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Synthesis, antimicrobial activity and acid dissociation constants of methyl 5,5-diphenyl-1-(thiazol-2-yl)pyrrolidine-2-carboxylate derivatives

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ABSTRACT

In this study, a series of polysubstituted methyl 5,5-diphenyl-1-(thiazol-2-yl)pyrrolidine-2-carboxylate derivatives were designed and synthesized by the cyclization reaction of methyl 1-(benzoylcarbamothioyl)-5,5-diphenylpyrrolidine-2-carboxylates and 2-bromo-1-(4-substituted phenyl)ethanones in 70–96% yield. The starting pyrrolidine derivatives were synthesized *via* a 1,3-dipolar cycloaddition reaction in 83–88% yield. The stereochemistry of one of these methyl 5,5-diphenyl-1-(thiazol-2-yl)pyrrolidine-2-carboxylate derivatives was characterized by a single crystal X-ray diffraction study and the acid dissociation constants of these compounds were determined. An antimicrobial screening was performed against different bacterial and fungal strains and against the *M. tuberculosis* H37Rv strain. Interesting antibacterial activity was observed for two compounds against the *A. baumannii* strain with MIC values of 31.25 μg/mL (Ampicillin: 125 μg/mL) and against the *M. tuberculosis* H37Rv strain with MIC values of 0.98–1.96 μg/mL (Isoniazid: 0.98 μg/mL, Ethambutol: 1.96 μg/mL). Therefore, these structures can be considered as good starting points for the development of new powerful antimycobacterial agents.

Tuberculosis (TB) is a major global health problem due to the fact that the control of this disease is very difficult.[1] Researchers have been carrying out very intensive studies to find new classes of antimicrobial agents against multi-drug resistant pathogens, because of the increasing emergence of multi-drug resistant strains during treatment of TB.[1,2] A number of studies have been carried out in this context on compounds containing a thiazole[2,3] and/or pyrrolidine[4] moiety in recent years and some important results were reported.[2–4]

The thiazole ring is a privileged scaffold in drug discovery studies.[5] This moiety is found in the molecular structure of many drugs, such as Abafungin, Cefdinir, Famotidin, Fanetizol, Meloxicam and Ritonavir,[5,6] and in natural products.[7] It is known that thiazole derivatives can exhibit a wide range of pharmacological activity[1] such as antibacterial,[8] antimycobacterial,[2,3,9] antifungal,[8b–d,10] and anticancer[11] activity. Furthermore, some thiazole derivatives also exhibit anti-inflammatory[12] and FabH inhibition[13] activity. The pyrrolidine ring is another scaffold which is one of the most studied pharmacophore groups in medicinal chemistry. It is known that this moiety is present in the structure of many pharmacologically active synthetic[14] or natural[15] products. Compounds containing a pyrrolidine ring were reported in studies on antimycobacterial[4,16] and various other pharmacological activities such as antiviral,[17] anticonvulsant[18] and anticancer[19] activity. In addition, there are also many synthetic and natural products which contain both pyrrolidine and thiazole rings.[7a]

As a continuation of our previous work,[16a] the design and synthesis of novel polysubstituted 2-(pyrrolidin-1-yl)thiazole derivatives containing both thiazole and pyrrolidine pharmacophore groups was established. Their effects on TB, the evaluation of their antimicrobial activity and the determination of their acid dissociation constants are reported.

The synthesis of the methyl 5,5-diphenylpyrrolidine-2-carboxylate derivatives **2a** and **2b** was performed according to a literature method.[16a,20] This synthesis proceeded *via* a 1,3-dipolar cycloaddition reaction of methyl 2-(diphenylmethyleneamino) acetate and methyl acrylate or dimethyl maleate, respectively, in

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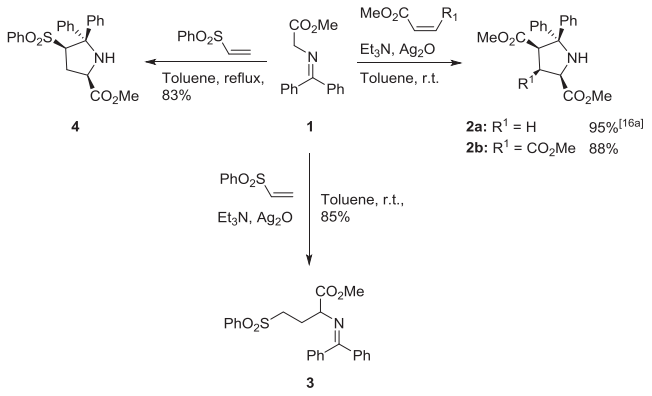
the presence of Ag_2O as a metal catalyst and Et_3N in toluene at room temperature (Scheme 1). When using phenyl vinyl sulfone as dipolarophile under the same reaction conditions, 1,4-addition reaction product methyl 2-(diphenylmethyleneamino)-4-(phenylsulfonyl)butanoate **3** was obtained unexpectedly in 85% yield. However, when the reaction was performed in refluxing toluene without Ag_2O, we obtained only the 1,3-dipolar cycloaddition product **4** in 83% yield. In addition, when the synthesis of compounds **2a** and **2b** was performed in refluxing toluene without using Ag_2O as a metal catalyst, **2a** and **2b** were obtained in 87% and 85% yield, respectively.

The methyl 1-(benzoylcarbamothioyl)-5,5-diphenylpyrrolidine-2-carboxylate derivatives **5a–c** were synthesized according to a literature method[16a] in 82–88% yield. Subsequent reaction with 2-bromo-1-(4-substituted phenyl)ethanone in acetone at reflux temperature[21] afforded the methyl 5,5-diphenyl-1-(thiazol-2-yl)pyrrolidine-2-carboxylates in 70–96% yield (Scheme 2, Table 1).

The stereochemistry of the compounds **6a–o** was unambiguously determined for **6e** by single crystal X-ray diffraction analysis.



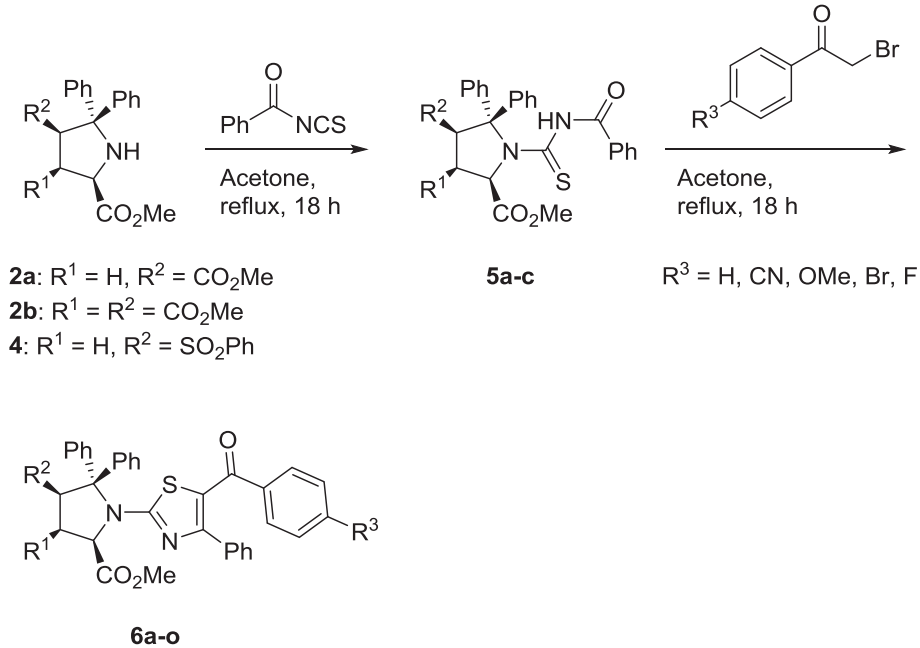
Scheme 1. Synthesis of the pyrrolidine derivatives and the product of 1,4-addition reaction.

The molecular structure with the atom labeling is shown in Fig. 1. Compound **6e** crystallizes in the monoclinic $P2_1/c$ space group with eighth molecules in the unit cell (see Supporting information). In the asymmetric unit there are two molecules with the same conformation. The structure contains two asymmetric carbon atoms and the stereogenic centers are as follows; C17(*R*) and C19(*R*). While the thiazole ring is planar, the pyrrolidine ring has an envelope conformation as expected. The N1 = C16 double bond in the thiazole unit is 1.315(4) Å. The S1-C8 and S1-C16 bond lengths are 1.733(4) and 1.727(4) Å respectively and have single bond character.

The antimicrobial activity screening of the polysubstituted methyl 5,5-diphenyl-1-(thiazol-2-yl)pyrrolidine-2-carboxylates **6a–o** was performed against five standard bacterial strains, with *S. aureus* and *B. subtilis* representing Gram-positive bacteria and *A. hydrophila*, *E. coli* and *A. baumannii* representing Gram-negative bacteria. Additionally, three standard fungal strains and the *M. tuberculosis H37Rv* strain were used for antimicrobial screening.

Table 1
Structure and yield of compounds **5** and **6**.

Compound	R^1	R^2	R^3	Yield (%)
5a[16a]	H	CO_2Me	–	95
5b	CO_2Me	CO_2Me	–	82
5c	H	SO_2Ph	–	87
6a	H	CO_2Me	H	91
6b	H	CO_2Me	CN	96
6c	H	CO_2Me	OMe	78
6d	H	CO_2Me	Br	77
6e	H	CO_2Me	F	85
6f	CO_2Me	CO_2Me	H	89
6g	CO_2Me	CO_2Me	CN	92
6h	CO_2Me	CO_2Me	OMe	75
6i	CO_2Me	CO_2Me	Br	70
6j	CO_2Me	CO_2Me	F	83
6k	H	SO_2Ph	H	88
6l	H	SO_2Ph	CN	93
6m	H	SO_2Ph	OMe	72
6n	H	SO_2Ph	Br	71
6o	H	SO_2Ph	F	80



Scheme 2. Synthesis of the methyl 5,5-diphenyl-1-(thiazol-2-yl)pyrrolidine-2-carboxylates.