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Synthesis and Characterization of New Thiazolidinones Which Are Used To Decrease Blood Glucose Level.

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ABSTRACT

This study is concerned with the synthesis and characterization deri**v**atives of Thiaszolidinones **3a-e**. These compounds were synthesized by reacting of thioglycolic acid with the appropriate Schiff base **2a-e**, in the presence of dry benzene in moderate yields (69-73%). The structures of Thiaszolidinone were established on the basis of the spectral data like FT-IR, ^{1}H-NMR, ^{13}C-NMR, Gcosy and Mass.

Keywords: Thiazolidinone , thioglycolic acid, ^{13}C NMR, Gcosy and mass spectral.

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INTRODUCTION

A number of protocols for the synthesis of 4-thiazolidinones are available in the literature, for this Schiff bases have played a vital role for the formation of 4-thiazolidinones [1]. Schiff bases have often been used as chelating ligands in coordination chemistry [2]. These Schiff bases are biologically as well as synthetically [3] important nitrogen containing compounds having azomethine group.

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five-member ring, 4-Thiazolidinones [4] have attracted considerable attention as they are endowed with wide range of pharmaceutical activities. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. The presence of N-C-S linkage in the compounds has been shown to have antimicrobial [5], antioxidant [6] and anti-HIV [7,8] activities etc.., 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group in the 4-position as reported with several biological [9,10], aspects together with antibacterial [11], antifungal [12], anti-inflammatory [13], antitumor [14,15] anti-tubercular [16] activity .

EXPERIMENTAL PART

Wherever necessary, the solvents were distilled/dried prior use by standard methods. All solvent extracts was dried over anhydrous sodium sulphate unless otherwise specified. The ^{1}H-NMR spectra were recorded, using VARIAN spectrophotometer (300 MHz). The ^{13}C-NMR spectra were recorded, using VARIAN spectrophotometer (75 MHz), the above measurements were recorded in National Hellenic Research Foundation, Institute of Biology Medicinal Chemistry and Biotechnology, Molecular analysis Group, Athens, Greece. The chemical shift values are expressed in δ (ppm), using tetramethylsilane (TMS) as internal standard and using DMSO-d_6 as solvent. The Mass spectra were recorded at 3 kV and 4 kV were using VARIAN spectrophotometer. IR spectra were recorded using Shimadzu FT-IR affinity spectrophotometer as KBr disks. Only principal absorption bonds of interest are reported and are expressed in cm^{-1}.

General Procedure for the preparation of imines 2(a-e)

In general, the imines **2(a-e)** were prepared [17,18] by reaction mixture of 0.01 mole amine with 0.01 mole aldehyde in 20 mL of methanol and 4-6 drops of glacial acetic acid was heated in water bath at (55-60˚C), The reaction mixture was refluxed for (1-3) h with stirring . The progress of the reaction was followed by TLC. After completion, the solvent evaporated and then recrystallized from ethanol. The physical data of imines **2a-e** and the reactants are shown in (Table 1).

1-(((6-Methoxybenzothiazol-2-yl)amino)methyl)naphthalene-2-ol **(2a)** it was prepared by reacting of 2-amino-6-methoxybenzothiazol (0.01 mol, 1.80 g) with 2-hydroxy-1-naphthaldehyde (0.01 mol, 1.72 g). Yield = 88%, m.p. = 193-194 ºC. IR (KBr disk): 1604 cm^{-1} (C=N).

1-(((5-Bromopyridine-2-yl)imino)methyl)naphthalene-2-ol **(2b)** it was prepared by the reaction of 2-amino-5-bromopyridine (0.01 mole 1.73g) with 2-hydroxy-1-naphthaldehyde (0.01mol, 1.72g) .Yield= 82% ,m.p =207-208 °C. IR (KBr disk): 1620 cm^{-1}(C=N).

1-(((5-Chloropyridine-2-yl)imino)methyl)naphthalene-2-ol **(2c)** it was prepared by reacting of 2-amino-5-chloropyridine (0.01 mole, 1.28 g) with 2-hydroxy-1-naphthaldehyde (0.01 mol, 1.72 g). Yield = 85 %, m.p. = 203-204 ºC. IR (KBr disk): 1620 cm^{-1} (C=N).

1-(((5-Methylpyridine-2-yl)imino)methyl)naphthalene-2-ol **(2d)** it was prepared by reacting of 2-amino-5-methylpyridine (0.01mole, 1.08g) with 2-hydroxy-1-naphthaldehyde (0.01mole, 1.72g). Yield = 89%, m.p.= 189-190 ºC. IR (KBr disk): 1620 cm^{-1} (C=N).

1-(((2-Amino-5-(3,4,5-trimethoxybenzyl)pyrimidine-4-yl)imino) methyl)naphthalen-2-ol **(2e)** it was prepared by reacting of trimethoprime (0.01mole, 2.90g) with 2-hydroxy-1-naphthaldehyde (0.01mole, 1.72g). Yield = 80%, m.p. = 204-205 °C. IR (KBr disk): 1612 cm^{-1} (C=N).

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Table (1) physical data of imines 2(a-e)

imines 2(a-e)	m.p °C	Yield %	Color
2a	193-194	88	yellow
2b	207-208	82	yellow
2c	203-204	85	yellow
2d	189-190	89	yellow
2e	204-205	80	yellow

General procedure for the preparation of thiazolidinones [19]

A mixture of compounds **2(a-e)** and thioglycolic acid in dry benzene (40) mL was refluxed for (6-12h). Progress of the reaction was checked by TLC using hexane-ethyl acetate (7:3) as eluent. After the completion of reaction benzene was removed by distillation to give solid. The solid obtained was filtered, washed with DCM and purified by crystallization from methanol to give compounds **3(a-e)**. the physical data of thiazoledinone **3(a-e)** and the reactants are shown in (Table 2).

2-(2-Hydroxynaphthalene-1-yl)-3-(6-methoxybenzo thiazol-2-yl)thiazolidin-4-one **(3a)** was prepared by reacting **(2a)** (0.01 mole, 3.34 g) and (0.01 mole, 0.92 gm, 0.67 ml) of thioglycolic acid. Yield =72 %, m.p. = 143-144 ºC. IR (KBr disk): 1674 cm^{-1} (–N–C=O). ^{1}H-NMR: 3.26 (d, J=15 Hz, 1H, C_5-H_2), 3.42 (q, J=15, 15 Hz, 1H,C_5-H_2), 6.23 (s, 1H, C_2-H). ^{13}C-NMR: 35.64 (C_5-H_2), 45.94 (C_2-H_1), 171.20 (-N-C=O).

3-(5-Bromopyridin-2-yl)-2-(2-hydroxynaphthalene-1-yl)thiazolidin-4-one **(3b)** was prepared by reacting **(2b)** (0.01 mole, 3.27 g) and (0.01 mole, 0.92 gm, 0.69 mL) of thioglycolic acid. Yield =70 %, m.p. = 133-134 ºC. IR (KBr disk): 1674 cm^{-1} (–N–C=O). ^{1}H-NMR: 3.27 (d, J=15 Hz, 1H, C_5-H_2), 3.43 (q, J=18, 15 Hz, 1H,C_5-H_2), 6.23 (s, 1H, C_2-H). ^{13}C-NMR: 35.64 (C_5-H_2), 45.94 (C_2-H_1), 171.20 (-N-C=O).

3-(5-Chloropyridin-2-yl)-2-(2-hydroxynaphthalene-1-yl) thiazolidin-4-one **(3c)** was prepared by reacting **(2c)** (0.01 mole, 2.82 g) and (0.01 mole, 0.92 gm, 0.69 mL) of thioglycolic acid. Yield =69 %, m.p. = 136-137 ºC. IR (KBr disk): 1674 cm-1 (–N–C=O). ^{1}H-NMR: 3.27 (d, J=15 Hz, 1H, C_5-H_2), 3.43 (q, J=15, 15 Hz, 1H,C_5-H_2), 6.23 (s, 1H, C_2-H). ^{13}C-NMR: 38.29 (C_5-H_2), 48.58 (C_2-H_1), 173.86 (-N-C=O).

2-(2-Hydroxynaphthalene-1-yl)-3-(5-methylpyridine-2-yl) thiazolidine-4-one **(3d)** was prepared by reacting **(2d)** (0.01 mole, 2.62 g) and (0.01 mole, 0.92 gm, 0.67 mL) of thioglycolic acid. Yield =73 %, m.p. = 157-158 °C. IR (KBr disk): 1689 cm-1 (–N–C=O). ^{1}H-NMR: 3.18 (d, J=15 Hz, 1H, C_5-H_2), 3.43 (q, J=15, 15 Hz, 1H,C_5-H_2), 6.16 (s, 1H, C_2-H). ^{13}C-NMR: 35.86 (C_5-H_2), 45.95 (C_2-H_1), 171.39 (-N-C=O).

3-(2-Amino-5-(3,4,5-trimethoxybenzyl)pyrimidine-4-yl)-2-(2-hydroxynaphthalene-1-yl)thiazolidin-4-one **(3e)** was prepared by reacting **(2e)** (0.01 mole, 4.44 g) and (0.01 mole, 0.92 gm, 0.67 mL) of thioglycolic acid. Yield =71 %, m.p. = 146-147 °C. IR (KBr disk): 1666 cm-1 (–N–C=O). ^{1}H-NMR: 3.27 (s, 1H, C_5-H_2), 3.4 (q, J=15, 15 Hz, 1H,C_5-H_2), 6.21 (s, 1H, C_2-H). ^{13}C-NMR: 35.94 (C_5-H_2), 56.31 (C_2-H_1), 171.20 (-N-C=O).

Table (2) physical data of Thiazoleinone 3(a-e)

Thiazoleinone 3(a-e)	m.p °C	Yield %	Colour
3a	143-144	72	White
3b	133-134	70	White
3c	136-137	69	White
3d	157-158	73	White
3e	146-147	71	Yellow

RESULTS AND DISCUSSION

Thiazolidinones and their derivatives are an important group of heterocyclic compounds , which are having several biological activities in the areas of medicine and agriculture [20,21], are obtained from reaction

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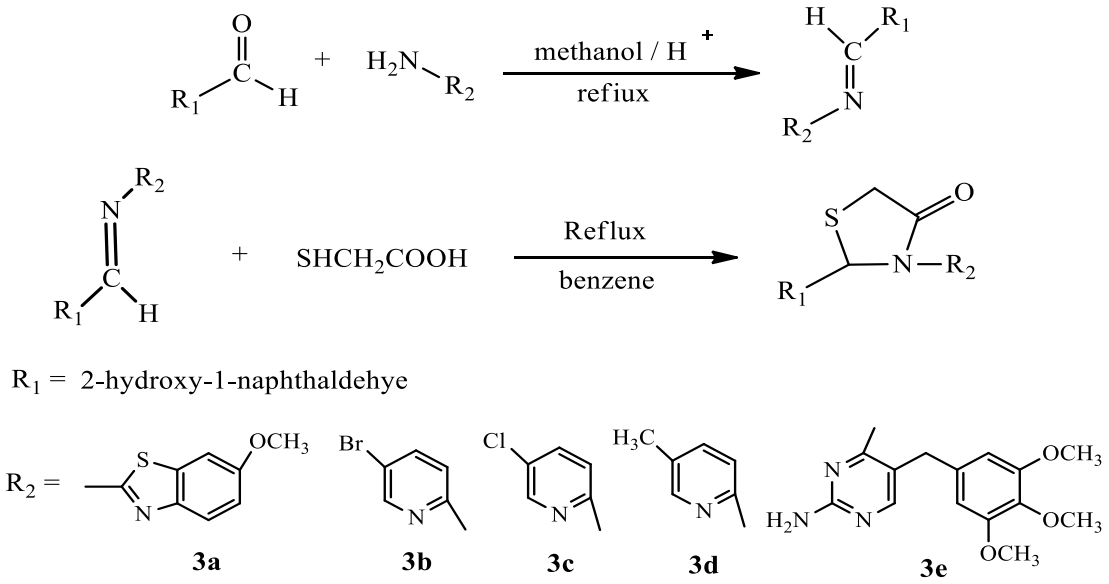
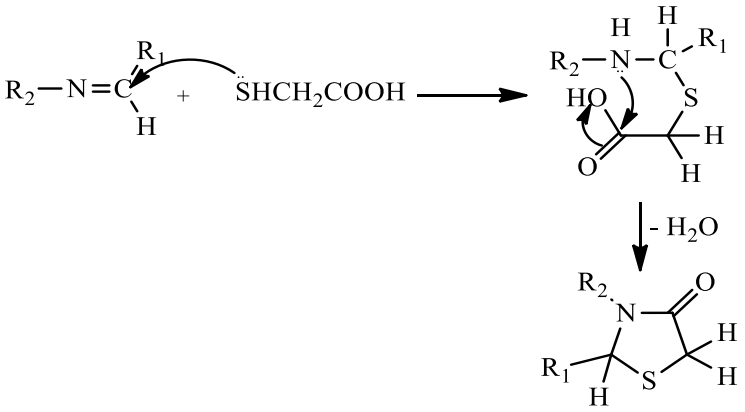
of imines with thioglycolic acid to give pure thiazolidinones as shown in these structure (figures 1-5). The key step in the synthesis of thiazolidinones 3(a-e) involved the treatment of imines 2(a-e) with thioglycolic acid in benzene to afford thiazolidinones 3(a-e), as shown in Schemes 1.



Scheme 1: Synthesis of thiazolidinones.

The general mechanism [22] of these reactions thiazolidinones are shown in (Scheme 2) involve, the cyclocondensation proceeds by the attack of the mercaptoacetic acid upon the C=N group. The mercaptoacetic acia adding to the carbon atom followed by the cyclisation.



Scheme 2: Mechanism of formation of thiazolidinones.

The IR spectra of imines **2(a-e)** as KBr disc shown absorption band at 1604-1620 cm^{-1} corresponding to the azomethine of imine compounds. The IR spectra of Thiazolidinones **3(a-e)** are characterized by the six bands corresponding to the stretching vibration of the aromatic C-H , aliphatic C-H , carbonyl amide group, aromatic C=C, C-N band , and bending vibration of S-C band , and substituted ring which occurs within the ranges 3147-3050, 2970-2880, 1689-1666, 1388-1342, 756-632, and 925-617 cm^{-1} respectively.

^{1}H-NMR spectral analysis

The ^{1}H-NMR spectral data of Thiazolidinones **3(a-e)** are included in **table (3)**. The ^{1}H-NMR spectra of **(3a)** shows a doublet signal at δ (3.26 ppm) with (J= 15 Hz) for one proton (d, 1H, C_5-H_2) of the thiazolidin-4-one ring. It also exhibited a quartet signal at δ (3.42 ppm) with (J=15, 15 Hz) for one proton (q,1H,C_5-H_2),.the thiazolidin-4-one ring shows a signal at δ (6.23 ppm) for one proton (s,1H,C_2-H).

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Table (3): Chemical shift data for ^{1}H-NMR of Thiazolidinone 3(a-e)

Thiazolidinone	C_5-H_2, J Hz C_5-H_2, J Hz	C_2-H J Hz	Ar-H
$C_{21}H_{16}N_2O_3S_2$ **3a**	3.26 (d) J= 15 Hz 3.42 (q) J= 15, 15 Hz	6.23 (s)	6.78 – 8.34 (m)
$C_{18}H_{13}BrN_2O_2S$ **3b**	3.27 (d) J= 15 Hz 3.43 (q) J= 18, 15 Hz	6.23 (s)	6.40 – 8.34 (m)
$C_{18}H_{13}ClN_2O_2S$ **3c**	3.27 (d) J= 15 Hz 3.43 (q) J= 15, 15 Hz	6.23 (s)	6.44 – 8.34 (m)
$C_{19}H_{16}N_2O_2S$ **3d**	3.18 (d) J= 15 Hz 3.34 (q) J= 15, 15 Hz	6.16 (s)	6.33 – 7.27 (m)
$C_{27}H_{26}N_4O_5S$ **3e**	3.27 (s) 3.4 (q) J= 15, 15 Hz	6.21 (s)	6.36 – 7.93 (m)

^{13}C-NMR spectral analysis

The ^{13}C-NMR spectral data of the Thiazolidinones **3(a-e)** are included in **table (4)**. The compound (3a) showed a signal at signal δ 35.64 ppm of one carbon (C_5-H_2) of thiazolidin-4-one ring, and showed signal at δ 45.94 ppm of one carbon (C_2-H). The ^{13}C-NMR spectra showed signals of aromatic carbons at δ 105.98-165-15 ppm. The signal for the (-N-C=O) carbon is exhibited at δ= 171.20.

Table (4): Chemical shift data for ^{13}C-NMR of Thiazolidinone 3(a-e)

Thiazolidinone	C_2 ring ppm	C_5 ring ppm	-N-C=O ppm	Ar-C
$C_{21}H_{16}N_2O_3S_2$ **3a**	45.94	35.64	171.20	105.98-154.72
$C_{18}H_{13}BrN_2O_2S$ **3b**	45.94	35.64	171.20	105.49-159.09
$C_{18}H_{13}ClN_2O_2S$ **3c**	48.58	38.29	173.86	112.37-161.58
$C_{19}H_{16}N_2O_2S$ **3d**	45.95	35.86	171.39	108.80-167.69
$C_{27}H_{26}N_4O_5S$ **3e**	56.31	35.94	171.20	106.59-163.01

Analysis of mass spectra

The Mass spectra of **(3a)** showed the important fragmentation peaks in 208 m/z (R 10%), 345 m/z (R 2%), 326 m/z (R 16%), 310 m/z (R 4%), 247 m/z (R 100%), 187 m/z (R 38%). The Mass spectra of **(3b)** showed the important fragmentation peaks in 283 m/z (R 35%), 327 m/z (R 1%), 187 m/z (R 7%), 131 m/z (R 36%), 129 m/z (R 100%). The Mass spectra of **(3c)** showed the important fragmentation peaks in 263 m/z (R 33%), 187 m/z (R 16%), 109 m/z (R 100%).

Gcosy spectral analysis

The Gcosy spectra of the 3-(5-Bromopyridin-2-yl)-2-(2hydroxy naphthalene-1-yl)thiazolidin-4-one (3b), don't show signals in aliphatic region indicating a absence of contiguous protons in this region, but the

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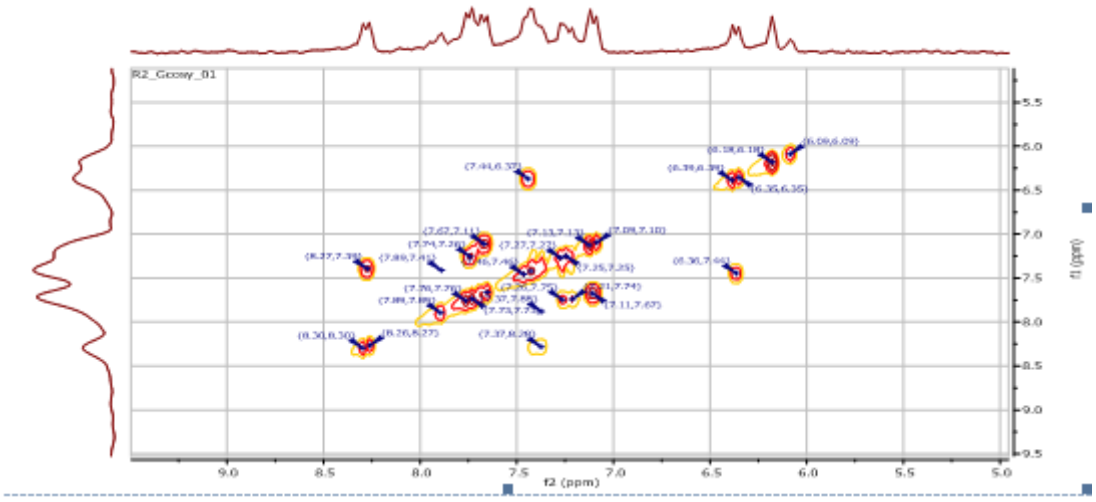
aromatic protons shown signals at δ (6.36 , 7.44), (7.11 , 7.67), (7.21 , 7.74), (7.26 , 7.75), (7.37 , 7.88) , (7.37 , 8.28), (7.44 , 6.37), (7.67 , 7.11), (7.74 , 7.26), (7.89 , 7.41), (8.27 , 7.39) ppm.



Anti-Hyperglycemic activity

Serum glucose concentration is changed as shown in table (3-5) during the experimental period. Thus, is a significant increase($P < 0.05$) in the serum concentration of glucose in group (3) compared with other group while groups (1 and 5) do not exhibit significant differences between them.

Treated group			Control positive	Control negatev	Groups / Average
DMSO	3b(100mg/kg)	3b(50mg/kg)			
101.017	110.600*	159.433*	203.383	99.9333	

LSD. (6.33), Significant = ($p<0.05$) *

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