Bioorganic & Medicinal Chemistry Letters 26 (2016) 3684–3689

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Click-based synthesis and antitubercular evaluation of dibenzofuran tethered thiazolyl-1,2,3-triazolyl acetamides

Goverdhan Surineni [a], Perumal Yogeeswari [b], Dharmarajan Sriram [b], Srinivas Kantevari [a,c,*]

[a] Organic Chemistry Division-II (CPC Division), CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, Telangana, India
[b] Medicinal Chemistry and Antimycobacterial Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science-Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500078, Telangana, India
[c] Academy of Scientific and Innovative Research, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, Telangana, India

ARTICLE INFO

Article history:
Received 15 December 2015
Revised 11 May 2016
Accepted 27 May 2016
Available online 2 June 2016

Keywords:
Dibenzofuran
Thiazole
Triazole
Antimycobacterial activity
Tuberculosis

ABSTRACT

A series of novel dibenzofuran tethered thiazolyl-1,2,3-triazolyl acetamides, designed by assembling antitubercular pharmacophoric fragments, dibenzofuran, 2-aminothiazole and substituted triazoles in one molecular architecture, were evaluated against *Mycobacterium tuberculosis*. The new analogues **6a–p** accomplished in four step synthetic sequence utilizing click chemistry in the penultimate step, was fully characterized by their NMR and mass spectral data. Among the compounds **6a–p** screened for in vitro antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv, three compounds **6j** (MIC: 1.56 μg/mL); **6a** and **6p** (MIC: 3.13 μg/mL) was found to be most active and exhibited lower cytotoxicity. Among these three, **6j** could be a candidate to consider as a drug like hit analogue for further development.

Tuberculosis (TB) is one of the biggest killers among the contagious diseases, despite the worldwide use of a live attenuated vaccine and several antibiotics.[1] It is a highly infectious disease caused by the bacterial pathogen *Mycobacterium tuberculosis* (*Mtb*).[2] According to the latest World Health Organization (WHO) report, 9.6 million people fell ill with TB and 1.5 million died from the disease in 2014 alone.[3] Coexisting with human immune deficiency syndrome and diabetes, TB is posing massive threat to global health.[4] Among the 1.5 million people killed by TB, 400,000 were HIV positive. Further TB threat has acquired a new dimension with the emergence of both multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).[5] The individuals infected with TB relied greatly on cocktail of 6–8 drugs such as isonicotinic acid hydrazide (INH), rifampicin (RIF), ethambutol (EMB), streptomycin (STR), *p*-aminosalicylic acid (PAS), pyrazinamide (PZA), fluoro quinolones etc. for prolonged period up to 24 months. However, most of these drugs have different drawbacks such as host toxicity, ineffectiveness against MDR-TB etc.[6] Consequently there is an urgent need to develop new antitubercular drugs to address the unmet demands of antituberculosis medical goals.[7]

Triazoles and 2-aminothiazole are important heterocyclic pharmacophore fragments possessing wide range of biological activity.[8] Few such analogs are being evaluated in clinical trials for the treatment of various diseases.[9] The naturally occurring antibiotic thiolactomycin analogs **I** and **II** (Fig. 1) primarily act by inhibiting the FAS-II β-ketoacyl-ACP syntheses condensing enzymes, halting mycolic acid biosynthesis and subsequently lead to *M. tuberculosis* cell death.[10] Another thiazole acetamide analogue **III** has moderate activity (MIC: 6.25 μg/mL) against bacterial pathogen *Mtb*. Recently, I-A09 (**IV**), a benzofuran salicylic acid containing triazolyl acetamide is emerged as promising antitubercular drug for clinical evaluations.[11] Further analogues of 1,2,3-triazolyl acetamides **V** and **VI** (Fig. 1) prepared in our lab exhibited antimycobacterial activity with MIC ranging 3.13–6.25 μg/mL and are undergoing detailed investigations.[12]

The lichen secondary metabolite usnic acid (**VII**, Fig. 2) having dibenzofuran architecture was shown to display an interesting antimycobacterial activity (MIC: 12.5 μg/mL), but its weak potency and associated myocardial toxicity did not permit its further development as an antitubercular drug.[13] Other dibenzofuran based natural product AB0022A (**VIII**) inhibited the gram positive bacteria with MIC 0.39 μg/mL.[14] Lucidafuran (**IX**) and Eriobofuran (**X**) were also reported inhibition of *f*MLP-induced superoxide production by human neutrophils.[15] Dibenzofuran analogs **XI–XIII** synthesized in our laboratory also exhibited in vitro antimycobacterial activity with MIC ranging 1.56–3.13 μg/mL.[16]

Continuing our work on development of novel antitubercular agents,[17] we herein report novel dibenzofuran tethered thiazolyl 1,2,3-triazolyl acetamides **6a–p** designed by combining pharmaco-

* Corresponding author. Tel.: +91 4027191437; fax: +91 4027198933.
E-mail addresses: kantevari@yahoo.com, kantevari@gmail.com (S. Kantevari).

http://dx.doi.org/10.1016/j.bmcl.2016.05.085
0960-894X/

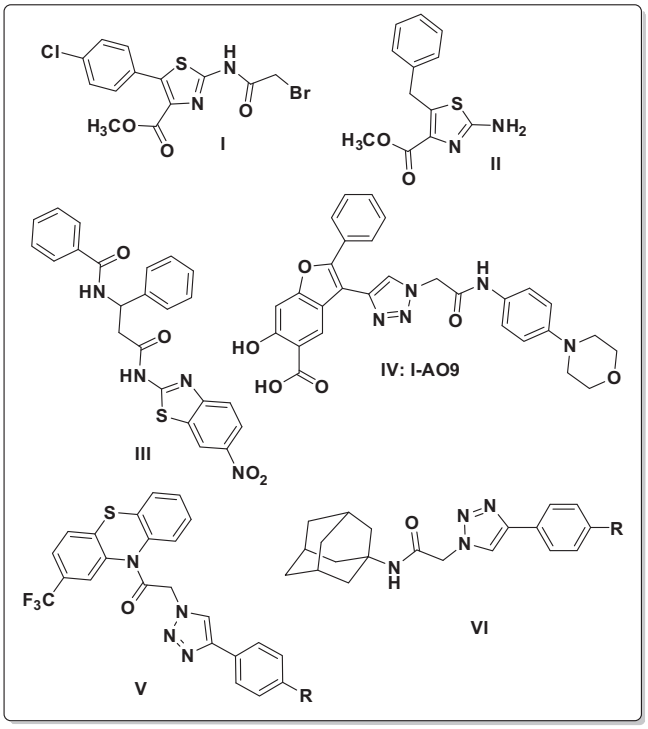


Figure 1. 2-Aminothiazole and 1,2,3-triazole containing bioactive analogs.

genic dibenzofuran, 2-aminothiazole and substituted 1,2,3-triazole fragments. Preparation of the desired compounds **6a**–**p** was accomplished in four step synthetic sequence utilizing click chemistry in the penultimate step. In vitro screening of all sixteen new analogs **6a**–**p** against *Mycobacterium tuberculosis* (*Mtb*) resulted in identification of **6a** and **6p** (MIC: 3.13 μg/mL) and **6j** (MIC: 1.56 μg/mL) as promising hit compounds with lower cytotoxicity profile.

The designed scaffold was broadly divided into three segments (Fig. 3). Substituted 1,2,3-triazolyl acetamide is an active pharmacophoric fragment of clinical antitubercular TB drug I-AO9 (Fig. 1). 2-Aminothiazole is another bioactive segment tethered with a

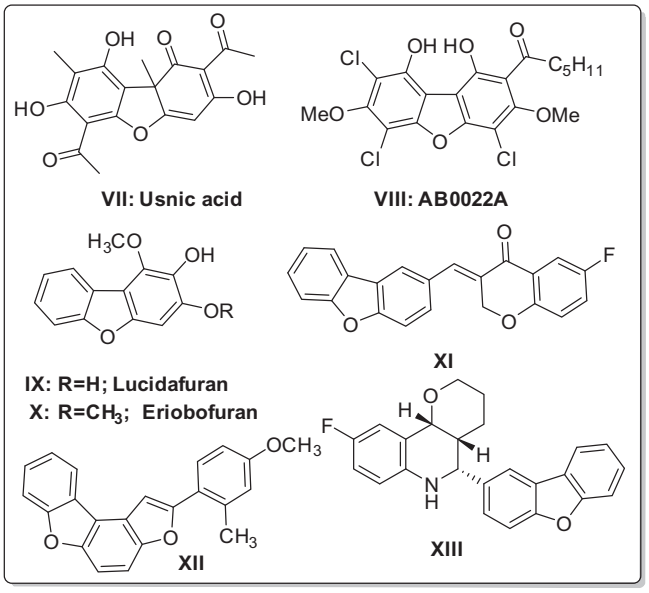


Figure 2. Natural and synthetic bioactive analogs of dibenzofuran core.

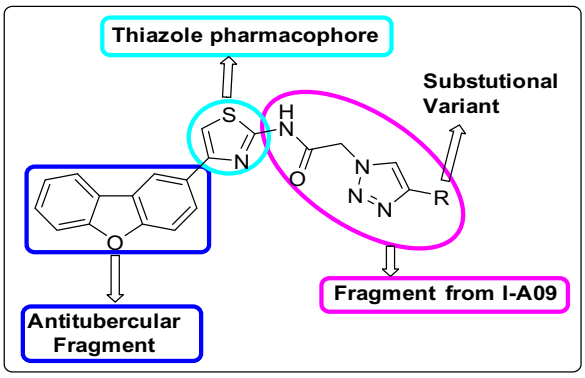


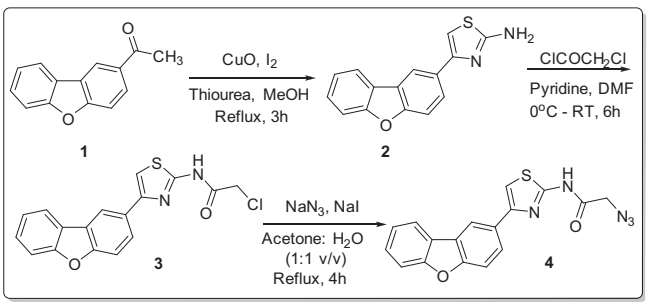
Figure 3. Design strategy for synthesis of dibenzofuran tethered thiazolyl 1,2,3-triazolyl acetamides.

pharmacophore dibenzofuran for desired pharmacological behavior. The lipophilicity control in the proposed scaffold could be accomplished with the choice of appended aliphatic, aromatic groups as variants on 1,2,3-triazole unit.

Initiating the synthesis (Scheme 1), 4-(dibenzofuran-2-yl)thiazol-2-amine (**2**) required was prepared by cyclization of 1-(dibenzofuran-2-yl)ethanone (**1**) with thiourea in the presence of CuO/iodine in methanol at reflux. Dibenzofuran tethered 2-aminothiazole **2** was next reacted with chloroacetyl chloride in dry DMF/pyridine at 0 °C to give 2-chloro-*N*-(4-(dibenzofuran-2-yl)thiazol-2-yl) acetamide (**3**) with 92% yield. Further reaction of compound **3** with NaN_3/NaI in acetone: water (1:1 v/v) at reflux gave 2-azido-*N*-(4-(dibenzofuran-2-yl)thiazol-2-yl)acetamide (**4**) in 93% yield. All these compounds **2**–**4** were fully characterized by their NMR, IR and ESI-Mass spectral data.[18]

To construct the desired analogues, 2-azido-*N*-(4-(dibenzofuran-2-yl)thiazol-2-yl)acetamide (**4**) was further reacted with various aliphatic and aromatic alkynes **5a**–**p** using click chemistry (Table 1). For example, compound **4** was reacted with alkyne **5b** in presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in *t*-butanol and water (1:1, v/v) to give *N*-(4-(dibenzofuran-2-yl)thiazol-2-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acetamide (**6b**) in 92% yield. Under similar conditions, all the compounds **6a**–**p** was synthesized and fully characterized by their ^1H and ^{13}C NMR, IR and Mass spectral data.[19] Log*P* and *C*log*P* required to assess the lipophilic character of new analogs was calculated using Chembiodraw 12.0 programme (Table 1).

All the newly synthesized thiazolyl 1,2,3-triazole derivatives **6a**–**p** were screened for in vitro antimycobacterial activity against *M. tuberculosis* H37Rv (ATCC27294) by agar dilution method[20] for the determination of MIC in triplicate. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth.



Scheme 1. Synthesis of 2-azido-*N*-(4-(dibenzofuran-2-yl)thiazol-2-yl)acetamide (**4**).