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Review

Quinoline: A promising antitubercular target

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ABSTRACT

Tuberculosis (TB) remains a global public health problem in recent years. TB originated mainly from various strains of *Mycobacterium tuberculosis*, is a highly infectious and chronic disease with high infection rate since ancient times. Since the last 50 years, the same long-duration, multidrug treatment plan is being followed for the treatment of tuberculosis. Due to the development of resistance to conventional antibiotics there is a need for new therapeutic strategies to combat *M. tuberculosis*. Subsequently, there is an urgent need for the development of new drug molecules with newer targets and with an alternative mechanism of action. Among hetrocyclic compounds, quinoline compounds are important privileged structure in medicinal chemistry, are widely used as "parental" compounds to synthesize molecules with medical benefits, especially with anti-malarial and anti-microbial activities. Certain, quinoline-based compounds, also show effective anti-TB activity. This broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinoline, which allows the generation of a large number of structurally diverse derivatives. 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 this versatile core to provide an insight so that its full therapeutic potential can be utilized for the treatment tuberculosis. It is hoped that, this review will be helpful for new thoughts in the quest for rational designs of more active and less toxic quinoline-based anti-TB drugs.

1. Introduction

Tuberculosis (TB) is a lung infection caused mainly by *Mycobacterium tuberculosis* (*M. tuberculosis* [MTB]). It is considered to be one of the most contagious and deadly diseases and is a major threat for public health. In combination with the HIV-1 infection TB is today amongst the biggest threat to the mankind. A large proportion of these new cases and deaths occur mostly in developing countries and the number of HIV-positive patients coinfected with *MTB* is constantly rising [1]. As a result, the TB situation may become even worse with the spread of HIV-1 worldwide, emergence of multi-drug (isoniazid and rifampin) resistant (MDR-TB) and the extensively drug resistant (XDR-TB) strains. Tuberculosis, also known as TB and 'white plaque', is caused by infection with members of the *MTB* complex, which includes *Mycobacterium tuberculosis* itself, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedii* and *Mycobacterium canettii* [2,3]. Robert Koch was the first scientist who isolatedthe bacteria, MTB in 1882 and got Nobel Prize for this discovery [4].

Abbreviations: AIDS, acquired immunodeficiency syndrome; CQ, 7-chloroquinoline; DOS, directly observed therapy short-course; DNA, deoxyribonucleic acid; EMB, ethambuthol; ETH, ethylenediamine spacer; GI, growth inhibition; HIV, human immunodeficiency virus; HTS, high throughput screening; INH, isoniazid; LORA, low-oxygen-recovery assay; LRP, luciferase reporter phage; LTBI, latent tuberculosis infection; MABA, Micro plate Alamar Blue Assay; *M. africanum*, *Mycobacterium africanum*; *M. smegmatis (MS)*, *Mycobacterium smegmatis*; *M. bovis (MB)*, *Mycobacterium bovis*; *M. caprae*, *Mycobacterium caprae*; *M. fortuitum (MF)*, *Mycobacterium fortuitum*; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; MDR-TB, multi-drug resistant tuberculosis; NTM, non-tubercular mycobacterial; MTB, *Mycobacterium tuberculosis (M. tuberculosis)*; *NR-MTB*, non-replicating *Mycobacterium tuberculosis*; PZA, prazinamide; R-Mtb, replicating *Mycobacterium tuberculosis*; RIF, rifampicin; RTK, receptor tyrosine kinases; SAR, structure activity relationship; SI, Selectivity index; TB, Tubercle Bacillus; TMC, Tibotec Medicinal Compound; WHO, World Health Organization; XDR-TB, Extensively drug-resistant tuberculosis.

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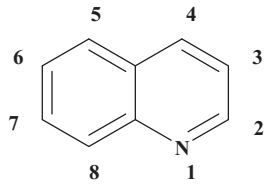
TB has been one of the deadliest diseases over the past few decades affecting nearly one-third of the world's population [5] with new infection occurring at 1% of population each year [6]. According to WHO studies, in 2011, there were 8.7 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB including one million HIV negative people [7]. The estimated 8.8 million new cases every year correspond to 52,000 deaths per week or more than 7000 each day [8,9]. These number shows ever, are only a partial depiction of the global TB threat. More than 80% of TB patients are in the economically productive age of 15–49 years, which results in tremendous economic and social problems. It was estimated that nearly 1 billion more people will be infected with TB in the next 20 years. About 15% of that group (150 million) will exhibit symptoms of the disease, and about 3.6% (36 million) will die from TB if new disease prevention and treatment measures are not developed [10]. In 2012, nearly nine million people around the world became sick with TB disease. There were around 1.3 million TB-related deaths worldwide. Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top three causes of death for women aged 15 to 44. In 2012, an estimated 530,000 children became ill with TB and 74,000 HIV-negative children died of TB [11]. These data facilitated chemists and biologist to discovery of novel drug targets, assisted the understanding of the biological phenomenon of *MTB*. Currently, the six to nine month multidrug protocol used in the treatment of TB is highly effective with drug-susceptible TB, but poor patient compliance promotes development of drug resistance [12]. Although the existing method of curing is very effective against TB, the length of treatment, the toxicity and the potential for drug-drug interactions are factors that highlight the need for new anti-TB drugs [13,14]. In addition, *MTB* is resistant to some of the first and second line drugs [15]. Therefore, effective new drugs [16] and strategies [17] are essential to treat the TB bacilli.

It has been established that heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications. Among pharmacologically important heterocyclic compounds, quinoline and its derivatives are significant because of their wide spectrum of biological activities and



(1)

Fig. 1. Chemical structure and numbering of quinoline.

their presence in naturally occurring compounds. Quinoline is a heterocyclic aromatic nitrogen compound characterized by a double-ring structure that contains a benzene ring fused to pyridine at two adjacent carbon atoms (Fig. 1) [18,19]. It can also be named as, benzopyridine, benzo[b]pyridine, 1-azanaphthalene, 1-benzazine and benzazine.

In the recent time, quinoline nucleus has gathered an immense attention among chemists as well as biologists as it is one of the key building elements for many naturally occurring compounds. In particular, quinoline alkaloids are found in many different plants including Berberidaceae, Fumariaceae, Papavaraceae and Rutaceae [20–24]. Quinoline and its derivatives are important class of bioactive molecules in the field of drugs and pharmaceuticals. They exhibit significant activity against several viruses including antimalarial [25–27], antibiotic [28,29], anticancer [30], anti-inflammatory [31], antihypertensive [32], tyrokinase PDGF-RTK inhibition [33] and anti-HIV [34,35] properties. To list a few quinoline derivatives quinine (antipyretic, antimalarial, analgesic, and anti-inflammatory properties), chloroquine (antimalarial), amidiaquine (antimalarial and anti-inflammatory agent), camptothecin (DNA enzyme topoisomerase I), and saquinavir (anti-retroviral drug), which are actively used in pharmacological field are given below (Fig. 2).

This broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinoline, which allows creating a large number of structurally diverse derivatives. Quinoline has been considered a pharmacophore for

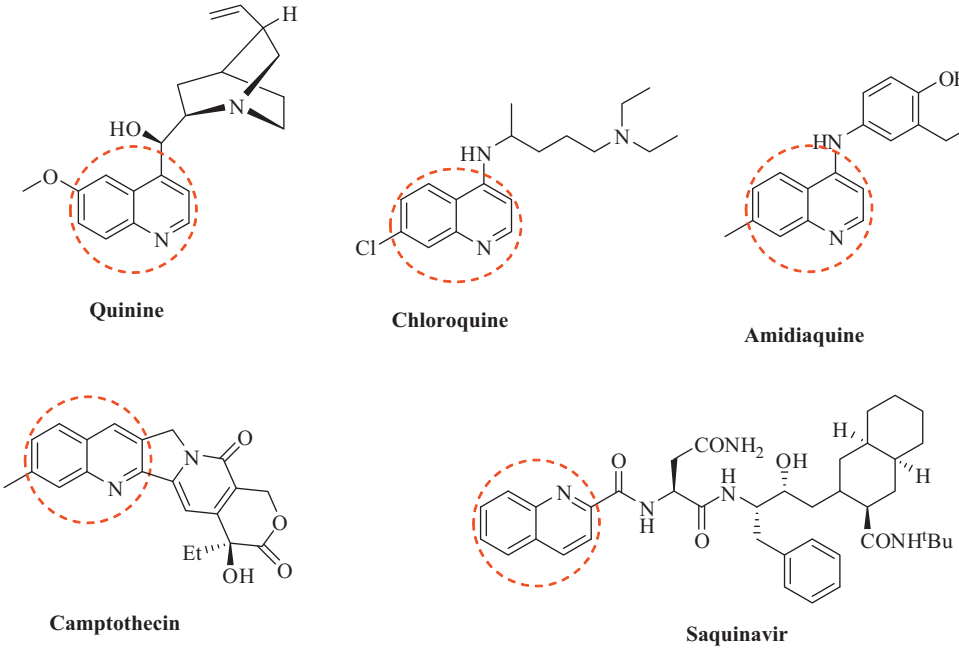


Fig. 2. A few quinoline derivatives in clinical use.