Bioorganic & Medicinal Chemistry Letters 27 (2017) 3643–3646

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design, synthesis and *in vitro* anti-mycobacterial evaluation of gatifloxacin-1H-1,2,3-triazole-isatin hybrids

Zhi Xu [a], Shu Zhang [b], Xufeng Song [c], Min Qiang [a], Zaosheng Lv [a,*]

[a] Key Laboratory of Hubei Province for Coal Conversion and New Carbon Materials, Wuhan University of Science and Technology, Hubei, PR China
[b] Pony Testing International Group (Wuhan), Hubei, PR China
[c] Beijing University of Technology, Beijing, PR China

ARTICLE INFO

Article history:
Received 26 May 2017
Revised 30 June 2017
Accepted 7 July 2017
Available online 8 July 2017

Keywords:
Gatifloxacin
Isatin
1,2,3-Triazole
Hybrids
Anti-tubercular activity
Anti-mycobacterial activity
Structure-activity relationship

ABSTRACT

A set of novel gatifloxacin-1H-1,2,3-triazole-isatin hybrids **6a-l** was designed, synthesized and evaluated for their *in vitro* anti-mycobacterial activities against *M. tuberculosis* (MTB) $H_{37}Rv$ and MDR-TB as well as cytotoxicity. The results showed that all the targets (MIC: 0.025–3.12 μg/mL) exhibited excellent inhibitory activity against MTB $H_{37}Rv$ and MDR-TB, but were much more toxic (CC_{50}: 7.8–62.5 μg/mL) than the parent gatifloxacin (**GTFX**) (CC_{50}: 125 μg/mL). Among them, **61** (MIC: 0.025 μg/mL) was 2–32 times more potent *in vitro* than the references **INH** (MIC: 0.05 μg/mL), **GTFX** (MIC: 0.78 μg/mL) and **RIF** (MIC: 0.39 μg/mL) against MTB $H_{37}Rv$. The most active conjugate **6** k (MIC: 0.06 μg/mL) was 16–>2048 times more potent than the three references (MIC: 1.0–>128 μg/mL) against MDR-TB. Both of the two hybrids warrant further investigations.

Introduction

Tuberculosis (TB), which is caused mainly by *Mycobacterium tuberculosis* (MTB), is one of the most devastating and common infectious disease threaten human for thousands of years. According to the World Health Organization (WHO) 2016 report, TB led to 1.4 million deaths and 10.4 million newly clinical cases in the year 2015.[1] Unfortunately, the numbers are in continual increase, especially in developing countries. The wide spread of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB) and co-infection with HIV, as well as the emergence of extensively drug-resistant TB (XDR-TB) and totally drug resistant TB (TDR-TB) making the situation even worse.[2,3] In the last 50 years, only a handful of compounds have entered human trials after the discovery of rifampicin (**RIF**). In particular, **sirturo** (**bedaquiline/TMC207**) and **delamanid** have recently received approval for treatment of MDR-TB infected patients, but both drugs are associated with side-effects and are only recommended for those MDR-TB patients without other treatment options.[4] Therefore, there is an urgent need to develop novel, potent and fast-acting anti-TB agents.

Great efforts have been put on synthesizing new analogues or modifying old drugs or existing compounds with an established activity for shortening and improving TB potency, since it's the most promising strategy to develop new anti-TB agents in the short time. Isatin and its derivatives exhibited various biological properties such as anti-TB, anti-malarial, anti-bacterial, anti-fungal, anti-virus, anti-tumor and anti-HIV profiles.[5] Fluoroquinolones are emerged as one of the widest used antibiotics, besides their classical anti-bacterial activity, **FQs** also displayed diverse biological activities including anti-TB potency.[6–10] Moreover, some **FQs** such as ciprofloxacin (**CPFX**) are currently recommended as the second-line agents by the WHO for the treatment of TB[11], so **FQs** derivatives caused continuous interests in searching new anti-TB agents.

Gatifloxacin (**GTFX**, has been withdrawn from the therapy due to dysglycaemia, but still worth to be investigated attribute to its excellent *in vitro* and *in vivo* anti-TB properties) methylene isatin hybrid **1** (Fig. 1) exhibited higher *in vitro* (16 and 64 folds against MTB $H_{37}Rv$ and MDR-TB) and *in vivo* potency than the parent **GTFX**.[6] Further studies revealed that the anti-TB activity of these derivatives was greatly influenced by the linkers between **FQs** and isatin.[9,12] The favorable properties of 1,2,3-triazole ring such as moderate dipole character, hydrogen bonding capability, rigidity making it as a promising linker for developing new drugs.[13] Indeed, 1,2,3-triazole derivative **I-A09** (Fig. 1) is in clinical evaluations currently, and may be used to treat TB infection in the near future.[14]

* Corresponding author.
E-mail address: chemorgchem@126.com (Z. Lv).

http://dx.doi.org/10.1016/j.bmcl.2017.07.023
0960-894X/

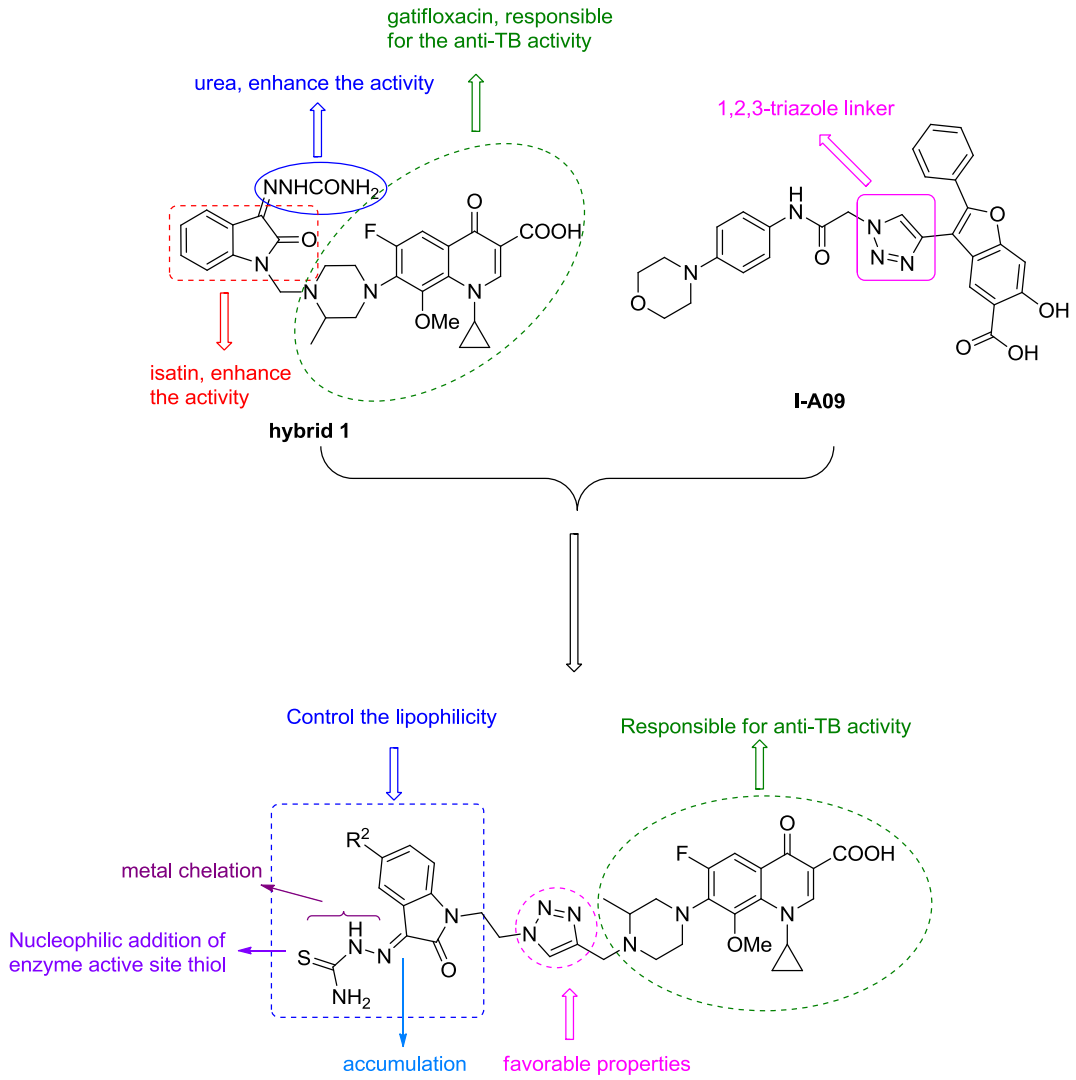

Fig. 1. Illustration of the design strategy for gatifloxacin-1H-1,2,3-triazole-isatin hybrids.

Inspired by the above research results and as a continuous program for developing new anti-TB agents, we synthesized and evaluated a set of novel gatifloxacin-1H-1,2,3-triazole-isatin hybrids in this study. Illustration of the design strategy for these hybrids is depicted in Fig. 1. These derivatives were screened for their *in vitro* anti-mycobacterial activity against MTB $H_{37}Rv$ and MDR-TB strains, along with Isoniazid (**INH**), rifampicin (**RIF**) and **GTFX** as references, and the cytotoxicity was also tested in VERO cell line.

Detailed pathways for synthesizing gatifloxacin-1H-1,2,3-triazole-isatin hybrids **6a-l** are depicted in Scheme 1. C-5 substituted *N*-(2-bromoethyl)isatins **2a-d** (yield: 51–67%) and propargyl GTFX **4** (yield: 39%) were obtained by alkylation of C-5 substituted isatins and **GTFX** with 1,2-dibromoethane and propargyl bromide, respectively, in the presence of anhydrous potassium carbonate *via* literature methods.[9,15,16] Treatment of C-5 substituted *N*-(2-bromoethyl)isatins **2a-d** with sodium azide at 60 °C gave the desired azido precursors **3a-d**.[17] The precursors **3a-d** and **4** were used for the synthesis of ketone gatifloxacin-1H-1,2,3-triazole-isatin hybrids **5a-d** (yield: 28–39%) *via* Cu-promoted azide-alkyne cycloaddition reaction in the presence of CuI in DMF.[18,19] Subsequent condensations of compounds **5a-d** with requisite substituted amine hydrochlorides in the presence of sodium bicarbonate formed the desired hybrids **6a-l** (21–54%).[18,19]

Compared with the parent **GTFX** (Log *P*: 1.51), all of the synthesized hybrids **6a-l** (Log *P*: 1.68–3.87) was much more lipophilic, and this profile may be rendering them more capable of penetrating various biomembrane, consequently improving their permeation properties toward mycobacterial cell membrane. All hybrids **6a-l** were initially evaluated for their *in vitro* anti-mycobacterial activity against MTB $H_{37}Rv$ and MDR-TB.[9] The MDR-TB strain was resistant to **INH**, **RIF** and ethambutol (**EMB**). The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give 90% inhibition of bacterial growth and MICs of the compounds are reported in Table 1.

The preliminary results indicated that all hybrids (MIC: 0.025–3.12 μg/mL) exhibited excellent inhibitory activity against MTB $H_{37}Rv$ and MDR-TB. Against MTB $H_{37}Rv$, all semicarbazone and thiosemicarbazone conjugates except **6e** were more active than that of the parent **GTFX** (MIC: 0.78 μg/mL). In particular, thiosemicarbazone **6l** (MIC: 0.025 μg/mL) was found to be the most active hybrid, and was 2–32 times more potent *in vitro* than the references **INH** (MIC: 0.05 μg/mL), **GTFX** (MIC: 0.78 μg/mL) and **RIF** (MIC: 0.39 μg/mL) against MTB $H_{37}Rv$. Against MDR-TB, all semicarbazone and thiosemicarbazone conjugates with MIC of 0.06–0.5 μg/mL were more active than the references **GTFX** (MIC: 1.0 μg/mL), **INH** (MIC: >128 μg/mL) and **RIF** (MIC: 32 μg/mL). The most potent hybrid **6k** (MIC: 0.06 μg/mL) were 16–>2048 times more active than the three references (MIC: 1.0–>128 μg/mL) against MDR-TB. The SAR revealed that the relative contribution