JCHR (2024) 14(2), 403-413

Journal of Chemical Health Risks

sanad.iau.ir/journal/jchr

ORIGINAL ARTICLE

Synthesis, Evaluation of New Imidazolidin-4-one and Thiazolidine -4- one compound on Insulin in the Serum of Type 1 Diabetes Albino Rats

Laith G. Atiya[1], Omar M.Yahya[2], Salim J.Mohmmed[*1]

[1]*Chemistry Department, College of Science, University of Mosul, Mosul, Iraq*

[2]*Department of Biochemistry, College of Medicine, Mosul University, Mosul, Iraq*

(Received: 11 August 2023 Accepted: 26 February 2024)

KEYWORDS

4-(2,4-di chlorophenoxy) butyric acid;
Hydrazide;
Hydrazine;
Imidazolidine;
Thiazolidine;
Molecular docking

ABSTRACT: This paper includes the synthesis of new imidazolidine-4-one and thiazolidine-4-one derivatives derived from 4-(2,4-dichlorophenoxy) butyric acid (1) by multistep reaction, the first step synthesis ester (2) by the esterification reaction of 4-(2,4-dichlorophenoxy) butyric acid with ethanol in the presence of sulfuric acid. Ester namely ethyl 4-(2,4-dichlorophenoxy) butanoate (2) was converted to the corresponding 4-(2,4-dichloro phenoxy)butane hydrazide (3) by reaction with hydrazine hydrate after those hydrazones (4a-f) derivatives were obtained by the reaction of carboxylic acid hydrazide (3) with various substituted aromatic aldehydes, this hydrazone were used to synthesize some new heterocyclic compounds by the hydrazones (4a-f) with Phenyl Alanine and thioglycolic acid to prepare imidazolidine-4-one(5a-e) and thiazolidine-4-one (6a-d) compounds respectively. The molecular docking study was carried out with the essential enzyme Insulin (PDB 1i144) responsible for Diabetes, suggesting that (4a-e) are the most active derivatives of the series that is responsible for diabetes, for some of the compounds that were prepared in this study. It was found that compounds (4a-e) are the most active derivatives. All newly synthesized compounds in this study were confirmed by physical and spectral (FT-IR, ^{1}H NMR, and ^{13}C NMR) analysis.

INTRODUCTION

As is well knowledge, diabetes mellitus type 1 (T1DM), also known as autoimmune disease, is a chronic illness marked by a lack of insulin that results in the death of pancreatic β cells and raises blood sugar levels.[1]. Diabetes is a chronic metabolic disease that is on the rise. Hyperglycemia, which is indicated by increased blood glucose levels, is its defining characteristic. It may be linked to chronic illness or failure in a number of the body's organs, including the heart, kidneys, and eyes. Generally speaking, diabetes comes in two varieties: The first kind is brought on by insufficient insulin synthesis. the On the other hand, insulin action deficiencies or resistance cause the second kind [2–5].Heterocyclic chemistry is an important and unique class among the applied branches of organic chemistry.[6] Imidazole, Imidazolidine-4-one and its derivatives represent important types of compounds that possess a wide spectrum of biological activities, such as anti-inflammatory[7], antimicrobial [8, 9], antibacterial [10], and anticonvulsant [11] activities. As well Also as antihypertensive, vasodilation properties [12], and .anti-cancer[13]. Many imidazole compounds function as a class of medications by binding to the adrenaline receptors [14]. Anti-α 2 has potential therapeutic

*Corresponding author: dr_salimjasim@yahoo.com (S. J.Mohmmed)
DOI: 10.22034/JCHR.2024.1088052

implications for depression, retinoid disease, as well as type II diabetes, and it is also utilized as an anxiety, relaxing, and antibacterial agent [15–17]. Thiazolidine-4-one a saturated form of thiazole has been considered a magic moiety that possesses almost all types of biological activities such as hypnotic [18],anti- HIV [19], antifungal [20], antibacterial [21], anti-tubercular [21], anthelmintic [21], antihistaminic(H1- antagonist) [21], antiviral [21], anti-inflammatory(COX-inhibitors) [22], analgesic [22], antimicrobial [23]and [24], diuretic [25]antitumor [26], anticancer [27], PAF antagonist [28], cardioprotective [29], anti-ischemic [30], Ca2+ channel blocker [31], cyclooxygenase inhibitory [32] and hypo-glycemic [33]activities.

MATERIALS AND METHODS

Materials

The chemicals were obtained from Fluka Chem Co. (Switzerland) and Aldrich-Sigma Chemistry Company. (Milwaukee, WI, USA) and were used as purchased without additional purification. They were used without further purification. Also, the melting points were set on the Stuard-SMP30 and were not corrected. The FTIR spectra were listed on FT-IR (400-4000 cm^{-1}) Bruker. tech engineering management spectrophotometer utilizing a KBr disc. The 1H-NMR and 13C-NMR spectrum were acquired on a Bruker (400 MHz), with TMS as the internal standards and DMSO-d6 as the solvent.

Synthesis of ethyl 4-(2,4-dichlorophenoxy) butanoate (2).

(2g, 0.008 moles)of compound (1) in absolute ethanol (30 ml) mixed with (1 ml) sulfuric acid then was based on Ultrasound Techniques for 1 hr. We used thin layer chromatography to see the reaction completion, and then we evaporated the solvent. The mixture was then poured into powdered ice water and, while continuing to stir, was neutralized with 10% sodium bicarbonate to obtain compound (2) in the form of oil.

Synthesis of 4-(2,4-dichlorophenoxy)butane hydrazide (3)

(0.001 moles) compound (2) mixed with hydrazine hydrate 80% (15ml) in ethanol (25ml) was based on Ultrasound Techniques for 1 to 1.5 hrs. The completion of the reaction was monitored by the thin -layer chromatography technique and the solvent was evaporated and cooled. The product was filtered, washed with water, dried, and recrystallized using ethanol to give a solid a white color [34].

Synthesis of hydrazones (4a-e)

Equimolar quantities of (3) (0.001 moles) and some substituted aldehydes (0.001 moels) With a few drops of glacial acetic acid in absolute ethanol , kept in an in Ultrasound Technique for (30 min). The completion of the reaction was monitored by the thin -layer chromatography technique. The mixture was concentrated, cooled. The solid product was filtered, washed with water, and dried. Then recrystallized from ethanol [34]. The physical properties are shown in Table 1.

Table 1. Physical data for compounds (4a-e)

Comp. No.	R	Color	Molecular Formula	M.P. °C	Yield%
4a	3-NO_2	white	$C_{17}H_{15}Cl_2N_3O_4$	151-152	81
4b	2,4-Cl	white	$C_{17}H_{14}Cl_4N_2O_2$	149-151	91
4c	1,3-dioxolane	light brown	$C_{18}H_{16}Cl_2N_2O_4$	152-154	87
4d	4-OH	pale yellow	$C_{17}H_{16}Cl_2N_2O_3$	163-165	91
4e	4-Br	white	$C_{17}H_{15}BrCl_2N_2O_2$	136-138	90

Synthesis of imidazolidine-4-one (5a-e)

Equimolar quantities of hydrazones (4a-e) (0.001 moles), and phenylalanine (0.165g, 0.001 moles) were dissolved in (20 ml) tetrahydrofuran . The mixture was refluxed for (24 hrs.) at a temperature of 80^0C. The reaction was then cooled and the resulting solid compounds were recrystallized from absolute methanol to obtain a precipitate of imidazolidine-4-one (5a-e). [35]. The physical properties are listed in Table 2.

Table 2. Physical data for compounds (5a-e).

Comp. No.	R	Color	Molecular Formula	M.P ^{0}C	Yield%
5a	3-NO_2	white	$C_{26}H_{24}Cl_2N_4O_5$	204-208	85
5b	2,4-Cl	white	$C_{26}H_{23}Cl_4N_3O_3$	158-160	86
5c	1,3-dioxolane	light brown	$C_{27}H_{25}Cl_2N3O_5$	158-160	85
5d	4-OH	yellow	$C_{26}H_{25}Cl_2N_3O_4$	192-194	77
5e	4-Br	white	$C_{26}H_{24}BrCl_2N_3O_3$	197-199	75

Synthesis of thiazolidine-4-one (6a-e)

Hydrazones (4a-e) (0.0005 mol) and thioglycolic acid (0.046 g, 0.0005 mol) were mixed in 15 mL of 1,4-dioxane, and the mixture was stirred under reflux condensation for 6 hours at 40-50 °C. The solvent is then evaporated under low pressure, then (15 ml of 10%) sodium bicarbonate solution is added and the solid precipitate is filtered and recrystallized with ethanol. To obtain the precipitate of thiazoline-4-one (6a-e).[36]. The physical data are recorded in Table 3.

Table 3. Physical properties of compounds, (6a-e).

Comp. No.	R	Color	Molecular Formula	M.P. $^\circ$C	Yield%
6a	3-NO_2	White	$C_{19}H_{17}Cl_2N_3O_5S$	147-150	77
6b	2,4-Cl	White	$C_{19}H_{16}Cl_4N_2O_3S$	148-150	63
6c	1,3-dioxolane	Pale yellow	$C_{20}H_{18}Cl_2N_2O_5S$	154-156	43
6d	4-OH	Yellow	$C_{19}H_{18}Cl_2N_2O_4S$	147-151	56
6e	4-Br	White	$C_{19}H_{17}BrCl_2N_2O_3S$	134-136	65

Molecular docking evaluation

In this research, the orientations and interactions of derivatives of powerful compounds that cause diabetes induced in mice (5a-b), represented by the known insulin enzyme, are simulated. The MCULE Docking program as well as the BIOVIA Discovery Studio (2021) program were applied. "The three-dimensional (3D) structure of the proteins selected from the site called PDB was also adopted. Finally, the proteins were added using the links in the Mcule base. [11]. Mcule Dock Company specialises in measuring biological effectiveness utilizing a new chemical substance. Enzymes are chosen for the purpose of investigating their interactions [12]. Enzymes are chosen from the existing enzyme database (BDP). Mcule typically assesses the bond strength between a chemical substance and particular enzymes by computing the ΔG value, which represents the free energy that causes the reaction. This aids in evaluating the intensity of the contact and the anticipated impact on the enzyme. Mcule docking can generate both 2D and 3D images illustrating the binding interaction between the chemical molecule and the enzyme, aiding in result interpretation [13].

In-vivo hypoglycemic study

Experimental animals

The Rats used had weights ranging from approximately 350 to ±10 g were used in the study. At first, all 40 male Rats were used and taken from the animal house of the

College of Veterinary Medicine at Tikrit University. Secondly transported to the animal facility at the University's College of Veterinary Medicine, University of Mosul. They were confined in specialized cages and given water and animal feed. They were separated into seven categories and given one week to adjust to laboratory settings regarding light and temperature before proceeding with the injections and dosing procedures.

In-vivo experiment

The study involved 40 male rats, divided into seven groups, each including 5 rats for each group. The first group was the control group and was fed a normal diet and distilled water. While the second group was used to determine the effect of the solvent on the mice. As for the third group, it was used to determine the LD50, while groups (4-7) were given doses of Alloxan 125 mg kg^{-1}, then groups 4, 5, 6, and 7 of the animals were treated with three different doses of the compound (5a-d) (15 - 25 - 35 mg kg^{-1}) by intraperitoneal injection for 7 days. The biochemical results showed that compounds 5c and 5d showed a response to reducing high blood sugar.

Induction of Diabetes with Alloxan

Feed was withheld from the animals for approximately 12 hours, after which the animals were injected ,intraperitoneally with a dose of alloxan equivalent to (150 mg-1) of body weight, after that replace drinking water with glucose sugar solution (10%) for (28) hours to relieve the shock of treatment with Alloxan After the Alloxan monohydrate injection, Confirmation of diabetes is done by measuring the fasting blood glucose level 24 hours later the injection given to rats. The blood glucose level of >200 mg dl^{-1} confirms diabetes in rats and was used further for the experiment. The animals were sorted into two groups: diabetic and non-diabetic animals by examination using a glucometer. For many studies, animals with high blood sugar levels (diabetes) were examined according to a previously reported procedure [37]**.**

1. The first group, which served as the control group, was provided with a standard food for the duration of the trial.
2. In the second group, the effect of the solvent on the rats was determined by giving them doses of DMSO.
3. In the third group, doses of the new heterocyclic compound that had been prepared were injected for one week for the purpose of determining the LD50 dose, and they were given additional DMSO a week before.
4. In the fourth group, they were treated with the new heterocyclic compound (5a) inside the peritoneal cavity for approximately 21 days at doses (15 - 25 - 35 mg kg-^{1}) of body weight daily.
5. In the fifth group, injections of the new heterocyclic compound (5b) were given into the peritoneal cavity for 21 days, at doses ranging from (15 - 25 - 35 mg kg^{-1}) of body weight daily, representing a therapeutic dose.
6. In the sixth group, a new heterocyclic compound (5c) was administered intraperitoneally for 21 days at doses ranging from (15 - 25 - 35 mg kg^{-1}) of body weight per day and represents a therapeutic dose.
7. In the seventh category, an injection of a novel heterocyclic drug (5D) was administered into the abdominal cavity for 21 days at doses of 15, 25, and 35 mg kg^{-1} per day, representing the therapeutic dose.

RESULTS AND DISCUSSION

Having potential medicinal and biological activity, in our present work, the synthesis of some imidazoline-4-one (5a-e) and thiazolidine-4-one (6a-e) derivatives was achieved. The reaction sequences leading to the formation of the ordered heterocyclic compounds are listed in Figure 1.

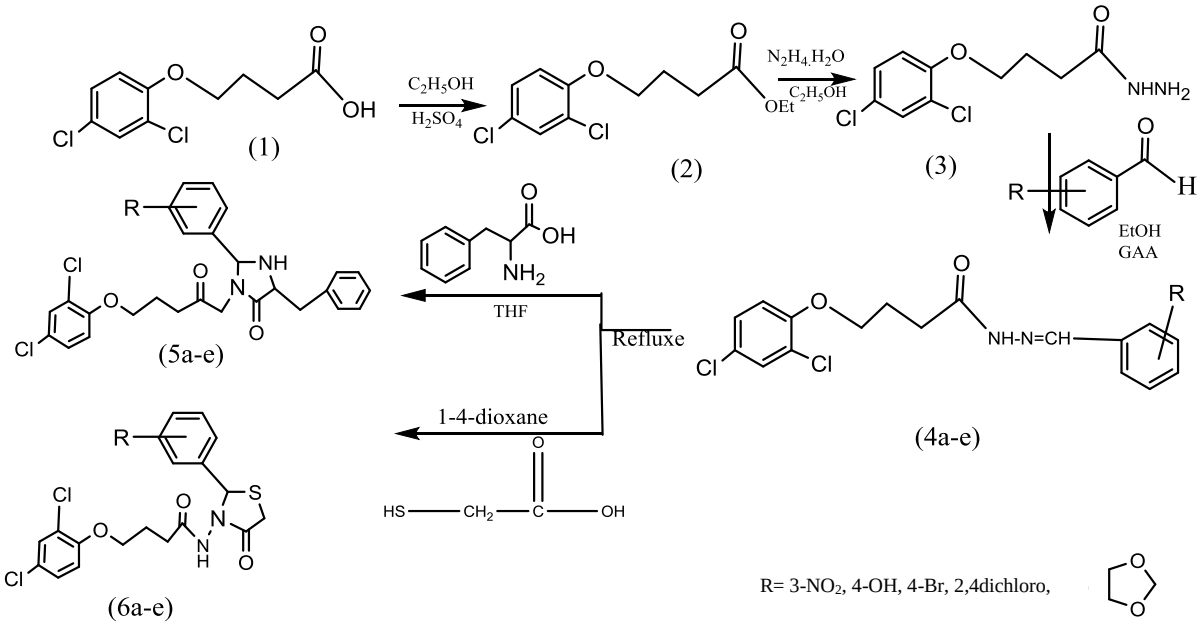

Figure 1. Synthesis of new compounds.

The starting material of carboxylic acid hydrazide (3)**,** which was made by reacting 4-(2,4-dichlorophenoxy) butyric acid (1) with ethanol in an sulfuric acid to produce 4-(2,4-dichlorophenoxy) butanoate (2).which, when combined with hydrazine hydrate in ethanol, yielded the corresponding hydrazide (3). When substituted benzaldehyde is added to carboxylic acid hydrazide (3), hydrazones (4a-e) are easily made with a good yield. Cyclization of hydrazones (4a-e) with amino acid namely Phenyl Alanine and thioglycolic acid to prepare imidazolidine-4-one (5a-e) and thiozolidine-4-one (6a-e) respectively. The structural compounds (4a-e), (5a-e), and (6a-e) were identified using the FT-IR, 1H-NMR, as well as 13C-NMR. The FT-IR spectrum for compounds (4a-e) revealed peaks in the area (1642-1675 cm-1) of vibration stretching of (C=O amide), (1596-1611 cm-1) stretch vibrating of azomethine (C=N) a group, and (3158-3213 cm-1) owing to (NH) group, as given in Table 4.

Table 4. FT-IR data for compounds (4a-e).

Comp. No.	FT-IR(KBr) γcm^{-1}					
	N-H	**C-H Ar.**	**CH Aliph.**	**C=O**	**C=N**	**others**
4a	3193	3085	2969	1668	1611	NO_2 Asym 1349 Sym 1203
4b	3185	3079	2960	1675	1594	C-Cl 778
4c	3172	3078	2963	1662	1596	C-0-C 1252
4d	3158	3070	2964	1642	1606	OH 3300
4e	3213	3077	2990	1672	1606	C-Br 744

The ^{1}H-NMR spectra studies of prepared compounds (4a, b, and c) showed up a singlet band at range (11.57-11.17 ppm) due to (NH) protons. Also, we noticed a peak at the range (8.89-8.10

ppm) for N=CH proton. In addition other packages for these compounds, are shown inTable 5.

Table 5. ^{1}H-NMR data of compounds (4 a-c).

Comp. No.	^{1}H-NMR δ (ppm)(400MHz DMSO-d_6)
4a	δ 11.57 (s, 1H , NH), 8.10 (s, 1H, CH=N), 7.55-7.19 (m, 3H, Ar_1H), 8.44– 7.2 (m, 4H, Ar_2H), 4.14 (t, 2H, O-CH_2), 2.07 (m, 2H,- C-CH_2-C-), 2.882 (*t*, 2H, - CH_2-C=O).
4b	δ 11.53 (s, 1H, -NH), 8.31 (s, 1H, -CH=N), 7.50-7.34 (m, 3H, Ar_1H), 7 .890– 7 .18 (m, 4H, Ar_2H), 4.13 (t, 2H, O-CH_2-), 2.06 (m, 2H, -C-CH_2-C-), 2.841 (*t*, 2H, CH_2-C=O).
4c	δ 11.17 (s, 1H, -NH), 8.89 (s,1H, -CH=N) ,7.23-7.05 (m , 3H, Ar_1H), 7.550– 7.18 (m, 3H, Ar_2H), 4.14 (t, 2H, O-CH_2), 2.07 (m, 2H, C-CH_2-C), 2.88 (*t*, 2H, -CH_2-C=O), 6.08, (m, 2H,- O-CH_2-O)

In the ^{13C}-NMR spectrum for compound (4a)

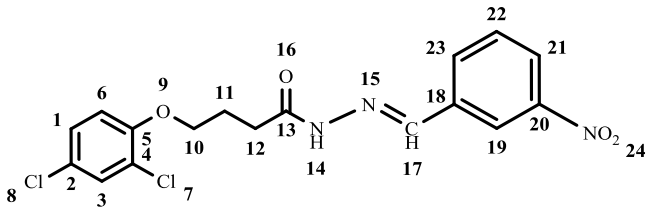

Figure 2. ^{13}C-NMR spectrum for compound (4a).

The following signs represent the carbon atoms in compound (4a)as shown in Figure 2: 121.14-153.42, (C1,2,3,4,5,6,19,20,21,22,23), 68.75(C10), 24.10(C11), 28.70(C12), 174.50(C13).

The FT-IR spectra for compounds (5a-e) showed absorption peak in the range (1635-1681 cm^{-1}) due to (C=O amide) group, (1153 - 1227 cm^{-1}) stretching vibration of (C-N) group, (3174-3293 cm^{-1}) due to (NH) group and as shown in Table 6.

Table 6. FT-IR data for compound (5a-e).

Comp. No.	FTIR(KBr) γcm^{-1}					
	N-H	**CH Ar.**	**CH Aliph.**	**C=O**	**C-N**	**others**
5a	3174	3084	2921	1661	1227	NO_2 Asym 1345 Sym 1210
5b	3181	3077	2991	1674	1172	Cl 776
5c	3293	3069	2953	1663	1183	C-O-C 1254
5d	3221	3064	2952	1635	1225	OH 3481
5e	3216	3034	2951	1681	1153	Br 744

^{1}H-NMR spectra for compounds (5 a-c), showed a single peak at (11.54-608ppm) due to NH cyclic and peaks (5.26-2.41 ppm) due to CH-C=O of imidazoline and other peaks as show in Table 7.

Table 7. ^{1}H-NMR data of compounds (5a- c).

Comp. No.	^{1}H-NMR δ (ppm)(400MHz DMSO-d_6)
5a	δ 11.58 (s, 1H , NH), 8.11 (s, 1H , NH cyclic), 8.44 – 7.27 (s, 12H, ArH), 4.14 (dt, 2H, O-CH_2), 2.06 (m, 2H, C-CH_2-C), 2.06 (*m* , 2H, -CH_2-C=O), 3.16 (m , 2H, CH_2), 7.56 (dd, 1H, N-CH-N), 2.46 (t, 1H, CH-C=O)
5b	δ 11.74 (s, 1H, NH), 11.54 (s, 1H, NH cyclic), 7.79 – 7.29 (s, 11H, ArH), 4.12 (dt, 2H, O-CH_2), 2.05 (m, 2H, C-CH_2-C), 2.050 (*m*, 2H , -CH_2-C=O), 4.12 (m, 2H, CH_2), 5..26 (d, 1H, - N-CH-N), 5.26 (s, 1H, -CH-C=O).
5c	δ 11.23 (s, 1H, NH), 6.08 (s, 1H, NH cyclic), 7.56 – 6.96 (s, 11H, ArH), 4.12 (dt, 2H, O-CH_2), 2.04 (m, 2H, CH_2-C-C), 2.06 (*m*, 2H, CH_2-C=O), 4.12 (m, 2H, CH_2-C-NH), 6.08 (m, 2H, O-CH_2-O sub) 7.24 (d, 1H, N-CH-N cyclic), 2.41 (t, 1H, CH-C=O cyclic).

Also, the ^{13}C-NMR spectrum for compound (5 a) showed a single peak at (169.22 C=0 cyclic) and (174.50 C=O amide), (68.76 CH cyclic) and the following signs represent the carbon atoms in compound (5a)as shown in Figure3:

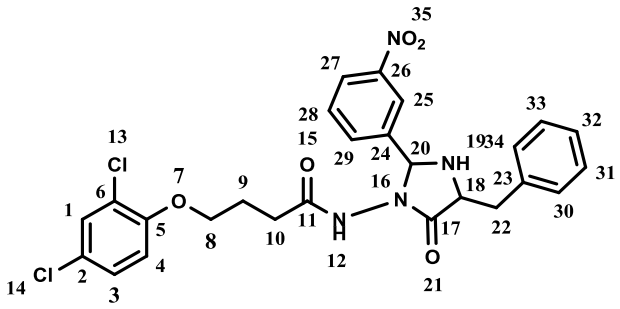

Figure 3. ^{13}C-NMR spectrum for compound (5a).

115.48-153.42 ,(C1,2,3,4,5,6,25,26,27,28,29,30,31,32,33,34), 68.75(C8), 24.11(C9), 30.83(C10), 174.50(C11), 169.22 (C17), 55.17 (C18), 68.76 (C20), 37.45 (C22)

The structures of the target compounds (6a and c) were elucidated , Thus,the FT-IR spectra for compounds (6a and c) showed two characteristic bands at 1788-1714 cm-1 due to C=O lactam and other bands as shown in Table 8.

Table 8. FT-IR data for compounds (6a and c).

Comp. No.	FTIR(KBr) γcm^{-1}						
	N-H	C-H Ar.	CH Aliph.	C=O	C=N	C-S	Others
6a	3198	3035	2972	1788	1678	703	NO_2 asym 1348 sym 1201 C-O-C
6c	3180	3077	2966	1714	1668	701	asym 1249 sym 1033

While ^{1}H-NMR spectra for compounds (6 a and c), showed a single peak at 3.43-2.81 due to (S-CH2), 7.19 - 6.08 due to (N-CH), and as shown in Table 9.

Table 9. ^{1}H-NMR data of compounds (6a and c).

Comp. No.	^{1}H-NMR δ (ppm)(400MHz DMSO-d_6)
6a	δ 11.580 (s, 1H, -NH), 8.24 – 7.19 (s, 7H, ArH), 4.15 (dt, 2H, O-CH_2), 1.08 (t , 2H, -C-CH_2-C), 2.09 (*t* , 2H,- CH_2-C=O), 3.43 (s, 2H, S-CH_2), 7.19(s, 1H, -N-CH).
6c	δ 11.21 (s, 1H, -NH), 7.56-7.06 (s, 6H, ArH), 4.13 (dt, 2H, O-CH_2), 2.40 (t, 2H,- C-CH_2-C), 2.04 (*m*, 2H,- CH_2-C=O), 2.81 (s, 2H, -S-CH_2), 6.08 (s, 1H, -N-CH), 6.08 (m, 2H, -O-CH_2-O)

As we mentioned previously in the practical part, the effectiveness of the compounds prepared in the research was evaluated (5a-d) on insulin enzymes in experimental animals. Experiments conducted on rats using the compounds prepared in this research showed that compounds 5c and 5d gave a response to reduce hyperglycemia. Where these compounds were shown positive effectiveness at concentrations of 35mg kg^{-1}, as shown in Table 10.

Table 10. Injection doses of selected compounds (5a-d).

Comp. No.	Results of injection doses anti-diabetes		
	15.0 mg kg^{-1}	25.0 mg kg^{-1}	35.0 mg kg^{-1}
5 a	-ve	-ve	-ve
5 b	-ve	-ve	-ve
5 c	-ve	-ve	+ve
5 d	-ve	-ve	+ve

There is no doubt that the strength of the association between chemical compounds with the selected enzymes is determined by calculating the value of (the free energy of the reaction). Which helps in estimating the strength of the interaction and the expected effect on the enzyme. Mcule docking can also produce 2D and 3D photographs of the bonding that happened among the chemical compound generated with the enzyme, resulting in an image of the results listed in Table 11 (Figures 4-7).

Table 11. Binding energies of the potent anti-diabetes (5a-d) with the examined proteins.

The ligand	Insulin [Kcal mol^{-1}]
5a	-8
5b	-7.4
5c	-8.7
5d	-7.9

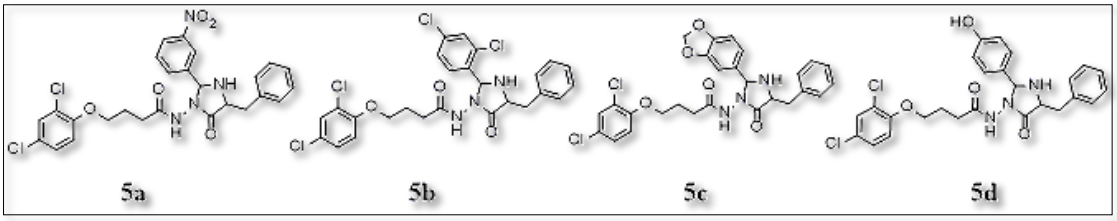

Figure 4. 3D and 2D images of the predicted interactions of compound 5a with insulin (PDB ID 1i144).

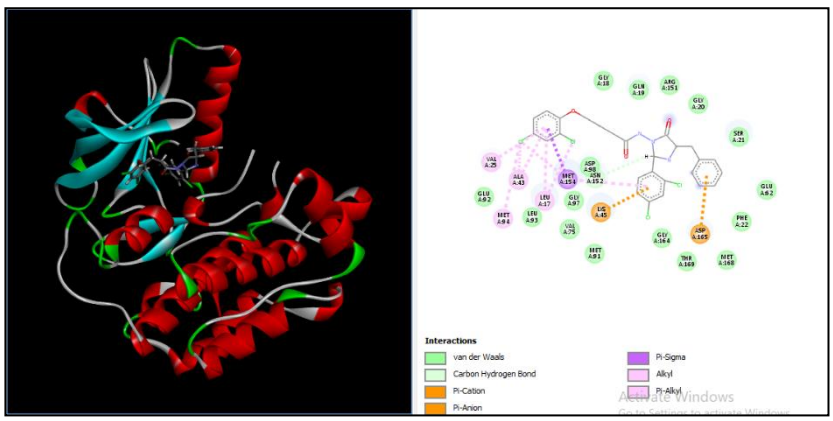

Figure 5. 3D and 2D images of the predicted interactions of compound 5b with insulin (PDB ID 1i144.

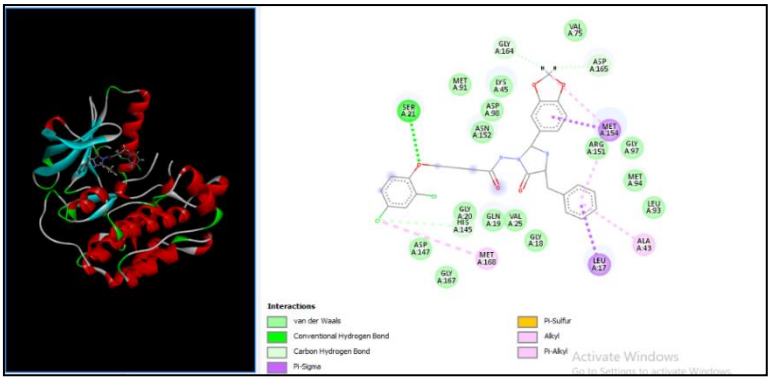

Figure 6. 3D and 2D images of the predicted interactions of compound 5e with insulin (PDB ID 1i144

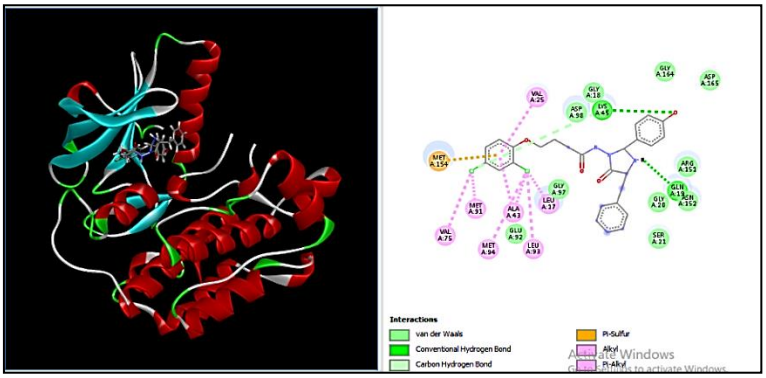

Figure 7. 3D and 2D images of the predicted interactions of compound 5 with insulin (PDB ID 1i144

CONCLUSIONS

The aim of the present study is to assess and investigate the influence of newly synthesized heterocyclic substances on the concentration of the enzyme insulin in the bloodstream of white the rats with type 1 diabetes caused by β cell loss in the pancreas and resulting in hyperglycemia. The compounds under investigation were analyzed theoretically through the utilization of the MCULE docking program, which identified a potential binding relationship between the compounds and the enzymes.

ACKNOWLEDGEMENTS

The authors appreciate and thank the Department of Chemistry, Factually of Science and College of Medicine in University of Mosul, for their invaluable assistance and support in completing of study.

Conflict of interests

The authors declare no conflict of interest.

REFERENCES

1. Katsarou A., Gudbjörnsdottir S., Rawshani A., Dabelea D., Bonifacio E., Anderson B.J., Ark Å., 2017. Type1 diabetes mellitus. Nature reviews Disease Primers. 3(1), 1-17.

2. Williams R., 2015. The economics of diabetes care: a global perspective. International Textbook of Diabetes Mellitus. 1113 - 1124.

3. Flores-Bocanegra L., Pérez-Vásquez A., Torres-Piedra M., Bye R., Linares E., Mata R., 2015. α-Glucosidase inhibitors from Vauquelinia corymbosa. Molecules. 20(8), 15330-15342.

4. Scully T., 2012. Diabetes in numbers. Nature. 485(7398), S2-S3.

5. Mohan V., Anbalagan V.P., 2013. Expanding role of the Madras diabetes research foundation-Indian diabetes risk score in clinical practice. Indian Journal of Endocrinology and Metabolism. 17(1), 31.

6. Kerru N., Gummidi L., Maddila S., Gangu K.K., Jonnalagadda S.B., 2020. A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules. 25(8), 1909.

7. Saleh M.Y., Al-barwari A.S., Ayoob A.I., 2022. Synthesis of Some Novel 1, 8-Naphthyridine Chalcones as Antibacterial Agents. Journal of Nanostructures.

12(3), 598-606.

8. Kumar R.S., Idhayadhulla A., Abdul Nasser A.J., Selvin J., 2010. Synthesis and characterization of new series of imidazolidin-2, 4-dione derivatives and its antimicrobial activity. Oriental Journal of Chemistry. 26, 1425-1430.

9. Kieć-Kononowicz K., Szymańska E., Motyl M., Holzer W., Białecka A., Kasprowic A., 1998. Synthesis, spectral and antimicrobial properties of 5-chloroarylidene aromatic derivatives of imidazoline-4-one. Die Pharmazie. 53(10), 680-684.

10. Ali D., Alarifi S., Chidambaram S.K., Radhakrishnan S.K., Akbar I., 2020. Antimicrobial activity of novel 5-benzylidene-3-(3-phenylallylideneamino) imidazolidine-2, 4-dione derivatives causing clinical pathogens: Synthesis and molecular docking studies. Journal of Infection and Public Health. 13(12), 1951-1960.

11. Godefroi E.F., Platje J.T.J., 1972. DL-1-(. alpha.-Methylbenzyl)-2-methylimidazole-5-carboxylate esters. Synthesis and pharmacological properties. Journal of Medicinal Chemistry. 15(3), 336-337.

12.Kacem Y., Hassine B.B., 2014. Solvent-free synthesis of new chiral 3-phenylamino-3, 5-dihydro-4H-imidazol-4-one derivatives from α-amino acid phenylhydrazides. Heterocycles. 89(1), 197-207.

13. Subtel'na I., Atamanyuk D., Szymańska E., Kieć-Kononowicz K., Zimenkovsky B., Vasylenko O., Gzella A., Lesyk R., 2010. Synthesis of 5-arylidene-2-amino-4-azolones and evaluation of their anticancer activity. Bioorganic & Medicinal Chemistry. 18(14), 5090-5102.

14. Alghamdi S.S., Suliman R.S., Almutairi K., Kahtani K., Aljatli D., 2021. Imidazole as a promising medicinal scaffold: Current status and future direction. Drug Design, Development and Therapy. 3289-3312.

15. Arkan Majhool A., Yakdhan Saleh M., Obaid Aldulaimi A.K., Mahmood Saeed S., Hassan S.M., El-Shehry M.F., Mohamed Awad S., Syed Abdul Azziz S.S., 2023. Synthesis of New Azo Dyes of Uracil via Ecofriendly Method and Evaluation for the Breast, Liver and Lung Cancer Cells In vitro. Chemical Review and Letters. 6(4), 442-448.

16. Arif I.A., Ahamed A., Kumar R.S., Idhayadhulla A., Manilal A., 2019. Cytotoxic, larvicidal, nematicidal, and antifeedant activities of piperidin-connected 2-thioxoimidazolidin-4-one derivatives. Saudi Journal of Biological Sciences. 26(4), 673-680.

17. Rodriguez F., Rozas I., Ortega J.E., Erdozain A.M., Meana J.J., Callado L.F., 2009. Guanidine and 2-aminoimidazoline aromatic derivatives as α2-adrenoceptor ligands: searching for structure− activity relationships. Journal of Medicinal Chemistry. 52(3), 601-609.

18. Ergenç N., Çapan G., Günay N.S., Özkirimli S., Güngör M., Özbey S., Kendi E., 1999. Synthesis and hypnotic activity of new 4- thiazolidinone and 2-thioxo- 4, 5- imidazolidinedione derivatives. Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry. 332(10), 343-347.

19. Ravichandran V., Kumar B.P., Sankar S., Agrawal R.K., 2009. Predicting anti-HIV activity of 1, 3, 4-thiazolidinone derivatives: 3D-QSAR approach. European Journal of Medicinal Chemistry. 44(3), 1180-1187.

20. Omar K., Geronikaki A., Zoumpoulakis P., Camoutsis C., Soković M., Ćirić A., Glamočlija J., 2010. Novel 4-thiazolidinone derivatives as potential antifungal and antibacterial drugs. Bioorganic & Medicinal Chemistry. 18(1), 426-432.

21. Verma A., Saraf S.K., 2008. 4-Thiazolidinone–A biologically active scaffold. European Journal of Medicinal Chemistry. 43(5), 897-905.

22. Tratrat C., Petrou A., Geronikaki A., Ivanov M., Kostić M., Soković M., Vizirianakis I.S., Theodoroula N.F., Haroun M., 2022. Thiazolidin-4-ones as potential antimicrobial agents: experimental and in silico evaluation. Molecules. 27(6), 1930.

23. Sabeeh Hasan I., Yakdhan Saleh M., Aldulaimi A. K., Saeed S. M., Adil M., Adhab A. H., 2024. A Review: Metal-Organic Frameworks Electrochemical Biosensors for Bioorganic Materials Detection. Analytical and Bioanalytical Electrochemistry. 16(1), 100-125.

24. Hassan S.A., Ziwar J.B., Muhammed Aziz D., Abdullah M.N., 2024. Sonochemical synthesis of New Thiazolidin-4-one derivatives as potent anticancer and antimicrobial agents with Docking design, and Energy gap estimation. Journal of Molecular Structure. 1301, 137282.

25. Sharma A., Sharma D., Saini N., Sharma S.V., Thakur V.K., Goyal R.K., Sharma P.C., 2023. Recent

advances in synthetic strategies and SAR of thiazolidin-4-one containing molecules in cancer therapeutics. Cancer and Metastasis Reviews. 1-43.

26. Roszczenko P., Holota S., Szewczyk O.K., Dudchak R., Bielawski K., Bielawska A., Lesyk, R., 2022. 4-Thiazolidinone-bearing hybrid molecules in anticancer drug design. International Journal of Molecular Sciences. 23(21), 13135.

27. Havrylyuk D., Zimenkovsky B., Lesyk R., 2009. Synthesis and anticancer activity of novel nonfused bicyclic thiazolidinone derivatives. Phosphorus, Sulfur, and Silicon. 184(3), 638-650.

28. Tanabe Y., Suzukamo G., Komuro Y., Imanishi N., Morooka S., Enomoto M., Kojima A., Sanemitsu Y., Mizutani M., 1991. Structure-activity relationship of optically active 2-(3-pyridyl) thiazolidin-4-ones as a PAF antagonists. Tetrahedron Letters. 32(3), 379-382.

29. Kato T., Ozaki T., Ohi N., 1999. Improved synthetic methods of CP-060S, a novel cardioprotective drug. Tetrahedron: Asymmetry. 10(20), 3963-3968.

30. Adachi Y., Suzuki Y., Homma N., Fukazawa M., Tamura K., Nishie I., Kuromaru O., 1999. The anti-ischemic effects of CP-060S during pacing-induced ischemia in anesthetized dogs. European Journal of Pharmacology. 367(2-3), 267-273.

31. Hara A., Suzuki T., Hashizume H., Shishido N., Nakamura M., Ushikubi F., Abiko Y., 1999. Effects of CP-060S, a novel Ca^{2+} channel blocker, on oxidative stress in cultured cardiac myocytes. European Journal of Pharmacology. 385(1), 81-88.

32. Ottaná R., Mazzon E., Dugo L., Monforte F., Maccari R., Sautebin L., Cuzzocrea S., 2002. Modeling and biological evaluation of 3, 3′-(1, 2-ethanediyl) bis [2-(4-methoxyphenyl)-thiazolidin-4-one], a new synthetic cyclooxygenase-2 inhibitor. European Journal of Pharmacology. 448(1), 71-80.

33. Saleh M., Sadeek G., Saied S., 2023. Preparation and characterization of a dual acidic Ionic Liquid functionalized Graphene Oxide nanosheets as a Heterogeneous Catalyst for the Synthesis of pyrimido[4,5-b] quinolines in water. Iranian Journal of Catalysis. 13(4), 499-516.

34. Nimbalkar U.D., Seijas J.A., Borkute R., Damale M.G., Sangshetti J.N., Sarkar D., Nikalje A.P.G., 2018. Ultrasound Assisted Synthesis of 4-(Benzyloxy)-N-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl) benzamide as challenging anti-tubercular scaffold. Molecules. 23(8), 1945.

35. Raauf A.M., 2019. Synthesis, characterization and antibacterial activity of new derivatives of imidazolidine having sulfamethoxazole moiety. Al Mustansiriyah Journal of Pharmaceutical Sciences. 19(4), 217-238.

36. Popiołek Ł., Stefańska J., Kiełczykowska M., Musik I., Biernasiuk A., Malm A., Wujec M., 2016. Synthesis, Dissociation Constants, and Antimicrobial Activity of Novel 2, 3- Disubstituted- 1, 3- thiazolidin- 4- one Derivatives. Journal of Heterocyclic Chemistry. 53(2), 393-402.

37. Hussain F., Khan Z., Jan M. S., Ahmad S., Ahmad A., Rashid U., Sadiq A., 2019. Synthesis, in-vitro α-glucosidase inhibition, antioxidant, in-vivo antidiabetic and molecular docking studies of pyrrolidine-2, 5-dione and thiazolidine-2, 4-dione derivatives. Bioorganic chemistry. 91, 103.