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Antimicrobial evaluation of new substituted hantzsch thiazole derivatives

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Abstract

New thiazole derivatives were synthesized and tested as antimicrobial agents. Synthesized compounds were assayed in vitro for their antimicrobial activity against a panel of selected Gram positive and Gram negative bacteria such as *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* by the disc diffusion and the serial dilution methods. Most of the thiazoles exhibited significant antibacterial activity compared to amoxicillin and ciprofloxacin as positive controls. The entire synthesized compounds and standard antibiotics have effective antibacterial properties against bacteria strains and are most active against Gram negative bacteria than the Gram positive one.

Keywords: Thiazoles; Antibacterial activity; Gram positive bacteria; Gram negative bacteria.

1. Introduction

Molecular entities bearing thiazole ring system(s) form an important class of natural and synthetic compounds because of their physicochemical properties [1–4]. Furthermore, they exhibit a wide range of biological activities such as cardiotonic [5], antifungal [6], analgesic [7], anticonvulsant [8], antituberculosis [9], antiviral [10], anti-inflammatory [11], anti-HIV [12], and anticancer activities [13].

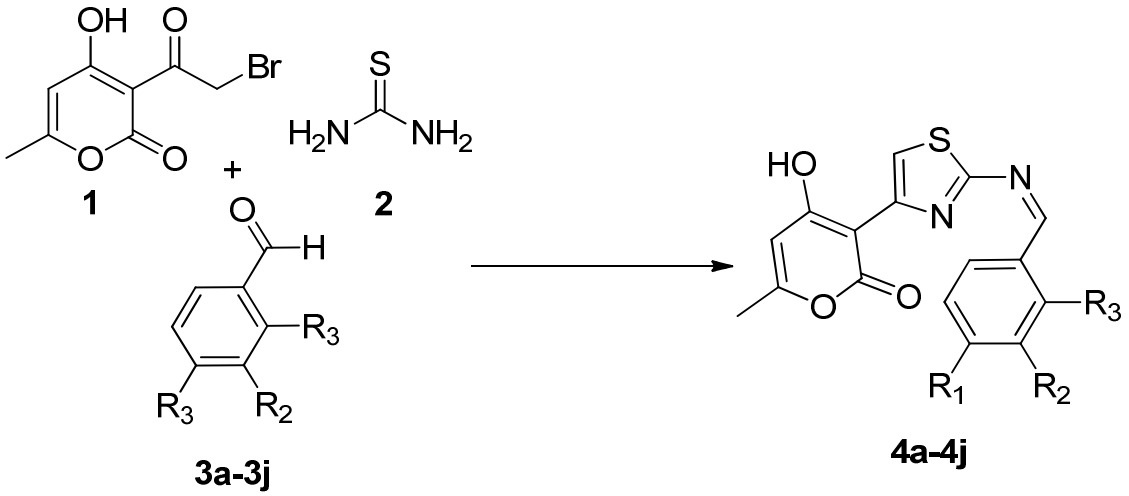
It is known that thiazoles can be synthesized from α-bromoketone and a thiourea via Hantzsch thiazole synthesis in high yields [14]. A literature survey revealed that there are numerous routes reported for the synthesis of substituted thiazoles according to Hantzsch thiazole synthesis [15].

Due to the importance of these heterocycles in medicinal and material chemistry, the development of new routes—which leads to these heterocycles in higher yields, shorter reaction time, milder or greener conditions—has received considerable attention in organic synthesis [16]. When designing organic synthesis, chemists have to face the ecocompatibility concern of their synthesis plan. Multi-component reactions (MCRs) are a special type of synthetically useful organic reaction, in which, three or more different starting materials react, to generate a single product in a one-pot procedure [17]. Thus, MCRs also represent a possible instrument to perform near ideal synthesis, because they possess one of the aforementioned qualities, namely the possibility of building up complex molecules with maximum simplicity and brevity [18]. Owing to the above facts and in continuation of our

research work on the development of MCRs for the synthesis of novel heterocyclic compounds, in this work, we report on the synthesis of functionalized thiazoles, in good yields, and their biological evaluation.

2. Synthesis

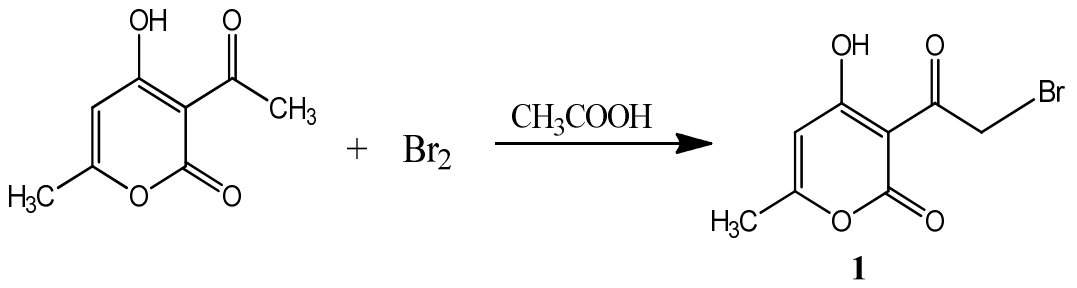
A mixture of 3-(bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one)((**1**)(1 mmol), thiourea (**2**) (1 mmol) and benzaldehyde (**3a**–**3j**) (1 mmol) was refluxed in ethanol/water 1/1 (5 mL) with stirring for 2h to 3.5h at 65 °C. The obtained solid was filtered off and washed with ethanol; the remaining solid was oven-dried (60 °C) and recristallised.



4a: R_1= H, R_2 = H, R_3 = H.
4b: R_1= H, R_2 = OH, R_3 = H.
4c: R_1= OH, R_2 = H, R_3 = OH.
4d: R_1= NO_2, R_2 = H, R_3 = H.
4e: R_1= Cl, R_2 = H, R_3 = H.
4f: R_1= OH, R_2 = H, R_3 = H.
4g: R_1= H, R_2 = OH, R_3 = OH.
4h: R_1= H, R_2 = H, R_3 = OCH_3.
4i: R_1= OCH_3, R_2 = H, R_3 = H.
4j: R_1= H, R_2 = OCH_3, R_3 = H.

Scheme 1. Synthesis of new Hantzsch thiazole derivatives **4a**–**4j**.

The required α-haloketone (**1**), 3-(bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one,is not commercially available. It could be easily obtained via the selective α-monobromination of dehydroacetic acid (DHAA) in 70% yield according to a known procedure.



Scheme 2. Synthesis of α-haloketone (**1**).

In that way, we decided to study the reactivity of (**1**) with several binucleophilic amines and initiate our studies with the reaction of thiourea (**2**) to afford the corresponding thiazoles. The thiazoles were assembled according to a slightly modified version of the Hantzsch thiazoles synthesis [48,49]. Herein, the three-component one-pot condensation of an equimolar amount of (**1**), (**2**) and substituted benzaldehydes (**3a**–**3j**), under conventional heating, yielded the corresponding thiazole derivatives (**4a**–**4j**) in good to excellent yield.

The scope and generality of this process are illustrated with respect to various substituted benzaldehydes as shown in Table 1.

Table 1. Synthesis of Hantzsch thiazole derivatives under conventional heating.

Product	Substitutions			Time (h)	Yield (%)
	R_1	**R_2**	**R_3**		
4a	H	H	H	2	87
4b	H	OH	H	2	85
4c	OH	H	OH	3.5	80
4d	NO_2	H	H	2	82
4e	Cl	H	H	2	84
4f	OH	H	H	2	85
4g	H	OH	OH	3.5	79
4h	H	H	OCH_3	3.5	75
4i	OCH_3	H	H	2	84
4j	H	OCH_3	H	2	82

All the new target compounds were completely characterized by using infrared (IR), ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. The spectroscopic data of the new compounds are given in the experimental section and are fully consistent with the proposed structures. IR spectra of **4a**–**4j** had strong N=C absorptions at about 1669cm^{-1}and displayed absorptions at about 1617–1546 cm^{-1}and 1582 cm^{-1}which were assigned to C=O and C=C functionalities respectively. This study confirmed the conservation of 2-pyroneby the presence of large elongation and intense bands in the absorption range at 1718–1693 cm^{-1}. The ^{1}H-NMRspectraof the compounds **4a**–**4j** exhibited broad signals at 6.02–6.92 ppm, which were assigned to the C–H proton of the thiazole ring. ^{13}C-NMR of compounds **4a**–**4j** showed peaks at about 111.98–115.10 and 164.33–167.46 for C-S (thiazole) and C=N (amide), respectively.

3. Microbiology

3.1. Antimicrobial activity evaluation

The new thiazoles were tested in vitro for their antimicrobial properties against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* by using the serial dilution method. Stock solutions of the compounds were prepared by dissolving them in dimethyl sulfoxide. Then, the solutions were diluted in the media (Mueller Hinton broth) so as to achieve concentrations of compound ranging from 50 to 150 µg/ mL. Amoxicillin and Ciprofloxacin, at the same concentrations of the test compounds, were used as standard control. Bacteria were inoculated at the concentration of 5x10^6 CFU/ mL. After an incubation period of 24 h at 37°C, the minimum inhibitory concentrations (MIC, µg/ mL) were detected as the lowest concentrations of compound that didn't show microbial growth. All the experiments were performed in triplicate and the reported results were obtained from three independent measurements. The entire synthesized compounds and standard antibiotics had higher antibacterial activity against bacteria strains and are most active against Gram-negative

bacteria than the Gram-positive bacteria (Figure 1). In general, all compounds are, approximately, behaving as the reference compounds with same activities.

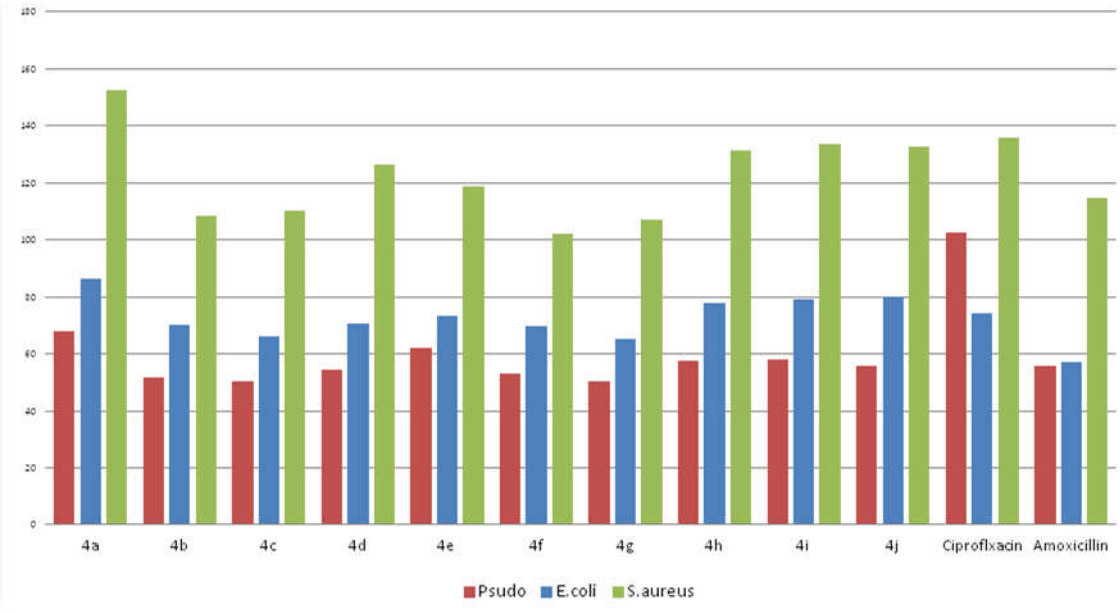


Figure 1. The antibacterial activity of compounds (**4a**–**4j**) compared to Ciprofloxacin and Amoxicillin (MIC = µg/ mL).

3.2. Structure-activity relationship

As regards the relationships between the structure of the heterocyclic scaffold and the detected antibacterial properties, it seems that there is no difference and both electron donating as well as electron withdrawing groups were found to increase the antibacterial properties. Moreover, the presence of substituents in different positions of benzene moiety causes a certain change of activity. Among benzothiazoles, compounds having a hydroxyl (OH) as substituent (compounds **4b, 4c, 4f** and **4g)** displayed moderate antibacterial activity whereas the remaining compounds showed less activity. From the obtained results it is clear that the potent antibacterial activity exhibited may is due to the thiazole ring.

4. Conclusion

In conclusion, an efficient and simple one-pot multi-component condensation procedure was introduced and developed for the synthesis of new thiazole derivatives, under conventional heating. The present method is bestowed with several advantages, such as an inexpensive, high reaction rate, high yield, simple workup procedure and high regioselectivity. This procedure would be a valuable addition to the current methodologies.

The new synthesized compounds have effective antibacterial activity against bacteria strains and are most active against Gram negative bacteria than the Gram positive one. The preliminary studies of these compounds proved that the thiazole ring enhances the antibacterial of the synthesis derivatives, which might serve as new templates in the synthesis and development of potent therapeutics.

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