Synthesis, Characterization and Biological Activity Study of some New Thiazolidine Derivatives

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Abstract

The study included the preparation of compound 2,2'-(1,4-phenylene) dithiazolidine-4-carboxylic acid (T) which were prepared from the reaction of Terphthaldehyde with cysteine under slightly conditions, This reaction afforded product as a mixture of diastereomers, Cis-(2R,4R) and Trans-(2S,2R), which could not be separated, An equilibrium resulting from epimerization at C(2) occurs between two isomers, The Cis/Trans ratios were strongly dependent on the nature of the solvent**.**Thiazolidine(T) react with acetic anhydride for the preparation of compound 2,2'-(1,4-phenylene) bis (N-acetyl thiazolidine-4-carboxylic acid) (AT) and which represents reaction protection for a amine group, then reacts compound (AT) with some aromatic amines to obtaincompound thiazolidine-4-carboxylic amide**.** The new synthesized compound were identified by melting points and FT-IR,^{1}HNMR, ^{13}CNMR and Mass Spectrum. The biological activity of some preparation compound were studied against two types of bacteria one of them were gram negative (E.coil) and other were gram positive (S.aureus) .

Key word: Cysteine, Thiazolidines derivatives, biological activity .

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1.Introduction

Currently, heterocyclic compounds have been extensively studied due to their important properties and applications. Among these compou-nds, thiazol and thiazolidine derivatives have become especially noteworthy in recent years,(Jan *et al*.2007; Gududuru *et al*. 2005). Thiazolidine-4-carboxylic acid is a cyclic sulfur amino acid analogous in molecular structure to proline and therefore has been named thioproline,(Weber *et al*. 1982). Thiazolidine derivatives has an interesting biological activities, some of these are anticancer activity (Wtodek *et al*.1996; Subr *et al*. 2006), antioxidant,(El-sharkawy 2011), and also has an interest-ingantimicrobial activity (influenza), (Dundar *et al*. 2007;Alhamadsheh *et al*. 2007),in addition to it found in some literature has antidiabitica agents, (El-sharkawy 2011). Thiazolidine Derivatives has been reported to inhibit the growth of bacteria such penicillin and cephacporinate, yeast and fungi. Thiazolidine and penicillin have similarities in their molecular structure. This may also account for similarities in antibacterial action, (Balsamo 1980). Thiazolidine and many other chemical relatives of penicillin were tested for antibiotic activity. However, none of the tested substances were found to be of chemotherapeutic value. Thiazol-idine also inhibits the growth of Escherichia coil. This inhibition is reversed when amino acids are added to the culture,(Weber *et al*. 1982). The synthesis, characterize-ation and biological activity of some Thiazolidine-4-carboxylic acid deri-veateives and Thiazolidine-4-carboxamide derivatives are described on this paper.

Materials and Methods

1.1

Melting points are uncorrected. ^{1}HNMR spectra were recorded on Brucker-400MHz spectrometer in DMSO-d6 in the presence of TMS as an internal standard. Chemical shifts are reported with reference to the respective residual solvent or deuterated peaks (δ_H2.5). Coupling constants are reported in hertz. The abbreviation used are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets) and m (multiblasty) .

2.1.1 General Procedure for the Preparation of 2,2'-(1,4-phenylene) dithiazolidine-4-carboxylic acid (T).

A mixture of L-cysteine (3.16 g,0.052 mole) and Terphthaldehyde (0.026 mole, 3.484g) in ethanol (300ml) and water (30ml) was stirred at room temperature for 8h, and the precipitated solid was collected by filtration, washed with diethyl ether, and dried afford a solid recrystallized from ethanol and water (3:1) give 2,2'-(1,4-phenylene) dithiazolidine-4-carbo-xylic acid as white crystals (m.p=170-172°C,80% yield),(Jain 2004). General structure is shown in Schema(3. 1).

2.1.2General procedure for the Synthesis of 2,2'-(1,4-phenylene) bis (N-acetyl thiazolidine-4-carboxylic acid) (AT) .

A solution of (T) (3.04 g, 0.01 mole) in 6% aqueous Na_2CO_3 (50 ml) cooled in ice- bath, followed by dropwise addition of acetic anhydride (3.77 ml,0.04 mole) over 2 min.. The mixture was left stirred for 1h, and the with the aid of saturation

with NaCl product was isolated by acidification of the reaction mixture and extraction with ethyl acetate (2x50 ml). The combined extracts was washed with saturated NaCl, dried over anhydrous Na_2SO_4. Evaporation of solvent afford a solid recrystallized from ethanol to give (AT) as white crystals,(Liu 2009),m.p 210-212 ° C, 90.5 % yield).

2.1.3 General procedure for the synthesis of 2,2'-(1,4-phenylene)bis(N-acetyl thiazolidine-4- carboxamide)

All compounds were synthesized using the same procedure,(Al-Masoudi *et al*. 2006). A represe-ntative example is described for 2,2'-(1,4-phenylene)bis(3-acetyl-N-(4-chlorophenyl) thiazolidine-4-carboxamide).

A mixture of appropriate protected carboxylic acids(AT) (0.01 mole), N,N-dicyclohexyl-carbodiimde (DCC, 0.02 mole) and hydroxybenzotriazole (HOBT, 0.02 mole) in CH_2Cl_2 (40 ml) was stirred at 0°Cfor 10 min. To this solution, appropriate amine(p-Chloro aniline (0.02 mole) was added and stirring was continued at room temperature for 24 h. Dicyclohexylurea (DCU) was filtered, and the reaction mixture was diluted with CH_2Cl_2 (40 ml) and sequentially washed successively with 5% $NaHCO_3$ solution, 10% citric acid, saturated NaCl solution and finally with water. The residue was dried ($MgSO_4$), filtered, evaporated to dryness and recrystalized from the mixture ethanol and water (1:1). Structures, physical data, and symbols of synthesized compounds are shown in table (2.1).

2.2 Biological study

The antibacterial test was performed according to the disc diffusion method. Compound(T, AT, ATA_3,ATA_5, ATA_6, ATA_7, ATA_8, ATA_9 and ATA_{11}) were assayed for antibacterial activity in vitro against two strains of bacteria(E.coil, S.aureus). prepared agar and petridishes were sterilized by autoclaving for 15 min. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganismsin the solidified medium suitably spaced apart holes were made all 6 mm in diameter. These holes were filled with 0.1 ml of the prepared compound, one concentration compound was prepared (1mg/ml), Ampicillin, cephalexin, ceftazidime and cloxacilline were used as references antibiotic drugs. DMSO was used as a solvent. one of these holes were filled with DMSO as control, to see the effect of solvent, these plates were incubated at 37 C for 24 h,(Jawad *et al*. 2012). .

(2S,2'S,4R,4'R)-2,2'-(1,4-phenylene) dithiazolidine-4-carboxylicacid) (T)*(Trans Isomer) (57%)*

Yield:80m.p:170-172C^o

^{1}HNMR(400MHz, DMSO-d_6)δ3.13 (dd,2H,J=8.14,3.6Hz)(H5b), 3.29(t,2H,J=7.44Hz)(H5a), 4.2 (t,2H,J=4.21Hz) (H4), 5.67 (d,2H,J=8.9Hz) (H2), 7.37-7.55(d,s, 4H, J=11.2Hz)(HAr). FT-IR(KBrdisk): 3390s(OH), 3300w (NH),3045w(C-H Ar.),2935w(C-H)

(2R,2'R,4R,4'R)-2,2'-(1,4-phenylene) dithiazolidine-4- carboxylic acid) (T) *(Cis isomer) (43%).*

Yield:80 ^{1}HNMR(400MHz, DMSO-d_6)δ3.09(m,2H,J=6.8Hz)(H5b),3.36(t,2H, J=7Hz)(H5a), 3.91 (t,2H,J=4.21Hz)(H4),

5.49 (d,2H,J=6.8Hz)(H2),7.39-7.5(d,s,4H, J= 7.95 Hz)(HAr).

(2R,2'R,4S,4'S)-2,2'-(1,4-phenylene) bis(N-acetylthiazolidine-4-carboxylicacid)(AT)*(Trans Isomer) (65%)*

Yield:90 m.p:210-212C^{o} ^{1}HNMR (400MHz, DMSO-d_6)δ1.82 (s,6H)(CH_3), 3.075(t,2H, J=6.5Hz) (H5b), 3.42(m,2H,J=6.5Hz)(H5a), 4.68 (dd,2H,J=14.12,6.5Hz) (H4), 6.38(d, 2H, J=6.1Hz) (H2), 7.5-7.82(d,s,4H, J=8.25Hz) (HAr), 13.03 (s,2H)(OH). FT-IR(KBr disk): 3590,3502s (OH),1732s (C=O Acid), 1665(C=Oamid).

(2R,2'R,4S,4'S)-2,2'-(1,4-phenylene) bis(N-acetylthiazolidine-4-carboxylicacid)(AT) *(Cis isomer) (35%).*

^{1}HNMR (400MHz, DMSO-d_6) δ2.05 (s,6H) (CH_3), 3.13(m)(H5b), 3.34 (m,2H, J=6.5Hz) (H5a), 5.157 (dd,2H,J=6,3.25Hz) (H4), 6.15 (d, 2H,J=6.1Hz) (H2), 7.45-7.86(d,s,4H, J=8.25Hz) (HAr), 13.06(s,2H) (OH).

(2R,2'R,4S,4'S)-2,2'-(1,4-phenylene) bis(3-acetyl-N-(4-Chlorophenyl)thiazolidine-4-carboxamide)(ATA_1)*(Trans Isomer) (82%)*

Yield:55 m.p:172-175C^{o} ^{1}HNMR (400MHz, DMSO-d_6)δ1.82 (s,6H) (CH_3), 3.09(dd,2H, J=20, 12Hz) (H5b), 3.43(dd,2H,J=12,8Hz) (H5a), 4.72 (dd,2H, J=16.8Hz)(H4), 6.46(s, 2H) (H2), 7.52-7.86(d,s,4H, J=8Hz) (HAr),7.69(d,4H, J=8) (HAr2`), 7.73(d,4H,J=8) (Ar3`),10.45 (s,2H) (NH).Mass(EI) [$M^{+\cdot}$]=642, $[M]^{+}$=127,^{13}CNMR (600MHz, DMSO-d_6), δ 22.5 (CH_3),30.7(CH_2) (C_5), 64.94(C_4), 66.24 (C_2),120-142(CAr) ,168.3 (C=O amide t),168.9 (C=Oamid). FT-IR (KBr disk): 3280w(NH amide),1689, 1635m (C=Oamid),3057w(C-H Ar).

(2R,2'R,4R,4'R)-2,2'-(1,4-phenylene) bis(3-acetyl-N-(4-Chlorophenyl)thiazolidine-4-carboxamide)(ATA_1)*(Cis isomer) (18%).*

Yield:55 m.p:172-175C^{o} ^{1}HNMR (400MHz, DMSO-d_6)δ2.05 (s,6H) (CH_3), 3.27(m,2H) (H5b), 3.63 (m,2H,J=8Hz) (H5a), 4.99 (m,2H,J=8Hz)(H4), 6.36(s, 2H) (H2), 7.5-7.82(d,s,4H, J=8Hz) (HAr), 7.67(d,4H,J=8)(HAr2`),7.75 (d, 4H ,J=8)(Ar3`),10.45(s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-p-tolylthiazolidine-4-carboxamide)(ATA_2)*(Trans Isomer) (80%)*

Yield:65 m.p:189-192C^{o} ^{1}HNMR (400MHz, DMSO-d_6) δ1.82(s,6H) (CH_3),2.28 (s,6H) (CH_3), 3.07 (dd,2H,J=22,8) (H5b), 3.45 (dd,2H, J=12, 8Hz) (H5a), 4.72 (t,2H,J=12Hz) (H4), 6.46(s, 2H) (H2), 7.15 (d,4H,J=8) (Ar3`),7.5-7.82 (d,s, 4H, J=8Hz) (HAr), 7.74 (d,4H, J=8) (HAr2`),10.19 (s,2H)(NH). Mass(EI) [$M^{+\cdot}$] =602, $[M]^{+}$=107. FT-IR(KBr disk): 3327w (NHamide), 1697s(C=Oamid), 3050w (C-HAr),2927w(C-H alph.)

(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-p-tolylthiazolidine-4-carboxamide)(ATA_2)*(Cis isomer) (20%).*

Yield:65 m.p:189-192C^{o} ^{1}HNMR (400MHz, DMSO-d_6)δ2.05 (s,6H) (CH_3),2.32(s,6H) (CH_3), 3.3 (m,2H) (H5b), 3.62(m,2H, J=8Hz) (H5a), 4.9 (m,2H,J=8Hz)(H4), 6.42(s, 2H) (H2), 7.15 (d,s,4H, J=8Hz) (HAr3`),7.52-7.82 (d,4H, J=8Hz) (HAr), 7.76 (d,4H,J=8)(Ar2`) ,10.22 (s,2H) (NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-(6-ethoxybenzo[d]thiazol-2-yl) thiazolidine-4-carboxamide)(ATA_3)*(Trans Isomer) (92%)*

Yield:45 m.p:277-280C° ^{1}HNMR (400MHz, DMSO-d_6)δ1.37 (t,6H,J=8) (CH_3),1.82 (s,6H) (CH_3), 3.145 (dd,2H, J=12,8Hz)(H5b), 3.41 (dd, 2H,J=20,12Hz) (H5a), 4.1 (t,4H,J=8Hz) (CH_2CH_3), 4.92 (t,2H,J=8Hz) (H4), 6.47(s, 2H) (H2), 7.52-7.86(d,s,4H, J=8Hz) (HAr),7.05-7.76(d,s,6H,J=4) (HAr2`),12.6 (s,2H) (NH). Mass(EI) [$M^{+\cdot}$]=776,[M]$^+$=194, ^{13}CNMR (600MHz ,DMSO-d_6), δ14.3 (CH_3), 22.4 (CH_3),31.5(CH_2) (C_5),63.6 (OCH_2),64.83(C_4),66.42 (C_2),105-155 (CAr),168.1(C=Oamide t),169.0 (C=O amid s). FT-IR(KBr disk): 3170w(NH amid),1701s (C=Oamid), 3040w (C-Halph).

(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-(6-ethoxybenzo[d] thiazol-2-yl) thiazolidine-4-carboxamide)(ATA_3)*(Cis isomer) (8%)*

Yield:45 ^{1}HNMR (400MHz, DMSO-d_6)δ1.37 (t,6H,J=8)(CH_3-), 2.05(s,6H) (CH_3), 3.3(m,2H,) (H5b), 3.48 (t,2H,J=8Hz) (H5a), 4.1(tt,4H,J=8Hz) (CH_2CH_3), 5.05 (t,2H) (H4), 6.42(s, 2H) (H2), 7.52-7.78(d, s,4H, J=8 Hz) (HAr),7.05-7.765(d,s,6H,J= 4)(HAr2`), 12.63 (s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-*m*-tolyl thiazolidine-4-carboxamide)(ATA_4)

(Trans Isomer) (77%)

Yield:35 m.p:161-165C° ^{1}HNMR (400MHz, DMSO-d_6) δ1.82(s,6H) (CH_3), 2.3 (s,6H) (CH_3), 3.08 (dd,2H,J=22,12Hz) (H5b), 3.41 (t,2H, J=6.3Hz) (H5a), 4.74 (dd,2H,J=12, 6.5Hz) (H4), 6.45(s, 2H) (H2), 6.92-8.15 (d,t,s,8H,J=8Hz) (Ar2`),7.5-7.82 (d,s,4H, J=8Hz) (HAr), 10.18(s,2H) (NH). FT-IR(KBr disk): 3186w (NHamid), 1697,1658s (C=Oamid), 3050w(C-H Ar).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-*m*-tolylthiazolidine-4-carboxamide)(ATA_4)*(Cis isomer) (23%).*

Yield:35 m.p:161-165C° ^{1}HNMR (400MHz, DMSO-d_6)δ2.05 (s,6H) (CH_3) ,2.32(s, 6H) (CH_3), 3.3 (m,2H,) (H5b), 3.5(m,2H) (H5a), 4.95 (m,2H,J=7.6Hz)(H4), 6.4 (s, 2H) (H2), 6.93-8.1 (d,t,s,8H, J=8Hz) (HAr2`),7.52-7.82(d,4H,J=8)(HAr), 10.3 (s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(4-Bromophenyl)thiazolidine-4-Carboxamide)(ATA_5)*(Trans Isomer) (78%)*

Yield:70 m.p:135-139C° ^{1}HNMR (400MHz, DMSO-d_6)δ2.08 (s,6H) (CH_3), 3.12(dd,2H, J=11,6.3Hz) (H5b), 3.42 (dd,2H,J=11.8,6Hz) (H5a), 4.73 (dd,2H,J=10,6.3Hz) (H4), 6.45 (s, 2H) (H2), 7.52-7.86 (d,s,4H, J=8Hz) (HAr),7.64 (d,4H,J=2.1) (HAr2`),7.62 (d,4H,J=2.12) (Ar3`), 10.42(s,2H) (NH). Mass(EI) [$M^{+\cdot}$]=731, [M]$^+$=171 FT-IR(KBr disk): 3266w(NH amid),1697,1635 (C=Oamid),3059w(C-HAr).

(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(4-Bromophenyl)thiazolidine-4-Carboxamide)(ATA_5)*(Cis isomer) (22%).*

Yield:70 m.p:135-139C° ^{1}HNMR (400MHz, DMSO-d_6)δ1.85(s,6H) (CH_3), 3.24(m,2H) (H5b), 3.62(t,2H,J=6Hz) (H5a), 4.99 (t ,2H,J=6.5Hz)(H4), 6.42(s, 2H) (H2), 7.5-7.82(d,s, 4H, J=8 Hz)

(HAr),7.67(d,4H,J=8)(HAr2`),7.72(d,4H,J=8)(Ar3`),10.5(s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(2-methoxyphenyl) thiazolidine -4-Carboxamide) (ATA_6) ***(Trans Isomer) (87%)***

Yield:72 m.p:198-165C° ^{1}HNMR (400MHz, DMSO-d_6) δ1.85(s,6H) (CH_3), 3.15(m,2H,J=5.8 Hz) (H5b), 3.415 (t,2H, J=6Hz) (H5a), 3.84(s ,6H)(OCH_3), 4.95 (t,2H,J=6.3Hz) (H4), 6.42(s, 2H) (H2), 6.94-8.12 (d,t,s,8H,J=7.5) (Ar2`),7.5-7.82 (d,s,4H, J=8Hz) (HAr), 9.44(s, 2H)(NH). FT-IR(KBr disk): 3388w (NH amide). Mass(EI) $[M^{+\cdot}]$= 634,$[M]^+$=123, FT-IR(KBr disk): 3287w (NH amide), 1662,1643m (C=Oamide),3050(C-HAr).

(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(2-methoxyphenyl) thiazolidine-4-Carboxamide)(ATA_6)*(Cis Isomer) (13%).*

Yield:72 m.p:198-165C° ^{1}HNMR (400MHz, DMSO-d_6) δ2.05(s,6H) (CH_3), 3.25(m,2H) (H5b), 3.61 (t,2H, J=4Hz) (H5a),3.86(s ,6H) (OCH_3), 5.12 (t,2H,J=4.1Hz) (H4), 6.35(s, 2H) (H2), 6.92-8.12 (d,t,s,8H,J=7.1) (Ar2`),7.5-7.82 (d,s,4H, J= 8Hz) (HAr), 9.64(s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(2,4-dibromophenyl) thiazolidine-4-Carboxamide)(ATA_7)*(Trans Isomer) (65%)*

Yield:55 m.p:144-147C° ^{1}HNMR (400MHz, DMSO-d_6) δ2.08(s,6H) (CH_3), 3.09(m,2H,J=5.8Hz)(H5b), 3.41 (m,2H, J=6) (H5a), 4.72 (dd,2H,J=15, 6.8Hz) (H4), 6.36(s, 2H) (H2), 7.632-7.7 (d,4H,J=7.7) (Ar2`),7.5-7.82 (d,s, 4H, J=8Hz) (HAr),8.1(s,2H)(Ar3`), 9.9(s,2H) (NH). Mass(EI) $[M^{+\cdot}]$=889, $[M]^+$ =250, FT-IR(KBr disk): 3327w (NHamide),1700,1627m(C=Oamid),3045 w(C-H Ar),2931(C-Halph.).

(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(*2,4*-dibromophenyl) thiazolidine-4-Carboxamide)(ATA_7)*(Cis Isomer) (35%)*

Yield:55 m.p:144-147C° ^{1}H NMR (400MHz, DMSO-d_6) δ1.82 (s,6H)(CH_3), 3.3(m,2H) (H5b), 3.62 (m,2H,) (H5a), 5.01 (m,2H,J=5. 4Hz) (H4), 6.23(s, 2H) (H2), 7.632-7.7 (d,4H,J=7.7) (Ar2`),7.52-7.86(d,s ,4H, J=8 Hz) (HAr), 8.12(s,2H)(Ar3`), ---(s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene) bis (3-Acetyl-N-(4-methyl-3- nitro phenyl) thiazolidine-4- carboxamide) (ATA_8) (*Trans Isomer) (80%)*

Yield:53 m.p:166-170C° ^{1}HNMR (400 MHz, DMSO-d_6) δ1.82(s,6H) (CH_3), 2.15(s,6H) (CH_3), 3.12 (m,2H,J=5.8Hz) (H5b), 3.44 (t ,2H, J=6Hz) (H5a), 4.73 (t, 2H,J=6.4Hz) (H4), 6.47(s, 2H) (H2), 7.76-7.81 (d, 4H,J=7.5)(Ar2`),7.5-7.82(d,s,4H, J=8Hz) (HAr),8.44(s,2H) (3`Ar), 10.7(s, 2H)(NH). Mass(EI) $[M^{+\cdot}]$=691, $[M]^+$=152 FT-IR(KBr disk): 3269w(NH amide), 1701,1654(C=Oamid),3049w(C-H).

(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene) bis (3-Acetyl-N-(4-methyl-3-nitrophenyl) thiazolidine-4-carboxamide)(ATA_8)*(Cis Isomer) (20%)*

Yield:53 m.p:166-170C° ^{1}HNMR (400MHz, DMSO-d_6) δ2.05(s,6H) (CH_3), 2.25(s,6H) (CH_3), 3.28 (m,2H) (H5b), 3.61 (t,2H, J=5.1 Hz) (H5a), 5.03 (t,2H,J=5Hz) (H4), 6.39(s, 2H) (H2), 7.76-7.86 (d, 4H,J=7.5)(Ar2`),7.5-7.82 (d,s,4H, J=8Hz) (HAr),8.4 (s,2H) (3`Ar), 10.66 (s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene) bis(3-Acetyl-N-(3-nitrophenyl) thiazolidine-4-carboxamide)(ATA_9)*(Trans Isomer) (83%)*

Yield:43 m.p:191-194C° ^{1}HNMR (400MHz, DMSO-d_6) δ1.81(s,6H) (CH_3), 3.13(m,2H,J=8.6Hz)(H5b), 3.45 (t ,2H, J=6.5Hz) (H5a), 4.76 (dd,2H,J=9.9,6.2Hz) (H4), 6.47(s, 2H) (H2), 7.76-7.95 (d,t, 6H,J=2.3)(Ar2`),7.5-7.82(d,s, 4H, J=8Hz) (HAr),8.69(s,2H) (3`Ar), 10.83(s, 2H)(NH)Mass(EI) [$M^{+\cdot}$]=664,[M]$^+$=137, FT-IR(KBr disk): 3267w(NH amide), 1697, 1635m(C=Oamide),3050(C-HAr).

(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene) bis(3-Acetyl-N-*(3-nitrophenyl)* thiazolidine-4-carboxamide)(ATA_9)*(Cis Isomer) (17%)*

Yield:43 m.p:191-194C° ^{1}HNMR (400MHz, DMSO-d_6) δ2.02(s,6H) (CH_3), 3.23(m,2H,J=5 Hz)(H5b), 3.5 (t ,2H, J=5.8Hz) (H5a), 5.05 (m, 2H) (H4), 6.43(s, 2H) (H2), 7.76-8.02 (d,t, 6H,J=2)(Ar2`),7.5-7.82(d,s,4H, J=8Hz) (HAr),8.64 (s,2H) (3`Ar), 10.8 (s ,2H)(NH).

(**2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(4-nitrophenyl)thiazolidine-4-Carboxamide)(ATA_{10})*(Trans Isomer) (83%)***

Yield:40 m.p:111-114C° ^{1}HNMR (400MHz, DMSO-d_6)δ2.05 (s,6H)(CH_3), 3.11(m,2H, J= 8.2Hz) (H5b), 3.45(m,2H,J=8.1 Hz) (H5a), 4.7 (dd,2H,J=18,8Hz) (H4), 6.5 (s, 2H) (H2), 7.52-7.86(d,s,4H, J=8Hz) (HAr),7.7(d,4H ,J=7.8) (HAr2`), 7.74(d,4H,J=8) (Ar3`),10.52(s,2H) (NH). FT-IR(KBr disk): 3253w(NH amide),1701,1654(C=Oamide),3070w(C-HAr).**(2R,2`R,4R,4`R)-2,2`-(1,4-phenylene)bis(3-Acetyl-N-(4-nitrophenyl)thiazolidine-4-Carboxamide)(ATA_{10})*(Cis Isomer) (17%)***

Yield:40 m.p:111-114C° ^{1}HNMR (400MHz, DMSO-d_6)δ1.85 (s,6H) (CH_3), 3.3(m,2H) (H5b), 3.62 (m,2H,J=6.2Hz) (H5a), 5.01 (t, 2H,J=5.8 Hz) (H4), 6.42 (s, 2H) (H2), 7.52-7.86(d,s,4H, J=8Hz) (HAr),7.73(d,4H,J=7.8)(HAr2`), 7.77(d,4H,J=8)(Ar3`),10.57(s,2H)(NH).

(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-*o*-tolyl thiazolidine-4-carboxamide)(ATA_{11})

(Trans Isomer) (80%)

Yield:60 m.p:154-157C° ^{1}HNMR (400MHz, DMSO-d_6)δ1.85 (s,6H)(CH_3),2.2(s,6H)(CH_3), 3.11(m,2H, J=5.8Hz)(H5b), 3.42 (m,2H,J=6.08Hz) (H5a), 4.88 (t,2H,J=9.5Hz) (H4), 6.44 (s, 2H) (H2), 7.52-7.86(d,s,4H, J=8Hz) (HAr) , 7.15-7.7 (t,d,8H,J=7.8), 9.6(s,2H) (NH). FT-IR(KBr disk): 3261w(NHamide),1692,1639m(C=Oamid)

.(2S,2`S,4R,4`R)-2,2`-(1,4-phenylene)bis (3-Acetyl-N-*o*-tolylthiazolidine-4-carboxamide)(ATA_{11})

(Cis Isomer) (20%)

Yield:60 m.p:154-157C° ^{1}HNMR (400MHz, DMSO-d_6)δ2.05 (s,6H)(CH_3),2.18(s,6H) (CH_3), 3.3(m,2H) (H5b), 3.64(m,2H) (H5a), 5.06 (m,2H,J=8Hz) (H4), 6.21(s, 2H) (H2), 7.52-7.86(d,s,4H, J=8Hz) (HAr),7.15-7.7(t,d,8H,J= 7.8), 9.67(s,2H) (NH).

3.Results and discussion

3.1 Chemistry

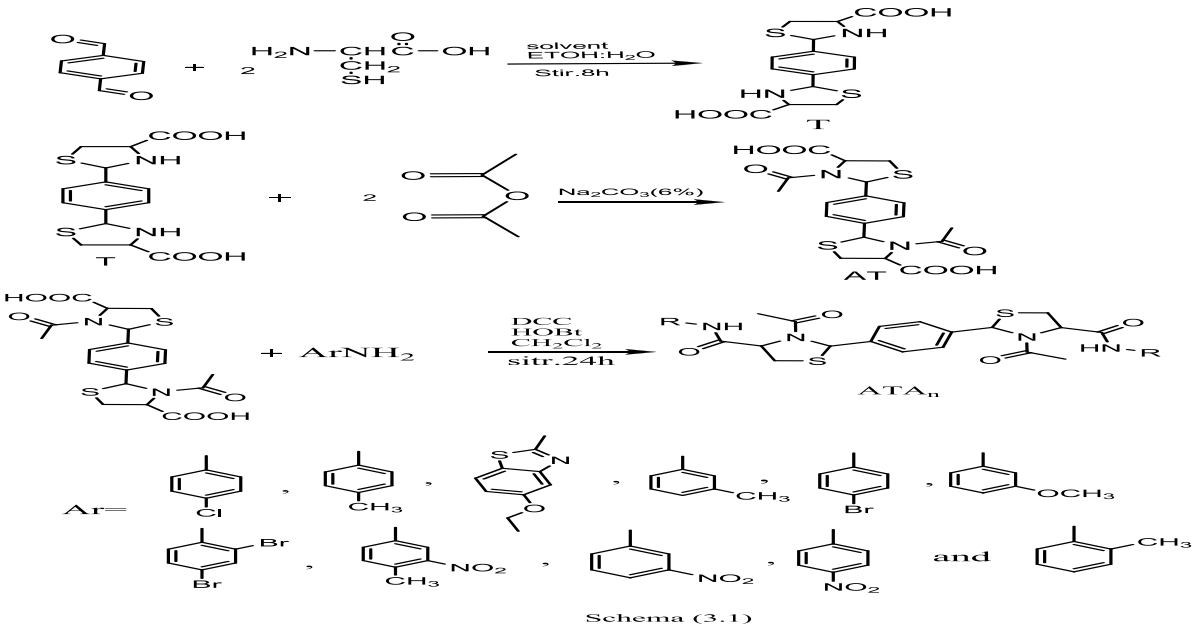
The reaction of L-cysteine with Terphthaldehyde in the presence of ethanol and water as solvent (10:1) in

either yields 2,2'-(1,4-phenylene) di thiazolidine-4-carboxylic acid (T), which in turn will react with acetic anhydride to form 2,2'-(1,4-phenylene)bis(N-acetyl thiazolidine-4- carboxylic acid) (AT), which react with aniline derivatives using 1-hydroxybenzotriazoleand N,N-dicyclohexyl carbodiimide (DCC) as coupling reagents in the presence of dichloromethane CH_2Cl_2 as solvent gave the corresponding amides**.** as shown in schema(3.1).

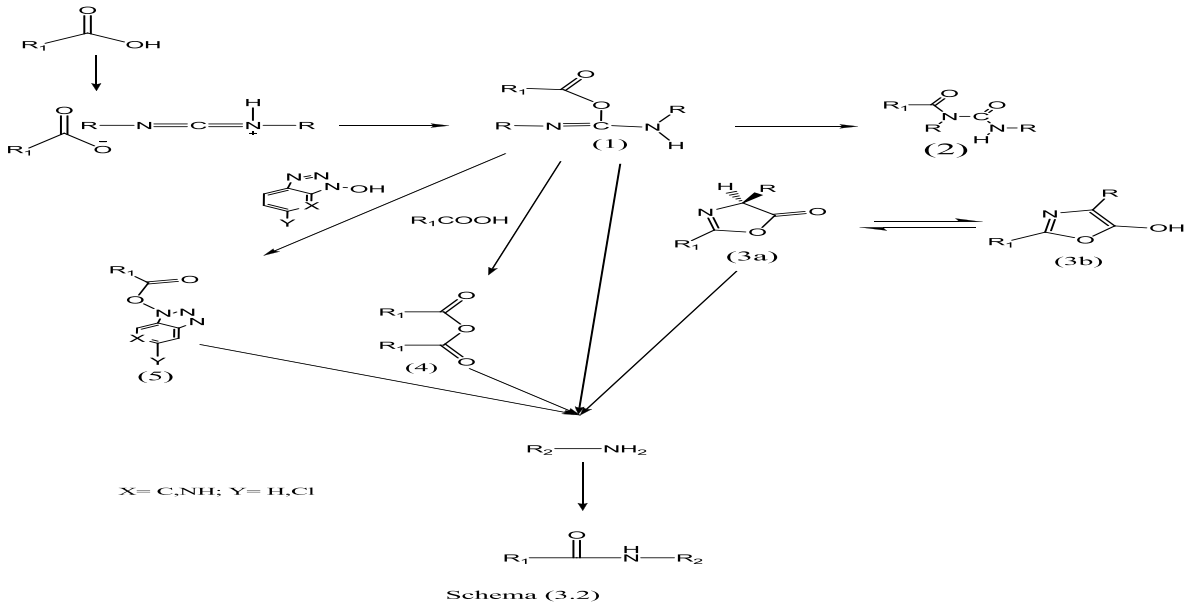
DCC is inexpensive, but it has a major problem that the DCU is being poorly soluble in most solvents and sometimes very difficult to remove completely from the product,(Amornraksa *et al*. 2009). Unfortunately, carbodiimide did not comply with the concept of ultimate coupling reagents because its high reactivity provokes racemization and side reactions during the coupling reaction as shown in Schema(3.2). Which,1-hydroxybenzotriazole (HOBT) was proposed as an additive to DCC to reduce racemization and from then on other benzotriazole derivatives such as 1-hydroxy-5-chlorobenz-otriazole (Cl-HOBt) or 1-hydroxy-7-azabenzotriazole (HOBt) have also been used. The OBt active esters (5) are less reactive than 1, but are more stable and less prone to racemize. All these factors make the addition of benzotriazole derivatives almost mandatory to preserve the amide bond formation by carbodiimde activation of low yields and undesired side reaction.

3.2 Biological activity

The inhibition zones caused by the various compound were examined. (1mg/ml) concentration for all of these compound). The results are listed in table (3.2) .



Schema 3.1:The steps for synthesis of compounds



Schema 3.2:The steps for synthesis of amide compounds

Table 2.1:Some physical properties for amide compounds

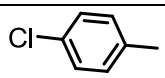
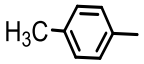
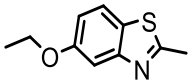
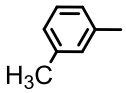
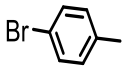
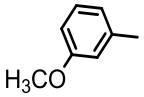
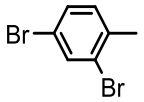
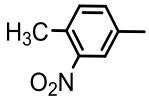
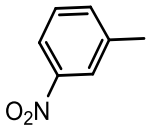
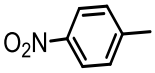
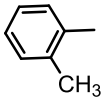
Comp. NO.	Ar	M.p	Rf. (Benzen:THf :Formicacid) (6:2:2)	Yield	Structure Molecular weight
ATA_1		172-175	0.65	55	$C_{30}H_{28}Cl_2N_4O_4S_2$ 643.5
ATA_2		189-192	0.62	65	$C_{32}H_{34}N_4O_4S_2$ 602.5
ATA_3		278-280	0.55	45	$C_{36}H_{36}N_6O_6S_4$ 776.97
ATA_4		161-165	0.59	35	$C_{32}H_{34}N_4O_4S_2$ 602.5
ATA_5		135-140	0.5	70	$C_{30}H_{28}Br_2N_4O_4S_2$ 732.5
ATA_6		198-202	0.655	72	$C_{32}H_{34}N_4O_6S_2$ 634.44
ATA_7		144-147	0.54	55	$C_{30}H_{26}Br_4N_4O_4S_2$ 890.3
ATA_8		166-170	0.45	53	$C_{32}H_{32}N_6O_8S_2$ 692.76
ATA_9		191-194	0.53	34	$C_{30}H_{28}N_6O_8S_2$ 664.7
ATA_{10}		111-114	0.6	40	$C_{30}H_{28}N_6O_8S_2$ 664.7
ATA_{11}		154-157	0.4	60	$C_{32}H_{34}N_4O_4S_2$ 602.5

Table3.2:Inhibition zones of compounds and the references antibiotics

NO.	**COM.**	**S.aureus**	**E.coil**
1	DMSO	0 mm	0 mm
2	T	15 mm	31 mm
3	AT	14mm	23mm
4	ATA_3	11mm	23mm
5	ATA_4	25mm	25mm
6	ATA_5	26mm	22mm
7	ATA_7	35mm	37mm
8	ATA_8	33mm	23mm
9	ATA_9	23mm	35mm
10	ATA_{11}	31mm	31mm
11	Cephalexin	7mm	17mm
12	Ceftazidime	3mm	17mm
13	Ampicillin	18mm	7mm
14	Cloxacillin	11mm	18mm

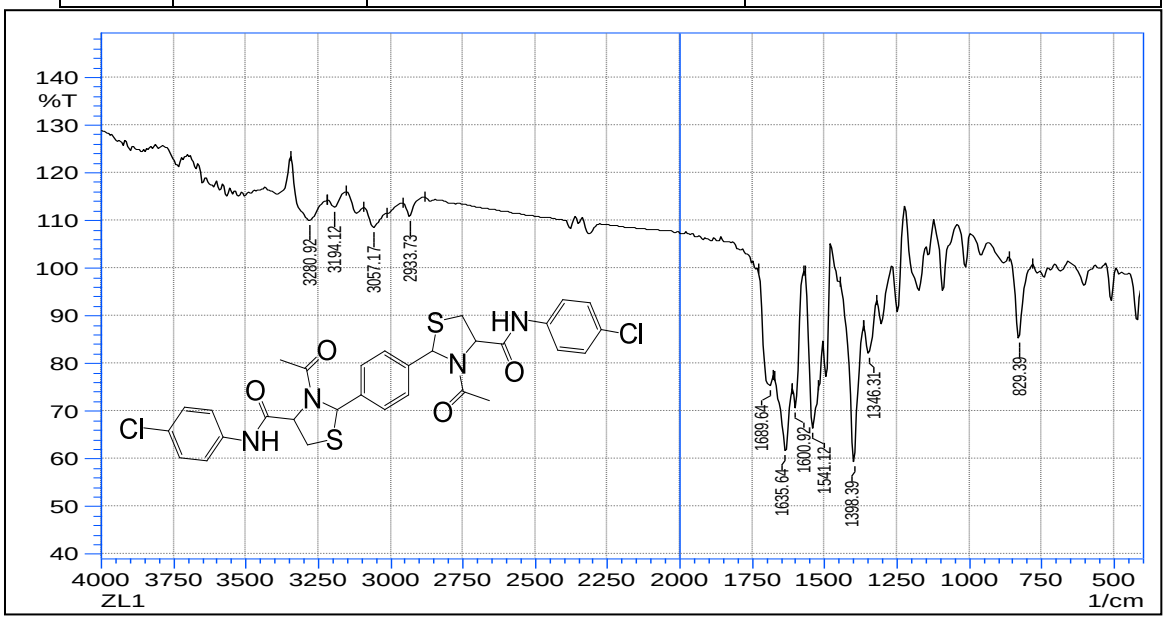


Fig.1:FT-IR spectrum for compound ATA_1

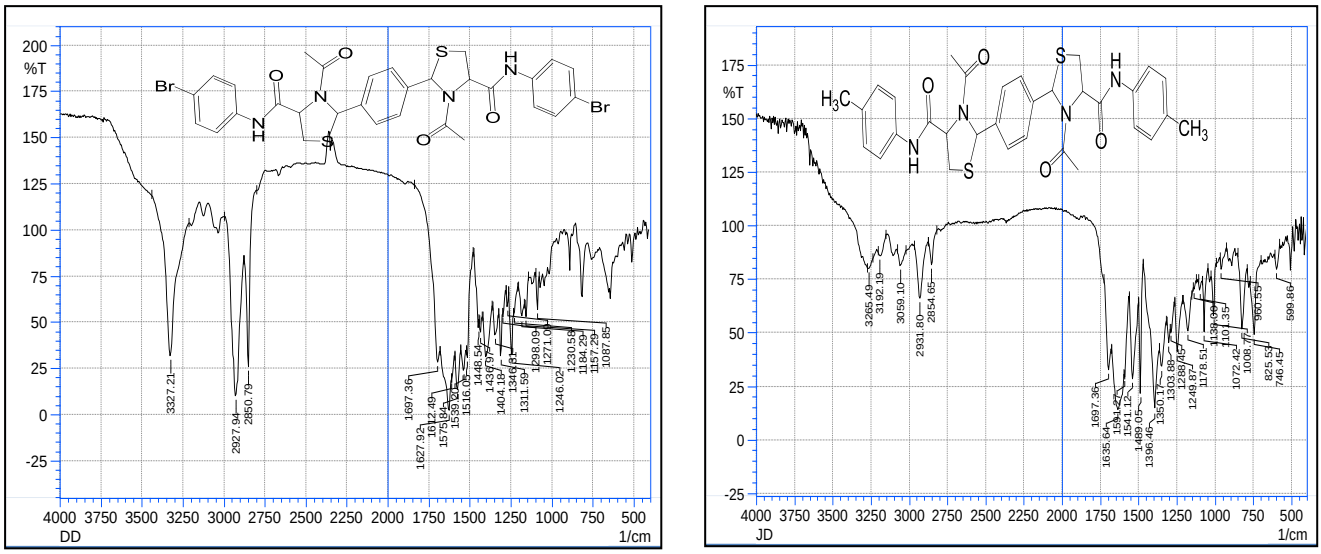


Fig.2:FT-IR spectrum for compound ATA_2,ATA_5

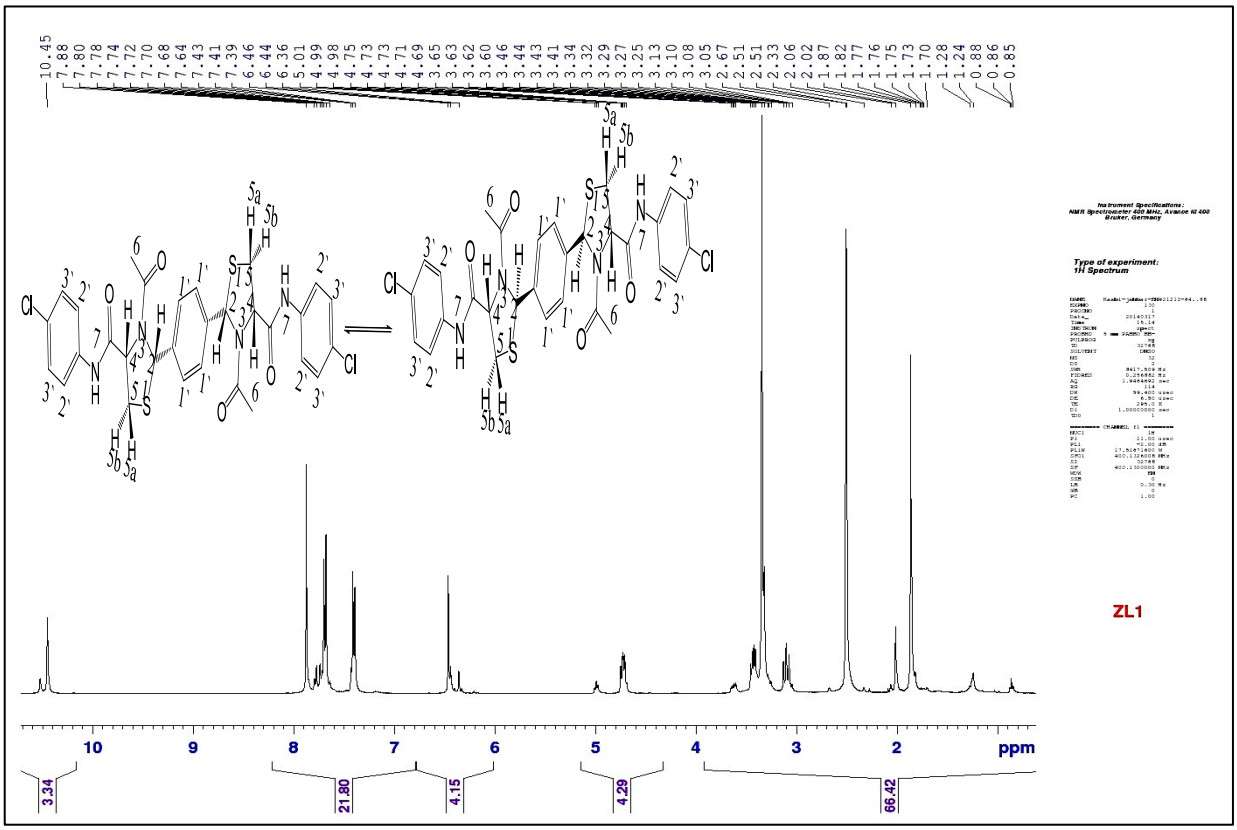


Fig.3:[1]HNMR spectrum for compound ATA_1

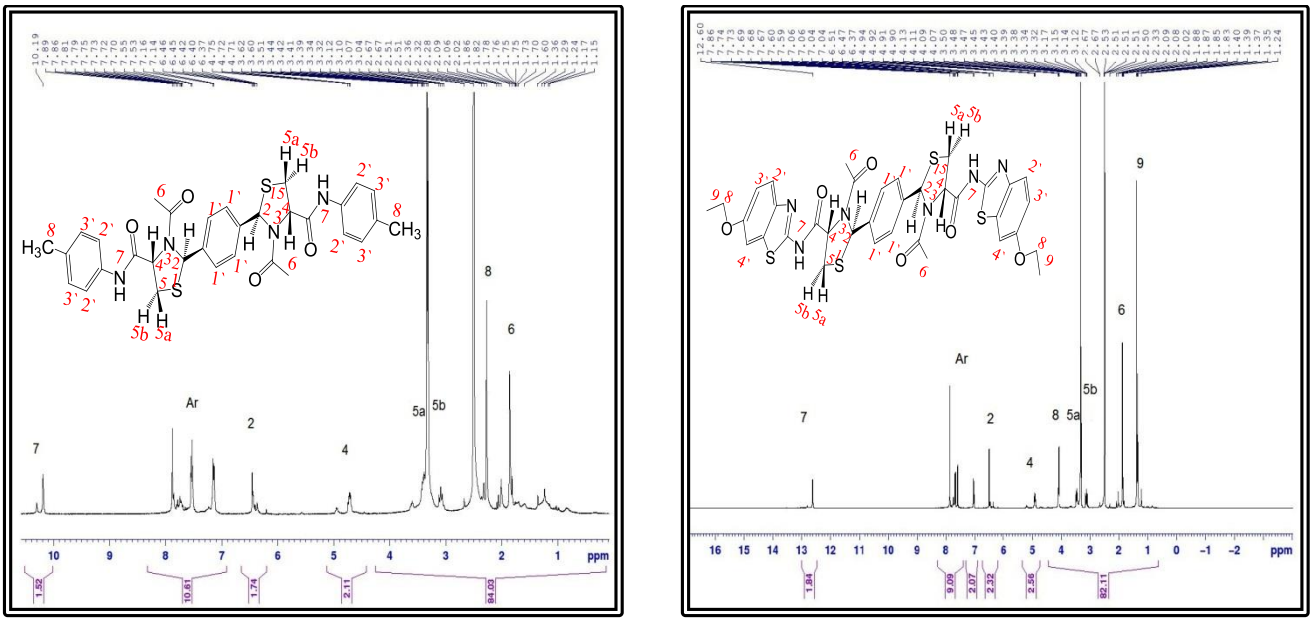


Fig.4:[1]HNMR Spectrum for compound ATA_2,ATA_3

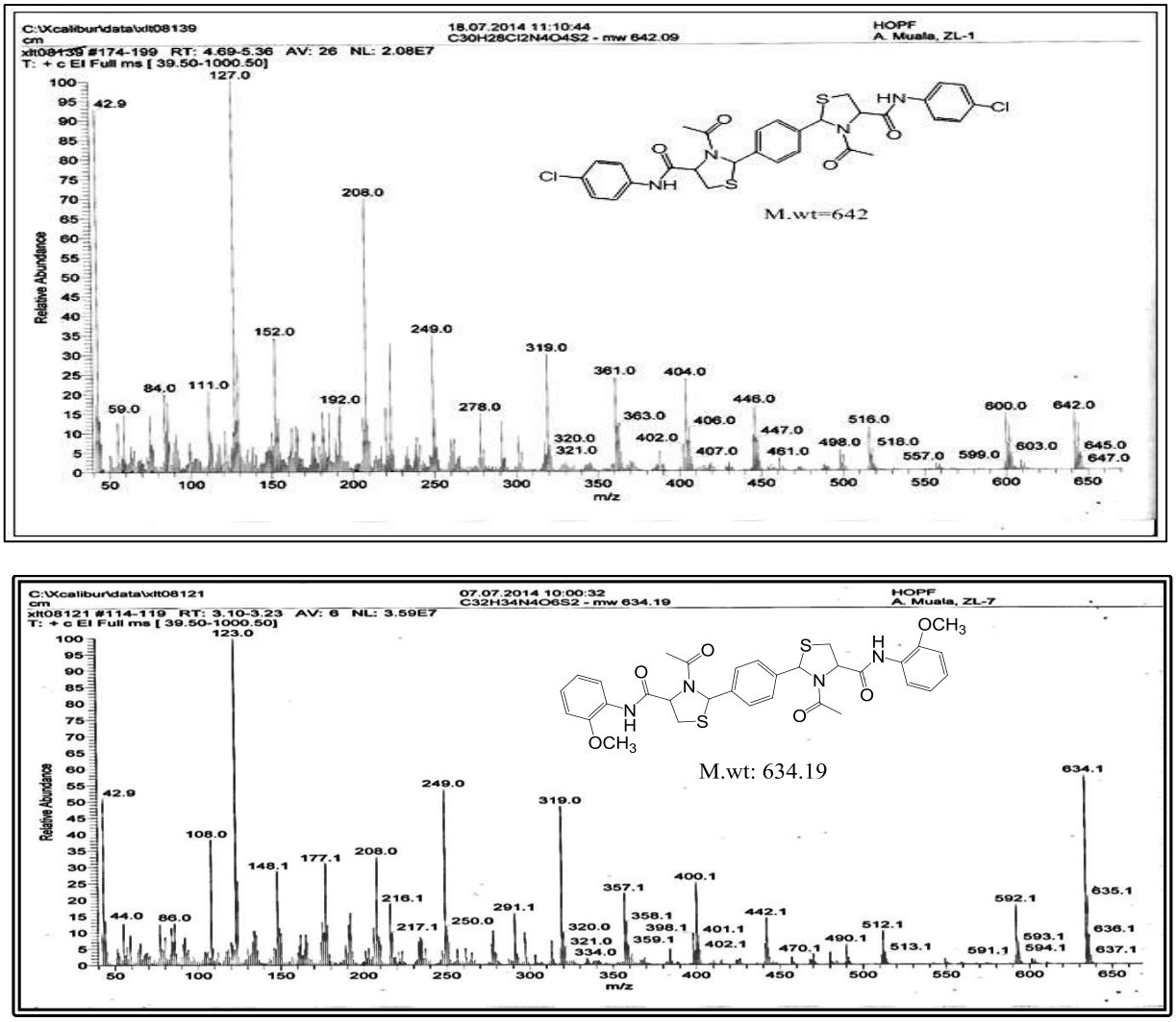
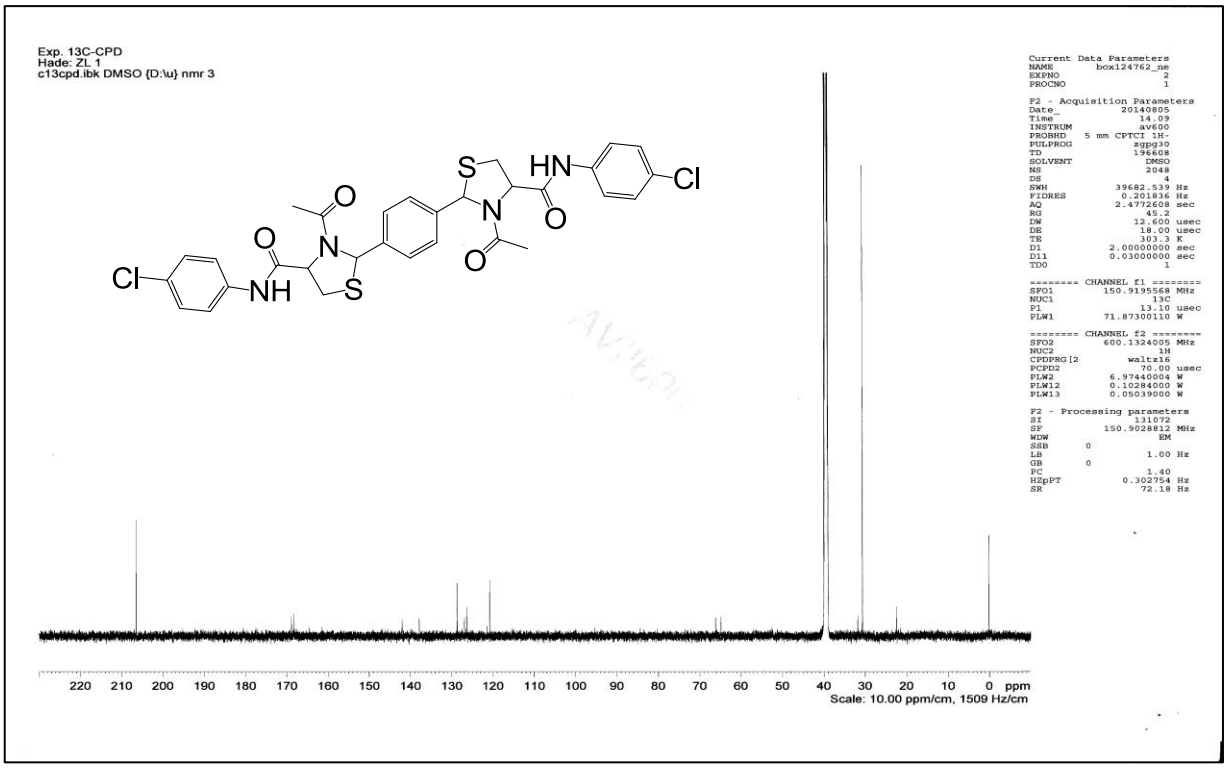


Fig.5:Mass Spectrum for compound ATA_1,ATA_6



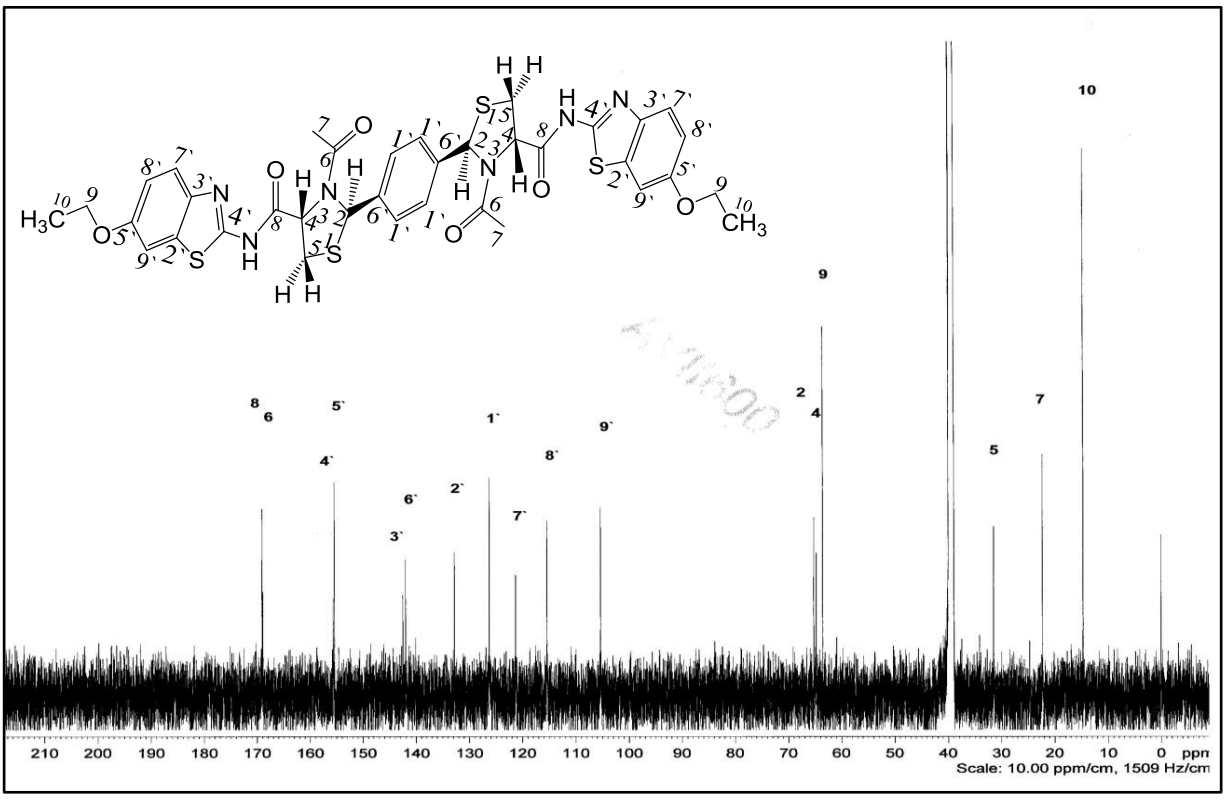


Fig.6:[13]CNMR Spectrum for compound ATA_1,ATA_3

4.Conclusion

Thiazolidines were easily obtained in yields of 80% from the condensation of L-Cysteine and Terphthaldehyde under slightly conditions. This condensation afforded product as a mixture of diastereomers, Cis-(2R,4R) and Trans-(2S,2R), which could not be separated. An equilibrium resulting from epimerization at C(2) occurs between two isomers. The Cis/Trans ratios were strongly dependent on the nature of the solvent. In CDCl3 the major isomer was the Cis Isomer while in DMSO-d_6, the trans diastereoisomer predominated after complete equilibration.

From the result we conclude that the all compounds have a good biological activities against two type of bacteria one of these were gram negative and the other was gram positive .

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تحضير وتشخيص ودراسة الفعالية البايولوجية لبعض مشتقات الثايازوليدين

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الخلاصة

تضمنت هذه الدراسة تحضير المركب (T) والمحضر من تفاعل الحامض الاميني السيستاين مع الترفثالدهايد تحت ظروف معينة، هذا التفاعل ينتج مزيج من الايزومرين السس (2R,4R) والترانس (2S,4R)،التي تكون صعبة الفصل و في حالة توازن و الايمر ينتج من ذرة الكاربون 2 بين كلا الايزومرين، نسبة الايزومرين السس والترانس تعتمد على طبيعة المذيب.الثايزولدين (T) يتفاعل مع انهدريد الخليك لتحضير المركب (AT) والذي يمثل تفاعل حماية لمجموعة الامين، ثم يتفاعل المركب (AT) مع بعض الامينات الاروماتية للحصول على مركبات الثايزولدين-4- كاربوكسيلك امايد. تم تشخيص المركبات المحضرة بقياس درجات الانصهار وقياس اطياف تحت الحمراء واطياف الكتلة واطياف الرنين النووي المغناطيسي البروتوني والكاربوني 13. درست الفعالية البايولوجية لبعض المركبات المحضرة اتجاه نوعين من البكتريا احدهما سالبة لصبغة كرام (E.coil) والاخرى موجبة لصبغة كرام (S.aureus)