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Mini-review

Recent progress in the drug development of coumarin derivatives as potent antituberculosis agents

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ABSTRACT

Tuberculosis (TB) is still a challenging worldwide health problem and *mycobacterium tuberculosis* (*MTB*) remains one of the most deadly human pathogens. TB is the second leading infectious cause of mortality today behind only HIV/AIDS. The impetus for developing new structural classes of antituberculosis drugs comes from the emergence of multi-drug resistant (MDR) strains. The development of MDR strains to commonly used drugs is due to, longer durations of therapy as results of resistance, and the resurgence of the disease in immune compromised patients. Therefore, there is an urgent need to explore new anti-tubercular (anti-TB) agents. Ironically, the low number of potentially new chemical entities which can act as anti-TB candidates is of great importance at present situation. Considering the severity of the problem, WHO has prepared a strategic plan in Berlin declaration 2007 to stop TB, globally. Among the oxygen heterocycles, coumarin derivatives are important motifs, which can be widely found in many natural products, and many of them displaying diverse biological activities. This spectacular spectrum of applications has intrigued organic and medicinal chemists for decades to explore the natural coumarins or their synthetic analogs for their applicability as anti-TB drugs. To pave the way for the future research, there is a need to collect the latest information in this promising area. In the present review, we collated published reports on coumarin derivatives to shed light on the insights on different types of methods reported for their preparations, characterizations and anti-TB applications, so that its full therapeutic potential class of compounds can be utilized for the treatment of tuberculosis. Therefore, the objective of this review is to focus on important coumarin analogs with anti-TB activities, and structure-activity relationships (SAR) for designing the better anti-TB agents. It is hoped that, this review will be helpful for new thoughts in the quest for rational designs of more active and less toxic coumarin-based anti-TB drugs.

1. Introduction

Tuberculosis (TB) is an acute or chronic infectious disease caused by several species of Mycobacterium, collectively called as tubercle bacilli. TB usually attacks the lungs but can also affect the central nervous system, lymphatic system, circulatory system, genitourinary system, gastrointestinal system, bones, joints, and even the skin. It is caused by the bacterium *Mycobacterium tuberculosis* complex, which includes *Mycobacterium tuberculosis* (*M. tuberculosis*, [*MTB*]) itself, *Mycobacterium microti*, *Mycobacterium pinnipedii* *Mycobacterium bovis*, *Mycobacterium caprae*, *Mycobacterium africanum*, and *Mycobacterium canettii* [1–3]. *MTB* also known as the “white plague” was identified by Robert Koch in 1882 [4]. Many people become symptom-free carriers of the tubercle bacilli bacteria. Although common and deadly in the third world, tuberculosis 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 immune deficiency syndrome (AIDS) [5]. Person can have active or inactive TB. Active TB disease means the bacteria are active in the body and the immune system is unable to stop them from causing illness. People with active TB in their lungs

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can pass the bacteria on to anyone they come into close contact with. When a person with active tuberculosis coughs, sneezes or spits, people nearby may breathe in the TB bacteria and become infected. Left untreated, each person with active TB will infect on average between 10 and 15 people every year [6].

According to the World Health Organization (WHO), one third of the world's population is infected with *MTB.* In 2008, WHO estimated about 9.4 million incident cases of TB, 11.1 million prevalent cases of TB, 1.3 million deaths from TB among HIV-negative people and an additional 0.52 million TB deaths among HIV-positive people [7,8]. Treatment of TB is protracted and burdensome [9] and its control is further complicated by the synergy between TB and HIV/AIDS [10,11] and by the development of multi-drug resistant tuberculosis (MDR-TB), which can be defined as strains that have resistance to at least isoniazid (INH) and rifampicin (RIF) that are important first line drugs used in TB treatment [12]. Another serious problem in the context of MDR-TB, is the extensively drug-resistant TB (XDR-TB), which is recently emerged as a public health threat [13,14]. Furthermore, common HIV *I* AIDS anti-retroviral therapies are not compatible with the current TB regimen because of shared drug toxicities and drug interactions, for example, as a consequence of RIF-induced cytochrome P450 activation [15,16].

Therefore, people with latent tuberculosis 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 tuberculosis disease and becoming infectious compared with non HIV people [17]. This has spurred for novel efforts to find new anti-TB drug candidates with novel modes of action. Which includes, developing pipelines for drug discovery and development and, in particular, trying to find new regimens that can considerably shorten the duration of effective therapy which would improve patient compliance and slow down the emergence of drug-resistant strains [18–23].

Natural, synthetic and semisynthetic heterocyclic compounds play an important role in drug discovery and chemical biology. The heterocycles are mainly of the classes of alkaloids, flavones, isoflavones, chromans, chromones, coumarins and chromenes. Synthetic compounds of these classes show different biological activity. It has been established that oxygen-containing heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications [24]. Among oxygen heterocyclic compounds, coumarin (*2H*-chromen-2-one or 2*H*-1-benzopyran-2-one) **(3)** and its derivatives are significant because of their wide spectrum of biological activities. In recent years, a number of coumarin derivatives have been isolated from various plant sources and their extracts are being employed as traditional medicines. These are naturally occurring lactones and are also being used as perfumery and food flavoring agents. The first time, parent coumarin was first isolated from Tonka beans by Vogel in the year 1820 [25]. Coumarin ring **(3)** can be viewed as arising out of the fusion of pyrone ring **(2)** with a benzene nucleus **(1)**. The numbering of coumarin starts from the ring oxygen i.e. oxygen receives position-1, carbonyl carbon-2 and goes round anti-clockwise along with the ring as shown below (Fig. 1.) [26].

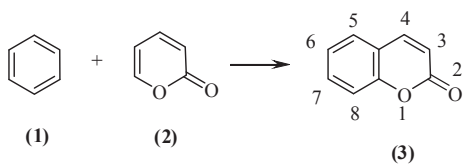

Fig. 1. Chemical structure and numbering of coumarin.

The synthesis of coumarin and their derivatives has attracted considerable attention from organic and medicinal chemists over the decades. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals [27] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable laser dye [28]. Coumarin and its derivatives have varied bioactivities such as antimicrobial [29–32], antidepressant [33], antioxidant [34], anti-inflammatory [35], antinociceptive [36], antitumor [37], antiasthmatic [38], antiviral [39,40], antituberculosis [41], anti-influenza [42], anti-Alzheimer [43,44], antihyperlipidemic [45], antipyretic [46], anti-HIV [47] activities. The discovery of coumarins having weak estrogenic activity resulted in the use of such derivatives as therapeutic agents in preventing the emergence of menopause-related diseases such as osteoporosis, increased risk of cardiovascular disease and cognitive deficiencies [48,49]. They also show inhibitory activity on viral proteases [50], and central nervous system modulating activities [51]. Coumarins also act as intermediates for the synthesis of furocoumarins, chromenes, coumarones and 2-acylresorcinols [52].

Some of the coumarin derivatives, which are already booming in the market, to quote a few, brodifacoum (**4**, anticoagulant), warfarin (**5**, anticoagulant), difenacoum (**6**, anticoagulant), auraptene (**7**, chemopreventative agent), acenocoumarol (**8**, anticoagulant), ensaculin (KA-672) (**9**, NMDA antagonist and a $5HT_{1A}$ agonist), armillarisin A (**10**, antibiotic), hymecromone (**11**, choleretic and antispasmodic), carbochromen (**12**, coronary disease), scopoletin **(13)**, phenprocoumon (**14**, anticoagulant) and novobiocin (**15**, antibiotic) (Fig. 2.) [53–55].

Therefore, the synthesis of coumarin and its derivatives have received an increasing attention to synthetic organic chemists and biologists. Some reviews on involvement of coumarin nucleus as antitumor [56,57], anti-HIV [58] and anti-Alzheimer's diseases [59,60] are available in the literature. Some compilation reports on all activities associated with coumarin nucleus are also reported [61–66]. But so far no review available in the literature where coumarin nucleated molecules with their application exclusively as anti-TB agents in detail. A significant amount of effort has been invested in the past decade to develop coumarin-based compounds as modulator of 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, it is thought to collect the data on coumarin derivatives as anti-TB agents (from 2000 to date), the indispensable anchor in medicinal chemistry. The present review reveals critical analysis of anti-TB research reports on development of different coumarin hybrids. It has been attempted to shed light and compile published reports on coumarin derivatives along with proposed of a suitable structure-activity relationship (SAR) studies. We also discussed different approaches to help the medicinal chemists in designing future generation potent yet safer coumarin-based anti-TB agents.

2. Coumarin: structural requirements for anti-TB activity

From the published data, it is evident that coumarin nucleus substituted at all positions with varied substituents has produced potent anti-TB activity except the position 1 and 2. The 3rd position of coumarin may be unsubstituted or substituents may vary from alkyl to aryl and heterocyclic groups. Among them, coumarin with fluorine, *n*-propyl and pyrazole substituents, demonstrated excellent anti-TB activity. Similarly, 4th position may be substituted with alkyl or bulky aryl/heteroaryl groups. Coumarins substituted with