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Synthesis, Characterization and Molecular Docking Simulation of Thioxothiazolidin-4-One Derivatives as Acetylcholinesterase Inhibitors

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ABSTRACT

Heterocyclic compounds play an important role in biological systems and present broadly in natural and synthesised compounds such as vitamins, drugs and hormones. A series of thioxothiazolidin-4-one derivatives (3a-d) were synthesised by reaction of 3-amino rhodanine with different benzaldehydes and the structures of these compounds were confirmed via different spectroscopic methods such as FT-IR, 1H-NMR, and 13C-NMR. The physical properties of the scaffolds like melting points and Rf values of pure compounds were determined as well. All derivatives were virtually screened by molecular docking study inside the active site of (AChE) enzyme. All derivatives were successfully synthesised with a high yield 84-90%. The docking result of compound 3c displayed the highest inhibitory activity against AChE, with docking score (-10.572 kcal/mol). The synthesized compounds showed significant activity as AChE inhibitors in comparison with standard drug Donepezil

Keywords: 2-Thioxothiazolidin-4-one; Rhodanine; Acetylcholinesterase; and Molecular docking.

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INTRODUCTION

Alzheimer's disease (AD) is an irreversible advanced brain disease that slowly damaged memory and it is one of the most public forms of dementia [1] which have the major effect on the person's talent to perform the daily activities [2]. According to the World Alzheimer report, this disease is one among the most significant social diseases and 17-25 million persons worldwide are predicted to fall targets of this disease in which its symptoms in most people appear after the age of sixty [3]. Regarding to 'cholinergic hypothesis', AD has been related to a shortage in the brain neurotransmitter, acetylcholine (Ach) [4]. Moreover, Acetylcholinesterase (AChE) catalyzes the hydrolysis of Ach in the healthy brain. Therefore, in order to sustain the level of acetylcholine (Ach) in brain and to protract its effect in exaggerated individuals, (AChEI) (acetylcholinesterase inhibitors) has been used as treatment of AD and these drugs inhibit the breakdown of acetylcholine [5]. Example of these drugs are: galantamine, rivastigmine, tacrine, and donepezil.

On the other hand, Schiff base compounds result from the condensation of aliphatic or aromatic aldehydes or ketones with primary amines; these compounds contain an azomethine group (-N=C) and their general formula is ($R\text{-}N{=}CR'R''$) [6,7,8]. Schiff bases have been reported to possess wide spectrum of biological activities [9,10]. Recently, there are limited studies for imine compounds as cholinesterase inhibitors [11].

Rhodanine (thioxothiazolidin-4-one) is a five-membered heterocyclic ring compound which has an interesting property due to its wide presence in many medicinal active natural or synthetic derivatives [12, 13]. thioxothiazolidin-4-one has a wide range of pharmaceutical activities, like analgesic, anticonvulsant [14], anti-inflammatory [15] antimalarial, antiviral, antibacterial, anticancer, and antidiabetic properties, as well as inhibitor of HCV NS3 protease and β-Lactamase [16-19].

Since thioxothiazolidin-4-one has this wide range of biological activities and great applications in medicine, the aim of this work is synthesis of Schiff base derivatives of rhodanine and study the binding interactions of these compounds in to the active site of the AChE by using molecular docking simulation.

MATERIALS AND METHODS

Materials

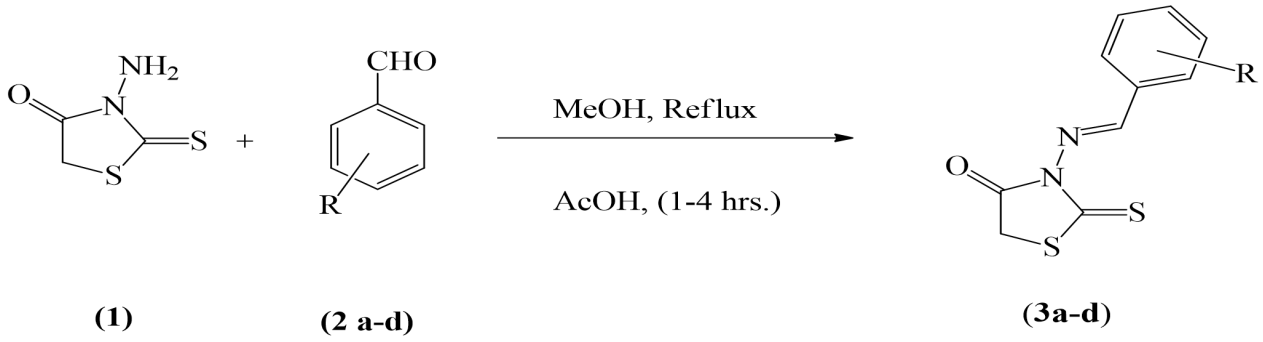
All chemicals used on this study were of an analytical grade and directly used without further purification, otherwise stated. 3-Aminorhodanine, 3-ethoxy-4-hydroxybenzaldehyde, 4-(dimethylamino)benzaldehyde, 3-benzyloxy-4-methoxybenzaldehyde and *n*-hexane were ordered from Sigma-Aldrich, whereas 3,5-dimethoxy-4-hydroxybenzaldehyde and silica gel aluminium 60 F254 plates were obtained from Merck, Germany. Furthermore, Glacial acetic acid, methanol and ethyl acetate were purchased from BDH limited, England.

Instrumentation

Melting points for all derivatives were measured using digital Stuart scientific SMP30 melting point apparatus, UK. Furthermore, the ^{1}H-NMR (500 MHz) and the ^{13}C NMR (125 MHz) spectra for all scaffolds were analyse using Varian NMR 500MHz, USA, while the Fourier Transform Infrared (FTIR) analysis was performed using FTIR-800 (SHIMADZU, Japan). Moreover, GC-MS analysis performed by Agilent GC-MS, USA.

Synthesis and Characterization

Four 2-thioxothiazolidin-4-one derivatives (**3a-d**) were synthesized according to the following protocols as shown in **scheme 1**.



(1) **(2 a-d)** **(3a-d)**

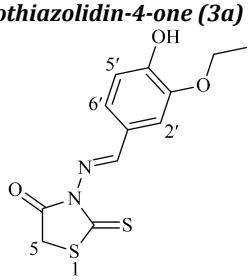
R:(**a**):3-OCH_2CH_3,4-OH; (**b**):4-$N(CH_3)_2$; (**c**):3-$OCH_2C_6H_5$,4-OCH_3; (**d**):3,5-OCH_3,4-OH.

Scheme 1: General scheme for synthesis of thioxothiazolidin-4-one derivatives (**3a-d**).

GENERAL CLASSICAL HEATING METHOD

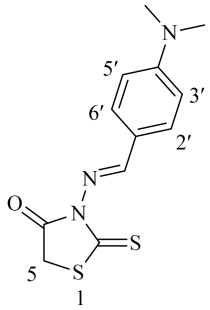
The conventional reflux method was performed according to Prabhu *et al.* 2015 with slight modifications [20]. In a 50-mL round bottom flask, each aldehyde (1.2 mmol) derivative was dissolved in methanol (1mL) and then added dropwise to 3-aminorhodanine (1 mmol, 0.14 g) which was dissolved in hot methanol (15 mL), followed by two drops of glacial acetic acid. The prepared mixture was heated to reflux with stirring at 95°C for 1-4 hrs. over an oil bath. The reaction progress was monitored by TLC every thirty minutes to check the reaction development. Then, it was cooled down to room temperature after its completion as evidenced by TLC. The target compounds obtained after drying and washing the crude product with suitable solvents to produce the precipitate of 84-90% yield.

Synthesis of (E)-3-((3-ethoxy-4-hydroxybenzylidene) amino)-2-thioxothiazolidin-4-one (3a)



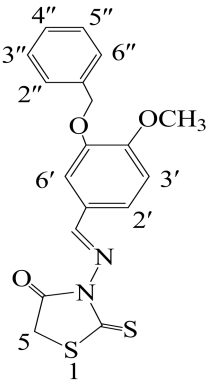
This compound was obtained as yellow powder; yield 84%; m.p.160-162; R_f: 0.40 in hexane :ethyl acetate (1:2) solvent system; FT-IR (KBr,cm^{-1}): 3527 (=**C-H** sp^2) , 3399 (**O-H** stretching), 2976 (-**C-H** sp^3 stretching), 1724 (**C=O** stretching), 1533 (**C=N** stretching), 1280 (**C-O** stretching), 1165 (**S=C** stretching). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 1.36 (t, 3H, C**H**$_3$), 4.08 (s, 2H, C**H**$_2$), 4.14 (s, 1H, OC**H**$_2$), 6.82 (d, 1H, **H-5'**), 7.15 (d, 2H, **H-6'**), 7.28 (s, 1H, **H-2'**), 8.63 (s, 1H, -N=C**H**), 9.67 (br. s, 1H, O**H**). ^{13}C NMR (125 MHz, *DMSO-d_6*) δ ppm 14.7 (**C**H$_3$), 35.3 (**C**H$_2$), 64.0 (O**C**H$_2$), 111.1 (**C-2'**), 115.7 (**C-5'**), 122.5 (**C-6'**), 134.7 (**C-1'**), 147.2 (**C-3'**), 152.1 (**C-4'**), 163.0 (-N=**C**H), 169.0 (**C**=O), 171.1 (**C**=S).

Synthesis of (E)-3-((4-(dimethylamino)benzylidene)amino)-2-thioxothiazolidin-4-one (3b)



This compound was obtained as red powder; yield 90%; m.p.270-272; R_f: 0.40 in hexane: ethyl acetate (1:1) solvent system; FTIR (KBr, cm^{-1}): 3473 (=**C-H** sp^2 stretching), 2904 (-**C-H** sp^3), 1689 (**C=O** stretching), 1579 (**C=N** stretching), 1373 (**C-O** stretching), 1167 (**C=S** stretching). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 3.04 (s, 6H, 2×C**H**$_3$), 3.65 (s, 2H, C**H**$_2$), 6.78 (d, 2H, **H-3'**, **5'**), 7.49 (d, 2H, **H-2', 6'**), 8.50 (s, 1H, -N=C**H**). ^{13}C NMR (125 MHz, *DMSO-d_6*) δ ppm 34.5 (2×**C**H$_3$), 52.2 (**C**H$_2$), 111.4 (**C-3'**), 111.7 (**C-5'**), 129.0 (**C-1'**), 130.6 (**C-2'**), 130.7 (**C-6'**), 130.8 (**C-4'**), 133.3 (-N=**C**H), 169.9 (**C**=O), 170.5 (**C**=S).

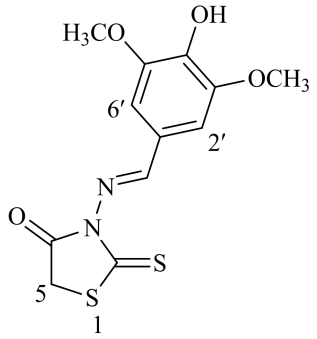
Synthesis of new (E)-3-((3-(benzyloxy)-4-methoxybenzylidene) amino)-2-thioxothiazolidin-4-one (3c)



This compound was obtained as yellow powder; yield 85%; m.p.140-142; R_f: 0.30 in hexane: ethyl acetate (1:1) solvent system; FTIR (KBr, cm^{-1}): 3437 (=**C-H** sp^2 stretching), 2926 (-**C-H** sp^3 stretching), 1739 (**C=O** stretching), 1597 (**C=N** stretching), 1280 (**C-O** stretching), 1139 (**C=S** stretching). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 3.6 (s, 3H, OC**H**$_3$), 4.16 (s, 2H, C**H**$_2$), 4.34 (s, 1H, OC**H**$_2$), 7.10 (d, 1H, **H-3'**), 7.20 (d, 2H, **H-2"**, **6"**), 7.30 (dd, 1H, **H-2'**), 7.40 (t, 34.6, 3H, **H-3"**, **4"**, **5"**), 7.50 (d, 1H, **H-6'**), 8.54 (s, 1H, -N=C**H**). ^{13}C NMR (125 MHz, *DMSO-d_6*) δ ppm 34.6 (**C**H$_2$), 55.8 (O**C**H$_3$), 69.9 (O**C**H$_2$), 111.2 (**C-5'**),

111.8 (**C-2'**), 124.9 (**C-6'**), 127.9 (**C-2"**, **6"**), 128.0 (**C-3",5"**), 128.4 (**C-1"**), 128.5 (**C-4"**), 136.6 (**C-1'**), 148.1 (**C-3'**), 153.4 (**C-4'**), 169.7 (**C**=O), 170.4 (**C**=S), 196.7 (-N=**C**H).

(E)-3-((4-hydroxy-3,5-dimethoxybenzylidene) amino)-2-thioxothiazolidin-4-one (3d)



This compound was obtained as yellow powder; yield 87%; m.p.195-197; R_f: 0.25 in hexane: ethyl acetate (1:1) solvent system; FTIR (KBr,cm^{-1}): 3394 (=**C-H** sp^2 stretching), 3309 (**O-H** stretching), 2941 (-**C-H** sp^3 stretching), 1722 (**C=O** stretching), 1581 (**C=N** stretching), 1336 (**C-O** stretching), 1162 (**C=S** stretching). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 3.84 (s, 6H, 2×OC**H**$_3$), 3.9 (s, 2H, C**H**$_2$), 7.3 (s, 2H, **H-2', 6'**), 8.6 (s, 1H, -N=C**H**), 9.6 (br. s, 1H, O**H**). ^{13}C NMR (125 MHz, *DMSO-d_6*) δ ppm 55.9 (**C**H$_2$), 56.1 (2×O**C**H$_3$), 108.8 (**C-2', 6'**), 123.3 (**C-1'**), 139.6 (**C-4'**), 148.3 (**C-3'**, **5'**), 169.0 (-N=**C**H), 186.2 (**C**=O), 187.0 (**C**=S).

Computational Method

All rhodanine derivatives structures drawn by ChemDraw 18.0 software. The geometry optimization calculations were performed by energy force field method using Hyperchem software 8.0 and the results were separately saved as .mol computer files format supported by semi-empirical mechanics optimization. The lowest geometrical conformation of all 2-thioxothiazolidin-4-one derivatives were kept as .sdf computer files format.

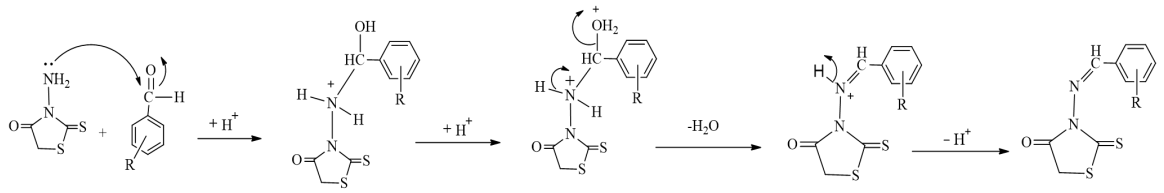
After that, the docking study was performed for binding evaluation by Glide tool used under SchrÖdinger Maestro 11.1 software. Furthermore, the crystal structures acetylcholinesterase (AChE) was obtained from Protein Data Bank under codes (PDB ID: 1EVE) with anti-Alzheimer's drug donepezil. Ligands of 2-thioxothiazolidin-4-one derivatives preparation processes were performed using LigPrep tool under the same package. Before docking processes, the receptor cite preparation of enzyme was performed using ProPrep tool using same software package for structure cleaning with optimization and energy minimization. Then, the filling of all missing loops was applied with preparation at target receptor quality.

The docking grid box was adjusted to 1.3 Å with an atomic charge of 0.30 and the obtained original ligands were docked back for validation process by applying flexibly XP calculation method (Glide-extra precision) for all ligands, while the enzyme active site receptor pocket was set aside rigid during all docking procedure. Finally, all obtained data was verified and sorted as .xlsx file format for future use.

RESULTS AND DISCUSSION

A series of four derivatives of thioxothiazolidin-4-one compounds (**3a-d**) were synthesized by reaction of 3-aminorhodanine with different benzaldehyde derivatives in presence glacial acetic acid as a catalyst and methanol as a solvent as shown in **Scheme1**. The purity of all the synthesized compounds was confirmed by TLC and R_f values were calculated for all derivatives, while their identifications were performed via study the physical properties (melting point) as well as spectroscopic data (FTIR, ^{1}H-NMR and ^{13}C-NMR).

The plausible mechanism of Schiff bases (**3a-d**) preparation involved nucleophilic addition of 3-aminorhodanine to carbonyl group as shown in **Scheme 2**:



(**3a-d**)

Scheme 2: Synthesis mechanism of Schiff bases **(3a-d)**

The physical analysis of the synthesized compounds are listed in **Table 1**. From the results, it is evident that all compounds melt within a 1-2 °C range which assures the compounds purity.

Table 1: Physical analysis of Schiff bases **(3a-d).**

Compounds	Molecular formula	Molecular Weight	Melting point °C
3a	$C_{12}H_{12}N_2O_3S_2$	296.37	160-162
3b	$C_{12}H_{13}N_3OS_2$	279.38	270-272
3c	$C_{18}H_{16}N_2O_3S_2$	372.46	140-142
3d	$C_{12}H_{12}N_2O_4S_2$	312.36	195-197

The ^{1}H-NMR spectrum of all Schiff base compounds displayed the most important singlets at the range of 3.65-4.16 ppm for C**H**$_2$ protons and 8.50-8.63 ppm for azomethine group (-N=C**H**$_2$) as shown in **Table 2** and his confirms the formation of the imine compounds (**3a-d**).

Table 2: Important protons in ^{1}H-NMR spectra of 2-thioxothazolidine -4-one derivatives **(3a-d)**.

Compound	^{1}H-NMR chemical shifts(δ, ppm)	
	C**H**$_2$ (s)	-N=C**H** (s)
3a	4.08	8.63
3b	3.65	8.50
3c	4.16	8.54
3d	3.90	8.60

The ^{1}H NMR spectrum of new compound **3c** is an example of these derivatives whereby this compound displayed the most important two sharp singlets at δ = 4.16 and 8.54 ppm which were belong to the C**H**$_2$ protons and the -N=C**H** proton, respectively. As displayed in **Fig 1**, this spectrum demonstrated another distinctive signals such as doublets at 7.10, 7.20, and 7.50 ppm for **H-3'**, **H-2"**, **6"**, and **H-6'**, respectively. Moreover, doublet of doublet resonances at 7.30 ppm is for **H-2'** and triplet signal at 7.40 is for **H-3"**, **4"**, and **5"**, respectively.

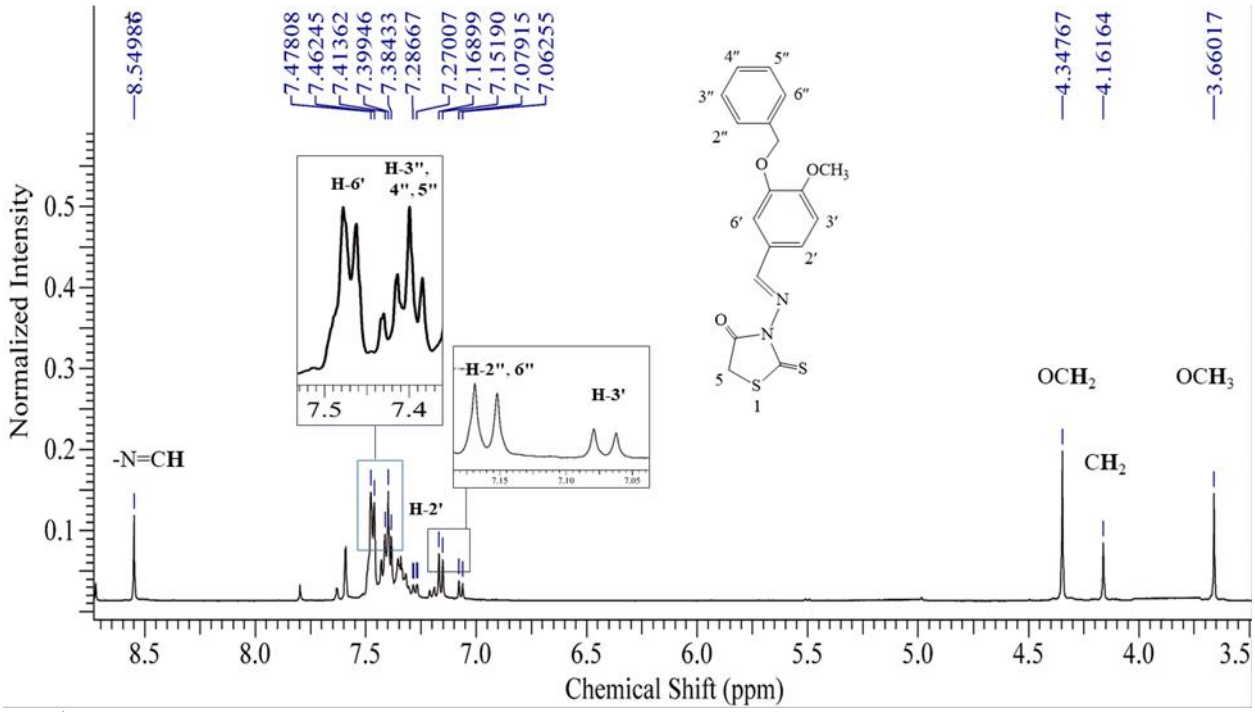


Figure 1: ^{1}H- NMR of (E)-3-((3-(benzyloxy)-4-methoxybenzylidene)amino)-2-thioxothiazolidin-4-one (**3c**)

The ^{13}CNMR spectra for the same derivatives showed the most significant peaks in the range of 34.6-55.9 ppm for **C**H$_2$ carbon and 133.3-196.7 ppm for –NH=**C**H carbon which affirm the structures of Schiff bases (**3a-d**) as shown in **Table 3**. For instance, new scaffold **3c** showed different signals at different chemical shifts as shown in **Fig 2**.

Table 3: Important proton in ^{13}C-NMR spectra of 2-thioxothazolidine -4-one derivatives **(3a-d)**

Compound	^{13}C-NMR chemical shifts (δ, ppm)	
	C**H**$_2$	-N=**C**H
3a	35.3	163.0
3b	52.2	133.3
3c	34.6	196.7
3d	55.9	169.0

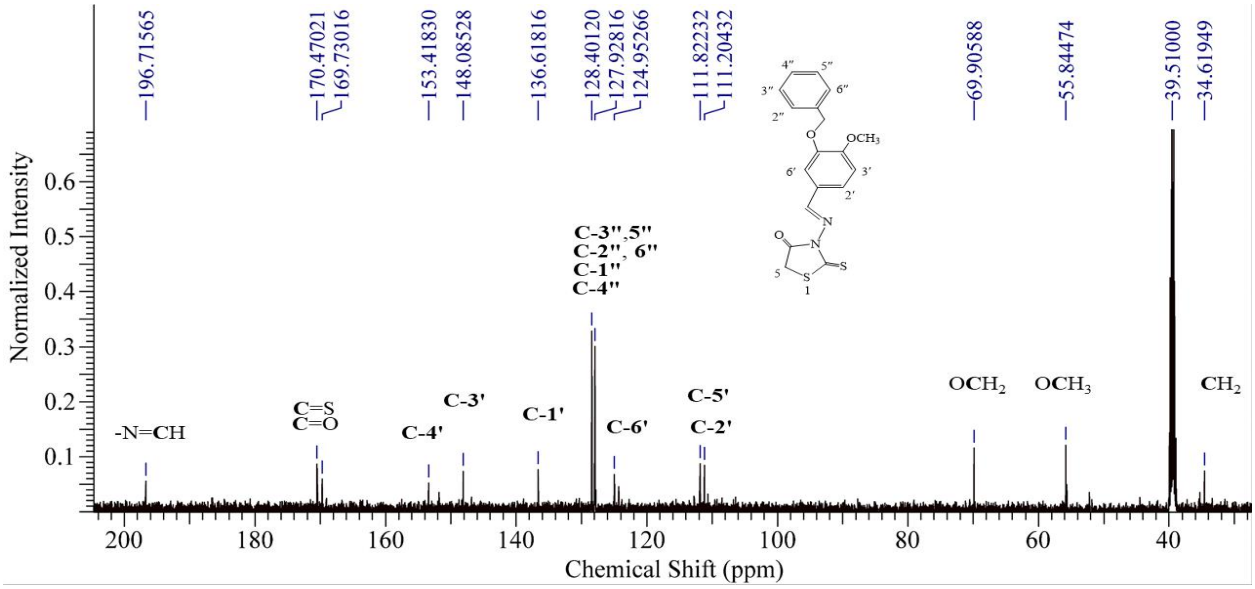


Figure 2: ^{13}C NMR of (E)-3-((3-(benzyloxy)-4-methoxybenzylidene) amino)-2-thioxothiazolidin-4-one (**3c**).

The studied thioxothiazolidin-4-one compounds were analyzed using Fourier Transform Infrared spectroscopy (FTIR) to identify what functional groups present in each particular derivative. FTIR spectra for all aromatic

thioxothiazolidin-4-one family exhibited the most important absorption bands around 1533-1597 cm^{-1} which belong to C=N stretching vibrations. These bands proved that the NH_2 group of the parent primary amine was disappeared and replaced by C=N group of Schiff bases.

Besides, FTIR spectra also showed distinctive peaks around 3394-3527, 2904-2976, 1689-1739, 1533-1597, 1280-1373, and 1139-1167 cm^{-1} regions, corresponded to **=C-H** sp^2, **-C-H** sp^3, **C=O**, **C=N**, **C-O**, and **C=S** stretching, respectively. All of these distinguished bands are displayed in **Table 4**. In addition, **Fig. 3** displays the FTIR spectrum for **3c** derivative.

Table 4: Infrared frequencies of the major functional groups **(3a-d)**

Compound	Important FTIR frequencies Frequency/wavelength (υmax in cm^{-1})					
	=C-H sp^2	**-C-H sp^3**	**C=O**	**C=N**	**C-O**	**C=S**
3a	3527	2976	1724	1533	1280	1165
3b	3473	2904	1689	1579	1373	1167
3c	3437	2926	1739	1597	1280	1139
3d	3394	2941	1722	1581	1336	1162

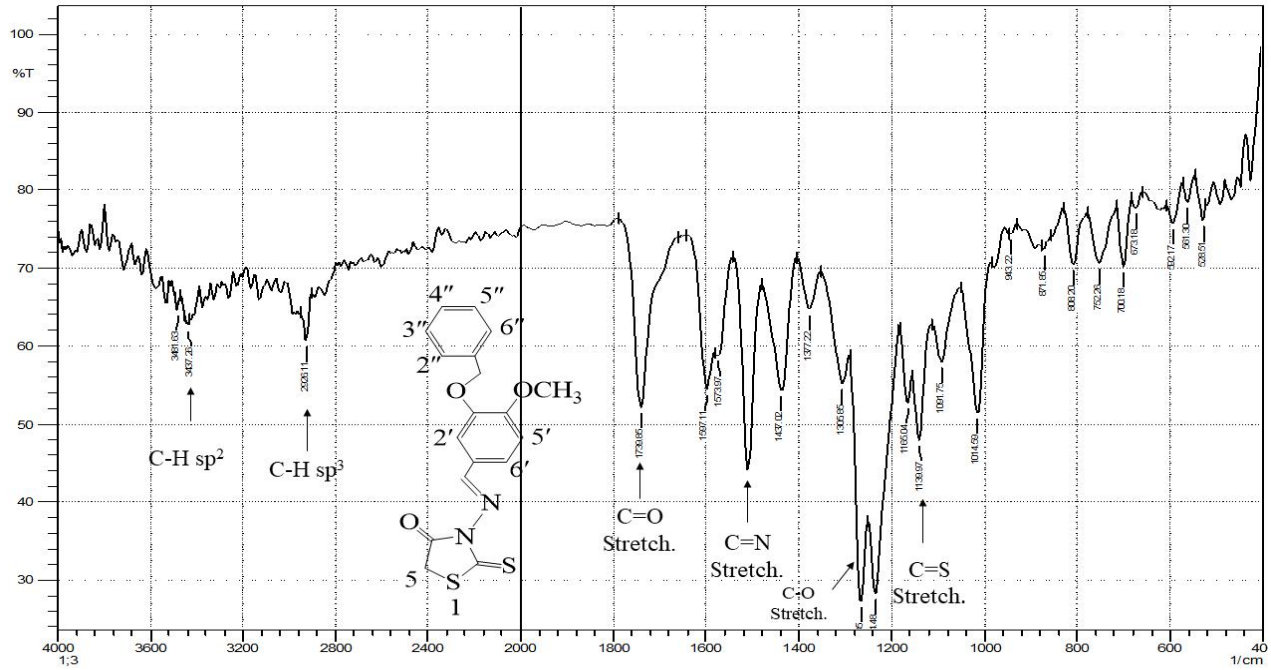


Figure 3: FTIR of (E)-3-((3-(benzyloxy)-4-methoxybenzylidene) amino)-2-thioxothiazolidin-4-one (**3c**).

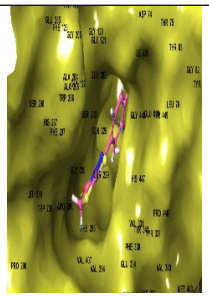
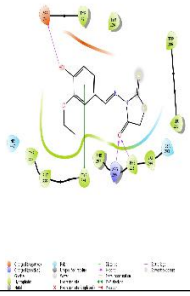
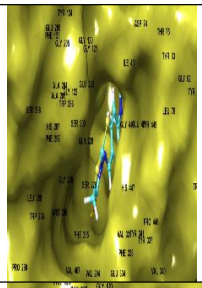
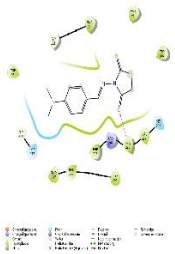
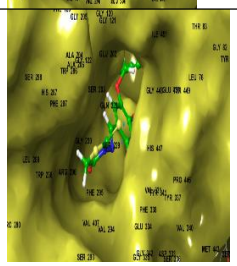
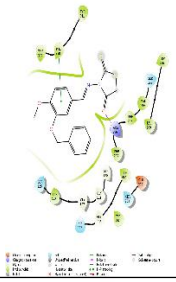
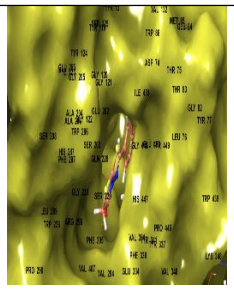
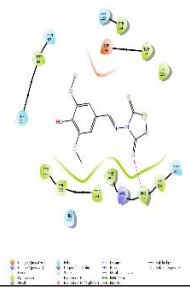
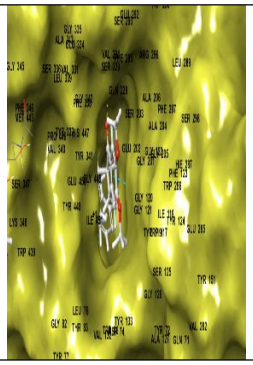
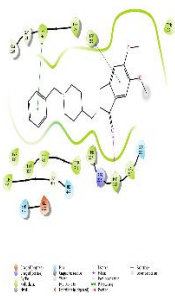
Thioxothiazolidin-4-one compounds which displayed better or comparable AChE inhibitory activities to that of the standard drug, Donepezil, were docked into the active site of AChE receptors. The orientation and binding interaction prototype to the main amino acid residues composing active site of AChE were investigated.

The main active site residues as well as orientation of each active inhibitor inside the AChE active site gorge were displayed and their binding interactions were briefly described in the following sections to disclose the inhibitor-enzyme interaction mechanism.

New compound **3c** showed better AChE inhibitory activities to that of the standard drug, Donepezil because of H-bond with ARG296 and Pi-Pi stacking with PHE338 as well as hydrophobic interactions which discloses that this compound can be accommodated efficiently inside the active site gorge and strongly attached with the receptor (AChE) enzyme, and the docking score of this compound (-10.572 kcal/mol) and compound **3a** was displayed good activity because three of (H-bond) with ASP74, ARG296 and PHE294 as well as Pi-Pi stacking with TYR341 with the docking score (-8.821 kcal/mol) as shown in **Table 5.**

Table 5: 2D & 3D interaction inside active site **(3a-3d)**

Comp. No.	Docking Score)kcal/mol)	3D Interaction	2D Interaction	Surrounding Amino Acids &Interactions

3a	-8.821			TRP286,TYR124,TYR72,ASP74,HIS447,TYR337,PHE338,TYR341,PHE297,ARG296,PHE295,VAL294,SER293,LEU289 and 3(H-bond)with ASP74,ARG296&PHE294 as well as Pi-Pi stacking with TYR341
3b	-8.694			TRP286,TYR72,TYR124,GLY121,TRP86,GLY448,HIS447,PHE297,ARG296,PHE295,VAl294, SER293and H-bonds with PHE295
3c	-10.572			TYR341,PHE338,TYR337,SER125, TYR124,GLY120,PHE297,ARG296, PHE295,VAL294,SER293& H-bond with ARG296 as well as Pi-Pi stacking PHE338
3d	-8.282			TRP286,TYR72,ASP74,ASN87,TRP86,THR83,TYR337,PHE338,TYR341,PHE297,ARG296,PHE295,VAL294,SER293 and H-bond with PHE295
Donepezil	-7.832			TYR72,TRP286,TYR124,TRP86,GLY121,GLY120,TYR133,TYR337,PHE338,TYR341,PHE297,ARG296,PHE295,VAL294,SER293 and H-bond with PHE295 as well as two Pi-Pi stacking with TRP286 and TRP86

CONCLUSION

Four rhodamine Schiff base scaffolds were successfully synthesised by single step with high yield 84-90% and were characterized by spectroscopic methods. All derivatives were docked into the active site of AChE enzyme and disclosed their binding model to cholinesterase enzyme; the synthesized compounds showed significant activity as AChE inhibitors in comparison with standard drug Donepezil

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