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Synthesis, antimicrobial and cytotoxic activities of pyrimidinyl benzoxazole, benzothiazole and benzimidazole

D. Seenaiah [a], P. Ramachandra Reddy [a], G. Mallikarjuna Reddy [a], A. Padmaja [a], V. Padmavathi [a,*], N. Siva krishna [b]

[a] Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, Andhra Pradesh, India
[b] Department of Molecular Reproduction Development and Genetics, Indian Institute of Science, Bangalore 560 012, Karnataka, India

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ABSTRACT

A variety of pyrimidinyl benzoxazoles, benzothiazoles and benzimidazoles linked by thio, methylthio and amino moieties were prepared and studied their antimicrobial and cytotoxic activities. The compound pyrimidinyl bis methylthio benzimidazole **22** was a potent antimicrobial agent particularly against *Staphylococcus aureus* (29 mm, MIC 12.5 μg/mL) and *Penicillium chrysogenum* (38 mm, MIC 12.5 μg/mL). The amino linked pyrimidinyl bis benzothiazole **24** exhibited cytotoxic activity on A549 cells with IC_{50} value of 10.5 μM.

1. Introduction

Organic compounds containing pyrimidine scaffold as a core unit are known to exhibit various biological and pharmaceutical activities such as antiviral [1], antibacterial [2], antitumor [3], anti-inflammatory [4], antifungal [5], *etc*. Benzoxazoles, benzothiazoles and benzimidazoles are important fragments in medicinal chemistry because of their wide range of biological activities. The benzoxazole ring is a core structure found in a wide class of natural and synthetic compounds showing antibacterial [6], antifungal [7], antimicrobial [8] and anti-measles virus activities [9]. Benzothiazole and their derivatives exhibit antitumor [10], antimicrobial [11] and antiviral [12] activities. Benzimidazoles have been frequently found to display anticancer [13], antiviral [14], anti-inflammatory [15], antimicrobial [16], antioxidant [17] and anticoagulant properties [18]. It is well known that the combination of two or more types of heterocycles into one molecule could afford a novel entity with increased bioactivities [19,20]. As part of an ongoing multifaceted program aimed towards the development of small molecules as therapeutic agents, herein we report the synthesis, antimicrobial and cytotoxic activities of thio, methylthio and amino linked pyrimidinyl benzoxazoles, benzothiazoles and benzimidazoles.

2. Chemistry

The synthetic intermediates 4-chloro-6-methylpyrimidine-2-thiol (**1**), 2-(chloromethyl)benzoxazole (**2**), 2-(chloromethyl)benzothiazole (**3**), 2-(chloromethyl)-1*H*-benzimidazole (**4**), benzoxazole-2-thiol (**5**), benzothiazole-2-thiol (**6**), 1*H*-benzimidazole-2-thiol (**7**), benzoxazol-2-ylmethanethiol (**8**), benzothiazol-2-ylmethanethiol (**9**), 1*H*-benzimidazol-2-ylmethanethiol (**10**), benzoxazol-2-amine (**11**), benzothiazol-2-amine (**12**) and 1*H*-benzimidazol-2-amine (**13**) were prepared as per the literature precedents [21–25]. The reaction of **1** with **2** in the presence of triethylamine in tetrahydrofuran resulted in 2-((4-chloro-6-methylpyrimidin-2-ylthio)methyl)benzoxazole (**14**). Similarly, the compounds 2-((4-chloro-6-methylpyrimidin-2-ylthio)methyl) benzothiazole (**15**) and 2-((4-chloro-6-methylpyrimidin-2-ylthio) methyl)-1*H*-benzimidazole (**16**) were prepared by treating **1** with **3** and **4** (Scheme 1). The reaction of **14** with **5** in the presence of a catalytic amount of methylsulfonic acid produced 2-(2-((benzoxazol-2-yl)methylthio)-6-methylpyrimidin-4-ylthio)benzoxazole

* Corresponding author.
E-mail address: vkpuram2001@yahoo.com (V. Padmavathi).

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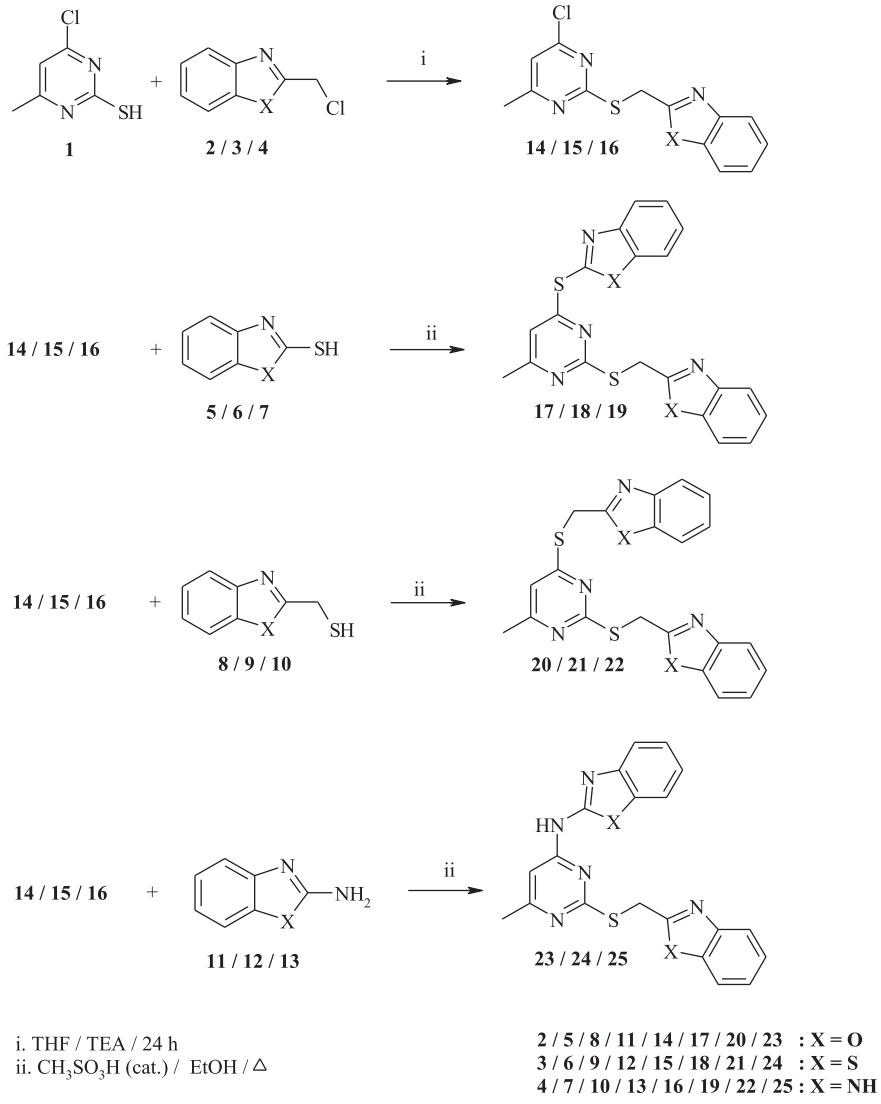

Scheme 1. Synthesis of Pyrimidine benzoxazole, benzothiazole, benzimidazole.

(**17**). Adopting similar procedure the compounds 2-(2-((benzothiazol-2-yl)methylthio)-6-methylpyrimidin-4-ylthio)benzothiazole (**18**) and 2-(2-((1*H*-benzimidazol-2-yl)methylthio)-6-methylpyrimidin-4-ylthio)-1*H*-benzimidazole (**19**) were prepared by performing the reaction of **15** with **6** and **16** with **7**, respectively. In a much similar way the compound 2-((4-((benzoxazol-2-yl) methylthio)-6-methyl-pyrimidin-2-ylthio)methyl)benzoxazole (**20**) was prepared by treating **14** with **8** in the presence of a catalytic amount of methylsulfonic acid. Likewise, the compounds 2-((4-((benzothiazol-2-yl)methylthio)-6-methylpyrimidin-2-ylthio) methyl)benzothiazole (**21**) and 2-((4-((1*H*-benzimidazol-2-yl) methylthio)-6-methylpyrimidin-2-ylthio)methyl)-1*H*-benzimidazole (**22**) were prepared by treating **15** with **9** and **16** with **10**, respectively. On the other hand, the compounds *N*-(2-((benzoxazol-2-yl)methylthio)-6-methylpyrimidin-4-yl)benzoxazol-2-amine (**23**), *N*-(2-((benzothiazol-2-yl)methylthio)-6-methylpyrimidin-4-yl)benzothiazol-2-amine (**24**) and *N*-(2-((1*H*-benzimidazol-2-yl)methylthio)-6-methyl-pyrimidin-4-yl)-1*H*-benzimidazol-2-amine (**25**) were prepared by the reaction of **14**, **15** and **16** with **11**, **12** and **13**, respectively. The structures of all the compounds were established by IR, NMR, Mass spectral data and elemental analyses.

3. Result and discussion

3.1. Antimicrobial activity

The compounds **14**–**25** were screened for antimicrobial activity at three different concentrations 25, 50 and 100 μg/well. The results of antibacterial activity presented in Table 1 indicated that all the tested compounds exhibited more activity towards Gram-positive bacteria than Gram-negative bacteria. The tris heterocyclic compounds exhibited greater activity than the bis heterocyclic systems. The compounds 4-chloro-pyrimidinylsulfanylmethyl benzoxazole (**14**), benzothiazole (**15**) and benzimidazole (**16**) displayed least activity. Replacement of chloro substituent by heterocyclic moiety enhanced the activity. Further, the amino linked heterocycles **23**–**25** showed slightly higher activity than those having thio group **17**–**19**. Amongst tris heterocyclic compounds, pyrimidinyl bis methylthio benzoxazole (**20**), benzothiazole (**21**) and benzimidazole (**22**) displayed greater activity. This may be due to more flexibility of these compounds. In fact, compound **22** showed activity higher than the standard Ciprofloxacin at all tested concentrations towards *Staphylococcus aureus*.