European Journal of Medicinal Chemistry 136 (2017) 122–130

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Mini-review

Recent developments of coumarin-containing derivatives and their anti-tubercular activity

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ARTICLE INFO

Article history:
Received 25 February 2017
Received in revised form
9 April 2017
Accepted 1 May 2017
Available online 2 May 2017

Keywords:
Coumarin derivatives
Hybrid compounds
Anti-tubercular activity
Anti-mycobacterial activity
Structure-activity relationship

ABSTRACT

Tuberculosis (TB) is a lift-threatening chronic deadliest infectious disease caused predominantly by *Mycobacterium tuberculosis* (MTB) which affects primarily the lungs (pulmonary TB) apart from other vital organs. The emergence of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB) and the recently cases of totally drug resistant (TDR) towards currently accessible standard drugs was increased up to alarming level in the recent decades. In pursuit of searching new anti-TB agents, numerous of derivatives have been synthesized and screened for their anti-TB activity. Coumarins are one of the most important classes of natural products that exhibited various biological activities, and their derivatives regarded as a new class of effective anti-TB candidates owing to their potential anti-TB activity. Thus, coumarin skeleton has attracted great interest in the development of new anti-TB agents. This review outlines the advances in the application of coumarin-containing derivatives as anti-TB agents and the critical aspects of design and structure-activity relationship of these derivatives.

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1. Introduction

Tuberculosis (TB), known as 'white plaque', is a potentially serious infectious disease caused by infection with members of *Mycobacterium tuberculosis* (MTB) complex including MTB itself, *M. africanum*, *M. bovis*, *M. caprae*, *M. microti*, *M. pinnipedii* and *M. canettii*, and MTB is predominantly pathogen which affects mainly the lungs (pulmonary TB) apart from other vital organs [1]. The World Health Organization (WHO) has estimated that one-third of the world's population (about 2 billion) harbor a latent infection by MTB, which has the strong ability to lie dormant for many years, result in around 5–10% of the latently infected individuals eventually develop an active TB. Although the first-line anti-TB drugs such as isoniazid (**INH**), rifampicin (**RIF**), ethambutol (**EMB**) and pyrazinamide (**PZA**) currently used for the treatment of TB infection are highly effective, are far from ideal, since the threat from TB is in continual increase, especially in developing countries, as evidenced by the fact that around 1.4 million deaths and 10.4 million clinical cases occurred in 2015 [2].

The current TB treatment regimens often leading to poor patient compliance due to the long-term therapy duration (often takes 6–12 months). Moreover, the increasing emergence of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB, resistant to at least two front-line drugs such as **INH** and **RIF**), extensively drug-resistant TB (XDR-TB) and the recently cases of totally drug resistant (TDR) towards currently accessible standard drugs was increased up to alarming level in the recent decades. 15 million of people have already been infected with DR-TB, and 0.48 million cases of MDR-TB infections with 0.19 million deaths in the year 2015 [2]. The MDR-TB cure rate is 40–80%, while in China the cure rate is only ~5%. Another contributing factor underlying the resurgence of TB is HIV co-infection with TB, which makes the patients more susceptible to reinfection with either drug-susceptible or drug-resistant strains. Indeed, TB is the leading cause of death among people living with HIV/AIDS, thus the TB situation may

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http://dx.doi.org/10.1016/j.ejmech.2017.05.004
0223-5234/Published by Elsevier Masson SAS.

become even worse with the spread of HIV worldwide [3,4]. Meanwhile the second-line anti-TB agents such as *p*-aminosalicylic acid, amikacin, cycloserine, capreomycin and ethionamide are less effective and more toxic. Accordingly, there is an urgent need to develop new anti-TB agents with a unique mechanism of action different from that of the currently used anti-TB drugs, well-tolerated, effective against both drug-susceptible and drug-resistant strains of MTB, low toxic and short therapy duration.

In recent years, the natural products play an important role in drug discovery. Coumarin (Fig. 1) and its derivatives, constitute an important class of benzopyrones that are found in nature and act as a structural subunit of more complex natural products, occupy an important position in medicinal chemistry ascribed to their ability to exert noncovalent interactions (π-π, hydrophobic, electrostatic interactions, hydrogen bonds, metal coordination and van der Waals force etc.) with the various active sites in organisms [5]. These molecules generally exhibit a fascinating array of pharmacological properties such as anti-proliferative [6], anti-cancer [7], anti-HCV [8], anti-HIV [9], anti-alzheimer [10], anti-malarial [11,12], anti-bacterial [13,14], anti-fungal [15,16], anti-oxidant [17], anti-convulsant [18], anti-inflammatory [19] and anti-TB [20,21] activities. To list a few coumarin based derivatives acenocoumarol, dicoumarolum, warfarin, hymecromone and carbochromen which are approved for therapeutic purposes in clinic are given below (Fig. 1) [21]. This broad spectrum of biological activities and successful usage of coumarin based drugs in clinic has been further inspires more research towards coumarin derivatives, which allows creating a large number of structurally diverse derivatives.

Coumarin skeleton has been considered a pharmacophore for the design of anti-TB agents attributed to the above favorable profiles. In pursuit of searching new anti-TB agents, numerous of coumarin-containing derivatives have been synthesized and screened for their anti-TB activity. Many derivatives showed promising activity, i.e. (+)-Calanolide A (Fig. 1), a naturally occurring coumarin derivative and an inhibitor of HIV-1 reverse transcriptase also have shown promising *in vitro* activity against MTB with an MIC value of 3.13 μg/mL, and its derivatives may be used to treat HIV co-infection with TB patents in the near future [22].

Further modification on coumarin skeleton may provide new anti-TB drugs with improved properties such as enhanced activity against both drug-susceptible and drug-resistant strains, reduced toxicity, shortened duration of therapy, rapid mycobactericidal mechanism of action and the ability to penetrate host cells and exert anti-mycobacterial effects in the intracellular environment, particularly, with activity against both TB and HIV infections.

This review aims to summarize the recent advances made towards the discovery of coumarin-containing derivatives as anti-TB agents and the critical aspects of design and structure-activity relationship (SAR) of these derivatives.

2. Azine/Azole coumarin derivatives

Dihydrofolate reductase (DHFR) is one of the well validated targets, has been successfully explored as a target for TB therapy. 1,3,5-triazine (also called *s*-triazine) moiety known to be targeting DHFR enzyme, so 1,3,5-triazine derivatives remain an attractive proposition, with their significant biological activities and further incorporation with coumarin skeleton may show promising *in vitro* and *in vivo* anti-TB activity and might be able to prevent the drug resistant to certain extent. Thus, *s*-triazine derivatives have gathered an immense attention.

A set of novel 2-[4-cyano-(3-trifluoromethyl)phenyl amino]-4-(4-coumarin-4-yloxy)-6-(fluoropiperazinyl)-*s*-triazines **1** (X = O) and corresponding quinoline hybrids (X = *N*-Me) have been tested for their *in vitro* anti-mycobacterial activity against MTB $H_{37}Rv$ using BACTEC MGIT and Lowenstein-Jensen MIC methods by Patel et al. [23–25]. In general, all *s*-triazine coumarin conjugates showed weak to moderate anti-mycobacterial activity with MIC > 6.25 μg/mL by BACTEC MGIT method and 100–1000 μg/mL by Lowenstein-Jensen method. Although the anti-mycobacterial activity of coumarin conjugates was less active than the corresponding quinoline hybrids, it can act as an ideal starting point for the synthesis of new pharmacological templates against MTB $H_{37}Rv$.

Azoles, such as 1,2,3-triazoles, thiazole, benzothiazole, imidazole, pyrazole and 1,3,4-oxadiazole are one of the most important classes of nitrogen containing heterocycles, and also regarded as a new kind of effective anti-TB candidates by inhibiting the growth of bacteria by blocking lipid biosynthesis and/or additional mechanisms which is one of the most attractive strategies for developing effective anti-TB agents [26]. In particular, triazoles have attracted continuous interest in the medicinal chemistry, due to their favorable properties such as moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions are responsible for their enhanced biological activities [27]. It's notable that 1,2,3-triazoles occupy a prominent place in drug discovery attributed to their facile synthesis through click chemistry.

A library of novel 3-trifluoromethyl pyrazolo-1,2,3-triazole hybrids were accomplished through click chemistry approach and were evaluated for *in vitro* anti-mycobacterial activity against *M. smegmatis* (MC^2 155) and also verified the cytotoxicity [28]. The hybrid **2** (Fig. 2) emerged as promising anti-TB candidate with MIC of 53.92 μg/mL, and with lowest cytotoxicity against the A549 cancer cell line (IC_{50} > 100 μM), indicating these triazole hybrids as

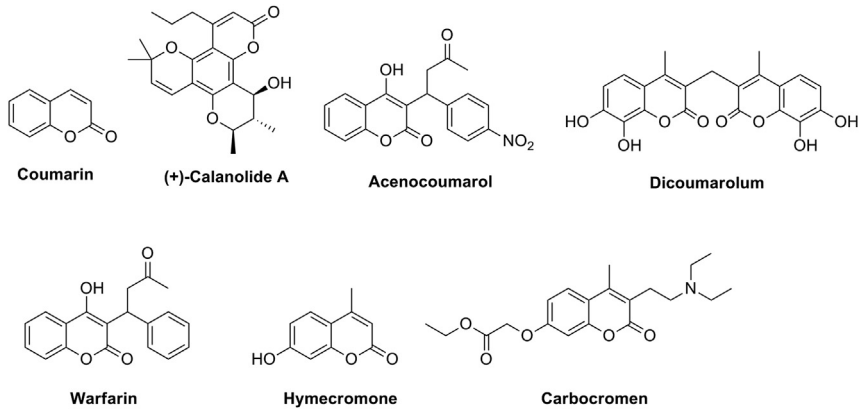

Fig. 1. Structures of coumarin, (+)-Calanolide A and drugs based on coumarin moiety.