K.A. El-Sharkawy /J. Pharm. Sci. & Res. Vol.3(1), 2011,1005-1014

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

# Synthesis and Antimicrobial Activity of 2-Substituted-3-Acetyl Thiazolidine -4-Carbonyl-Amino acid Derivatives

K. A. El –Sharkawy
Organic Chemistry Department, Faculty of Pharmacy, October University for Modern Sciences and Arts (M.S.A), El-Wahat road, 6 October City, Egypt.

**Abstract:**
The synthesis of different 2-substituted-3-acetyl-thiazolidine-4-carbonyl amino acid methyl esters (3-11) by coupling 2-substituted-3-acetyl-thiazolidine-4-carboxylic acid with amino acid methyl ester hydrochloride, corresponding amino acid hydrazides (12-20) via hydrazinolysis using hydrazine hydrate and 2-substituted-3-acetyl–thiazolidine–4–carbonyl-N-benzylidine glycine hydrazone derivatives (21-26) were prepared via the condensation reaction of 2-substituted-3-acetyl-thiazolidine-4-carbonyl amino acid hydrazides with benzaldehyde and 4-chlorobenzaldehyde . The structures of the synthesized compounds were established by IR, $^1$H-NMR and MS data and elemental analysis results. The synthesized compounds were tested against different types of microorganism included gram-positive, gram-negative microorganisms *Bacillius subtilis* , *Bacillus pumilus, ,Pesudomonas aeruginosa and Escherichia coli* and the fungi *Candida utilis*.
Some of the synthesized compounds were found to possess antimicrobial activities towards different type of microorganisms.

**Keywords:** Thiazolidine, amino acid derivatives, antimicrobial.

## INTRODUCTION:

Thiazolidine derivatives has an interesting biological activities, some of these are anticancer activity[1,2] , antioxidant[3,4] and also it has an interesting antimicrobial activity [5-8], in addition to it found in some literature has antidiabitic agents[9-11].therefore they seemed desirable to synthesize some of 2-substituted-thiazolidine--4-carbonyl amino acid derivatives to try to improve it's antibacterial activity.

As a part of our efforts to synthesis amino acids containing hetero cyclic compounds and studying their biological activities [12-14] are demonstrate here. The synthesis and antimicrobial evaluation of some 2-substituted-3-acetyl-thiazolidine-4-carbonyl amino acid methyl esters (3-11), corresponding amino acid hydrazides (12-20) and 2-substituted-3-acetyl–thiazolidine–4–carbonyl-N-benzylidine-glycine-hydrazone-derivatives (21-26) are described on this paper.

## MATERIALS AND METHODS:

Thin layer chromatography (TLC, Rf values) was carried out on silica gel 60 (Merck), using benzene ethyl acetate mixture (10:1) as a solvent system and an iodine – potassium iodide (20%) solution as detection reagent. Benzidine, ninhydrin, silver nitrate and hydroxomate reactions were used for the detection of amino acid derivatives on whatman No.1 paper chromatograms (spot reactions). Optical rotation [$\alpha^{20}$] were taken in Bellingham Stanley polarimeter, 1 dm tube (c = 5, in acetone). The IR spectra (KBr, υ max in $cm^{-1}$) were taken using FTIR system 2000 instrument. The nuclear magnetic resonance $^1$HNMR spectra were measured in DMSO – $D_6$ using fx 900 Fourier transform NMR spectrometer and the mass spectra were performed using shimadzu GC, MS – QP 1000 EX using the direct inlet system. Elemental analysis were carried out by Micro Analytical Data Unit Cairo University, Melting points are uncorrected.

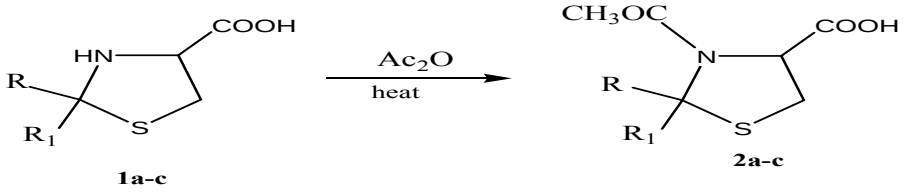
Synthetic pathways are presented in Scheme 1, 2. The pharmacological data are indicated through Tables 1.

## EXPERIMENTAL SECTION:

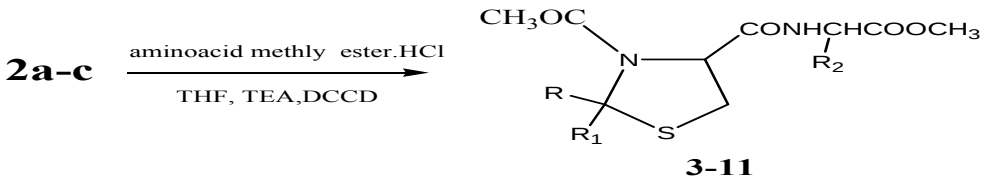
### 2-Substituted-thiazolidine-4-carboxylic acid derivatives (1a, b, c) :

The titled compounds 1a,b,c were prepared by the reaction of cystiene solution with appropriate carbonyl compounds, acetaldehyde, acetone and benzaldehyde at room temperature with stirring for 3h according to method described before[15-16]

**Scheme 1**




| 1,2 | R | R1 |
|---|---|---|
| a | H | $CH_3$ |
| b | $CH_3$ | $CH_3$ |
| c | H | Ph |





| *Comp. No.* | *R* | *$R_1$* | $R_2$ |
|---|---|---|---|
| **3** | H | $CH_3$ | H |
| **4** | H | $CH_3$ | $CH_3$ |
| **5** | H | $CH_3$ | $CH_2CH_2SCH_3$ |
| **6** | $CH_3$ | $CH_3$ | H |
| **7** | $CH_3$ | $CH_3$ | $CH_3$ |
| **8** | $CH_3$ | $CH_3$ | $CH_2CH_2SCH_3$ |
| **9** | H | Ph | H |
| **10** | H | Ph | $CH_3$ |
| **11** | H | Ph | $CH_2CH_2SCH_3$ |

| *Comp.No.* | *R* | *$R_1$* | $R_2$ |
|---|---|---|---|
| **12** | H | $CH_3$ | H |
| **13** | H | $CH_3$ | $CH_3$ |
| **14** | H | $CH_3$ | $CH_2CH_2SCH_3$ |
| **15** | $CH_3$ | $CH_3$ | H |
| **16** | $CH_3$ | $CH_3$ | $CH_3$ |
| **17** | $CH_3$ | $CH_3$ | $CH_2CH_2SCH_3$ |
| **18** | H | Ph | H |
| **19** | H | Ph | $CH_3$ |
| **20** | H | Ph | $CH_2CH_2SCH_3$ |

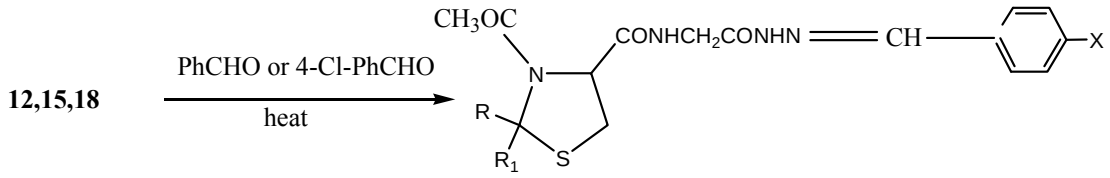
**2-substituted-3-acetyl -thiazolidine–4-carboxlic acid derivatives (2a, b, c) :**

The 3-acetyl-2-substituted-thiazolidine-4-carboxylic acid derivatives 2a,b,c were prepared via the reaction of 2-Substituted-thiazolidine-4-carboxylic acid derivatives **(1a, b, c)** with acetic anhydride at 90 C° according to the procedure described earlier[17-18].

**GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-SUBSTITUTED-3-ACETYL-THIAZOLIDINE–4-CARBONYL AMINO ACID METHYL ESTERS (3-11) :**

2-methyl, 2,2 dimethyl and 2-phenyl-3-acetyl thiazolidine-4- carboxylic acid ( 2a, b, c ,0.01 mole) and amino acid methyl ester hydrochloride (0.01 mole) were dissolved in tetrahydrofurane THF (50mL) containing triethylamine TEA ( 1mL). The mixture was cooled to 0 C° and dicyclohexyl carbodiimide (0.01 mole) was added. The reaction mixture was allowed to proceed: i) for 3 hr at 0 C°

**Scheme 2**




**21-26** X = H or Cl

| *Comp.No.* | *R* | *R1* | X |
|---|---|---|---|
| **21** | H | $CH_3$ | H |
| **22** | H | $CH_3$ | Cl |
| **23** | $CH_3$ | $CH_3$ | H |
| **24** | $CH_3$ | $CH_3$ | Cl |
| **25** | H | Ph | H |
| **26** | H | Ph | Cl |

with stirring . ii) for 24 hr at 0 C° and iii) for 24 hr at room temperature. The dicyclohexyl urea was removed by filtration and the solvent was evaporated to dryness under reduced pressure. The residual material was recrystallized from ethanol – water the products **(3–11)** were chromatographically homogeneous when developed with benizidine.

**3-acetyl-2-methyl -thiazolidine-4-carbonyl glycine methyl ester (3).**Yield: 46%, m.p.118-120 °C; Anal.Calcd. for $C_{10}H_{16}N_2O_4S$ : C, 46.15; H, 6.15; N, 10.76. Found: C, 46.22; H, 6.15; N, 10.82; IR (KBr, $cm^{-1}$): 3312, 3181 (stretching of CONH) , 2984 (stretching of CH aliph.) , 1665 , 1373 (stretching of $COOCH_3$) ,1572 (stretching of CONH) and 1112 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.46 (3H, *d*, $CH_3$) , 2.32 (3H, *s*, $COCH_3$), 3.27 (2H, *s*, $CH_2$), 3.91 (3-H, *s*, $COOCH_3$) , 5.14 (2H, *d*,5-H of thiazolidine ring), 5.33 (1H, *b* ,NH, $D_2O$ exchangeable), 5.42 (1H, *s*, 2-H of the ring) and 6.21 (1H, *t*, 4-H) . Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.6.

**3-acetyl-2-methyl- -thiazolidine-4-carbonyl L-alanine methyl ester (4).**Yield: 40%, m.p.242-244 °C; Anal.Calcd. for $C_{11}H_{18}N_2O_4S$ : C, 48.17; H, 6.56; N, 10.21. Found: C, 48.25; H, 6.46; N, 10.19; IR (KBr, $cm^{-1}$): 3348, 3156 (stretching of CONH) , 2995 (stretching of CH aliph.) , 1767 , 1364 (stretching of $COOCH_3$) ,1605 (stretching of CONH) and 1123 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.35 (3H, *d*, $CH_3$) , 1.83 (3H, *d*, $CH_3$), 1.92 (3H, *s*, $COCH_3$), 3.76 (3-H, *s*, $COOCH_3$), 4.45 (H, *q*, CH), 5.12 (2H, *d*,5-H of thiazolidine ring), 5.49 (1H, *b* ,NH, $D_2O$ exchangeable), 5.53 (1H, *s*, 2-H of the ring) and 6.12 (1H, *t*, 4-H). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -30.6 ; TLC chromatography (Rf) value, 0.64.

**3-acetyl-2-methyl-thiazolidine-4-carbonyl L-methionine methyl ester (5).**Yield: 53%, m.p.194-196 °C; Anal.Calcd. for $C_{13}H_{22}N_2O_4S_2$ : C, 46.7; H, 6.58; N, 8.38. Found: C,46.66; H, 6.49; N, 8.44; IR (KBr, $cm^{-1}$): 3316, 3187 (stretching of CONH) , 2995 ,2883 (stretching of CH aliph.) , 1694 , 1393 (stretching of $COOCH_3$) ,1632 (stretching of CONH) and 1125 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 0.97 (3H, *d*, $CH_3$) , 1.93 (3H, *s*, $COCH_3$), 3.17 (2H, *m*, $CH_2$), 3.52 (2H, *t*, $CH_2$), 3.66 (3H, *s*, $CH_3$), 3.77 (3H, *s*, $COOCH_3$) , 4.93 (2H, *d*,5-H of thiazolidine ring), 5.14 (1H, *t*, CH ), 5.25 (1H, *b* ,NH, $D_2O$ exchangeable), 5.36 (1H, *s*, 2-H of the ring) and 5.97 (1H, *t*, 4-H). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -18.8 ; TLC chromatography (Rf) value, 0.75.

**3-acetyl-2,2-dimethyl -thiazolidine-4-carbonyl glycine methyl ester (6).**Yield: 46%, m.p.167-169 °C; Anal.Calcd. for $C_{11}H_{18}N_2O_4S$ : C, 48.17; H, 6.56; N, 10.21 Found: C, 48.24; H, 6.47; N, 10.25; IR (KBr, $cm^{-1}$): 3284, 3164 (stretching of CONH) , 2995 (stretching of CH aliph.) , 1663 , 1365 (stretching of $COOCH_3$) ,1574 (stretching of CONH) and 1122 (stretching of C-C bond of the ring); MS (m/z,(relative abundance, %)): 232 ($M^+$, 11.5), 201, 273, 259, 244 (BP,100).Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.73.

**3-acetyl-2,2-di-methyl-thiazolidine-4-carbonyl L-alanine methyl ester (7).**Yield: 41%, m.p.158-160 °C; Anal. Calcd. for

$C_{12}H_{20}N_2O_4S$ : C, 50.00; H, 6.94; N, 9.72. Found: C, 49.93; H, 6.88; N, 9.66; IR (KBr, $cm^{-1}$): 3384, 3217 (stretching of CONH) , 2985 ,2892 (stretching of CH aliph.) , 1703 , 1371 (stretching of $COOCH_3$) ,1684 (stretching of CONH) and 1130 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.16(3H, *d*, $CH_3$), 1.42 (6H, *s*, $2CH_3$) , 2.33 (3H, *s*, $COCH_3$), 3.46 (3-H, *s*, $COOCH_3$) , 4.45 (1H, *q*, CH), 4.8 (2H, *d*,5-H of thiazolidine ring), 5.47 (1H, *b* ,NH, $D_2O$ exchangeable), and 5.53 (1H, *t*, 4-H). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -45.2 ; TLC chromatography (Rf) value, 0.7.

**3-acetyl-2,2di-methyl-thiazolidine-4-carbonyl L-methionine methyl ester(8).**Yield: 40%, m.p.179-181 °C; Anal.Calcd. for $C_{14}H_{24}N_2O_4S_2$ : C, 48.27; H, 6.89; N, 8.04. Found: C, 48.33; H, 6.82; N, 8.11; IR (KBr, $cm^{-1}$): 3365, 3153 (stretching of CONH) , 2982 ,2871 (stretching of CH aliph.) , 1685 , 1388 (stretching of $COOCH_3$) ,1669 (stretching of CONH) and 1107 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.35 (6H, *s*, $2CH_3$) , 2.14 (3H, *s*, $COCH_3$), 3.25 (3H, *s*, $CH_3$), 3.66 (2H, *m*, $CH_2$), 3.87 (2H, *t*, $CH_2$), 3.9 (3H, *s*, $COOCH_3$) , 4.72 (2H, *d*,5-H of thiazolidine ring), 5.43 (1H, *t*, CH ), 5.63 (1H, *b* ,NH, $D_2O$ exchangeable), and 5.96 (1H, *t*, 4-H).Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -52.5 ; TLC chromatography (Rf) value, 0.68.

**3-acetyl-2-phenyl-thiazolidine-4-carbonyl-glycine methyl ester (9).**Yield: 54%, m.p.115-117 °C; Anal.Calcd. for $C_{15}H_{18}N_2O_4S$ : C, 55.90; H, 5.59; N, 8.69. Found: C, 55.82; H, 5.62; N, 8.77; IR (KBr, $cm^{-1}$): 3361, 3163 (CONH) , 3062 (CH arom.), 2991 ( CH aliph.) , 1670 , 1456 (stertching $COOCH_3$) ,1596 (stertching CONH) , 1104 (stertching of C-C bond of the ring) and other bands characteristic for remaining part of molecule. ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 2.15 (3H, *s*, $COCH_3$), 3.46 (2H, *s*,$CH_2$), 4.25 (3-H, *s* , $COOCH_3$) , 5.23 (2H, *d*, 5-H of thiazolidine ring), 5.48 (1H, *s*,2-H of the ring) , 5.99 (1H, *t*, 4-H of the ring) ,7.37 (5H arom, *m*.) and 8.45 (1H, *b*, CONH, $D_2O$ exchangeable);Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.6.

**3-acetyl-2-phenylthiazolidine-4-carbonyl L-alanine methyl ester (10).**Yield: 51%, m.p.128-130 °C; Anal.Calcd. for $C_{16}H_{20}N_2O_4S$ : C, 57.14; H, 5.95; N, 8.33 Found: C, 57.12; H, 5.87; N, 8.40; IR (KBr, $cm^{-1}$): 3291, 3116 (CONH) , 3063 (CH arom.), 2977 ( CH aliph.) , 1687 , 1444 (stertching $COOCH_3$) ,1588 (stertching CONH) , 1112 (stertching of C-C bond of the ring) and other bands characteristic for remaining part of molecule. ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.67 (3H, *d*,$CH_3$), 2.38 (3H, *s*, $COCH_3$), 4.12 (3-H, *s* , $COOCH_3$) , 4.95 (1H, *q*,CH), 5.12 (2H, *d*, 5-H of thiazolidine ring), 5.55 (1H, *s*,2-H of the ring) , 5.87 (1H, *t*, 4-H of the ring) ,7.15 (5H arom, *m*.) and 8.96 (1H, *b*, CONH, $D_2O$ exchangeable);Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -19.2 ; TLC chromatography (Rf) value, 0.71.

**3-acetyl-2-phenyl -thiazolidine-4-carbonyl L-methionine methyl ester (11).**Yield: 45%, m.p.135-137 °C; Anal.Calcd. for $C_{18}H_{24}N_2O_4S_2$ : C, 54.54; H, 6.06; N, 7.07. Found: C, 54.60; H, 6.10; N, 7.02; IR (KBr, $cm^{-1}$): 3364, 3192 (stretching of CONH) , 3045 (CH arom.), 2983 ,2880 (stretching of CH aliph.) , 1714 , 1415 (stretching of $COOCH_3$) ,1663 (stretching of CONH) and 1126 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.76 (3H, *s*, $COCH_3$), 3.35 (2H, *m*, $CH_2$), 3.44 (2H, *t*, $CH_2$), 3.64 (3H, *s*, $CH_3$), 3.97 (3H, *s*, $COOCH_3$) , 4.71 (2H, *d*,5-H of thiazolidine ring), 4.92 (1H, *t*, CH ), 5.47 (1H, *s*, 2-H of the ring) 5.81 (1H, *t*, 4-H). 6.78 (1H, *b* ,NH, $D_2O$ exchangeable) and 7.32 (5H arom, *m*.) . Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, +15.7 ; TLC chromatography (Rf) value, 0.76.

## GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-SUBSTITUTED-3-ACETYL-THIAZOLIDINE-4-CARBONYL AMINO ACID HYDRAZIDES (12-20):

The methyl esters **(3 –11**, 0.005 mole**)** were dissolved in 1 M alcoholic hydrazine hydrate solution (prepared from 6.6 mL hydrazine hydrate in 100 mL ethanol). The reaction mixtures were heated on water bath for 2 hr

and kept 24 hr at 0 C°, the crystalline products were filtered and washed with ether and recrystallized from ethanol. All the hydrazides **(12–20)** were found to be homogeneous on TLC using benzidine and silver nitrate as the spray reagent.

**3-acetyl-2-methyl-thiazolidine-4-carbonyl-glycine-hydrazide (12).** Yield: 42%, m.p.199-201 °C; Anal.Calcd. for $C_9H_{16}N_4O_3S$ : C, 41.53; H, 6.15; N, 21.53. Found: C, 41.6; H, 6.2; N, 21.6; IR (KBr, $cm^{-1}$): 3332, 3211 ($NH_2$, NH and CONH stretching ), 2965 ( CH stretching aliph.), 1734,1702, 1627 (C=O stertching) and other bonds characteristic for the rest of the molecule; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.61 (3H , *d*, $CH_3$ ) , 2.55 (3H , *s*, $COCH_3$), 3.47 (2H, *s*,$CH_2$), 5.02 (2H, *d*, 5-H of thiazolidine ring), 5.17, 5.38 (2H, *b*, 2NH, $D_2O$ exchangeable), 5.46 (1H, *s*, 2-H of the ring), 6.25 (1H, *t*,4-H) and 9.65 (2H, *b* ,$NH_2$, $D_2O$ exchangeable), Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.56.

**3-acetyl-2-methyl- -thiazolidine-4-carbonyl L-alanine hydrazide (13).**Yield: 50%, m.p.164-166 °C; Anal.Calcd. for $C_{10}H_{18}N_4O_3S$ : C, 43.79; H, 6.56; N, 20.43. Found: C, 43.72; H, 6.61; N, 20.50; IR (KBr, $cm^{-1}$): 3366, 3275, 3155 ($NH_2$, NH and CONH stretching), , 2987 (stretching of CH aliph.) , 1698 , 1382 (stretching of CONH) ,1711 (stretching of $COCH_3$) and 1132 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.77 (3H, *d*, $CH_3$) , 1.92 (3H, *d*, $CH_3$), 2.35 (3H, *s*, $COCH_3$), 4.33 (H, *q*, CH), 5.34 (2H, *d*,5-H of thiazolidine ring), 5.44, 5.72 (2H, *b* ,2NH, $D_2O$ exchangeable), 5.88 (1H, *s*, 2-H of the ring), 6.21 (1H, *t*, 4-H) and 10.75 (2H, *b* ,$NH_2$, $D_2O$ exchangeable), Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -7.8 ; TLC chromatography (Rf) value, 0.81.

**3-acetyl-2-methyl-thiazolidine-4-carbonyl L-methionine hydrazide (14).**Yield: 52%, m.p.234-236 °C; Anal.Calcd. for $C_{12}H_{22}N_4O_3S_2$ : C, 43.11; H, 6.58; N, 16.76. Found: C,43.20; H, 6.63; N, 16.84; IR (KBr, $cm^{-1}$): 3356, 3225 (stretching of CONH) , 2992 ,2865 (stretching of CH aliph.) , 1693 , 1396 (stretching of CONH) , and 1123 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.14 (3H, *d*, $CH_3$) , 1.83 (3H, *s*, $COCH_3$), 3.22 (2H, *m*, $CH_2$), 3.45 (2H, *t*, $CH_2$), 3.74 (3H, *s*, $CH_3$), 4.53 (2H, *d*,5-H of thiazolidine ring), 4.98 (1H, *t*, CH ), 5.12, 5.53 (2H, *b* ,2NH, $D_2O$ exchangeable), 5.66 (1H, *s*, 2-H of the ring) 5.97 (1H, *t*, 4-H) and 10.12 (2H, *b* ,$NH_2$, $D_2O$ exchangeable),.Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -66.9 ; TLC chromatography (Rf) value, 0.86.

**3-acetyl-2,2-dimethyl -thiazolidine-4-carbonyl glycine hydrazide (15).**Yield: 44%, m.p.227-229 °C; Anal.Calcd. for $C_{10}H_{18}N_4O_3S$ : C, 43.79; H, 6.56; N, 20.43 Found: C, 43.71; H, 6.6; N, 20.36; IR (KBr, $cm^{-1}$): 3290, 3166 ($NH_2$, NH and CONH stretching ), 2946 ( CH stretching aliph.), 1722, 1710, 1657 (C=O stertching) and other bands characteristic for the rest of the molecule; MS (m/z,(relative abundance, %)): 274 ($M^+$, 20.5), 258, 243, 215, 201,186 (BP,100). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.84.

**3-acetyl-2,2-di-methyl-thiazolidine-4-carbonyl L-alanine hydrazide (16).**Yield: 46%, m.p.217-219 °C; Anal.Calcd. for $C_{11}H_{20}N_4O_3S$ : C, 45.83; H, 6.94; N, 19.44. Found: C, 45.89; H, 6.87; N, 19.50; $^1$H-NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.77 (6H, *d*, $2CH_3$) , 1.95 (3H, *d*, $CH_3$) , 2.34 (3H , *s*, $COCH_3$), 5.13 (2H, *d*, 5-H of thiazolidine ring), 5.72 (1H, *t*, 4-H of the ring), 5.95 (1-H, *q*, CH), 6.23, 6.55 (2H, *s*, 2CONH, $D_2O$ exchangeable), and 8.38 (2H, *b* ,$NH_2$, $D_2O$ exchangeable). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -26.1 ; TLC chromatography (Rf) value, 0.67.

**3-acetyl-2,2-di-methyl-thiazolidine-4-carbonyl-L-methionine-hydrazide(17).** Yield: 62%, m.p.222-224 °C; Anal.Calcd. for $C_{13}H_{24}O_3S_2$ : C, 44.82; H, 6.89; N, 16.09. Found: C, 44.89; H, 6.87; N, 16.05; IR (KBr, $cm^{-1}$): 3316, 3205 (stretching of CONH) , 2987 ,2846 (stretching of CH aliph.) , 1675 , 1403 (stretching of CONH) , and 1105 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.36 (6H, *s*, $2CH_3$) , 1.72 (3H, *s*, $COCH_3$), 3.3 (2H, *m*, $CH_2$), 3.63 (2H, *t*, $CH_2$), 3.84 (3H, *s*, $CH_3$), 4.44 (2H, *d*,5-H of thiazolidine ring), 4.81 (1H, *t*, CH ), 5.12, 5.54 (2H, *b* ,2NH, $D_2O$ exchangeable), 5.76 (1H, *t*, 4-H) and 10.91

(2H, *b* ,$NH_2$, $D_2O$ exchangeable),Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -34.8 ; TLC chromatography (Rf) value, 0.71.

**3-acetyl-2-phenyl-thiazolidine-4-carbonyl-glycine hydrazide (18).**Yield: 66%, m.p.179-182 °C; Anal.Calcd. for $C_{14}H_{18}N_4O_3S$ : C, 52.17; H, 5.59; N, 17.39 Found: C, 52.22; H, 5.58; N, 17.47; IR (KBr, $cm^{-1}$): 3383, 3176 ($NH_2$, NH and CONH stretching ), 3052 (CH stretching arom..) 2876 ( CH stretching aliph.), 1734, 1685 (C=O stertching) and other bonds characteristic for the rest of the molecule; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 2.34 (3H , *s*, $COCH_3$), 3.55 (2H, *s*,$CH_2$), 5.12 (2H, *d*, 5-H of thiazolidine ring), 5.23, 5.62 (2H, *b*, 2NH, $D_2O$ exchangeable), 5.75 (1H, *s*, 2-H of the ring), 6.16 (1H, *t*, 4-H), 7.44 (*m*, 5H.arom.) and 9.33 (2H, *b* ,$NH_2$, $D_2O$ exchangeable), Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.55.

**3-acetyl-2-phenyl-thiazolidine-4-carbonyl-L-alanine hydrazide (19).**Yield 70%; m.p.212-214 °C; Anal.Calcd. for $C_{15}H_{20}N_4O_3S$ : C, 53.57; H, 5.95; N, 8.33. Found: C, 53.61; H, 6.03; N, 8.26; IR (KBr, $cm^{-1}$): 3330,3216 ($NH_2$, NH and CONH stretching), 3075 (CH stretching arom..) , 2986 ( CH stretching aliph.), 1761, 1715, 1673 (C=O stretching), 1612 (C=C stretching) and other bands characteristic for the rest of the molecule; $^1$H-NMR (DMSO-$d_6$, δ, ppm): 1.27 (3H, *d*, $CH_3$), 1.82 (3H , *s*, $COCH_3$), 5.31 (2H, *d*, 5-H of thiazolidine ring), 5.59 (1H, *b*, NH, $D_2O$ exchangeable); 5.68 (1H, *s*,2-H of the ring), 5.93 (1H, *q*, CH) , 6.18 (1H, *t*, 4-H) , 6.95 (1H, s, CONH, $D_2O$ exchangeable), 7.28 (*m*, 5H.arom.) and 8.99 (2-H, *s*, $NH_2$, $D_2O$ exchangeable). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -23.3 ; TLC chromatography (Rf) value, 0.61.

**3-acetyl-2-phenyl-thiazolidine-4-carbonyl-L-methionine hydrazide (20).**Yield 63%; m.p.169-171 °C; Anal.Calcd. for $C_{17}H_{24}N_4O_3S_2$ : C, 51.51; H, 6.06; N, 14.14. Found: C,51.46; H,6.02; N,14.21; IR (KBr, $cm^{-1}$): 3332, 3143 ($NH_2$, NH and CONH stretching ) , 3045 (CH arom.), 2996 ,2865 (stretching of CH aliph.) , 1715 , 1417 (stretching of C=O) ,1675 (stretching of CONH) and 1139 (stretching of C-C bond of the ring) ; $^1$H NMR (200 MHz, DMSO-$d_6$, δ, ppm): 1.55 (3H, *s*, $COCH_3$), 3.12 (2H, *m*, $CH_2$), 3.37 (2H, *t*, $CH_2$), 3.7 (3H, *s*, $CH_3$), 4.66 (2H, *d*,5-H of thiazolidine ring), 4.88 (1H, *t*, CH ), 5.24 (1H, *s*, 2-H of the ring), 5.53 (1H, *t*, 4-H). 6.25, 6.77 (2H, *b* ,2NH, $D_2O$ exchangeable), 7.62 (5H arom, *m*.) and 8.78 (2-H, *s*, $NH_2$, $D_2O$ exchangeable).. Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, -38.9 ; TLC chromatography (Rf) value, 0.68.

**GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-SUBSTITUTED-3-ACETYL–THIAZOLIDINE–4–CARBONYL-N-BENZYLIDINE GLYCINE HYDRAZONE DERIVATIVES (21-26) :**

2-substituted-3-acetyl-thiazolidine-4-cabonyl amino acid hydrazides **(12, 15, 18,** 0.01 mole**)**, the appropriate aromatic aldehydes (0.01 mole), ethanol (50 ml) were heated under reflux for 5 hours in presence of 2 drops of conc. Sulphoric acid .

The crude product which precipitated by cooling were filtered and recrystallized from ethanol.-water.

**3-acetyl-2-methyl-thiazolidine-4-carbonyl-N-benzylidine-glycine-hydrazone (21).** Yield 71%; m.p.264-266 °C; Anal.Calcd. for $C_{16}H_{19}N_4O_3S$ : C, 55.33; H, 5.47; N, 16.13. Found: C, 55.26; H, 5.42; N, 16.21; IR (KBr, $cm^{-1}$): 3410, 3062 (NH and CONH stretching), 3061 (CH arom.), 2988 (CH stretching aliph.) , 2832 ( CH stretching aliph.), 1718, 1709, 1666 (C=O stretching), 1622 (C=C stretching) and other bands characteristic for the rest of the molecule; $^1$H-NMR (DMSO-$d_6$, δ, ppm): 1.47 (3H, *d*, $CH_3$), 2.23 (3H , *s*, $COCH_3$), 3.83 (2H, s, $CH_2$ ), 4.92 (1-H, s, CONH, $D_2O$ exchangeable), 5.07 (2H, *d*,5-H of the ring), 5.55 (1-H, *b*, CONH, $D_2O$ exchangeable), 5.73 (1H, *s*, 2-H of the ring) , 6.09 (1H, *t*, 4-H) , 6.89 (1H, *s*, CH=N ) and 7.53 (*m*, 5H.arom.) .Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.59.

**3-acetyl-2-methyl-thiazolidine-4-carbonyl-N-4\-chloro-benzylidine-glycine-hydrazone (22).** Yield 60%; m.p.288-290 °C; Anal.Calcd. for $C_{16}H_{18}N_4O_3SCl$ : C, 50.32; H, 4.71; N, 14.67. Found: C,50.26; H,4.63; N,14.74; IR (KBr, $cm^{-1}$): 3373, 3142 ( NH and CONH stretching), 3055 (CH arom.),

2998 (CH stretching aliph.) , 2855 ( CH stretching aliph.), 1725, 1683, 1664 (C=O stretching), 1634 (C=C stretching) and other bands characteristic for the rest of the molecule; $^1$H-NMR (DMSO-$d_6$, δ, ppm): 1.22 (3H, *d*, $CH_3$), 2.47 (3H , *s*, $COCH_3$), 3.67 (2H, s, $CH_2$ ), 4.54 (1-H, s, CONH, $D_2O$ exchangeable), 5.11 (2H, *d*,5-H of the ring), 5.42 (1-H, *b*, CONH, $D_2O$ exchangeable), 5.63 (1H, *s*, 2-H of the ring) , 6.14 (1H, *t*, 4-H) , 6.55 (1H, *s*, CH=N ) and 7.23 (*d. d*, 4H.arom.). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.66.

**3-acetyl-2,2-dimethyl-thiazolidine-4-carbonyl-N-benzylidine-glycine-hydrazone (23).** Yield 73%; m.p.244-246 °C; Anal.Calcd. for $C_{17}H_{21}N_4O_3S$ : C, 56.50; H, 5.81; N, 15.51. Found: C, 56.45; H, 5.88; N, 15.45; IR (KBr, $cm^{-1}$): 3345, 3193 (NH and CONH stretching), 3052 (CH arom.), 2986 (CH stretching aliph.) , 2865 ( CH stretching aliph.), 1716, 1685, 1675 (C=O stretching), 1624 (C=C stretching) and other bands characteristic for the rest of the molecule; $^1$H-NMR (DMSO-$d_6$, δ, ppm): 1.17 (6H, *s*, $2CH_3$), 2.25 (3H , *s*, $COCH_3$), 3.46 (2H, s, $CH_2$ ), 4.72 (1-H, s, CONH, $D_2O$ exchangeable), 5.18 (2H, *d*,5-H of the ring), 5.66 (1-H, *b*, CONH, $D_2O$ exchangeable), 5.92 (1H, *t*, 4-H) , 6.2 (1H, *s*, CH=N ) and 7.43 (*m*, 5H.arom.). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.58.

***3*-acetyl-2,2-dimethyl-thiazolidine-4-carbonyl-N-4′-chloro-benzylidine-glycine-hydrazone (24).** Yield 55%; m.p.>300 °C; Anal.Calcd. for $C_{17}H_{20}N_4O_3SCl$ : C, 51.58; H, 5.05; N, 14.15. Found: C, 51.69; H, 5.11; N, 14.09; IR (KBr. $Cm^{-1}$): 3372 , 3213 (NH and CONH stretching ), 3072 (CH of stretching arom.) , 2975 ( CH of $CH_3$ stretching aliph.), 2855 (CH of $CH_2$ stretching aliph.), 1765,1723, 1677 (C=O stretching), 1612 (CH=N stretching) and other bonds characteristic for the rest of the molecule; $^1$H-NMR (DMSO-$d_6$, δ, ppm): 1.34 (6H, *s*, $2CH_3$), 2.43 (3H , *s*, $COCH_3$), 3.26 (2H, s, $CH_2$ ), 4.56 (1-H, s, CONH, $D_2O$ exchangeable), 5.59 (2H, *d*,5-H of the ring), 5.85 (1-H, *b*, CONH, $D_2O$ exchangeable), 5.92 (1H, *t*, 4-H) , 6.4 (1H, *s*, CH=N ) and 7.11 (*d. d*, 4H.arom ).

**3-acetyl-2-phenyl-thiazolidine-4-carbonyl-N-benzylidine-glycine-hydrazone (25).** Yield 70%; m.p.229-231 °C; Anal.Calcd. for $C_{21}H_{21}N_4O_3S$ : C, 61.61; H, 5.13; N, 13.69. Found: C, 60.54; H, 5.15; N, 13.59; IR (KBr, $cm^{-1}$): 3310, 3156 (NH and CONH stretching), 3056 (CH arom.), 2995 (CH stretching aliph.) , 2876 ( CH stretching aliph.), 1715, 1673, 1661 (C=O stretching), 1612 (C=C stretching) and other bands characteristic for the rest of the molecule; $^1$H-NMR (DMSO-$d_6$, δ, ppm): 1.93 (3H , *s*, $COCH_3$), 3.22 (2H, s, $CH_2$ ), 4.81 (1-H, s, CONH, $D_2O$ exchangeable), 5.38 (2H, *d*,5-H of the ring), 5.54 (1H, *s*, 2-H of the ring),5.54 (1-H, *b*, CONH, $D_2O$ exchangeable), 5.76 (1H, *t*, 4-H) , 6.17 (1H, *s*, CH=N ) and 7.66 (*m*, 10H.arom.). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.70.

**3-acetyl-2-phenyl-thiazolidine-4-carbonyl-N-4′-chloro-benzylidine-glycine-hydrazone (26).** Yield 64%; m.p.192-194 °C; Anal.Calcd. for $C_{21}H_{20}N_4O_3SCl$ : C, 56.82; H, 4.50; N, 12.62. Found: C, 56.77; H, 4.58; N, 12.54; IR (KBr, $cm^{-1}$): 3272, 3133 (NH and CONH stretching), 3045 (CH arom.), 2993 (CH stretching aliph.) , 2877 ( CH stretching aliph.), 1695, 1681, 1667 (C=O stretching), 1616 (C=C stretching) and other bands characteristic for the rest of the molecule; $^1$H NMR (DMSO-$d_6$, δ, ppm): 2.88 (3H , *s*, $COCH_3$), 4.63 (2H, *s*, $CH_2$) , 5.0 (1-H, *s*, CONH, $D_2O$ exchangeable) , 5.25 (2H, *d*, 5-H of thiazolidine ring), 5.54 (1H, *s*, 2-H of the ring), 5.71 (1H, *t*, 4 –H of thiazolidine ring), 5.93 (1-H, *b*, CONH, $D_2O$ exchangeable) , 6.9 (*s*, CH=N) , 7.49 (5H, *m*, arom.) and 7.86 (4H, *d.d,* arom.). Specific rotation [$\alpha^{20}$] deg $dm^{-1}g^{-1}cm^3$, zero ; TLC chromatography (Rf) value, 0.52.

## ANTIMICROBIAL ACTIVITY:

The *in vitro* activities of the synthesized compounds (3-26) were tested using the hole plate method and filter paper disc method [19-20]. The used microorganisms included gram-positive, gram-negative microorganisms *Bacilliu subtilis , Bacillus pumilus , Pesudomonas aeruginosa and*

**Table : 1- Antimicrobial Activity**

| COMPOUND | MIC( µg/mL) | | | | |
|---|---|---|---|---|---|
| | B. subtilis | B.pumilus | P. aeruginosa | E. coli | C. utilis |
| 1 | - | + | - | ++ | - |
| 1b | - | + | - | + | - |
| 1c | - | - | - | + | - |
| 2a | + | + | - | + | - |
| 2b | + | + | - | + | - |
| 2c | + | ++ | - | - | - |
| 3 | +++ | - | - | - | - |
| 4 | - | + | + | - | - |
| 5 | ++ | - | - | + | - |
| 6 | + | - | - | - | - |
| 7 | + | + | - | + | - |
| 8 | - | + | + | - | + |
| 9 | + | ++ | - | - | - |
| 10 | ++ | ++ | - | + | - |
| 11 | ++ | - | - | - | - |
| 12 | + | + | - | - | - |
| 13 | +++ | ++ | + | ++ | - |
| 14 | ++ | + | + | + | - |
| 15 | ++ | ++ | - | ++ | - |
| 16 | + | + | - | + | - |
| 17 | + | + | - | + | - |
| 18 | +++ | + | + | - | - |
| 19 | + | ++ | + | + | - |
| 20 | +++ | ++ | + | ++ | - |
| 21 | + | ++ | + | - | - |
| 22 | ++ | + | - | + | - |
| 23 | + | + | + | - | + |
| 24 | + | - | ++ | - | - |
| 25 | ++ | - | - | + | - |
| 26 | ++ | +++ | ++ | ++ | - |
| Sulfadimidine | ++ | ++ | ++ | ++ | - |
| Amoxycillin trihydrate | ++++ | ++++ | ++++ | ++++ | - |

*Escherichia coli* and the fungi *Candida utilis*. The results were compared with the parent compounds (1a, b, c and 2a, b, c) and Sulfadimidine, amoxycilline trihydrate as reference standard in table 1.

All 2-substituted-3-acetyl-thiazolidine-4-carbonyl amino acid methyl esters (3-11) were found to possess moderate activities (at MIC 75-250 µg/mL against *B. subtilis, B. pumilus,P. aerugenosa and E.coli.* Some compounds in the series of 2-substituted-3-acetyl-thiazolidine-4-carbonyl amino acid methyl esters showed marked antimicrobial activity such as 2-phenyl-3-acetylthiazolidine-4-carbonyl-L-Ala-OMe (10) was found to be active (at MIC 125 µg/mL) against *B.subtilis* and *B.biomilus* only .

Some of the 2-substituted-3-acetyl-thiazolidine-4-carbonyl amino acid hydrazides (12-20) were found to possess good activities (at MIC 75-250 µg/mL) against *B. subtilis , B.biomilus, p-aeruginosa and E.coli* like 2-methyl-3-acetyl-thiazolidine-4-carbonyl L-Ala-hydrazide (13) and 2-phenyl-3-acetyl-thiazolidine-4-carbonyl-L-Meth-hydrazide (20) were found to be active (at MIC 125 µg/mL). All 2-substituted-3-acetyl-thiazolidine-4-arbonyl-N-benzylidine glycine hydrazone derivatives (21-26) were detected and gave a good results as antimicrobial agent (at MIC 75-250 µg/mL) against *B. subtilis , B.biomilus, p-aeruginosa and E.coli,* some of these compounds such as 2-phenyl-3-acetyl-thiazolidine-4-carbonyl- N-4′-chloro

benzy lidine -gly-hydrazone (26) has a marked growth inhibitory effect against *B.subtilis, B.pumilus, P.aeruginosa and E.coli* (at 75-125 μg/mL).

## RESULTS AND DISCUSSION:

The synthesis of 2-substituted-3-acetylthiazolidine-4-carbonyl amino acid methyl esters (3-11) were performed by coupling 2-Methyl or 2,2-Dimethyl and 2-Phenyl -3-acetylthiazolidine -4-carboxylic acid (2a or 2b and 2c ) respectively with amino acid methyl ester hydrochloride using DCC technique in THF/TEA medium.

All the products (3-11) were obtained in crystalline form and gave chromatographically homogenous spots reactions. Hydrazinolysis of the methyl esters (3-11) in ethanol were occurred using water bath for 2h to gave the corresponding hydrazides (12-20) as crystalline products and gave the positive benzidine and silver nitrate reactions.

The hydrazone compounds, 2-substituted-3-acetyl–thiazolidine–4–carbonyl-N-benzyl idine-glycine-hydrazone derivatives (21-26) were prepared by condensation reaction of 2-substituted-3-acetyl-thiazolidine-4-cabonyl amino acid hydrazides (12,15,18) with the appropriate aromatic aldehydes in presence of acidic medium and ethanol as solvent. The synthesized products were obtained in crystalline form .

Compounds (3-26) in schems1 and 2 were supported by their elemental analysis, IR, $^1$H-NMR and mass spectral data, chromatographic and spot reactions.

## CONCLUSIONS:

New compounds were synthesized containing 2-substituted-3-acetyl- thiazolidine ring to study the effect of 2- substituted alkyl or aryl groups on its antimicrobial activity with respect to another compounds containing 3-acetyl-thiazolidine ring it self .

Finally we can concluded that the synthesis of 2-substituted-3-acetyl-thiazolidine-4-carbonyl -amino acid derivatives has a marked effect of the antimicrobial activity on the same type of microorganisms much more than that of the corresponding each 2-substituted-thiazolidine-4-caboxylic acid (1a,b,c) and 2-substituted-3-Acetyl –thiazolidine–4-carboxlic acid derivatives (2a,b,c) and 3-acetyl thiazolidine-4-cabonyl amino acid derivatives [21].

## REFERENCES:


[1]. Wtodek, L., Wróbel, M., and Czubak, J., *General Pharmacology: The Vascular System*, 1996,*27,* 1373

[2]. Šubr, V., Ulbrich, K., *Reactive and Functional Polymers*, 2006, *66,* 1525

[3]. Yan, Y., Shun, L.W., Qin, H. B., Zhou, S. H., *Nutrition Research*, 2006, *6,* 369

[4]. Ferrández, M. D., Correa, R., Del Rio, M., De la Fuente, M., *Experimental Gerontology* 1999, *34***,** 675

[5]. Krishna, C. J., Dandia, A ., Sunita, B., *Journal of Fluorine Chemistry*. 1990,*48,*169

[6]. Sriharsha, S. N., Satish, S., Shashikanth, S., Raveesha, K. A., *Bioorganic & Medicinal Chemistry.* 2006,*14,* 7476

[7]. [7] Dündar, O. B., Özgen Ö., Menteşe, A., Altanlar, N., Atlı, O., Kendi, R, E., *Bioorganic & Medicinal Chemistry.* 2007, *18,* 6012

[8]. [8] Alhamadsheh, M. M., Waters, C. N., Huddler, D. P., Deitrick, M. K., Florova, G., Reynolds, K. A., *Bioorganic & Medicinal Chemistry Letters*, 2007, *17,* 879.

[9]. Norisada, N., Masuzaki, H., Fujimoto, M., Inoue, G., Hosoda, K., Hayashi, T., Watanabe, M., Muraoka, S., Yoneda, F., Nakao, K., *Metabolism*, 2004, *53,* 1532

[10]. Desai, R.C., Han, W., Metzger, E. J., Bergman, J. P., Gratale, D. F., MacNaul, K. L., Berger, J. P., Doebber, T. W., Leung, K., Moller, D. E., Heck, J. V., Sahoo, S. P. *Bioorganic & Medicinal Chemistry Letters* 2003, *13***,** 2795

[11]. Madhavan, G. R., Chakrabarti, R., Kumar, S. K. B., Misra, P., Mamidi, R. N. V. S., Balraju, V., Kasiram, K., Babu, R. K., Suresh, J., Lohray, B. B., Lohray, V. B., Iqbal, J., Rajagopalan, R., *European Journal of Medicinal Chemistry* 2001, *36,* 627

[12]. Van Bogaert, I ., Haemers, A., Bollaert, W., Van Meirvenne, N., Brun, R., Smith, K.,Fairlam, A. H., *Europian Journal of MedicinalChemistry.* 2007, *28*, 387

[13]. Nagase, M., Yukawa, Y., Inomata, Y., Takeuchi, T., *Inorganica Chimica Acta* .1988, *152*, 211

[14]. Cremonesi, G., Croce, P. D., Fontana, F., Forni, A., La Rosa, C., *Tetrahedron: Asymmetry*. 2007, *18***,** 1667
[15]. Nagasawa, H. T., Goon, D. J., Muldoon, W. P., Zera, R. T.. *J. Med. Chemistry* 1984, *27(5),* 591
[16]. Sutcliffe, O. B., Storr, R. C., Gilchrist, T. L., Rafferty, P., *J. Chem. Soc., Perkin Trans.* 2001, *1*, 1795
[17]. Pader, M., Albert, S., *Farmaceutic Italia Soc .anon. Brit* 1959, 811
[18]. Oeriu et al, Chem.Abstr., 1974, *81*, 3916m
[19]. Manoussakis, G., Bolos, C., Ecateriniadou, L., Sarris, C., *European Journal of Medicinal Chemistry*.1987, *22*, 421
[20]. Sulaxna, M. N., Song, X., Eng, G., Kumar, A., *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 2008, *70*, 766
[21] Ahmed, F. S. M., El-Gazzar, A.M., Shedid, S. A., and El-Sharkawy, K. A., *Egypt J.Biomed . Sci*. 2007, *25,* 257 .