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Synthesis of new 4-thiazolidinone derivatives as potential anti H-pylori

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Abstract: As part of ongoing studies in developing new antimicrobials, a structurally novel class of 4-thiazolidinone derivatives was synthesized by the two-step reaction, which is known as bioactive nuclei. New 4-methyl thiazole and 5-methyl isoxazole on ylimino were synthesized by displaying 3,4,5-trimethoxy groups on the benzene ring of ylimino-5-arylidene-4-thiazolidinone and then were assayed in vitro test for analyzing their antibacterial activity. These new compounds have important effects on H-pylori.

Keywords: 4-Thiazolidinone, Anti H-pylori, Thiazolidinone derivatives, 5-Arylidene.

Introduction

Because of combination of factors including emerging infectious disease and increasing number of multi-drug resistant microbial pathogens [1-3], treatment of infectious disease still remains as a challenging problem. By our recent findings of new class of antibacterial agents, the ylimino-5-benzylidene-4-thiazolidinones [4-6], we decided to extend our research to classes of analogues and focuse on them. It was found that 4-thiazolidinone ring system which has a core structure in various synthetic pharmaceuticals display a broad spectrum of biological activity including antibacterial properties [7-9]. Our analogue-based design encompasses to synthesis of two new ylimino-5-(3,4,5-trimethoxybenzylidene) 4-thiazolidinone derivatives (Figure **1**) , to be tested for their in vitro anti H-pylori properties.

Results and discussion

As part of our ongoing studies in developing new antimicrobials [5,6] we report the synthesis of new class of structurally novel 4-thiazolidinone derivatives incorporating one known bioactive nuclei such as thiazolidinone.

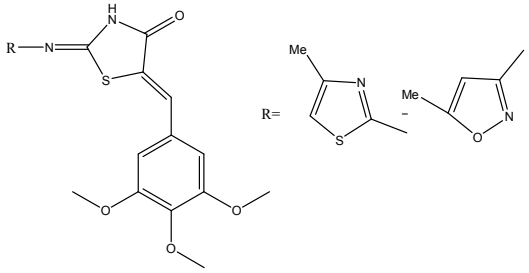

Fig. 1: Structure of the synthesized compounds

The compounds described in this paper were synthesized by the multi-step reaction (Fig. **2**). 2-Chloro-N-(4-methylthiazol-2-yl) acetamide (1a) and 2-chloro-N-(5-methylisoxazol-3-yl) acetamide (1b), synthesized using procedure reported earlier [10] from 4-methyl-2-aminothiazole and 5-methyl-3-aminoisoxazole. Heterocyclization in the presence of ammonium thiocyanate in refluxing ethanol [11,5], produced 2-(4-methylthiazol-2-ylimino) thiazolidin-4-one (2a) and 3-(5-methylisoxazole-2-

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ylimino)thiazolidin-4-one (2b). The ylimino-5-arylidene-4-thiazolidinones (3a-b) were obtained by refluxing with appropriate aldehyde in buffered glacial acetic acid (Figure **2**). All the new compounds (3a-b) were characterized by mp, elemental analysis and spectroscopic data (^{1}H-NMR and IR). The spectral data and the elemental analysis of the new compounds reported in this study correlate with the proposed structures.

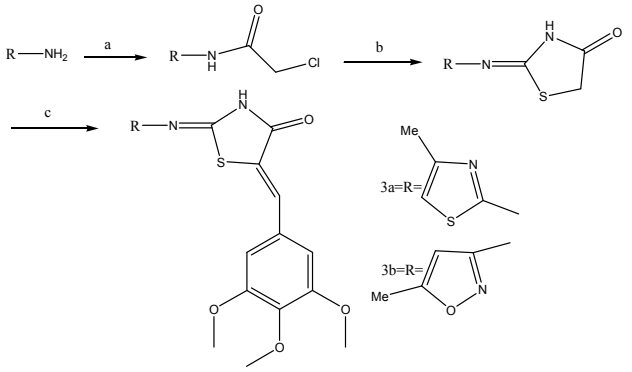

Fig. 2: Synthesis of the compounds. Reagents and conditions: (a) $ClCOCH_2Cl$, DMF, rt, 1h: (b) NH_4SCN, EtOH, reflux, 3h: (c) ArCHO , MeCOOH , MeCOONa.

Conclusion

All of these new compounds have important effects on H-pylori. It should be noticed that all compounds tested exhibited better activity than commercial antimicrobial agents used as reference drugs. All the compounds 3a-b showed excellent antibacterial activity indicating that the diverse substitutions were well tolerated on amine for proper fit at the potential receptor site. The outstanding properties of this new class of antibacterial substances deserve further investigation in order to clarify the mode of action at molecular level responsible for the activity observed.

Experimental

Chemistry-general aspects

Melting points were taken in glass capillary tubes on a Haake Bucher apparatus and are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer in splid phase KBr. All proton NMR spectra were determined by a varian 400 MHz spectrometer using deuterated dimethylsulfoxide (DMSO-d_6). Thin layer chromatography (TLC) was performed in E Merck precoated silica gel plates.

Synthesis of 2-chloro-N-(4-methylthiazol-2-yl) acetamide (1a):

To a solution of 2-amino-4-methylthiazole (1mmol, 0.12gr) in 3 ml of *N,N*-dimethylformamide was added chloroacetylchloride (1.5mmol). The mixture was stirred for 1 h. After this time the precipitate was filtered, washed with water and then recrystallised with ethanol. ^{1}H-NMR (PPm, DMSO): 2.73 (S,3H,-CH_3), 4.37 (s,2H,-CH_2), 6.81 (S,1H,Ar-H), 7.95 (S,1H,-NH).

Synthesis of 4-methyl-2-(thiazole-2-ylimino) thiazolidin-4-one (2a):

A solution of 2-chloro-N-(4-methylthiazol-2-yl) acetamide (1mmol) and ammonium thiocyanate (2mmol) in 10 ml of 96% ethanol was refluxed for 3 h. The precipitate was filtered, washed with water and then recrystallised with ethanol. ^{1}H-NMR (PPm, DMSO): 2.28 (S,3H,-CH_3), 3.96 (S,2H,-CH_2), 6.92 (S,1H,Ar-H), 7.96 (S,1H,-NH).

Synthesis of 2-chloro-N-(5-methylisoxazol-3-yl) acetamide (1b):

To a solution of 3-amino-5-methylisoxazole (1mmol, 0.09gr) in 3 ml of N,N-Dimethylform amide was added chloroacetylchloride (1.5mmol). The mixture was stirred for 1 h. After this time the precipitate was filtered, washed with water and then recrystallised with ethanol. ^{1}H-NMR (PPm, DMSO): 2.50 (S, 3H,-CH_3), 4.29 (S, 2H,-CH_2) 6.62, (S, 1H, Ar-H), 11.27 (S, 1H,-NH).

Synthesis of 5-methyl-3-(isoxazole-2-ylimino) thiazolidin-4-one (2b):

A solution of 2-chloro-N-(5-methylisoxazol-3-yl) acetamide (1mmol) and ammonium thiocyanate (2mmol) in 10 ml of 96% ethanol was refluxed for 3 h. The precipitate was filtered, washed with water and then recrystallised with ethanol. ^{1}H-NMR (PPm, DMSO): 2.39 (S, 3H,-CH_3), 4.04 (S, 2H,-CH_2), 6.09 (S, 1H,Ar-H), 11.26 (S,1H,-NH).

General procedure for synthesis of 2-ylimino-5-arylidene-4-thiazolidinones (3a-b)

A well-stirred solution of 1 mmol of 2-ylimino thiazolidin-4-one in 35 ml of glacial acetic acid was buffered with sodium acetate (8mmol) and added with the appropriate arylaldehyde (0.5mmol). The solution was refluxed for 24 h and then poured into ice-cold water. The precipitate was filtered and washed with water and the resulting crude product was purified by recrystallisation from dioxane.

5-(3,4,5-Trimethoxybenzylidene)-2-(4-methylthiazol-2-ylimino)thiazolidin-4-one (3a):

Yield: 70% . mp 254-258 (dioxane) . IR cm^{-1}: 3093.7 (NH), 1711.7 (C=O), 1582.5 (C=N). ^{1}HNMR (PPm, DMSO): 2.32 (S, 3H,-CH_3), 3.86 (S, 9H,3-OMe), 6.56 (S, 2H,H benzylidene), 7.03 (S, 1H,H thiazolyl), 7.68 (S, 1H, =CH), 7.95 (S, 1H,-NH).

5-(3,4,5-Trimethoxybenzylidene)-2-(5-methylisoxazol-3-ylimino)thiazolidin-4-one (3b)

Yield: 76% . mp 260-262 (dioxane) . IR cm^{-1}: 3124.4 (NH), 1614.8 (C=O), 1505.1 (C=N). ^{1}HNMR (PPm, DMSO): 2.40 (S, 3H,-CH_3), 3.83 (S, 9H,3-OMe), 6.22 (S, 2H, H benzylidene), 6.94 (S, 1H, H isoxazolyl), 7.67 (S, 1H, =CH) , 11.27 (S,1H,-NH).

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