africanum* is not widely distributed, but it is a significant cause of tuberculosis in parts of Africa. *M. bovis* was once a prevalent cause of tuberculosis, but in developing countries, the introduction of pasteurized milk has largely removed this as a public health problem. *M. canetti* is uncommon and appears to be restricted to Africa, though a few cases of African emigrants have been recorded. M. *microti* is most commonly found in immunocompromised persons, though its prevalence may have been underestimated [4].

4. Mechanism of the spread of infection

- **Transmission**

M. Tuberculosis is spread through the air through droplet nuclei that are 1– 5 microns in diameter. When people with pulmonary or laryngeal tuberculosis cough, sneeze, yell or sing, infectious droplet nuclei are formed. These tiny particles will stay suspended in the air for several hours depending on the atmosphere. M. tuberculosis is spread through the air, not through contact with the skin. When a person inhales M. tuberculosis-containing droplet nuclei, the droplet nuclei travel through the mouth or nasal passages, upper respiratory tract, and bronchi to enter the lungs' alveoli [5].

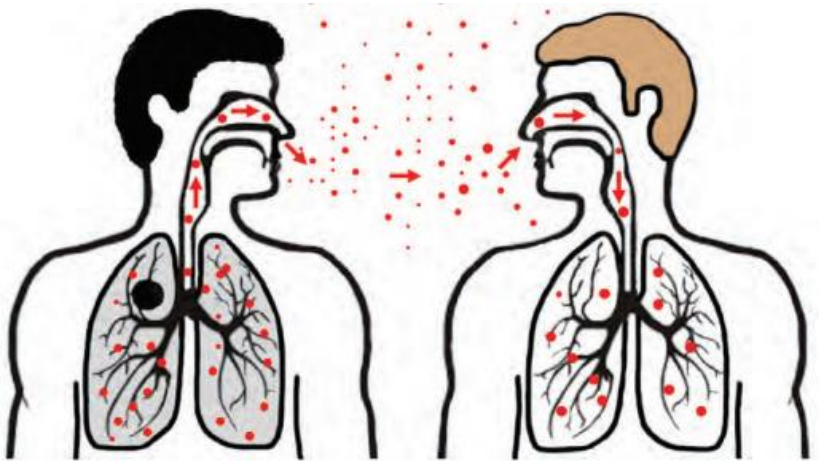
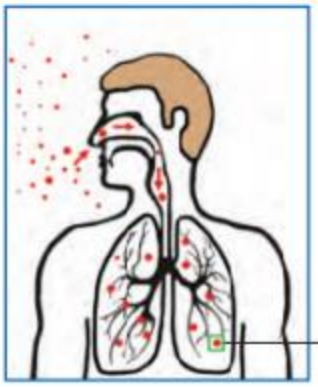
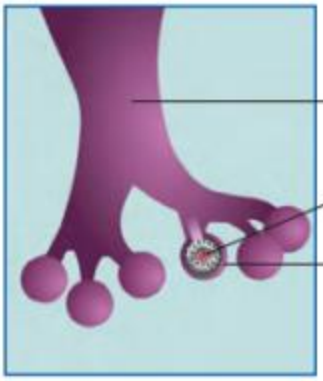


Figure No. 3: Mechanism of Transmission of M. TB

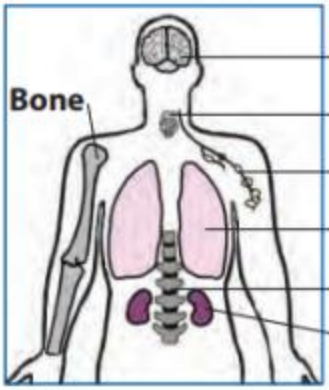
- **Pathogenesis**



Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

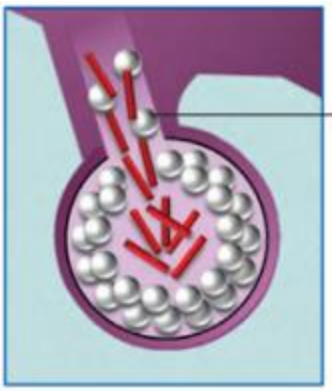


Tubercle bacilli multiply in the alveoli.



A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control(LTBI).



If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone.

Figure No. 4: Pathogenesis of Tuberculosis

5. Diagnosis

M. tuberculosis is detected in sputum and pus samples to diagnose tuberculosis. Other radio imaging and tuberculin monitoring techniques are used where these identifiability checks are not practical. Physical tests, X-ray imaging, microbiological smears, and cultures can all be used to do a thorough analysis. Tuberculin tests have the drawback of yielding false negatives, especially when the patient has sarcoidosis, Hodgkin's lymphoma, malnutrition, or, most importantly, active tuberculosis disease [6].

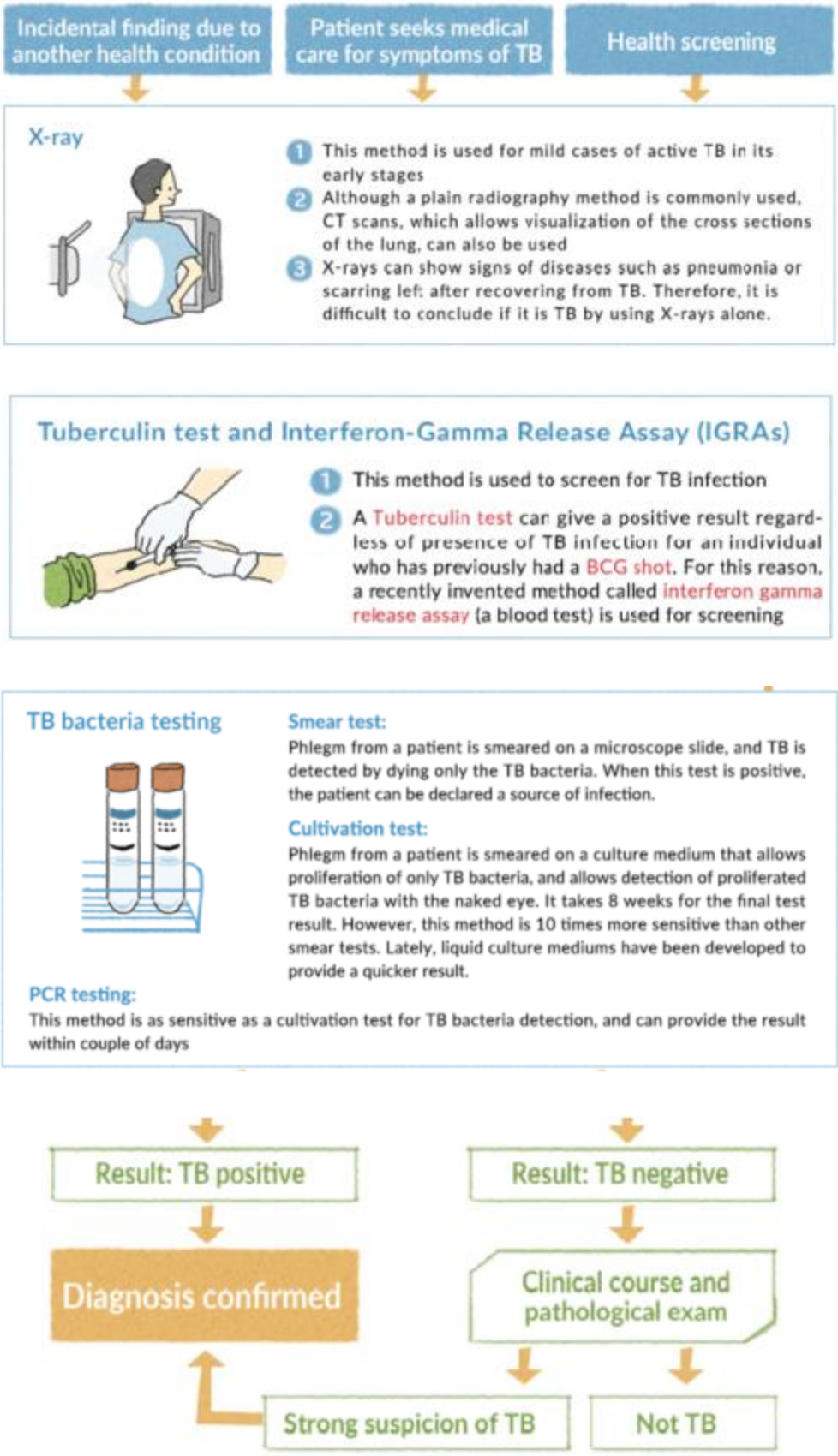


Figure No. 5: Diagnosis of Tuberculosis

6. Global & Regional incidence

According to WHO, the area of South-East Asia had the highest number of new tuberculosis cases in 2008, accounting for 34% of all cases worldwide. However, with over 350 cases per 100,000 people, the reported incidence rate in Sub-Saharan Africa is nearly twice that of South-East Asia. In 2008, an estimated 1.3 million people died of tuberculosis. The area with the most deaths was South-East Asia, while the region with the highest mortality per capita was Africa.

Global tuberculosis countermeasures are connected to the eradication of tuberculosis in Japan.

The value of (TB) countermeasures has been recognized internationally since the invention of DOTS. The growth of tuberculosis in Asia and Africa in today's world, with frequent global travel, is not simply "someone else's problem," which is why a global effort is being made to devise new strategies to eradicate the disease.

The World Health Organization (WHO) declared tuberculosis (TB) to be a global health emergency in 1993 and urged developing and developed countries to work together to resolve the issue.

The World Bank started granting large-scale financial assistance (loans) for TB countermeasures to countries such as China and India after recognizing the economic value of DOTS-based TB countermeasures.

Several public and private groups and organizations came together to form the Stop TB Alliance, which became a strong supporter for global TB countermeasure promotion, with an emphasis on developing countries, with the WHO at its heart.

At the G8 summit in Okinawa in 2000, Japan proposed raising awareness of the fact that infectious diseases were preventing developed countries from expanding. Under the leadership of the United Nations, the Global Fund to Fight AIDS, Tuberculosis, and Malaria were created and began providing substantial funding to combat these diseases.

The number of patients in developing countries in Asia and Africa is particularly high.

Tuberculosis Worldwide

Per year, 10.4 million new cases of tuberculosis are diagnosed, and 1.4 million people die from the disease (chart/figure 10)*. In recent years, these figures have begun to gradually decline. The number of patients in developing countries is the largest. TB is known as a "re-emerging infectious disease" because it refuses to go away, and complications including TB/HIV co-infection and MDR-TB (multidrug-resistant tuberculosis) have recently emerged as a problem [7].

When the number of deaths due to TB/HIV co-infection is added to the number shown in the graph, the total number of deaths per year is 390,000 worldwide.

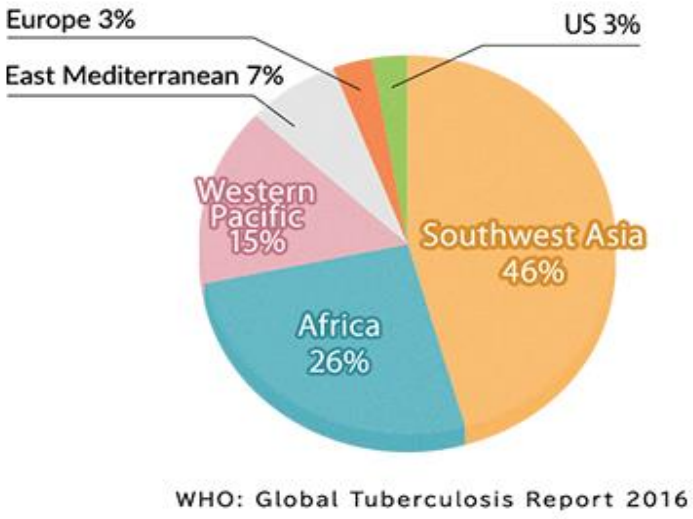


Figure No. 6: Global Tuberculosis Report 2016

7. Estimated TB. Incidence, prevalence & mortality, 2008

Table No. 1: Estimated TB, incidence, prevalence and mortality, 2008

Table 1
Estimated tuberculosis (TB) incidence, prevalence and mortality, 2008.

WHO region	Incidence			Prevalence		Mortality	
	nº in thousands	% of global total	Rate per 100,000 pop	nº. in thousands	Rate per 100,000 pop	nº in thousands	Rate per 100,000 pop
Africa	2828	30%	351	3809	473	385	48
The Americas	282	3%	31	221	24	29	3
Eastern Mediterranean	675	7%	115	929	159	115	20
Europe	425	5%	48	322	36	55	6
South-East Asia	3213	34%	183	3805	216	477	27
Western Pacific	1946	21%	109	2007	112	261	15
Global total	9369	100%	139	11093	164	1322	20

Incidence is the number of new cases arising during a defined period; prevalence is the number of cases (new and previously occurring) that exists at a given point in time; pop: population.

The life cycle of M. Tuberculosis

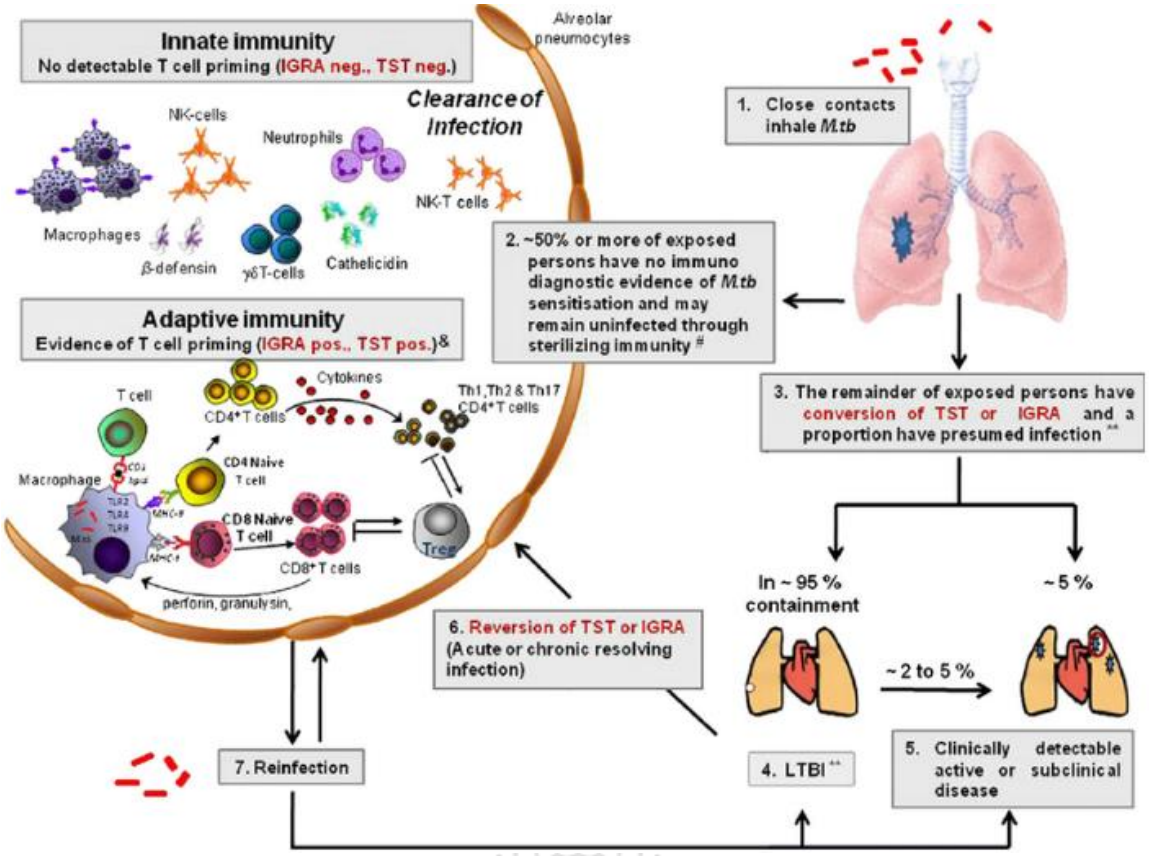


Figure No. 7: Life cycle of M. Tuberculosis

8. Quinazoline

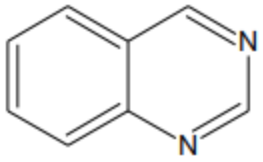


Figure No. 8: Structure of Quinazoline

Quinazoline is a heterocyclic organic compound with the molecular formula $C_8H_6N_2$[8]. Quinazoline is a yellow-colored solid that is crystalline in nature and water soluble. It has a melting point of 48^0C.

Gabriel prepared quinazoline (1, 3- diazanaphthalene) in 1903, but Griess synthesized the first derivative. Widdege suggested the term, but it has also been referred to as phenmiazine,

benzo-1, 3-diazine, and 5; 6-benzopyrimidine. Paal and Busch's proposed numbering scheme is still in use [9].

The existence of a fused benzene ring significantly changes the properties of the pyrimidine ring. The two nitrogen atoms are not identical, and quinazoline reactions show the marked polarisation of the 3, 4-double bond [10].

Substituted quinazolines' properties are mainly defined by:

(a) The substituent's essence.

(b) Regardless of whether they are in the pyrimidine or benzene rings.

(c) And whether or not the pyrimidine ring has full conjugation.

Covalent hydration in acidic solution complicated the reduction of quinazoline because the hydrated species were difficult to reduce. The anhydrous species were reduced to dihydro and then to tetrahydro quinazoline in an alkaline medium, and the dihydro radical intermediate was capable of dimerization. The polarographic technique was used to evaluate the protonation concentrations of N-heterocyclic in an aqueous solution. The rates of quinazoline and pyrimidine were too fast to calculate, as predicted by quantum chemical calculations.

Quinazoline has a wide range of biological activities, including analgesic, anti-inflammatory, antibacterial, diuretic, antihypertensive, antimalarial, sedative, hypoglycemic, antibiotic, and antitumor. These examples illustrate quinazoline derivatives' potential as a source of useful pharmacophore for new drug development [11].

We pursued an unexplored, synthetically accessible heterocyclic template (quinazoline) capable of bearing some possible pharmacophore to evoke and enhance inherent biological activity as part of our quest for biological heterocycles. Additionally, quinazoline derivatives can be used as an anti-invasive agent in early and advanced solid tumors, metastatic bone disease, and leukemia. Some of the known quinazoline derivatives have been shown to have potent anti-cancer properties. However, the quest for more potent lead molecules is ongoing, as these molecules are gaining resistance over time.

Because of the importance of these molecules, we focused our efforts on developing novel quinazoline derivatives to develop more potent molecules. The quinazoline has played an

important role in medicinal chemistry and has subsequently emerged as a pharmacophore among a wide variety of nitrogen heterocyclics that have been explored for developing pharmaceutically important molecules. Because of their biological importance, the chemistry of 4(3H)-quinazoline has piqued people's interest.

8.1 Chemistry of Quinazoline

Paal and Busch[18] suggested the quinazoline ring numbering scheme that is still used today. Williamson studied the chemistry of quinazoline in 1957, and Armarego did the same in 1963, bringing it up to date. Quinazolines are found to be stable in cold acid and alkali solutions but destabilize in boiling acid and alkali solutions. Ammonia, o-amino benzaldehyde, and formic acid are formed when quinazolines are boiled with HCl. Quinazoline undergoes reactions of oxidation, reduction, amination, and nitration [12].

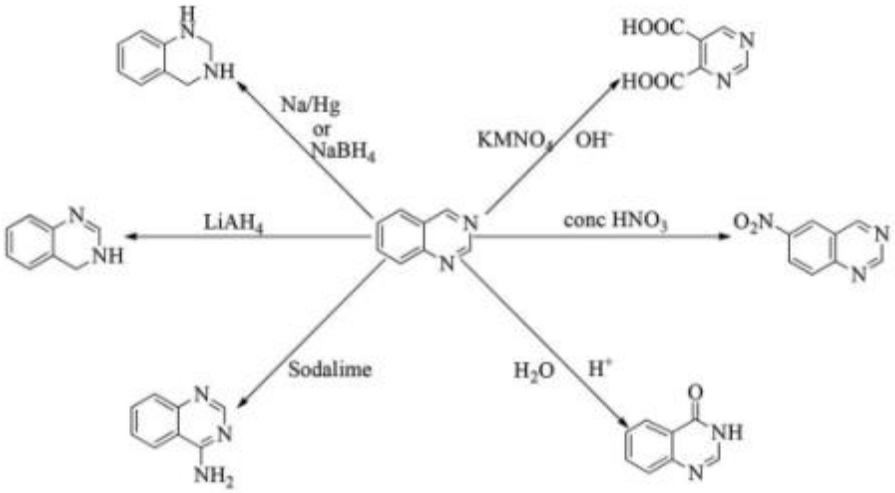


Figure No. 9: Chemistry of Qinazoline

8.2 Pharmacological Activity of Quinazoline

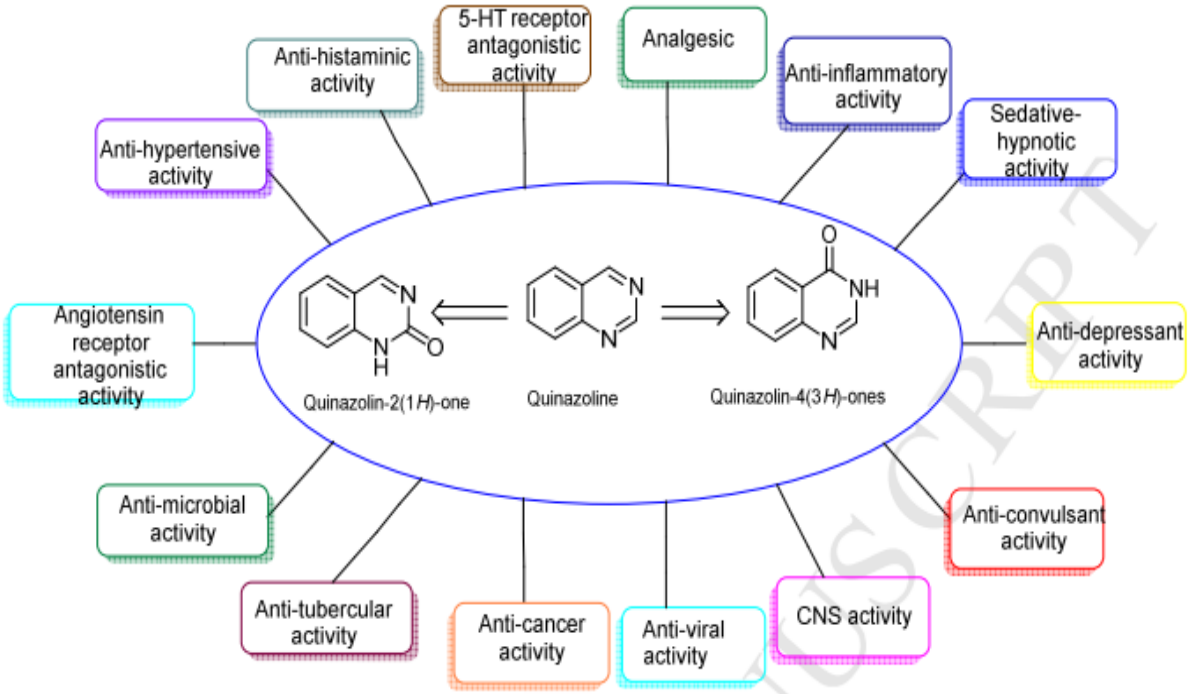
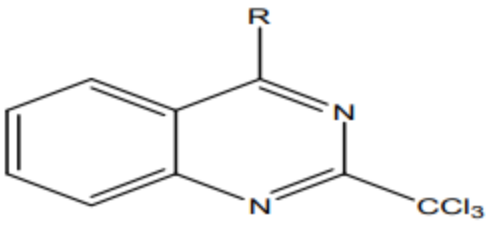


Figure No. 10: Flowchart of Pharmacological Activity of Quinazoline

a) Anti-tubercular Activity

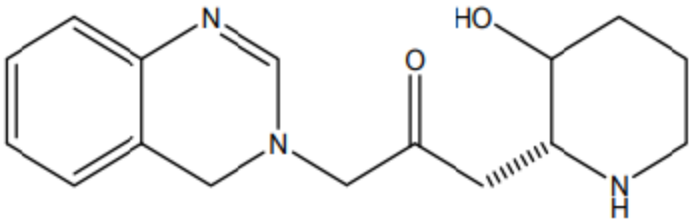
Maneesh et al [18] created a series of novel 2-trichloromethyl quinazoline derivatives with a substituted secondary amine group at the 4th position and tested their anti-tubercular activity in vitro against M. tuberculosis bacteria. By using the Alamar Blue assay method, tuberculosis H37Rv ATCC (American Type Culture Collection) tuberculosis H37Rv tuberculosis H37Rv tuberculosis tuberculo (MABA).



b) Antimalarial Activity

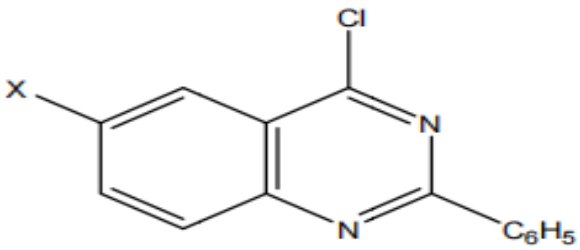
Centered on the structure of febrifugine, a sequence of 2- and 2,3-substituted quinazolin -4(3H)-one derivative was synthesized. At a dose of 5 mg/kg, *in-vivo*, biological activity tests

showed that certain compounds had antimalarial activity against Plasmodium berghei in mice. These drugs, in comparison to Chloroquine and Artemisinin, have shorter synthetic routes and are thus more cost-effective.



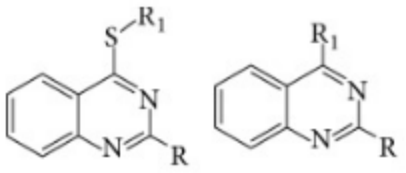
c) Antibacterial Activity

Synthesized some novel 4,6-disubstituted derivatives and evaluated their antimicrobial activity starting from anthranilic acid derivatives through conventional methods. Initially, acylation was followed by cyclization to obtain benz-oxazinones which on further treatment with ammonia yielded the crucial intermediate, 2-substituted benzamide. The products were subsequently cyclised to obtain quinazolones, chlorinated, then hooked to have various 4,6-substituted quinazoline derivatives.



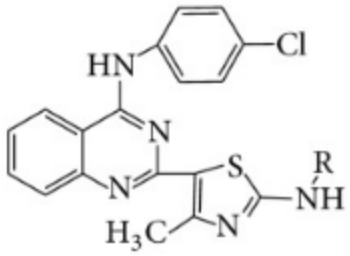
d) Antimalarial activity

A series of 4-thiophenoxy-2-trichloromethylquinazolines derivatives evaluated for their antiplasmodial activity against the human malarial parasite Plasmodium falciparum was determined. Those compounds showed good activity against K_1 Plasmodium falciparum.



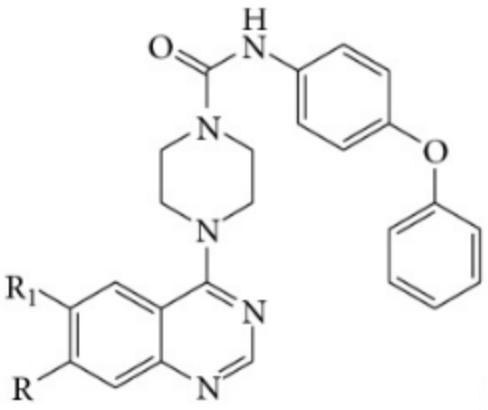
e) Anti-inflammatory and Analgesic activity

A series of novel 2-(2,4-disubstituted-thiazolee-5-yl)-3-aryl-3H-quinazoline-4-ones derivative which became good inhibitors of NFxB and AP-1 medicated transcription activation.



f) Anticancer Activity

A series of 4-[4-(N-substituted(thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives were evaluated for their potential antagonizing activity against Platelet-Derived Growth Factor Receptor (PDGF).



9. CONCLUSION:

Traditional synthetic methods for quinazoline derivatives,still in general use, including Aza-synthetic method, refluxing, oxidative cyclization, are fundamental methods for the synthesis of this important heterocyclic compounds. As can be observed from the examples provided above, new synthetic methods are constantly being developed, and various methods are used in the synthesis of various quinazoline analogues, such as phase-transfer synthesis, ultrasound-promoted synthesis, and so on. Synthesis research on quinazoline derivatives has increased as a result of improved synthetic methods, which have a propensity to be faster,

more diversified, and more convenient. Furthermore, it is well known that substituents in different locations have distinct effects on activity. Quinazoline derivatives with imidazole substituted at the 2-position of the side chain, for example, have a potent anti-tubercular function; and quinazoline derivatives with amine or substituted amine on the 4-position and either halogens or electron rich substituent groups on the 6-position could promote anti-cancer and antimicrobial activities, among other things. According to current studies, 2-, 4-, and 6-position substituted quinazoline analogues are the most common among the products. However, as research progresses, substituent groups at other positions are increasingly accomplished and examined, such as the synthesis of N-heterocyclic quinazolines through the introduction of active groups into the 3-position of the quinazoline core. It's worth noting that N-heterocyclic quinazolines with a more rigid and sophisticated structure were synthesised in the following steps, with some of them exhibiting good antibacterial characteristics. Furthermore, it can be deduced from the previous research that improving activity through the splicing approach of installing numerous active groups is and will continue to be the primary strategy for drug design and reconstruction of quinazoline derivatives.

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