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Synthesis and evaluation of the antibacterial activities of aryl substituted dihydrotriazine derivatives

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ABSTRACT

Five series of dihydrotriazine derivatives containing chalcone (**13a–i**), phenoxy acetophenone (**14a–b**), benzyl benzene (**15a–c**), naphthoxyl acetophenone (**16a–b**) and benzyl naphthalene (**17a–h**) moieties were designed and synthesized. The antibacterial and antifungal activities of these compounds were evaluated against several strains of Gram-positive and Gram-negative bacteria, as well as a single fungus. Compound **17h** was found to be the most potent of all of the compounds tested, with an MIC value of 0.5 μg/mL against several Gram-positive (*Staphylococcus aureus* 4220 and QRSA CCARM 3505) and Gram-negative (*Escherichia coli* 1924) strains of bacteria. However, this compound was inactive against *Pseudomonas aeruginosa* 2742 and *Salmonella typhimurium* 2421, indicating that its antibacterial spectrum is similar to those of the positive controls gatifloxacin and moxifloxacin. The cytotoxic activity of the compound **13i**, **16b** and **17h** was assessed in Human normal liver cells.

Many different types of disease are caused by bacterial infection. In principle, pathogenic bacteria and conditional pathogens can produce toxins and secondary metabolites that can lead to a variety of physical discomforts such as rashes, fever and chills during blood circulation. The discovery of antibiotics and other antimicrobial agents has played a critical role in the fight against bacteria. However, recent increases in drug-resistant bacteria mean that the standard-of-care antibacterial drugs currently used in clinical practice could soon become ineffective, making it difficult to manage these diseases. There is therefore an urgent need for the development of new antibacterial drugs that exert their activity through unique mechanisms of action, enabling them to inhibit the growth of drug-resistant bacteria. The importance of this task is highlighted by the large number government agencies, scientific institutions and clinicians involved in the search for new antimicrobial agents.[1]

1,3,5-triazine derivatives have been reported to exhibit a wide range of interesting biological properties including anticancer, anti-HIV and antimicrobial activities.[2–6] For example, Feng et al. reported that N^2-methyl-6-(5-methylisoxazol-3-yloxy)-N^4-(4-(trifluoromethyl)phenyl)-1,3,5-triazine-2,4-diamine displayed an antimicrobial activity of up to 97.7% when it was used at a concentration of around 200 μg/mL.[7] Furthermore, Singga et al. reported that the growth some Gram-positive and Gram-negative bacteria could be inhibited by triazine derivatives, which exerted their activity by restricting the growth of the bacterial cell membranes.[8] In our previous work, we reported the identification of a series of 2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid derivatives, and demonstrated that all of the compounds belonging to this series showed outstanding bacteriostatic activity against Gram-positive bacteria, as exemplified by compounds A, B, C and D (MIC = 2 μg/mL) (Fig. 1).[9–12] Unfortunately, however, compounds belonging to this series did not show any bacteriostatic activity against Gram-negative bacteria. In this study, we designed and synthesized five novel series of compounds (**13a–i**, **14a–b**, **15a–c**, **16a–b**, **17a–h**) (Fig. 2) using a hybrid strategy with compounds A–D (Fig. 1) as the lead compounds. Notably, the 2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid moiety in these lead compounds was replaced with a dihydrotriazine ring. These compounds were subsequently evaluated in terms of their antibacterial activities with an aim of identifying a new series of potent antimicrobial agents.

The route used to synthesize the five different series of dihydrotriazine derivatives is shown in Scheme 1. Metformin hydrochloride was prepared by the reaction of dicyandiamide with

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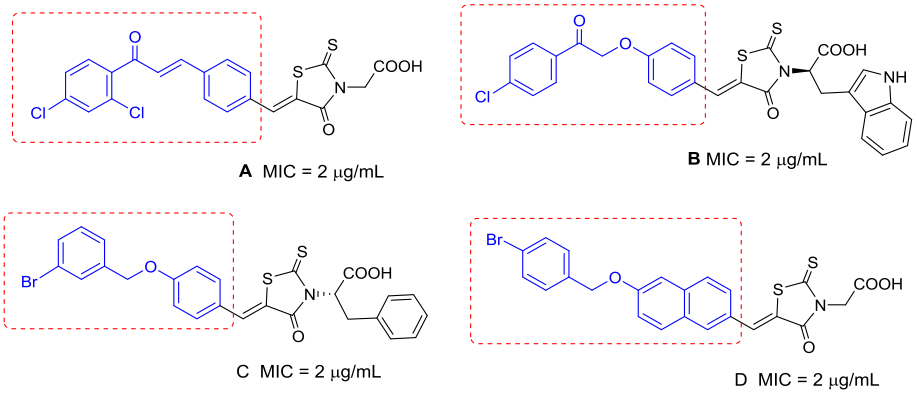
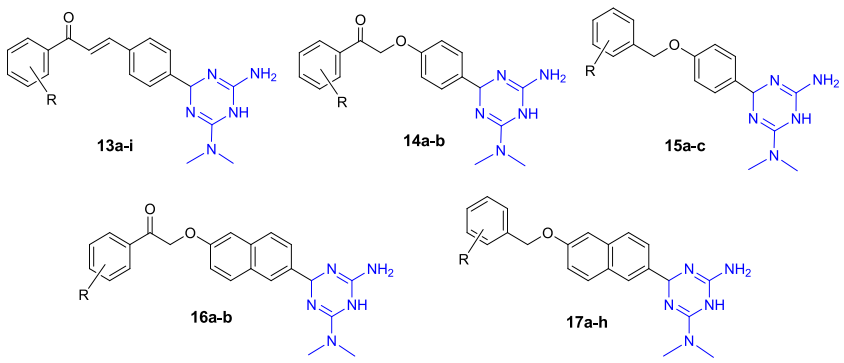


Fig. 1. Previously reported antibacterial compounds.



13a: R= H	13i: R= 2,4-$(Cl)_2$	17a: R= H
13b: R= 4-F	14a: R= H	17b: R= 4-CH_3
13c: R= 2-Br	14b: R= 4-Br	17c: R= 2-Cl
13d: R= 4-Br	15a: R= H	17d: R= 3-Cl
13e: R= 2-OCH_3	15b: R= 4-CH_3	17e: R= 4-Cl
13f: R= 3-OCH_3	15c: R= 4-F	17f: R= 2-F
13g: R= 4-CH_3	16a: R= H	17g: R= 4-Br
13h: R= 2,4-$(Cl)_2$	16b: R= 4-Br	17h: R= 2,4-$(Cl)_2$

Fig. 2. Designed target compounds.

minocycline hydrochloride according to a previously reported method.[13] Acetophenone was reacted with terephthalaldehyde in the presence of ethylene glycol to afford a series of (*E*)-4-(3-oxo-3-phenylprop-1-en-1-yl)benzaldehydes (**8a–i**). Two 4-(2-oxo-2-phenylethoxy)benzaldehydes (**9a–b**) were prepared by reacting the corresponding substituted 2-bromo-1-phenylethanones (**2**) with 4-hydroxybenzaldehyde in the presence of K_2CO_3. Two 6-(2-oxo-2-phenylethoxy)-2-naphthaldehydes (**11a–b**) were prepared using the same method by reacting **2** with 6-hydroxy-2-naphthaldehyde (**6**). Three 4-(benzyloxy)benzaldehydes (**10a–c**) and eight 6-(benzyloxy)-2-naphthaldehydes (**12a–h**) were obtained by reacting substituted chloromethylbenzene (**3**) with 4-hydroxybenzaldehydes (**5**) and **6**, respectively. The reductive cyclization reactions of the five intermediate series (**8a–i**, **9a–b**, **10a–c**, **11a–b**, **12a–h**) with metformin hydrochloride (**7**) afforded the corresponding novel dihydrotriazine derivatives (**13a–i**, **14a–b**, **15a–c**, **16a–b**, **17a–h**). The structures of the synthesized dihydrotriazine compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS analyses. The purity (≥95%) of the compound is verified by the HPLC study performed on Develosil C18 (4.6 mm × 250 mm, 5 μm) column using a mixture of solvent 0.1FA acetonitrile/0.1FA water at the flow rate of 1 mL/min and peak detection at 334 nm under UV.[14]

The *in vitro* antimicrobial and antifungal activities of the synthesized compounds were evaluated against various bacteria, including multidrug-resistant clinical isolates, as well as one fungus. These screening assays were conducted in 96-well microtiter plates to obtain the minimum inhibitory concentration (MIC) values of the different compounds.[15] Gatifloxacin, moxifloxacin and fluconazole were used as positive controls. The compounds were screened against several Gram-positive strains (*S. aureus* 4220, QRSA CCARM 3505, MRSA CCARM 3167, *S. mutans* 3289) and Gram-negative strains (*Escherichia coli* 1924, *Pseudomonas aeruginosa* 2742, *Salmonella typhimurium* 2421), as well as one fungus (*Candida albicans* 7535), and the results are shown in Table 1. Most of the newly synthesized compounds exhibited potent inhibitory activities against the different bacteria and single fungus tested in the current study with MICs in the range of 0.5 to 64 μg/mL.

Compounds belonging to series **13**, **14**, **15** and **16** showed moderate levels of antimicrobial activity against the different strains of Gram-positive bacteria and fungus, whereas compounds belonging to series **17** exhibited potent activity against the Gram-positive