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Synthesis, Characterization and Antibacterial Study of 2 ((E) -Cinnamoyl imino) 4-methyl thiazole with Some Amino Acids

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Abstract:

New compounds of 2 ((E) -2 (cinnamoyl imino) 4-methyl thiazole with amino acids were prepared by base catalyzed cyclization of (E) -2 (3-cinnamoyl thioureido) derivatives with α-haloketon in the presence of triethyl amine (Et_3N).

All new compounds were characterized by IR, ^{1}HNMR spectroscopic and the antibacterial activity of these compound was determined against some pathogenic bacteria.

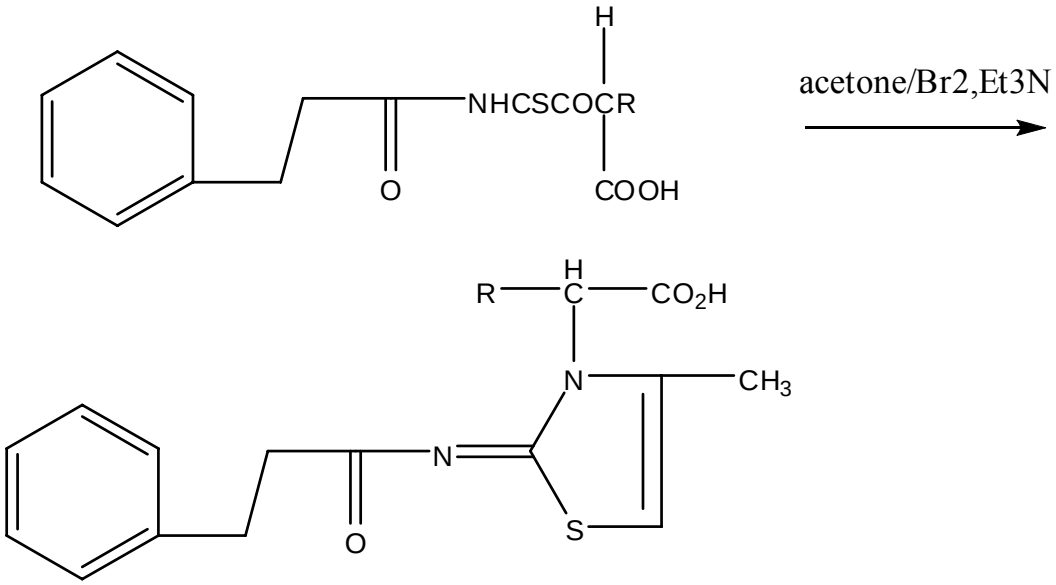
Introduction :

Thiazole, CH_3H_5N, first described by Hantzch Weber in 1887, Is a five member hetrocyclic organic compounds that is a part of vitamin B (Thaimine) structure as well with penicillins [1].

Thiazole compounds are useful in manufacture of Pesticides, drug, dye and other compounds. Some of them exhibits antibacterial [2-4] anti cancer [5] antiflamtory [6], antiemetic [7], anti HlV [8, 9], antifungal[10] and sedative hypnotic[11].

Cinnamic acid derivatives also are important in Pharmaceuticals [12]. Shakir [13] reported some new cinnamoyl thiouredio amino acid derivatives.

In continution of our work on amino acid derivatives, we report here in synthesis, characterization and antibacterial activity of 2 (E) 2-cinnamoyl imino) 4-methyl thiazole compound, namely 2 ((E) -cinnamoyl imino) 4-methyl thiazole 3 (2H) -3 (4-hydroxy phenyl) propanoic acid (1), 2 ((E) -cinnamoyl imino) 4-methyl thiazole -3 (2H) - (1) pentadioic acid (11), 2 ((E) 2-cinnamoyl imino) 4-methyl thiazole 3 (2H) -y1-3 (H-imadazol-yl) propanoic acid (111). as ahown in (Scheme 1) :



No.	R	Amino acid
(i)	p-Cresol	L-thyrsine
(ii)	$(CH_2)_2CO_2H$	L-glutamic acid
(iii)	CH_2-3-imidazole	L-histidine

Scheme 1: Synthetic of 2 ((E) -cinnamoyl imino) 4-methyl thiazole (R-substitution) propanoic acid

Experimental:

Physical measurements:

Melting points are uncorrected and were measured on a Gallen –Kemp melting point apparatus. IR spectra were recorded with Ft-IR 8400 s spectra photometer model (2000) from SHIMADZU Japan. The ^{1}HNMR spectra were obtained in deatrated solution DMSO-by using Broker 300 MHZ, type advance Mltrashield instrument in general laboratories of Institute of earth and everyone science of the university of Ahlal-Bayt, Jordan.

General procedure preparation:

New three compounds were synthized according to the reported procedure [, 12]. To stirred solution of (1.0 mmole) from compound (cinnamoyl thiouredio amino acid) in dry acetone (20 mL) was added Et_3N (1.0 mmole), followed by drop wise addition to bromine solution (1.0 mmole) in acetone (10 mL). The reaction mixture was stirred at room temperature for 2 h, and then the mixture was evaporated to dryness to give the desired products which were crystallized from EtOH to afford compounds (1-111).

2 ((E) -cinnamoyl imino) 4-methyl thiazole 3 (2H) 3- (4-hydroxy phenyl) propanoic acid (1).

From thyrosine (0.5 g, yield (0.39gm, 60%)), mp. (250-252 ^{o}C). IR (KBr). pellet, ; Ʊ

(C=O) carboxylic acid 1660, ʊ (C=O) cinnomyl 1130, ʊ (C=N) 1450, (b=C-H) 750, ^{1}HNMR (DMSO-d6) S (ppm) :12.57 (S, H, CO_2H), 9.4 (S, 1H, ArCOH) 5.8 (q, H thiazol), 2.12 (d, 3H) ($H3_{thiazole}$) 7.6 (d, 2H ArH), 7.3 (d, 2H, ArH), 7.4 (S, 1H, ArH). 7.7 – 7.8 (d) 2H cinnomoyl $_{(HC=CH),}$ 3.88 (SCH-N), 3.18 (S, 2H, CH_2Ar).

2 ((E) -cinnamoyl imino) 4-methyl thiazole -3 ((2H) -Y1) Pentanedoic (11).

From glutamic acid (0.5 g). Yield (0.4 g, 80 %.), mp (200-202 ^oC). IR (KBr pellet, ʊ (C=O) carboxylic) 1665, ʊ (C=O) cinnamoyl) 1630, ʊ (C=N) 1450, (b=C-H) 770, ^{1}HNMR (DMSO-d6), S (ppm) : 12.16 (S, 1H, CO_2H), 12.3 (S, 1H, CO_2H), 5.8 (q, 1H thiazol) 2.12 (d, 3H, $CH_{3\ thiazol}$), 7.3-7.6 (m, 5H, ArH) 7.31 (t, 2H, $CH_2CO_2H_{\ glutamic)}$ 2.05 (t, 2H, $CH_{2\ glutamic)}$, 7.7-7.8 (d, 2Hcinnamoyl), 3.7 (s, H, CH glutamic).

2 ((E) -cinnamoyl imino) 4-methyl thiazole 3 (2H) Yl-3 (1H) imidazol-5-yl) propanoic acid (111).

From L-Histidine (0.5 g), yield (0.4 g, 74%), mp (239-240 ^oC). IR (KBr pellet, Cm^{-1}) : $ʊ_{(C=O)\ carboxylic}$ 1700, $ʊ_{(C=O)\ cinnoyl}$ 1630, $ʊ_{(C=N)}$ 1420, (b=C-H) 780. ^{1}HNMR (DMSO-d6) S (ppm) : 12.8 (S, H, CO_2H), 5.8 (q, H thiazol) 2.13 (d, 3H, CH_3 thiazole), 7.3-7.6 (m, SH, ArH), 7.7-7.8 (d, 2H, HC=CH cinnomyl), 4.7 (S, 1H, N), 8.47 (S, 1H, CH imidazol), 2.88 (S, 2H, $CH_{2\ histidin)}$, 3.11 (s, $CH_{\ histidine}$).

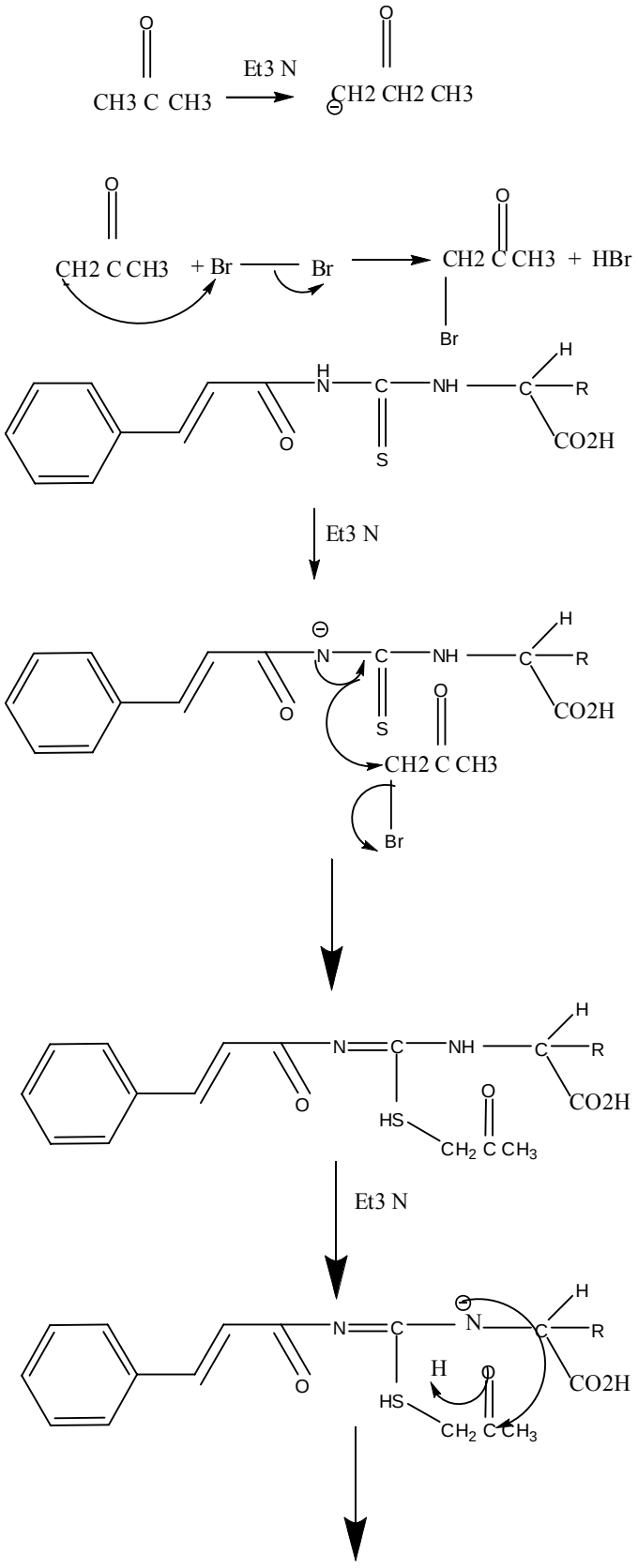
Determination of the antibacterial activity of the prepared compounds

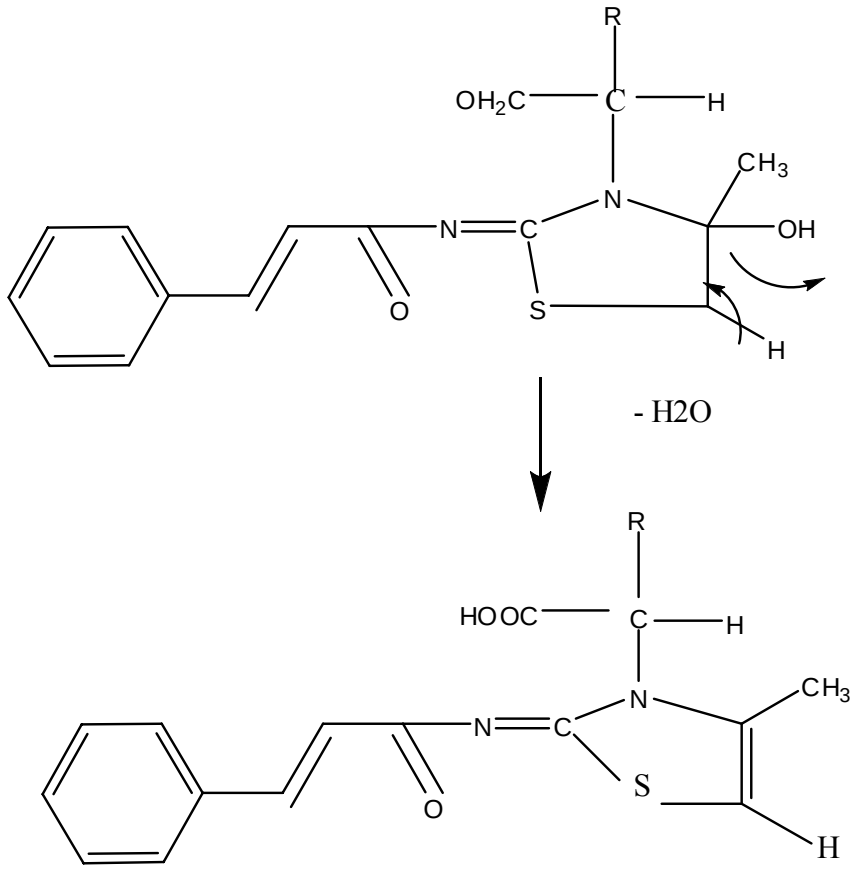
A filter disk assay was used to determine the antibacterial activity of the prepared compounds against strains of gram positive and gram negative bacteria which are (*Staphylococcus aureus* and *Escherichia coli*), which were tested using plates of Muller- Hinton agar. The biological activity was defined as the clear zone of growth inhibition [18].

Results and Discussion:

Condensation of (E) -2 (3-cinnamoyl thioureido) amino acid with α-haloketone in the presence of Et_3N for 1-2h to produce 2 ((E) -cinnamoyl imino) 4-methyl thiazole amino acid (1-111) as show in schem1.

The mechanism followed the classical Hautzsch thiazole synthesis [14-17] as show in Scheme 2:


Et3 N
CH3 C CH3
CH2 CH2 CH3
CH2 C CH3
+ Br
Br
CH2 C CH3 + HBr
Br
H
N
C
NH
C
R
CO2H
O
S
Et3 N
CH2 C CH3
Br
HS
CH2 C CH3
Et3 N
H



Scheme 2: The mechanism of formation compounds (1-111).

The structures (1-111) were indicated by IR and ^{1}HNMR spectra.

IR spectra showed absorption bands in the reglon λ_{max} = 1665 – 1700 and 1420-1440 Cm^{-1} attributed to $C=O_{carboxilic}$ and C=N groups. While (C=S) at 740-760 and υ_{N-H} at 3051-3200 Cm^{-1} for thioureido derivatives was hidden and that ensure the formation of the products (1-111).

^{1}HNMR spectra, the doublet in the region 2.11-2.12 ppm was assign to the methyl group at C_4 position thiazole ring, while the quartet in the region 5.8 ppm was assigned to the H at C_5 position of thiazole ring.

The results of antibacterial activity of the prepared compounds (different concentrations ranging between (25 – 100 mg \ ml.)) were shown in table (1). The prepared compounds in this study appear very effective against both Gram negative (*Escherichia coli*) and gram positive (*Staphylococcus aureus*). The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. It is well known that a number of heterocyclic compounds containing nitrogen, oxygen and sulphur exhibit a wide variety of biological activity. [18]. Compounds carrying the thiazolidinone ring have reported to demonstrate a wide range of pharmacological activities which include anti microbial [20 -30] antifungal activity [31], antitumor [32], antidiabetic activity [33, 34] anti inflammatory [35, 36] anticonvulsant [37].

Table 1: The anti bacterial activity of the prepared compounds against pathogenic (G+) and (G-) bacterial strains.

Extracts & conc. (mg\ml) \ Bacteria		*S. aureus* (Pathogenic)	*E. coli* (Pathogenic)
1	100	10	20
	50	18	15
	25	20	17
2	100	10	18
	50	5	25
	25	---	25
3	100	10	18
	50	10	10
	25	---	---

Conculsion:

New compounds have been prepared by base-catalyzed syclization of E-2 (3-cinnamoyl thiourido) derivatives with amino acids. These compounds carrying thiazol ring that give them to be biological activity.

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