Bioorganic & Medicinal Chemistry Letters 28 (2018) 1610–1614

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Dibenzofuran, dibenzothiophene and *N*-methyl carbazole tethered 2-aminothiazoles and their cinnamamides as potent inhibitors of *Mycobacterium tuberculosis* ☆

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ARTICLE INFO

Article history:
Received 4 January 2018
Revised 6 March 2018
Accepted 17 March 2018
Available online 19 March 2018

Keywords:
Dibenzofuran
Dibenzothiophene
N-Methyl carbazole
2-Aminothiazole
Cinnamamide
Antimycobacterial activity

ABSTRACT

Herein described the design, synthesis and antitubercular evaluation of novel series of dibenzofuran, dibenzothiophene and *N*-methyl carbazole tethered 2-aminothiazoles and their cinnamamide analogs. One pot condensation of *N*-methyl carbazole, dibenzofuran and dibenzothiophene methyl ketones with thiourea in the presence of Iodine and CuO gave respective 2-aminothiazoles **4**–**6** in very good yields. Aminothiazoles were further coupled with substituted cinnamic acids using acid-amine coupling conditions to give desired cinnamamide analogs **8a**–**e**, **9a**–**e** and **10a**–**e**. All the newly synthesized compounds were fully characterized by their NMR and mass spectral analysis. *In vitro* screening of new derivatives against *Mycobacterium tuberculosis* H37Rv (*Mtb*) resulted **8c**, **10d** and **10e** (MIC: 0.78 μg/mL) and 2-aminothiazoles **5** and **6** (MIC: 1.56 μg/mL) as potent compounds with lower cytotoxicity profile.

Among infectious diseases, tuberculosis (TB) remained most prevalent and deadliest pandemic disease worldwide. The causative pathogen, *Mycobacterium tuberculosis* (*Mtb*) is responsible for more deaths than any other bacterial infection.[1] World Health Organization (WHO) *Global tuberculosis report* 2017 estimated that globally 1.3 million people died from tuberculosis and 10.4 million new tuberculosis cases were identified. It is remarkable to note that today TB is responsible for more deaths than HIV and ranked as leading killer in infectious diseases.[2] 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).[3] In 2016, there were 600,000 new cases with resistance to rifampicin (RRTB), the most effective first-line drug, of which 490,000 had multidrug-resistant TB (MDR-TB). Almost half (47%) of these cases were from India, China, and the Russian Federation. Standard treatment for the individuals infected with drug-sensitive TB involves four drugs for 2 months and two of them for an additional 4 months, a far longer treatment than for most bacterial infections, whereas treatment of drug-resistant TB often requires >24 months.[4] Moreover none of the first- and second-line TB drugs that are active against replicating (R) *Mtb in vitro* are comparably active against non replicating (NR) *Mtb*.[5] These considerations have prompted to develop new anti-tubercular drugs to address the unmet needs of antituberculosis medical goals.[6]

Recent years, heterocyclic natural products have gained renewed interest in discovering new antitubercular leads possessing novel architectures.[7] Among them carbazole alkaloids such as Micromeline (**I**) and Clausine K (**II**) isolated from several plants possess greater antitubercular activity.[8] Dibenzofuran lichen secondary metabolite usnic acid **(III)** exhibit good antimycobacterial activity (MIC: 12.5 μg/mL).[9] Some of the synthetic analogs of carbazole, dibenzofuran and dibenzothiophene **IV**–**VII** (Fig. 1) synthesized in our laboratory, exhibited promising antitubercular activity and are undergoing detailed mechanistic studies.[10]

2-Aminothiazole is a familiar heterocycle possessing a wide range of pharmacological activities.[11] Thiazole nucleus is main integral part of all the available penicillin's, which has metamorphose the therapy of bacterial diseases.[12] The synthetic carbazolo–thiazole, dibenzofuran – thiazole conjugates **VIII** & **IX** and

☆ CSIR-IICT communication no. IICT/Pubs/2018/0010.

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https://doi.org/10.1016/j.bmcl.2018.03.048
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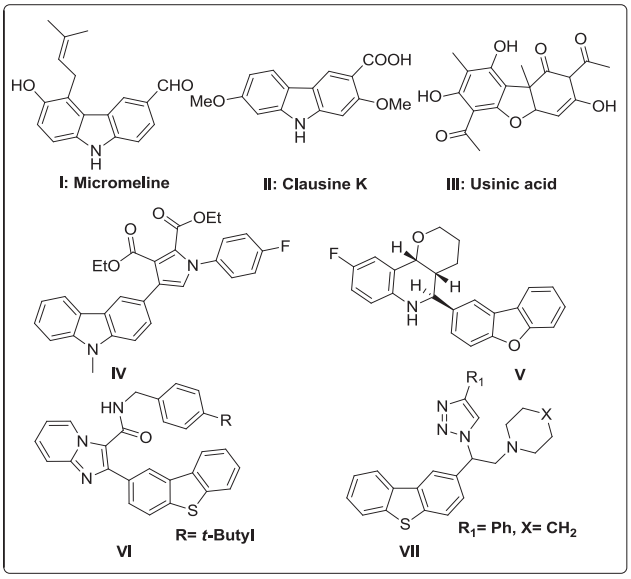


Fig. 1. Natural and synthetic bioactive analogs of carbazole, dibenzofuran & dibenzothiophene.

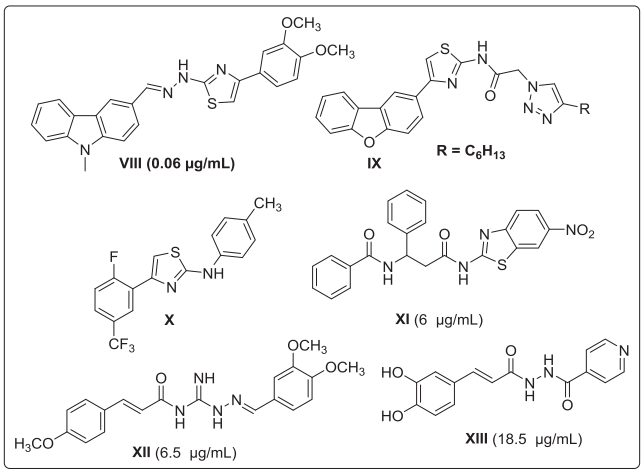


Fig. 2. Bioactive synthetic thiazole and cinnamamide analogs.

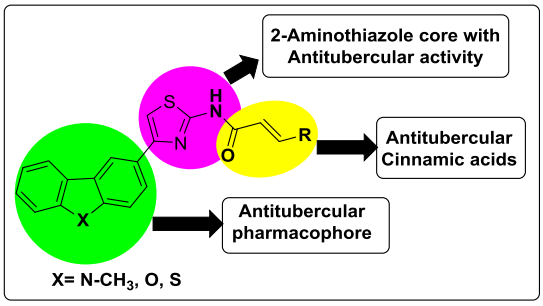
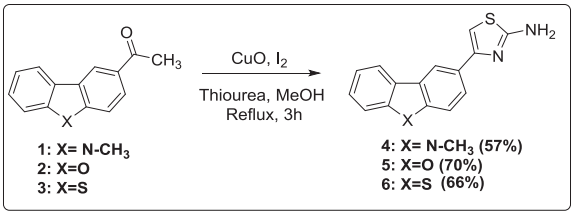


Fig. 3. The Design strategy for the synthesis of *N*-methylcarbazole, dibenzofuran and dibenzothiophene derived thiazolyl cinnamides.



Scheme 1. Synthesis of 2-aminothiazoles **4**, **5** & **6**.

thiazole derivatives **X** & **XI** reported showing potential antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain.[13] Further cinnamic acid derivatives **XII**–**XIII** possess synergism to some first line antitubercular agents.[14] These high therapeutic properties of the carbazole, dibenzofuran, dibenzothiophene, 2-aminothiazole and cinnamamide related drugs have encouraged medicinal chemists to synthesize a number of novel clinical agents for treating various types of diseases.

Continuing our work on the development of new antitubercular agents,[15] we herein report a series of novel *N*-methylcarbazole, dibenzofuran, dibenzothiophene tethered thiazolyl cinnamamides **8a**–**e**, **9a**–**e** and **10a**–**e** designed by combining pharamcogenic *N*-methyl carbazole, dibenzofuran, dibenzothiophene, 2-amino thiazole and substituted cinnamic acid fragments. The desired compounds **8a**–**e**, **9a**–**e** and **10a**–**e** were accomplished in two-step synthetic sequence utilizing acid-amine condensation in the ultimate step. *In vitro* screening of all fifteen new derivatives **8a**–**e**, **9a**–**e** and **10a**–**e** against *Mycobacterium tuberculosis* H37Rv (*Mtb*) resulted **8c**, **10d** and **10e** (MIC: 0.78 μg/mL) and 2-amino thiazoles **5** and **6** (MIC: 1.56 μg/mL) as effective hit compounds with lower cytotoxicity profile.

The designed scaffold (Fig. 3) is originated from the structure of an antitubercular agent's **IX**, **X**, and **XII** (Fig. 2). The new scaffold is in three parts: thiazole ring as an antitubercular pharmacophoric fragment linked to *N*-methylcarbazole, dibenzofuran and dibenzothiophene and substituted cinnamamide groups appended to amine moiety of thiazole for enhancing pharmacophoric nature and to induce lipophilicity. Variations in the proposed scaffold can be accomplished with the choice of substituted cinnamic acids.

Initiating the synthesis (Scheme 1), of 2-amino thiazole from easily available heteroaryl (*N*-methylcarbazole, dibenzofuran, dibenzothiophene) ketones and thiourea in presence of CuO, I_2. For example, compound **5** required was prepared by cyclization of 1-(dibenzo[*b*,*d*]furan-2-yl)ethanone (**2**) with thiourea in the presence of CuO/Iodine in methanol at reflux to form required 5-(dibenzo[*b*,*d*]furan-2-yl)thiazol-2-amine (**5**) in 70% yield. All the compounds **4**, **5** & **6** were fully characterized by their NMR, IR and ESI-Mass spectral data.[16]

To build the desired analogs, 2-aminothiazole **4**, **5** & **6** were further reacted with substituted cinnamic acids **7a**–**e** utilized by an acid-amine condensation reaction (Table 1). For example, compound **2** was reacted with *p*-tolyl cinnamic acid (**7b**) in presence of *N*-(3-Dimethylaminopropyl)-*N*′-ethyl carbodiimide hydrochloride (EDCI.HCl), hydroxybenzotriazole (HOBT) and triethylamine in dry dichloromethane at reflux to gave (*E*)-*N*-(5-(dibenzo[*b*,*d*]furan-2-yl) thiazol-2-yl)-3-(*p*-tolyl) acrylamide (**9b**) in 65% yield. Under similar conditions, all the compounds **8a**–**e**, **9a**–**e** & **10a**–**e** was synthesized and fully characterized by their ^{1}H & ^{13}C NMR, IR, and Mass (ESI-MS & HR-MS) spectral data.[17] LogP and ClogP required assessing the lipophilic character of new analogs was calculated using Chembiodraw 12.0 programme (Table 1).

All the newly synthesized thiazolyl cinnamamide derivatives **8a**–**e**, **9a**–**e** & **10a**–**e** were screened for *in vitro* antimycobacterial activity against *M. tuberculosis* $H_{37}Rv$ (ATCC27294) by agar dilution method for the determination of MIC in triplicates.[18] The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values (μg/mL) of **8a**–**e**, **9a**–**e** & **10a**–**e** along with the standard drugs for comparison are listed in Table 1. Fifteen new compounds and three 2-aminothiazoles were screened showed