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Synthesis and antimicrobial evaluation of novel ethyl 2-(2-(4-substituted)acetamido)-4-subtituted-thiazole-5-carboxylate derivatives

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ABSTRACT

A series of novel molecules containing thiazole ring structure were designed and synthesized. The structures of the synthesized compounds were elucidated and confirmed by ^{1}H NMR, ^{13}C NMR, Mass spectrum and the purity was checked through HPLC analysis. Among these synthesized compounds, **3a**–**3i** and **6a**–**6c** were tested for their antimicrobial activity (minimum inhibitory concentration) against a series of strains of *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli* for antibacterial activity and against the strains of *Candida albicans*, *Aspergillus flavus* and *Aspergillus niger* for antifungal activity respectively. The results of the antimicrobial screening data revealed that most of the tested compounds showed moderate to good microbial inhibitions.

The thiazole nucleus is an important component for a huge spectrum of therapeutic agents including anticancer, anticonvulsants, antifungal and antibacterial agents.[1] This structure has found applications in drug development for the treatment of cardiotonic, fungicidal, HIV infection, mental retardation in children, age related and neurodegenerative brain damage (Alzheimer's disease, Parkinson's disease).[2] This class of heterocyclic compounds are found in many potent biologically active molecules such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycin and Tiazofurin (antineoplastic drug).[3]

Furthermore, some thiazoles are used in agriculture as pesticides and plant growth regulators. Several novel thiazole derivatives have been reported in literatures such as, introduction of fluorine into thiazoline and synthesis of sydnonyl substituted thiazolidinone and thiazoline derivatives.[4] Thiazole ring is an important pharmacophore and its coupling with other rings could furnish new biologically active compounds.[5]

In recent times, the applications of thiazoles were found in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, HIV infections, and hypnotics and more recently for the treatment of pain, as fibrinogen receptor antagonists with antithrombotic activity and as new inhibitors of bacterial DNA gyrase B.[3]

Thiazole moiety has been already reported for its antimicrobial activity. Thiazole ring is an important pharmacophore and their couplings with other rings could furnish new biologically active compounds. Thiazole containing compounds exhibit a wide range of biological properties, such as antitumor, anticonvulsant,[6] cardiotonic,[7] IMP dehydrogenase inhibiton,[8] analgesic,[9] anticancer.[10] It was observed that, benzotriazole and thiazole rings present in the same molecule could be convenient models for investigation of their biological activity.[5] Literature revealed that syntheses of such thiazolyl-benzotriazole showed anti-convulsant and anti-inflammatory activity,[11] anti-tumoral activity.[12] After extensive literature search, it was observed that, thiazole coupling with a piperidine moiety would increase the chances of potent antimicrobial activity of the thiazole containing compound.[13–19] We herein report the synthesis of new substituted thiazole derivatives (Schemes 1 and 2) with the aim of investigating their antimicrobial activity.

Thiazoles show many biological activities so we planned to study its antimicrobial activity along with the incorporation of

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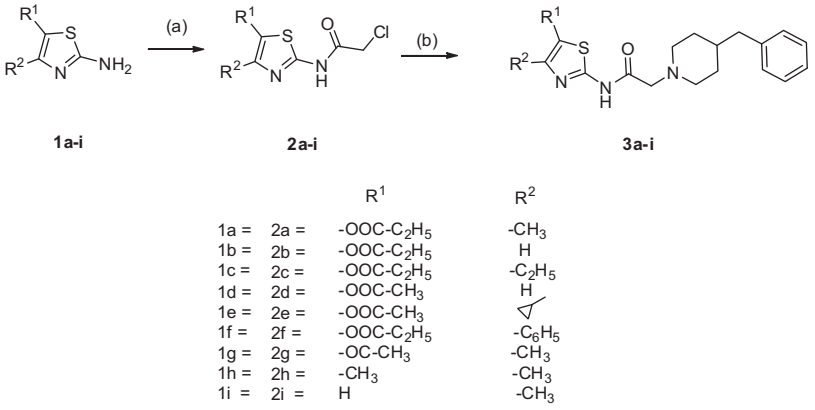
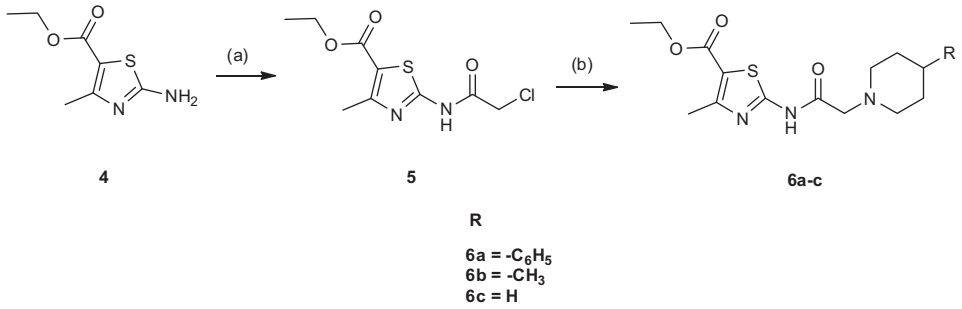


Scheme 1. Synthesis of ethyl 2-(2-(4-substituted)acetamido)-4-subtituted-thiazole-5-carboxylate derivatives (**3a**–**3i**). Reagents and conditions: (a) 2,6-leutidine, DMAP, DCM, chloroacetyl chloride at 0 °C; (b) 2,6-leutidine, DMAP added in 4-benzylpiperidine solution in THF.



Scheme 2. Synthesis of ethyl 2-(2-(4-substituted)acetamido)-4-subtituted-thiazole-5-carboxylate derivatives. Reagents and conditions: (a) 2,6-leutidine., DMAP, DCM, Chloroacetyl chloride at 0 °C; (b) 2,6-leutidine, DMAP, 4-phenylpiperidine (**2a**)/4-methylpiperidine (**2b**)/piperidine (**2c**) solution in THF.

substituted piperidones, as substituted piperidones shows variety of biological activities. The piperidine moiety is a very important pharmacophore because of its presence in numerous alkaloids, pharmaceuticals and diverse applications in medicinal chemistry.[20] The nucleus, as like piperidine and its derivatives are reported in literature for varied pharmacological activities like antifungal,[21] antibacterial,[22] AChE inhibitors,[23] antitubercular,[24] antihistaminics,[25] antitumor agents[26] and anticancer activity.[27] The piperidine and its derivatives are important building blocks in the synthesis of pharmaceutical drug molecules like paroxetine, methylphenidate, raloxifene, minoxidil, risperidone and pethidine. The biologically active alkaloids containing substituted piperidine ring systems have been targeted by medicinal chemists, for their complete or partial synthesis.[28]

Our research group previously reported synthesis, characterization and antimicrobial evaluation of derivatives of thiazole and thiazolidinone.[29] Here, we wish to mention the development and incorporation of thiazole and substituted piperidine scaffold in one framework.

The synthetic methods adopted for the preparation of the title compounds **3a**–**3i** and **6a**–**6c** care depicted in the schemes presented below.

We have optimized condition for the preparation of our substituted products by varying different bases, varying solvents and reaction time. We presented optimization conditions for both the schemes of step (a) and (b) in Tables 1 and 2 respectively. For the step (a), in the base TEA with DMF solvent gives the corresponding product in a 45% yield, which was the worst among these solvents (Table 1, entry 1). Nevertheless, all of these yields were generally low before further optimizations. To increase the efficiency of the condensation reaction, the effects of different solvents were investigated (Table 1, entries 1–10). DCM exhibited

Table 1
Screening of base and solvent for synthesis of compounds **2a**–**2i** and **5** step (a)

Entry	Base	Solvent	Time (h)	Yield[a] (%)
1	TEA (2 equiv)	DMF	6	45
2	DIPEA(2 equiv)	DMF	16	30
3	DMAP (2 equiv)	DMF	16	55
4	2,6-Leutidine (2 equiv)	DMF	6	58
5	Pyridine (2 equiv)	DMF	16	40
6	DMAP (2 equiv)	DCM	16	60
7	2,6-Leutidine (2 equiv) and DMAP (0.2 equiv)	DCM	3	80
8	DIPEA(2 equiv)	DCM	16	40
9	TEA (2 equiv) and DMAP (0.2 equiv)	DCM	3	40
10	Pyridine (2 equiv)	DCM	16	30

[a] Isolated yield.

the best performance of the solvent; the product yield was 80%, reaction completion time only 3 h (Table 1, entries 7). The DMF gave lower yields as a solvent with used bases (Table 1, entries 1–3, and 5). But interestingly in the base 2,6-Leutidine the product yield was 58%, All the reactions were carried out with various amounts of each bases in 1 mL of solvent. Among these reactions same amounts of the solvent, 1 mL of DCM turned out to be the best choice with 2,6-Leutidine (2 equiv) and DMAP (0.2 equiv) gives yield of 80% (Table 1, entry 7). We like to mention here in DCM as a solvent and with 2,6-Leutidine (2 equiv) and DMAP (0.2 equiv) were the best choice and less time required for reaction completion. We decided to carry out the further reaction in DCM.

For the step (b), we have again used different bases and solvents and finally optimized one condition that gives good yield along with reduced reaction time (Table 2, entry 1) without purification and crude used further for next reactions.