Synthesis and antibacterial activity of novel 3-substituted 1-(2-methyl-5-nitrophenyl)-5-oxopyrrolidine derivatives

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Abstract – ***The synthesis of novel azole derivatives has been accomplished during chemical transformations of the 1-(2-methyl-5-nitrophenyl)-5-oxopyrrolidine-3-carbohydrazide. The structure of the synthesized compounds was determined by NMR and IR spectroscopies. Most of the synthesized compounds were screened for their antibacterial activity against S. aureus, L. monocytogenes, E. coli, and P. aeruginosa bacteria strains.***

Keywords – pyrrolidin-2-ones, thiazoles, sulphonylamides, antibacterial activity.

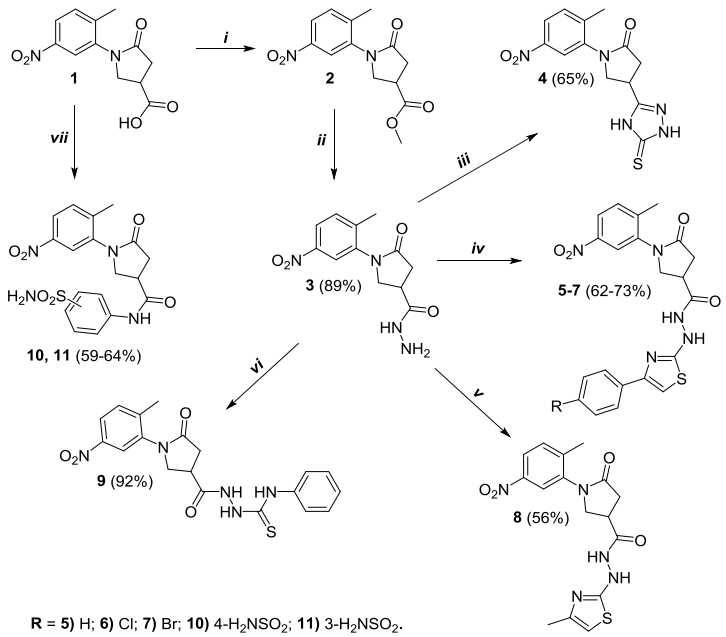
Introduction

Pyrrolidinone derivatives are widely known for their biological activities such as antimicrobial [1], antiviral [2], etc. Furthermore, thiazole is an important pharmacophore associated with varied biological activities including antimicrobial [3], antiviral [4]. In the view of this interesting pharmacological content we have decided to design and synthesize the molecular framework of new pyrrolidinone derivatives with heterocyclic or acyclic fragments and investigate their antibacterial activity.

Results and discussion

Chemistry

Scheme 1. Synthesis of 1,3-disubstituted 5-oxopyrrolidines 2–11.



R = **5)** H; **6)** Cl; **7)** Br; **10)** 4-H_2NSO_2; **11)** 3-H_2NSO_2.

i) methanol, H_2SO_4,reflux, 8 h; ***ii)*** $N_2H_4 \cdot H_2O$, propan-2-ol, 5 h, reflux; ***iii)*** KSCN, 30% acetic acid, reflux, 48 h; ***iv)*** 1-(4-Substituted phenyl)-2-thiocyanatoethan-1-one, 1,4-dioxane, reflux, 72 h; ***v)*** 1-thiocyanatopropan-2-one, 1,4-dioxane, reflux, 48 h; ***vi)*** phenyl isothiocyanate, methanol, rt, 8 h; ***vii)*** benzenesulfonamide, 160 °C, 4 h.

1-(2-Methyl-5-nitrophenyl)-5-oxopyrrolidine-3-carbohydrazide (**3**) was prepared from carboxylic acid **1** via esterification reaction with methanol in the presence of sulphuric acid as a catalyst which resulted in formation of methyl ester **2** (Scheme 1). Finally, the subsequent reaction of the ester **2** with hydrazine monohydrate was carried out providing hydrazide **3**. 1,2,4-Triazole-5-thione **4** was obtained by the reaction of hydrazide **3** and KSCN in 30% acetic acid. Corresponding 2,4-disubstituted-1,3-thiazoles **5**–**8** were synthesized by the reaction of respective thiocyanatoethan-1-ones or 1-thiocyanatopropan-2-one with

hydrazide **3** in dry 1,4-dioxane. Thiosemicarbazide **9** was obtained from the reaction of hydrazide **3** and phenylisothiocyonate in good yield (Scheme 1). Sulphanilamides **10**, **11** were synthesized by heating 1-(2-methyl-5-nitrophenyl)-5-oxopyrrolidine-3-carboxylic acid (**1**) with corresponding benzenesulfonamides.

Biology

The antimicrobial activity of the compounds **4**–**11** was screened by testing their different concentrations against the Gram-positive cocci *Staphylococcus aureus* and Gram-negative rods *Escherichia coli*, *Pseudomonas aeruginosa*, and Listeria *monocytogenes* using the broth and spread-plate methods. The minimum inhibition concentration (MIC, μg/ml) and the minimum bactericidal concentration (MBC, μg/ml) values are presented in Table 1. A broad-spectrum antibiotic oxytetracycline was used as a positive control.

Table 1

Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values for the tested compounds

Compound	*S. aureus*		*E.coli*		*P. aeruginosa*		*L. monocytogenes*	
	MIC, μg/ml	MBC, μg/ml	MIC, μg/ml	MBC, μg/ml	MIC, μg/ml	MBC, μg/ml	MIC, μg/ml	MBC, μg/ml
9	250	250	250	250	250	250	250	250
10	15,6	31,25	15,6	15,6	15,6	15,6	31,25	31,25
11	15,6	31,25	15,6	15,6	7,8	7,8	15,6	15,6
C*	62,5	62,5	250	250	250	250	62,5	62,5

*Oxytetracycline was used as a control for *S. aureus*, *E. coli*, *P. aeruginosa*, and *L. monocytogenes*.

Compounds **5**–**8** possessed moderate antibacterial activity against the tested bacterial strains. Thiosemicarbazide **9** exhibited the same antibacterial activity against *E. coli* and *P. aeruginosa* as the control sample. Sulphanilamides **10**, **11** have showed an exceptional antibacterial activity.

Conclusion

A series of 5-oxopyrrolidine derivatives containing functionalized azole or acyclic fragments were synthesized. Most of the obtained structures were tested for their antibacterial properties and exhibited moderate biological activity. However, the results of sulphanilamides **10**, **11** antimicrobial screening showed that their antibacterial properties were better than broad-spectrum antibiotic oxytetracycline, which was used as a positive control.

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