Journal of Materials Science and Engineering A 2 (2) (2012) 220-231

Discovery of Potent of New 4-oxothiazolidin-2-ylidene Derivatives Containing Piperidinyl Moiety against Aldose Reductase

Awatef A. Farag[1], Ali.Khalil[2], Shaban Ibrahim Mohamed[3], Ahmed A. El-Henaway[4], Gameel Ahamed Mohamed El-Hag Ali[4] and Yuosry Ahmed Ammar[5]

1. Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City(Girls) Cairo, Egypt

2. Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt

3. Technology Engineering Institute, Tamoh,Giza , Egypt

4. Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo(boys) Egypt

5. Chemistry Department, Faculty of Science, King Khaled University, Saudi Arabia, Abha

Received: September 06, 2011 / Accepted: November 01, 2011 / Published: February 10, 2012.

Abstract: 2-(2-Oxo-2-(piperidin-1-yl)ethylidene)thiazolidin-4-one **(1)** was used as a key intermediate for the synthesis of many thiazolo[3,2-a] pyridine derivatives. Thus, 4-thiazolidinine **(1)** was refluxed with aromatic aldehydes where the corresponding 4-thiazolidinone derivatives **(2a,b)** were afforded. Cyclization of **(2a,b**) with malononitrile and aldehydes gave the corresponding thiazolo[3,2-a] pyridines **(5a,b)**. Thiazolo[3,2-a] naphthyridine derivatives **(6a,b)** were obtained from the reaction of compounds **(5a,b)** with formic acid. Acylation of **(5a,b)** with acetic anhydride or benzoyl chloride for 2 h produced the corresponding amide derivatives **(7,8)**. While, upon treatment of **(5b)** with acetic anhydride for 5 h furnished tricyclic structure **(9)**. Furthermore, compounds **(5a,b)** were refluxed with either chloroacetonitrile to give thiazolo[3,2-a] pyrrolo [2,3-c] pyridines **(10a,b)** or with malononitrile to afford the corresponding thiazolo[3,2-a] naphthyridine derivatives **(14a,b)**. In addition, the corresponding thiourea and Pyrazolo [3,4:4',5] thiazolo derivatives **(15)** and **(16)** were produced via the reaction of **5** ethyl with ethylisothiocyanate and phenyl hydrazine. Molecular docking simulations into the active site of ALR2 were performed, and showed that, some of the synthesized compounds more suitable inhibitor against ALR2 with farther modification in future.

Key words: 4-Thiazolidinones, thiazolo[3,2-a]pyridines, pyrrolo [2,3-c] pyridines,thiazolonaphthyridines and docking.

1. Introduction

Diabetes mellitus (DM) is a common chronic, more than 220 million people worldwide suffer from DM, this figure is expected to increase by 2030 to 400 million cases [1, 2]. Diabetic complications (retinopathy, neuropathy, nephropathy or cataract) are serious and disabling pathologies associated with DM [3]. Hyperglycemia is a typical condition of DM and plays a crucial role in the development and advancement of these complications, which arise from acute, and are thus largely responsible for the morbidity and mortality observed in these patients [1, 4-6].

Increasing flux of glucose through the polyol pathway, that occurs under hyperglycemic conditions in tissues possessing insulin-independent glucose transport is a well examined factor involved in the appearance and progression of such chronic complications [3, 6-13]. Aldose reductase (EC 1.1. 1.21, ALR2) is the first enzyme of the polyol pathway, which responsible for reduction of glucose to sorbitol [14]. Glucose metabolism, specifically via ALR2 and the polyol pathway, is often linked to the development of chronic complications of diabetes mellitus. Therefore, ALR2 has been considered an attractive target enzyme, to develop drugs to control or prevent

Corresponding author: Gameel Ahmed Mohamed Mohamed, professor, research field: heterocyclic chemistry. E-mail: Elhag1970@yahoo.com.

the progression of chronic diabetic complications, but remain many problems with toxicity and lack of targeted specificity towards the enzyme [11, 13-16].

In fact, many thiazolidinediones derivatives have been marketed for the treatment of non-insulin-dependent diabetes mellitus (NIDDM or type 2 diabetes) [17-20]. In view of the above mentioned findings and in continuation of our previous work on the synthesis of 4-thiazolidinine derivatives [21-29], we disclose a new synthetic protocol for the synthesis of thiazolo[3,2-a] pyridine and thiazolo [3,2-a]-1,8- naphthyridines derivatives having piperidinyl moiety with expected ALR2 inhibitor activity. Furthermore, induced-fit docking (IFD) studies were performed in order to gain new insight concerning the possible binding modes of our compounds, which should also be useful to guide the future synthesis of improved compounds.

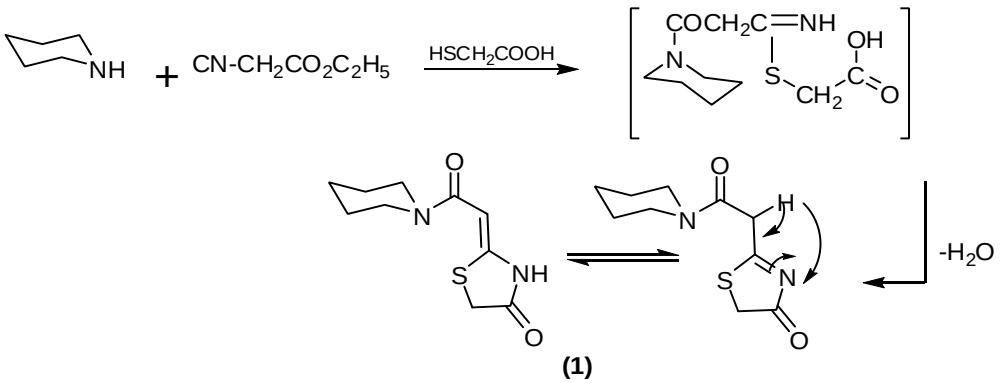
2. Results and Discussion

2.1 Chemistry

The starting 2 2-(2-oxo-2-(piperidin-1-yl) ethylidene) thiazolidin-4-one (1) was easily prepared in one pot reaction from the corresponding ethyl cyanoacetate , thioglycollic acid, and piperidine according to the previously reported procedure [30].

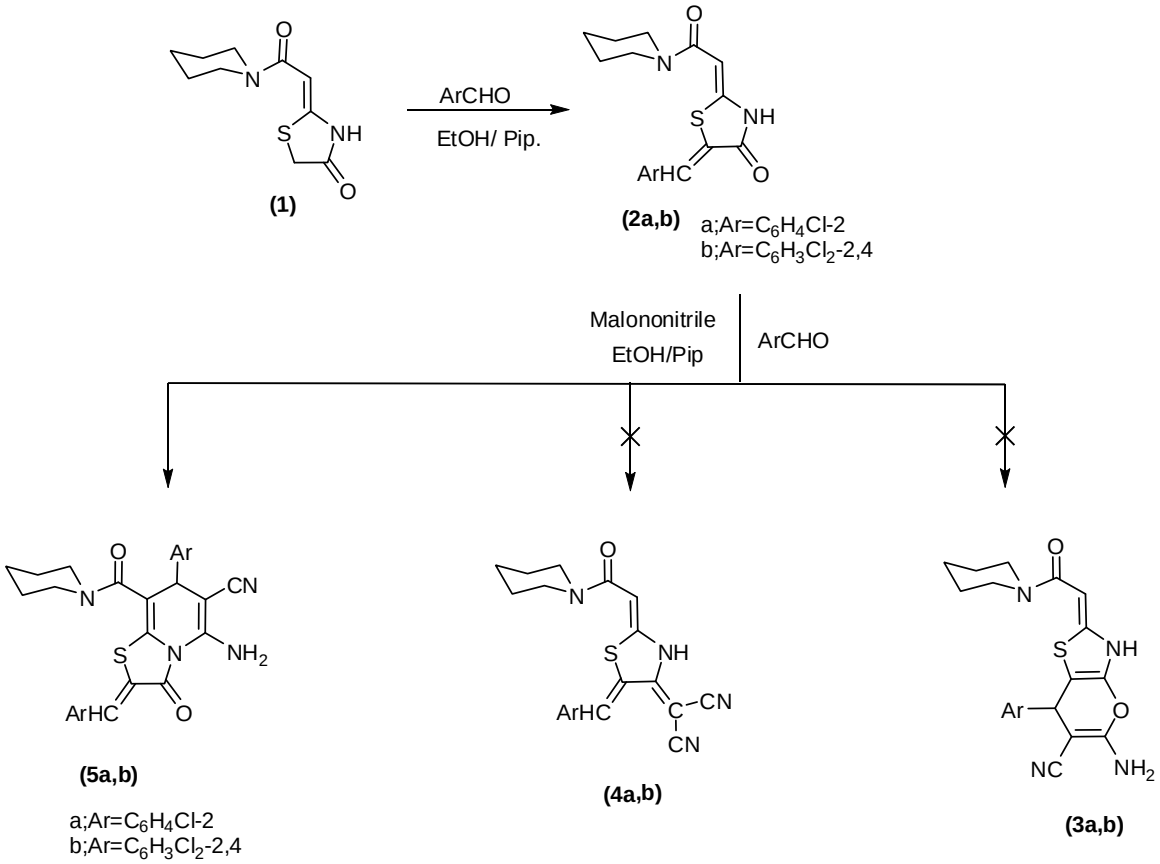
2-Aryl methylidine-4-thiazolidinone derivatives **(2a,b)** were synthesized from the reaction of 4-thiazolidinone **(1)** with different aromatic aldehydes in ethanolic solution catalyzed with piperidine. The elemental and spectral data were in compete agreement with 4-thiazolidinone structure **(2a,b)**, the IR spectrum of compound **(2a)** exhibited intensive absorption bands for (NH, and C=O thiazolidinone and amide functional groups) at 3,158, 1,708 and 1,628 cm^{-1}, respectively. Moreover, ^{1}HNMR spectrum of **(2b)** revealed a characteristic signal corresponding to methine-H at δ 6.15 ppm, mass spectrum of **(2b)** assigned a molecular ion peak at m/z (382; 5.51%), Scheme 2. Thiazolidinones were used for the synthesis of thiazolo[3,2-a]pyridine derivatives. Thus, reaction of **(2a,b)** with malononitrile and aldehydes in ethanolic piperidine solution led to the formation of thiazolo[3,2-a]pyridines **(5a,b)**, while, structures **(3)** and **(4)** were excluded on the basis of correct elemental analysis and spectral data, (Scheme 2).The structure of **(5)** was identified with spectral data, where ^{1}HNMR spectrum of **(5b)** revealed a singlet signal to a characteristic signal at δ 5.07 ppm, corresponding to pyridine-H, other significant signals were observed at δ 0.97, 3.97 ppm for piperidinyl protons.

The reactivity of thiazolo [3,2-a] pyridines **(5a,b)** towards some electrophiles like carboxylic acids and their derivatives was investigated. Thus, treatment of thiazolo[3,2-a] pyridnies **(5a,b)** with formic acid under reflux conditions resulted in the formation of thiazolo[3,2-a]-3-aza-1,8-naphthyridines **(6a,b)** as a single product. The structure of compounds **(6a,b)** was confirmed by the correct elemental analysis and spectral data. IR spectra of **(6a,b)** showed disappearance of absorption band in the region 2,000-2,200 cm^{-1} for C≡N group. ^{1}HNMR spectrum of



(1)

Scheme 1 Synthesis of 4- thiazolidinone derivatives.



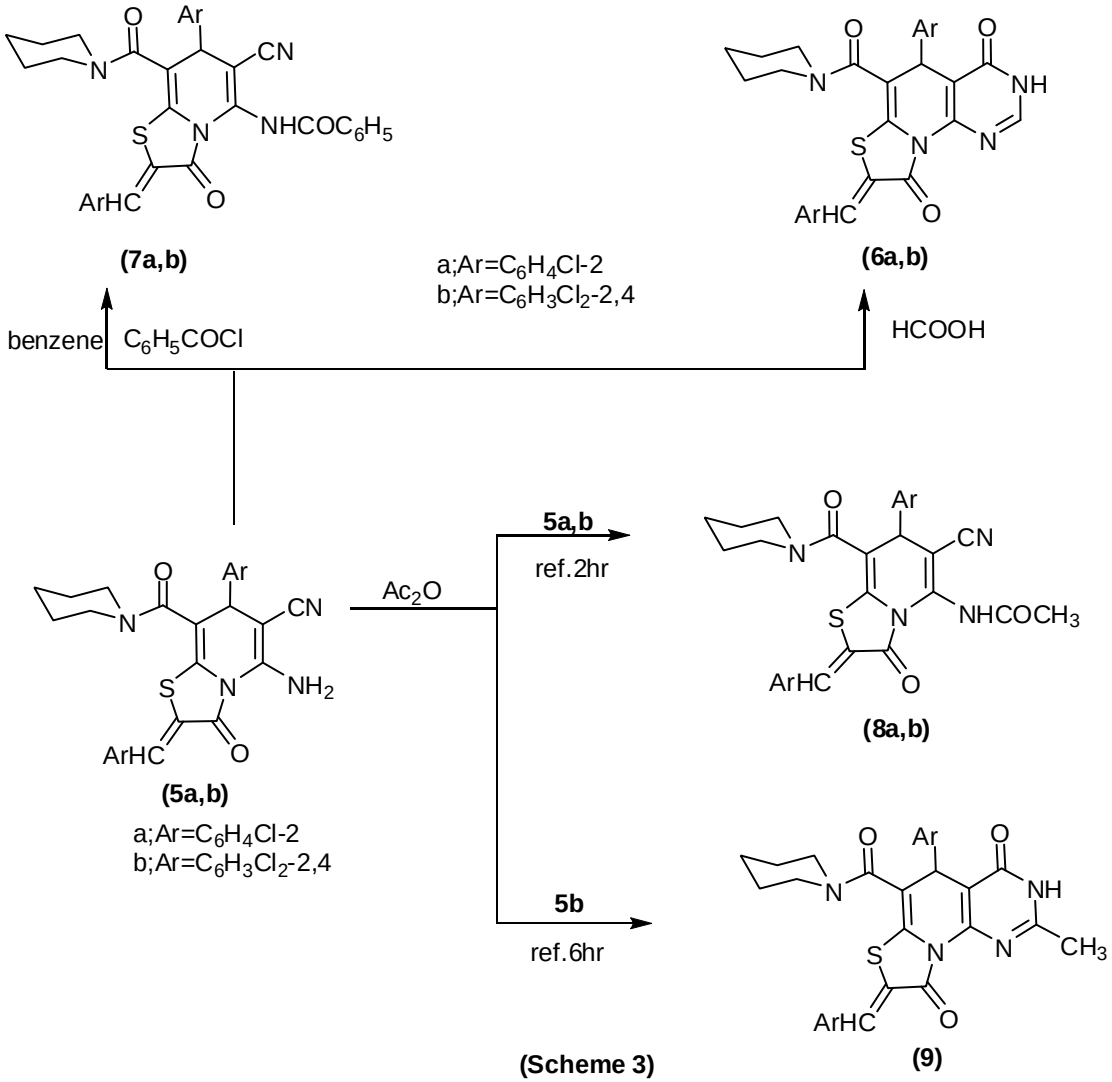
Scheme 2

Scheme 2 Synthesis of thiazolo[3,2-a] pyridine derivatives.

(6b) showed signals at δ 1.17, 3.61, and 6.14 ppm due to piperidinyl and pyrimidine protons , respectively, in addition to aromatic protons in the region δ 7.52-7.74 ppm (Scheme 3).

In addition, acylation of **(5a,b)** with benzoyl chloride and acetic anhydride for two hr yielded the corresponding amide derivatives **(7a,b)** and **(8a,b)**. On the other hand upon heating compound **(5b)** with acetic anhydride for 6 h caused cyclization to furnish the corresponding thiazolo[3,2-a]-3-aza-1,8-naphthyridine **(9)**. Elemental analyses and spectral data were in complete agreement with the assigned structures. IR Spectrum of **(8a)** as example revealed presence of absorption band at 2190 due to C≡N group, where as IR Spectrum of **(9)** showed the complete disappearance of nitrile absorption band. The mass spectrum of **(7a)** revealed a molecular ion peak at m/z (640;5.02%) and a base peak at m/z 74. ^{1}HNMR spectrum of **(8a)** showed signals at δ 0.96, 3.99, 2.25 and 5.06 ppm due to piperidinyl, methyl and pyridine-H , respectively.

Our investigation was extended to study the reactivity of thiazolo[3,2-a] pyridines **(5a,b)** towards some activated nitrile derivatives. Thus, treatment of **(5a,b)** with chloroacetonitrile in ethanolic solution containing few drops of triethylamine under reflux conditions gave a single product for which two structures **(10a,b)** and **(11a,b)** are possible. Structure **(11)** was discarded based on spectral data. However, elemental analysis and spectral data were in complete accordance with pyrrolo [2,3-c] thiazolo [3,2-a] pyridines structure **(10a,b)**. The IR spectra of **(10a,b)** revealed absorption bands for cyano and amino groups at 2,196, 2,190, 3,392, 3,318, and 3,396, 3,296 cm^{-1}. ^{1}HNMR spectrum in (DMSO-d6) of **(10a)** displayed

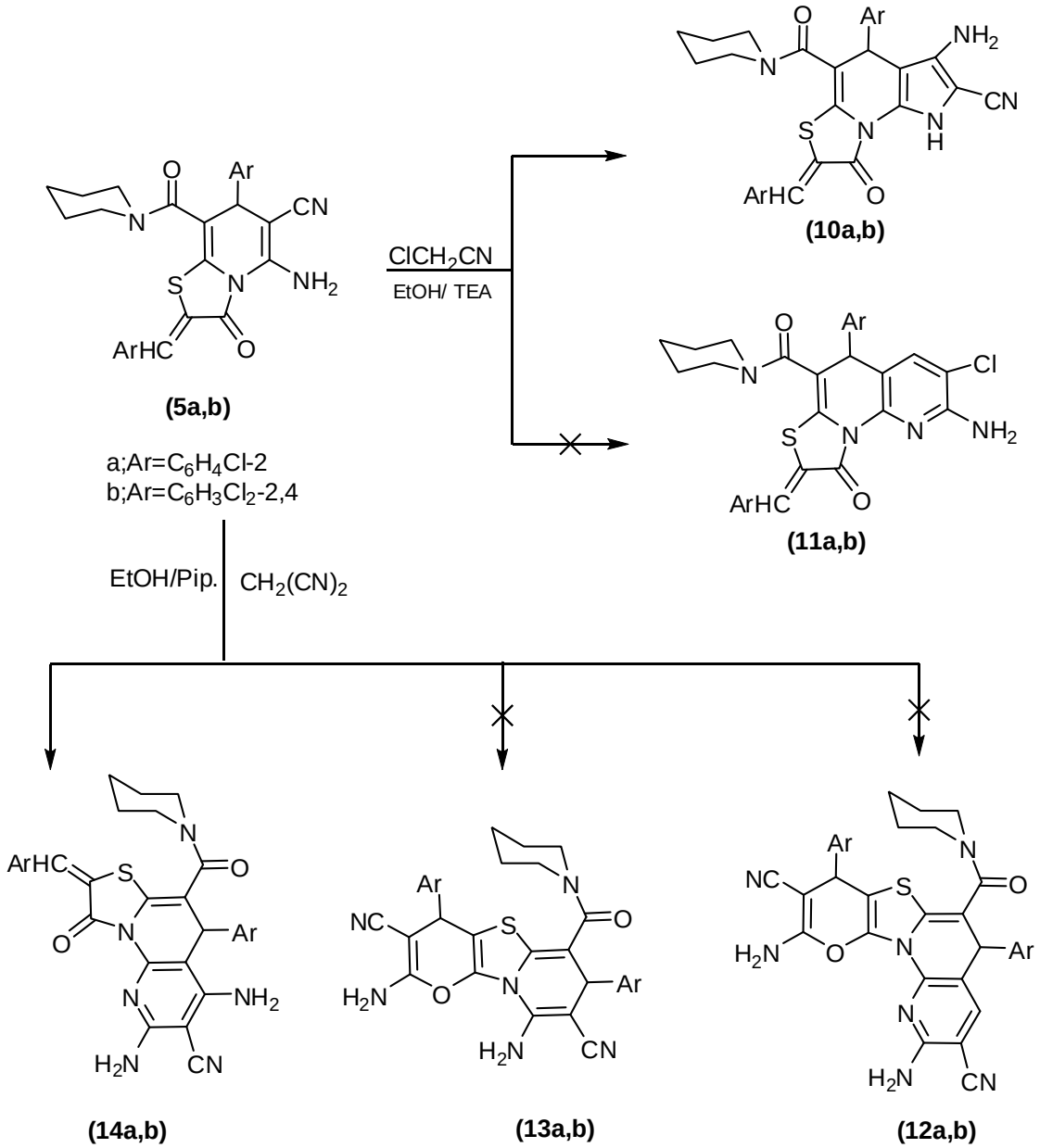


Scheme 3 Synthesis of thiazolo[3,2-a]1,8-naphthyridines.

signals at δ 0.91, 3.94, and 5.07 ppm for piperidinyl, pyridine-H protons. The reaction can be proceeding through nucleophilic substitution to the chlorine atom followed by addition of the metylene to the cyano group. Furthermore thiazolo[3,2-a] 1,8-naphthyridine enaminonitriles **(14a,b)** were produced via the reaction of thiazolo [3,2-a] pyridines **(5a,b)** with malononitrile in ethanolic piperidine solution. Elemental analysis and spectral data were in complete agreement with thiazolo[3,2a]-1,8-naphthyridines while, the other possible structures **(12a,b)** and **(13a,b)** were excluded. ^{1}HNMR spectra in (DMSO-d6) of **(14a,b)** displayed a significant signals at δ 5.07, and 4.15 ppm for pyridine-H protons, respectively (Scheme 4).

Finally, thiazolo [3,2-a] pyridines **(15a,b)** and **(16)** were obtained via the reaction of (**5a** or **5b)** with ethyl isothiocynate and phenyl hydrazine, respectively (Scheme 5). The IR spectrum of compounds **(15a,b)** showed absorption bands at 2,196 and 2,190 cm^{-1} due to cyano, and carbonyl functional group,. ^{1}H NMR spectrum in (DMSO-*d*6) of **(15a)** displayed signals at δ 5.07, 1.44, and 4.01 ppm for pyridine and ethyl protons.

The IR spectrum of compound **(16)** showed disappearance of absorption band at 1,704 cm^{-1} due to thiazolidinone functional group. Its, ^{1}HNMR spectrum



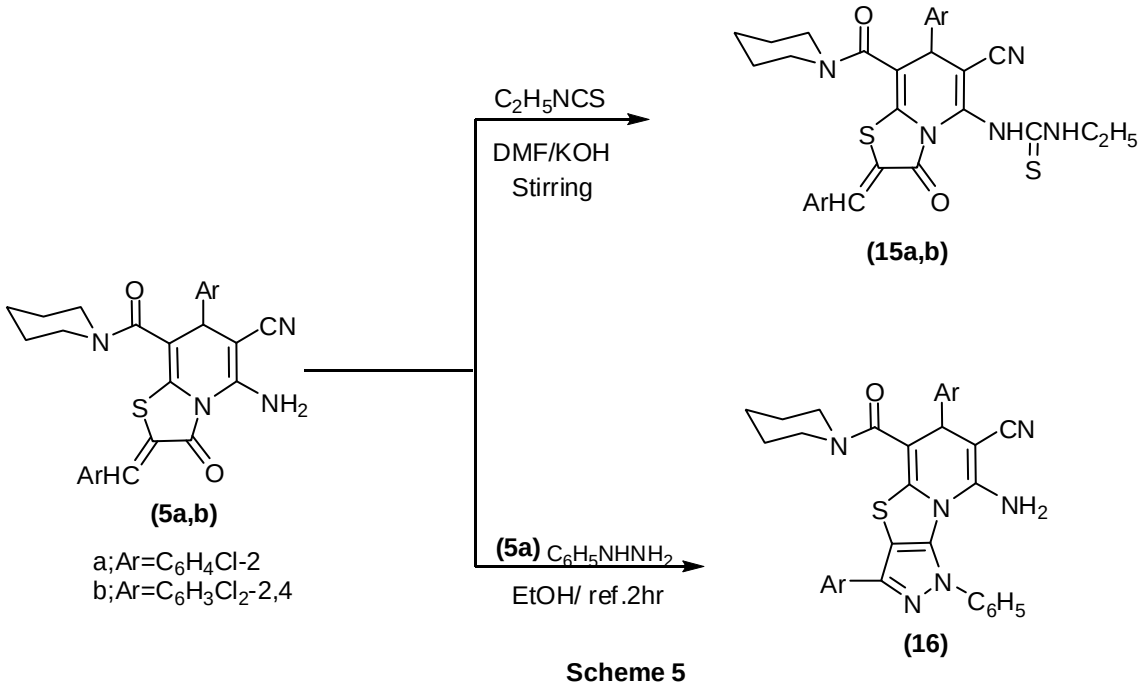
Scheme 4

Scheme 4 synthesis of thiazolo[3,2-a] 1,8-naphthyridines.

in (DMSO-*d*6) displayed signals at δ 4.27, 1.29, and 3.68 ppm due to pyridine and piperidinyl protons.

2.2 ***Molecular Modeling Studies***

Molecular structures: At last few years, various X-ray crystal structures of ALR2 have been recognized in the PDB database [31]. From the analysis of the ALR2 active site experimental data showed that, binding site of the ALR2 can be divided into two sub-pockets, (1) catalytic pocket (also called the recognition region), (2) specificity pocket. The catalytic pocket is rather stable in all the various reported crystal structures. In contrast, the specificity pocket can adopt different conformations, adapting itself to the size of the bound ligands via movement of the loop region between Cys298 and Cys303 and the



Scheme 5

Scheme 5 Synthesis of thiazolo[3,2-a] pyridines and Pyrazolo [3,4:4',5] thiazolo derivatives.

different rotameric states of the surrounding amino acid side chains, especially of Leu300, which acting as a gate-keeper between the open and closed states. Until recently, only three different conformations of the specificity pocket were known, which called by Zentgraf et al. [32]. The binding pocket conformations were exemplified by the PDB structures (1PWM), which used in this study. In order to understand the binding mode of protein-ligand interactions, docking study was carried out using SYBYL version 7.3. Tripos Inc [33]. The crystal structure of the human ALR2 enzyme (1PWM) complexed with (ligand Fidarestat, Fig.1, sorbinil conformation) as an inhibitor, was downloaded from a protein data bank PDB [34]. The Mol Dock scoring function was applied to evaluate the binding affinities between the (1PWM) and selected synthesized inhibitors. (FID) was re-docked into the active site of the enzyme, and then replaced it with the tested compounds in order to compare the binding mode of ligand, and the tested compounds.

From Figs. 1 and 2 and Table 1, the following results can be drawn: FID (original ligand) reveals MVD score (-116.6 Kcal/J) and forms 4 hydrogen bonds with: Leu-300, Trp-111, His-110 and Tyr 48 respectively (Fig. 1). Compound **(2a)** gives moderately binding affinity with MVD score (-227.0 Kcal/J) and forms 4 bonds with the active binding site: three important hydrogen bonds(one hydrogen bond with His-110 and two hydrogen bonds (Tyr-48), and one bond with Cys-298 (Fig. 2).

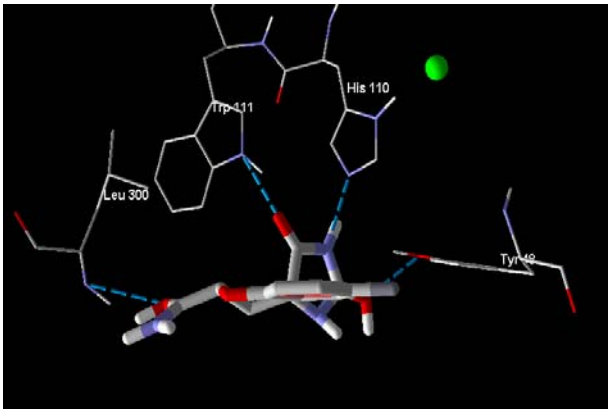
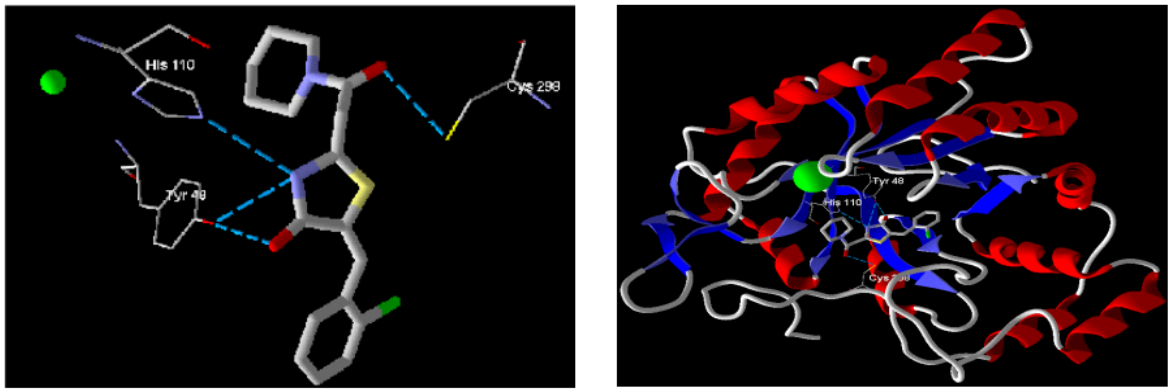


Fig. 1 Interaction between ligand (FID) and binding site of ALR2 (1PWM, PDB code), which blue dot lines represented hydrogen bonding interaction of ligand (Fid) with binding site. Ligand (Fid) are represented in stick mode, which atoms are colored in dark grey, oxygen in red, nitrogen in blue and sulfur in yellow. Hydrogen atoms of the amino acid residues and ligand were removed to improve clarity.



A B

Fig. 2 A) Interaction between ligand (2a) and binding site of ALR2 (1PWM, PDB code), which blue dot lines represented hydrogen bonding interaction of ligand (2a) with binding site. B) A plot of docked ligand (2a) in active site where the backbone of protein is shown in flat ribbon. Ligand (2a) are represented in stick mode, which atoms are colored in dark grey, oxygen in red, nitrogen in blue and sulfur in yellow. Hydrogen atoms of the amino acid residues and ligand was removed to improve clarity.

Table 1 Different scores derived from the MVD docking tools.

NO.	MolDock score	Rerank score	Interaction-E	H-Bond -E	LE1 -E	LE2 -E	Docking score
FID	-116.682	-96.5913	-121.92	-10	-5.834	-4.829	-115.281
2a	-227.071	-144.098	-229.329	-14.397	-4.730	-3.002	-235.532
6a	-101.363	-88.0007	-104.444	-8.25567	-6.757	-5.866	-101.42
15a	-130.758	-101.324	-133.644	0	-5.685	-4.405	-129.31
16a	-161.2	-114.846	-172.797	0	-4.477	-3.190	-158.878

MVD Score(KJ/mol): Energy score used during docking; Re-rank Score(Kj/mol): The re-ranking score; H. Bond Enrgy(Kj/mol): Hydrogen bonding energy between protein and ligand; Interaction affinity (Kj /mol): The total interaction energy between the pose and the protein; LE1(Kj/mol): MolDock Score divided by Heavy Atoms count; LE2 (Kcal/mol): Rerank Score divided by Heavy Atoms count; Docking Score: Evaluated before post-processing.

3. Conclusions

In the present work aimed to the development of novel antidiabetes molecules containing piperidinylthiazolidinediones pharmacophore. Systematic structure based virtual screening of the synthesized compound library, identified synthesized compounds as putative ALR2 binders. The results point the 5-(2-chlorobenzylidene)- 2-(2-oxo -2-(piperidin-1-yl) ethylidene) thiazolidin-4-one considers suitable inhibitor against ALR2 with farther modification in the future.

4. Experiment

4.1. Instrumentation and Materials

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^{1}HNMR spectra were recorded on a Varian Gemini spectrometer (δ; ppm) 200 MHz using TMS as internal standard. Mass spectra were recorded on a Jeol-JMS-600 mass spectrometer. Micro analytical data were obtained from the Micro analytical Research Centre, Faculty of Science, Cairo University.

4.2 Synthesis

5-(2-chlorobenzylidene)-2-(2-oxo-2-(piperidin-1-yl) ethylidene)thiazolidin-4-one ***(2a,b)***.

To a solution of (1) (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL) either o-chlorobenzaldeyde or 2,4-dichloro -benzaldehyde (0.01 mol) was added. The reaction

mixture was heated under reflux for 3 h. The solid product formed was collected by filtration and recrystallized from ethanol.

2a: yellow crystals, yield 72%, m.p. 205-07 ºC. IR (KBr, cm^{-1}): 3,158 (NH), 1,708 and 1,628 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 0.93 (s, 6H, $3CH_2$-mor), 3.95 (t, 4H, $2CH_2$-mor), 6.72 (s,1H, methine-H), 7.33-7.76 (m, 5H, Ar-H and NH, exchangeable with D_2O). MS m/z (%): 348 (M^+, 5.08). Anal. Calcd for $C_{17}H_{17}ClN_2O_2S$ (348): C: 58.62, H: 4.88, N: 8.04. Found: C: 58.23, H: 5.10, N: 8.21.

2b: orange crystals, yield 82%, m.p. 210-12 ºC. IR (KBr, cm^{-1}): 3,160 (NH), 1,708 and 1,608 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 6H, $3CH_2$-mor), 3.91 (s, 4H, $2CH_2$-mor), 6.15 (s, 1H, methine-H), 7.33-7.76 (m, 4H, Ar-H+ NH, exchangeable with D_2O) . MS m/z (%): 382 (M^+, 5.51). Anal. Calcd for $C_{17}H_{16}Cl_2N_2O_2S$ (382): C: 53.40, H: 4.18, N: 7.32. Found: C: 52.63, H: 3.92, N: 7.45.

*2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-amino-6-cyano-7-aryl-8-piperidinyl carbaldehydo thiazolo [3,2 -a] pyridine**(5a,b)***

Malononitrile (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL) was added to either **(2a)** or **(2b)** (0.01mol). The reaction mixture was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized from ethanol to give **(5a,b)**

5a: yellow crystals, yield 78%, m.p. 249-51 ºC. IR (KBr, cm^{-1}): 3,396, 3,328 (NH_2), 2,198 (C≡N), 1696, and 1646 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 0.94 (m, 6H, $3CH_2$-Pip.), 3.95 (t, 4H, $2CH_2$-Pip.), 5.09 (s, 1H, Pyridine-H), 7.26-7.88 (m, 11H, Ar-H, methine-H and NH_2; exchangeable with D_2O). Anal. Calcd for $C_{27}H_{22}Cl_2N_4O_2S$ (536): C: 60.44, H: 4.10, N: 10.44. Found: C: 60.51, H: 3.85, N: 10.01.

5b: yellow crystals, yield 70%, m.p. 255-57 ºC. IR (KBr, cm^{-1}): 3,396, 3,298 (NH_2), 2,192 (C≡N), 1,718, and 1,642 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 0.97 (m, 6H, $3CH_2$-Pip.), 3.97 (t, 4H, $2CH_2$-Pip.), 5.07(s, 1H, Pyridine-H), 7.52-7.86 (m, 9H, Ar-H, methine-H and NH_2; exchangeable with D_2O). Anal. Calcd for $C_{27}H_{20}Cl_4N_4O_2S$ (604): C: 53.64, H: 3.31, N: 9.27. Found: C: 53.21, H: 3.85, N: 9.61.

*2,3,9-Trihydro-2-arylmethylidine-3,8-dioxo--6-cyano-9-aryl-10-piperid-inyl carbaldehyd thiazolo [3 2-a] -3-aza-1,8-naphthyridines **(6a,b)***

To a solution of either **(5a)** or **(5b)** (0.01 mol) formic acid (20 mL) was added. The reaction mixture was heated under reflux for 5 h. The solid product formed was collected by filtration and recrystallized from ethanol to give **(6a,b)**

6a: yellow crystals, yield 65%, m.p. 143-45 ºC. IR (KBr, cm^{-1}): 3112(NH), 1,706 and 1,620(C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 0.94 (m, 6H, $3CH_2$-Pip.), 3.95 (t, 4H, $2CH_2$-Pip.), 5.09 (s, 1H, Pyridine-H), 6.14 (s, 1H, pyrimidine-H), 7.26-7.88 (m, 10H, Ar-H, methine-H and NH; exchangeable with D_2O). Anal. Calcd for $C_{28}H_{22}Cl_2N_4O_3S$ (564): C: 59.57, H: 3.90, N: 9.92. Found: C: 60.23, H: 3.95, N: 10.03.

6b: yellow crystals, yield 69%, m.p. 218-20 ºC. IR (KBr, cm^{-1}): 3,084 (NH), 1,706 and 1,622(C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 1.17 (m, 6H, $3CH_2$-Pip.), 3.61 (t, 4H, $2CH_2$-Pip.), 5.01(s, 1H, Pyridine-H), 6.14 (s, 1H, Pyrimidine-H), 7.52 -7.74 (m, 8H, Ar-H, methine-H and NH; Cancelled with D_2O). Anal. Calcd for $C_{28}H_{20}Cl_4N_4O_3S$ (632): C: 53.16, H: 3.16, N: 8.86. Found: C: 53.51, H: 3.42, N: 9.01.

*2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-bezoylamino-6-cyano-7-aryl-8-piperidinyl carbaldehydo thiazolo[3,2-a] pyridine **(7a,b)***

To a solution of either **(5a)** or **(5b)** (0.01 mol) in (20 mL) benzene, bezoyl chloride (0.01 mol) was added. The reaction mixture was heated under reflux for 5h. The solid product formed was collected by filtration and recrystallized from ethanol to give **(7a,b)**

7a: yellow crystals, yield 63%, m.p. 280-82 ºC. IR (KBr, cm^{-1}) 3,226 (NH), 2,198 (C≡N), 1706 and 1,644 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 0.92 (m, 6H, $3CH_2$-Pip.), 3.94 (t, 4H, $2CH_2$-Pip.), 5.06(s, 1H, Pyridine-H), 7.25-7.67(m, 14H, Ar-H and

methine-H), 7.84(s, 1H, NH; exchangeable with D_2O) MS m/z (%): 640 (M^+, 0.98). Anal. Calcd for $C_{34}H_{26}Cl_2N_4O_3S$ (640): C: 63.75, H: 4.06, N: 8.75. Found: C: 63.21, H: 3.95, N: 8.10.

7b: yellow crystals, yield 63%, m.p. 233-35 ºC. IR (KBr, cm^{-1}): 3,396 NH, 2,190 (C≡N), 1,706 and 1,636 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO -d_6) δ 0.95 (m,6H, $3CH_2$-Pip.), 3.91 (t, 4H, $2CH_2$-Pip.), 5.06 (s, 1H, Pyridine-H), 7.33-7.81 (m, 13H, Ar-H ,methine-H and NH; exchangeable with D_2O), Anal. Calcd for $C_{34}H_{24}Cl_4N_4O_3S$ (708): C: 57.62, H: 3.38, N: 7.90. Found: C: 57.12, H: 3.21, N: 8.10.

*2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-acetylamino-6-cyano-7-aryl-8-piperid-inyl carbaldehydo thiazolo[3,2-a]pyridine**(8a,b)**; 2,3,9-Trihydro-2- arylmethylidine-3,8-dioxo-6-methyl-9-aryl-10-piperidinylcarbaldehydo thiazolo [3 ,2-a] -3-aza-1,8 –naphthyridine **(9)***

A solution of either **(5a)** or **(5b)** (0.01 mol) in acetic anhydride (20 mL) was heated under reflux conditions. The solid product formed was collected by filtration and recrystallized from ethanol to give **(8a,b)** and **(9)**

8a: yellow crystals, yield 63%, m.p. 205-07 ºC. IR (KBr, cm^{-1}): 3,148 (NH), 2,222 (C≡N), 1,726 and 1,644 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 0.96 (m, 6H, $3CH_2$-Pip.), 2.25 (s,3H,CH_3) 3.99 (t, 4H, $2CH_2$-Pip.), 5.06 (s, 1H, Pyrid-ine-H), 7.33-7.69 (m,9H, Ar-H, and methine-H), 7.83 (s, 1H,NH; exchangeable with D_2O) MS m/z (%): 520 (M^+= M-$NHCOCH_3$; 0.192). Anal. Calcd for $C_{29}H_{24}Cl_2N_4O_3S$ (578): C: 60.20, H: 4.15, N: 9.68. Found: C: 60.51, H: 3.95, N: 9.31.

8b: yellow crystals, yield 63 %, m.p. 230-32 ºC. IR (KBr, cm^{-1}): 3,392 (NH), 2,198 (C≡N), 1,712 and 1,632 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 1.46 (m, 6H, $3CH_2$-Pip.), 2.46 (s, 3H, CH_3) 3.46 (t, 4H, $2CH_2$-Pip.), 5.07 (s, 1H, Pyridine-H), 7.35-7.76 (m, 8H, Ar-H, methane and NH; exchangeable with D_2O). Anal. Calcd for $C_{29}H_{22}Cl_4N_4O_3S$ (646): C: 53.86, H: 3.40, N: 8.66. Found: C: 54.01, H: 3.95, N: 8.41.

9: brown crystals, yield 59%, m.p. 177-79 ºC. IR (KBr, cm^{-1}): 3,210(NH), 1,712 and 1,622(C=O thiazolidinone and amide). ^{1}HNMR (DMSO -d_6) δ 0.92 (m, 6H, $3CH_2$-Pip.), 2.23 (s, 3H, CH_3) 3.94 (t, 4H, $2CH_2$-Pip.), 5.06(s, 1H, Pyridine-H), 7.34-8.11 (m, 7H, Ar-H,and methine-H), 8.37 (s, 1H, NH; exchangeable with D_2O). Anal. Calcd for $C_{29}H_{22}Cl_4N_4O_3S$ (646): C: (646): C: 53.86, H: 3.40, N: 8.66. Found: C: 54.03, H: 3.95, N: 8.31.

*2,3,8-Trihydro-2-arylmethylidine-3-oxo--6-cyano-7-amino-8-aryl-9-piperidinyl carbaldehydo thiazolo [2 ,3-a] pyrollo[2,3-c]pyridines**(10a,b)***

To a solution of either **(5a)** or **(5b)** (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.05 mL) chloroacetonitrile (0.01 mol) was added. The reaction mixture was heated under reflux conditions. The solid product formed was collected by filtration and recrystallized from ethanol to give **(10a,b)**

10a: yellow crystals, yield 60%, m.p. 275-77 ºC. IR (KBr, cm^{-1}): 3,392, 3,318 (NH_2), 2,196 (C≡N), 1,694 and 1,646 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO -d_6) δ 0.91 (m, 6H, $3CH_2$-Pip.), 3.94 (t, 4H, $2CH_2$-Pip.), 5.07(s, 1H, Pyridine-H), 7.25-7.84 (m,11H, Ar-H, methine-H andNH_2; exchangeable with D_2O).Anal. Calcd for $C_{29}H_{23}Cl_2N_5O_2S$ (575): C: 60.52, H: 4.00, N: 12.17. Found: C: 60.22, H: 3.92, N: 12.23.

10b: yellow crystals, yield 60%, m.p. 278-80 ºC. IR (KBr, cm^{-1}): 3396, 3296 (NH_2), 2,190 (C≡N), 1,696 and 1,640 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 0.91 (m, 6H, $3CH_2$-Pip.), 3.94 (t, 4H, $2CH_2$-Pip.), 5.05 (s, 1H, Pyridine-H), 7.25-7.84 (m, 9H, Ar-H, methine-H- and NH_2; exchangeable with D_2O). Anal. Calcd for$C_{29}H_{21}Cl_4N_5O_2S$ (643): C: 54.12, H: 3.26, N: 10.88. Found: C: 54.02, H: 3.80, N: 11.00.

*2,3,9-Trihydro-2-arylmethylidine-3,8-dioxo-6,8-diamino-7--cyano-9-aryl-10-piperidinylcarbaldehydo thiazolo[3,2-a]-1,8-naphthyridine**(14a,b)***

To a solution of either **(5a)** or **(5b)** (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.05 mL) malononitrile (0.01 mol) was added. The reaction mixture was heated under reflux

conditions. The solid product formed was collected by filtration and recrystallized from ethanol to give **(14a,b)**

14a: yellow crystals, yield 60%, m.p. 274-76 ºC. IR (KBr, cm^{-1}): 3,392, 3,147 (NH_2), 2,202 (C≡N), 1,704 and 1,626 (C=O thiazolidinone and amide), ^{1}HNMR (DMSO-d_6) δ 1.19 (m, 6H, $3CH_2$-Pip.), 3.93 (t, 4H, $2CH_2$-Pip.), 5.07(s, 1H, Pyridine-H), 6.15 (s, 2H, NH_2; exchangeable with D_2O), 7.42-7.61 (m, 11H, Ar-H, methine-H-and NH_2; exchangeable with D_2O). Anal. Calcd for $C_{30}H_{24}Cl_2N_6O_2S$ (602): C: 59.88, H: 3.98, N: 13.95. Found: C: 60.01, H: 3.92, N: 12.82.

14b: yellow crystals, yield 60%, m.p. 280-82 ºC. IR (KBr, cm^{-1}): 3,392, 3147 (NH_2), 2,196 (C≡N), 1,702 and 1,642 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO -d_6) δ 0.79 (m, 6H, $3CH_2$-Pip.), 3.85 (t, 4H, $2CH_2$-Pip.), 4.15(s, 1H, Pyridine-H), 6.15 (s, 2H, NH_2; exchangeable with D_2O), 6.89-7.81 (m, 9H, Ar-H, methine-H-and NH_2; exchangeable with D_2O).Anal. Calcd for $C_{30}H_{22}Cl_4N_6O_2S$ (670): C: 53.73, H: 3.28, N: 12.53. Found: C: 53.62, H: 3.52, N: 12.73.

*2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-N-ethylthiourea--6-cyano-7-aryl-8-piperidinylcarbaldehydo thiazolo[3,2-a] pyridine**(15a,b)***

To a solution of either **(5a)** or **(5b)** (0.01 mol) in DMF(20 mL) containing KOH (0.01 mol) ethyl isothiocynate (0.01 mol) was added. The reaction mixture was stirred at room temperature. The solid product formed was collected by filtration and recrystallized from ethanol to give **(15a,b)**

15a: yellow crystals, yield 60%, m.p. 180-82 ºC. IR (KBr, cm^{-1}): 3,156 (NH), 2,196 (C≡N), 1,704 and 1,626 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 0.92 (m, 6H, $3CH_2$-Pip.), 1.44 (t, 3H, CH_3) 3.93 (t, 4H, $2CH_2$-Pip.) 4.01 (q, 2H ,CH2), 5.07 (s, 1H, Pyridine-H), 6.15 (s, 1H, NH; exchangeable with D_2O), 7.41-7.68 (m, 9H, Ar-H, and methine-H), 12.05 (s, 1H, NH; exchangeable with D_2O), Anal. Calcd for $C_{30}H_{27}Cl_2N_5O_2S_2$ (623): C: 57.78, H: 4.33, N: 11.23. Found: C: 56.91, H: 4.40, N: 11.01.

15b: yellow crystals, yield 60%, m.p. 190-92 ºC. IR (KBr, cm^{-1}): 3,156 (NH_2), 2,190 (C≡N), 1,708 and 1,628 (C=O thiazolidinone and amide). ^{1}HNMR (DMSO-d_6) δ 1.01 (m, 6H, $3CH_2$-Pip.), 1.44 (t, 3H, CH_3) 3.41 (t, 4H, $2CH_2$-Pip.) 4.01 (q, 2H, CH_2),5.07 (s, 1H, Pyridine-H), 6.15 (s, 1H, NH; exchangeable with D_2O), 7.53-7.76 (m, 7H, Ar-H, and methine-H), 12.04(s, 1H, NH; exchangeable with D_2O), Anal. Calcd for $C_{30}H_{25}Cl_4N_5O_2S_2$ (693): C: 52.09, H: 3.61, N: 10.13. Found: C: 52.71, H: 3.35, N: 9.85.

*2,10-diaryl-5-phenyl-8-amino-9-cyano-11-piperidinylcarbaldehydo pyrazolo[3,4:4',5']thiazolo[3,2-a] pyridine**(16)***

To a solution of either **(5a)** (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.05 mol) phenyl hydrazine(0.01 mol) was added The reaction mixture was heated under reflux conditions. The solid product formed was collected by filtration and recrystallized from ethanol to give **(16)**

16: yellow crystals, yield 60%, m.p. 178-80 ºC. IR (KBr, cm^{-1}): 3,412, 3,210 (NH_2), 2,190 (C≡N), 1,628 (C=O amide). ^{1}HNMR (DM SO-d_6) δ 1.01 (m, 6H, $3CH_2$-Pip.), 3.41 (t, 4H, $2CH_2$-Pip.) 4.27 (s, 1H, Pyridine-H) 6.27-7.55 (m ,13H, Ar-H), 9.93 (s,2H,NH_2; exchangeable with D_2O), Anal. Calcd for $C_{33}H_{26}Cl_2N_6OS$ (624): C: 63.46, H: 4.16, N: 13.46. Found: C: 63.72, H: 3.95, N: 13.55.

4.3 Molecular Modelling Study

4.3.1 Generation of Ligand and Enzyme Structures

Docking study was carried out for the target compounds into (ALR2), the crystal structure of the (1PWM) complexed with (FID) was uploaded from the protein data bank PDB [34].

4.3.2 Preparation of Small Molecule

Molecular modeling of the target compounds was built using ChemDraw Ultra version 8.0.3, and minimized their energy through Chem3D Ultra version 8.0.3/MOPAC, Job Type: Minimum RMS Gradient of 0.010 kcal/mol and RMS distance of 0.1 °A, and saved as MDL MolFile (*.mol) [35]. Our compounds were

introduced into the (1PWM) binding site accordance the published crystal structures of (FID) bound to a\kinase.

References

[1] P. Zimmet, K.G.M.M. Alberti, J. Shaw, Global and societal implications of the diabetes epidemic, Nature 414 (2001) 782-787.

[2] S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes Care 27 (2004) 1047-53.

[3] P.F. Kador, The role of aldose reductase in the development of diabetic complications, Med. Res. Rev. 8 (1988) 325-52.

[4] J. Diamond, The double puzzle of diabetes, Nature 423 (2003) 599-602.

[5] H. King, R.E. Aubert, W.H. Herman, Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections, Diabetes Care 21 (1998) 1414-1431.

[6] M. Brownlee, Biochemistry and molecular cell biology of diabetic complications, Nature 414 (2001) 813-820.

[7] S. Suzen, E. Buyukbingol, Recent studies of aldose reductase enzyme inhibition for diabetic complications, Curr. Med. Chem. 15 (2003) 1329-52.

[8] D.J. Porte, M.W. Schwartz, Diabetes complications, why is glucose potentially toxic, Science 272 (1996) 699-700.

[9] P.F. Kador, J.H. Kinoshita, N.E. Sharpless, Aldose reductase inhibitors: a potential new class of agents for the pharmacological control of certain diabetic complications, J. Med. Chem. 28 (1985) 841-849.

[10] C.Y. Nishimura, Aldose reductase in glucose toxicity: A potential target for the prevention of diabetic complications, Pharmacol. Rev. 20 (1998) 21-33.

[11] L. Costantino, G. Rastelli, G. Cignarella, P. Vianello, D. Barlocco, New aldose reductase inhibitors as potential agents for the prevention of long-term diabetic complications, Exp. Opin. Ther. Patents 7 (1997) 843-858.

[12] B.H. Wollfenbuttel, T.W. Haeften, Prevention of complications in Non-Insulin-Dependent Diabetes Mellitus (NIDDM), Drugs 50 (1995) 263-288.

[13] S. Miyamoto, Molecular modeling and structure-based drug discovery studies of aldose reductase inhibitors, Chem-Bio Info. J. 2 (2002) 74-85.

[14] S. Narayanan, Aldose reductase and its inhibition in the control of diabetic complications, Ann. Clin. Lab. Sci. 23 (1993) 148-158.

[15] E.R. Larson, C.A. Lipinski, R. Sarges, Medicinal chemistry of aldose reductase inhibitors, Med. Res. Rev. 8 (1988) 159-186.

[16] L. Costantino, G. Rastelli, P. Vianello, G. Cignarella, D. Barlocco, Diabetes complications and their potential prevention: aldose reductase inhibition and other approaches, Med. Res. Rev. 19 (1999) 3-23.

[17] L. Costantino, G. Rastelli, M.C. Gamberoni, D. Barlocco, Pharmacological approaches to the treatment of diabetic complications, Exp. Opin. Ther. Patents 10 (2000) 1245-1262.

[18] P. Alexiou, K. Pegklidou, M. Chatzopoulou, I. Nicolaou, V.J. Demopoulos, Aldose reductase enzyme and its implication to major health problems of the 21st century, Curr. Med. Chem. 16 (2009) 734-752.

[19] R. Maccari, R. Ottanà, 2,4-Thiazolidinedione and 2-thioxo-4-thiazolidinone derivatives as aldose reductase inhibitors in the search for drugs to prevent long-term diabetes complications, in: M. Stefek (Ed.), Advances in Molecular Mechanisms and Pharmacology of Diabetic Complications, Transworld Research Network, Kerala, 2010, pp. 219-245.

[20] D.E. Moller, New drug targets for type 2 diabetes and the metabolic syndrome, Nature 414 (2001) 821-827.

[21] G.A.M. Ali, Studies on thiazolopyridines: Part 3. Reactivity of thiazolo[3,2-a]-3-aza-1,8-naphthyridines towards some nucleophiles, Phosphorus, Sulfur and Silicon 178 (4) (2003) 711-720.

[22] G.A.M. Ali, A. Khalil, A.H.A. Ahmed, M.S.A. El-Gaby, Study on thiazolopyridines: Part 2. Synth esis and activity of novel thiazolo[2,2-a]pyridines and thiazolo [3,2-a]1,8-naphthyridines having two different aryl moieties, Acta. Chim. Slov. 49 (2002) 365-376.

[23] M.E. Azab, G.A.M. Ali, A.H.F. Abd El-Wahab, A novel synthesis of bisthiazolopyridines as promising antibacterial agents, Acta Pharm. 53 (2003) 213-221.

[24] A.A. El-Maghraby, G.A.M. Ali, A.H.A. Ahmed, M.S.A. El-Gaby, Antimicrobial activity of some novel fluorinated thiazolo[3,2-a]pyridines, and [2,3-1,6]pyrimidines, Phosphorus, Sulfur and Silicon 177 (2) (2002) 293-302.

[25] M.S.A. El-Gaby, M.M. Khafagy, G.A.M. El-Hag Ali, H.A. Eyada, A.A. El-Maghraby, M.H. Helal, Study on thiazolopyridines: Part 4. Synthesis of hitherto unkown 1,4-bis(thiazolopyridines) benzene derivatives, Phosphorus, Sulfur and Silicon 178 (8) (2003) 1681 -1688.

[26] R.Q. Lamphon, M.S.A. El-Gaby, M.M. Khafagy, G.A.M. Ali, A.A. El-Maghraby, H.A. Eyada, et al., Study on thiazolopyridines: Part 5. Synthesis of hitherto unkown thiazolidinone and thiazolo[3,2-a]pyr idines having in their structures the morpholine -4- yl-moiety, Phosphorus, Sulfur and Silicon 179 (7) (2004) 1279-1292.

[27] G.A.M. El-Hag Ali, R.Q. Lamphon, A. Khalil, A. El-Maghraby, Stydy on thiazolopyridines: Part 6. Synthesis and antimicrobial evaluation of some novel thiazolo[2,3-1,6] pyrido[2,3-d]pyridines, Phosphorus, Sulfur and Silicon 180 (8) (2005) 1909-1919.

[28] T.I. El-Emary, G.A.M. El-Hag Ali, A. Khalil, A.A.A. El-Adasy, A facile synthesis of new thiazolo[3,2-a] pyridines containing pyrazoloyl moiety and their antimicrobial activities, Phosphorus, Sulfur and Silicon 180 (1) (2005) 19-30.

[29] G.A.M. El-Hag Ali, M.T. Abd El-Rahman, M.H.M. Helal, M.S.A. El-Gaby, Novel synthesis of pyrano [2,3 -d] thiazole, thiazolo[3,2-pyridines, pyrazolo [3,4 -4',5']and thiazolo[3,2-a]pyridine derivatives, Phos- phorus, Sulfur and Silicon 183 (2008) 3023-3036.

[30] G.A.M. El-Hag Ali, H. Eltamamy, M. Elsonousy, Z.A.E. AlAzhar, Utility of thioglycollic acid in the synthesis of some newly thiazolidinone and thiazolo[3,2-a] pyridine derivatives as antimicrobial agents, Bull Science 21 (2010) 175-188.

[31] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, et al., The protein data bank, Nucleic Acids Res. 28 (2000) 235-242.

[32] M. Zentgraf, H. Steuber, C. Koch, C. Motta, S. Sartini, C. A. Sotriffer, et al., How reliable are current docking approaches for structure-based drug design? Lessons from Aldose Reductase 46 (2007) 3575-3578.

[33] R. Thomsen, H. Christensen, MolDock: A new technique for high-accuracy molecular docking, J. Med. Chem. 49 (11) (2006) 3315-3321.

[34] O. El-Kabbani, C. Darmanin, T.R. Schneider, I. Hazemann, F. Ruiz, M. Oka, et al., Ultrahigh resolution drug design: Part 2. Atomic resolution structures of human aldose reductase holoenzyme complexed with Fidarestat and Minalrestat: implications for the binding of cyclic imide inhibitors, A Proteins 55 (2004) 805-813.

[35] Chem Draw Software, http://www.cambridgesoft.com/ software /ChemDraw/, lliams, Pharm. Biol. 32 (1994) 337-345.