Frontiers in Health Informatics www.healthinformaticsjournal.com
ISSN-Online: 2676-7104
2024; Vol 13: Issue 2 Open Access

Study of Molecular Docking (Intraction and Connucation) of Drugs Metformin and Pioglitazone for Thyroid Dysfunction in Patients with Diabetes

Idries Muhson Abeed Al-Mashkor[1], Iqbal J. Al-assadi[2], Hanan A. Al-Hazam[3]
[1,2,3]Department of Chemistry, Faculty of Science, University of Basrah, Iraq
E-mail : idris_m@utq.edu.iq [1], Iqbal.bader@uobasrah.edu.iq [2], hanan.radhy@uobasrah.edu.iq [3]

Article Info

Article type:

Research

Article History:

Received: 2024-03-10

Revised: 2024-05-02

Accepted: 2024-06-20

Keywords:

molecular docking, Intraction, connucation, thyroid dysfunction, diabetes

A B S T R A C T

In this study, docking analysis and scores were obtained from the compounds against the receptor (insulin hormone). The yield of all ligands was given by energy values in kcal/mole. ligands show remarkable degrees of docking. The docking score of the target compounds was compared with the docking score of the drug (metformin and pioglitazone), which is used as an effective drug to treat diabetes, which showed higher docking scores. The interactions were the bond strength of the compounds. The strength of the compounds' binding to the receptor was strong and close, and the results in (metformin and pioglitazone) showed that the best association with the protein and separate from it was the strongest association with compound (metformin and pioglitazone). With the protein, it was found to be strongly associated with the amino acid (LYS 75, PHE 106, LYS 40, ARG 67) and (NH1 ARG 18) bound to the functional group (Amine, hydroxide,) H-donor and pi-H of the H receptor, pi-caten. compound metformin that binds strongly to the amino acid, and then the bonding strength of compound pioglitazone is less than the previous compound, and at the same time they have a good bond with the pharmaceutical compound (metformin and pioglitazone) and how the images of these compounds are presented through the figures taken from MOE program.

INTRODUCTION

Long regarded as the benchmark for determining the biological activity of compounds, High-Throughput Screening (HTS) consists of comparing extensive collections of chemical compounds to collections of molecular targets. The substantial expenses associated with establishing and maintaining these screening platforms render them seldom utilized in the pharmaceutical discovery sector [1]. Furthermore, the increasing prevalence of computational techniques, also known as "in silico approaches," can be readily explained by the rapid expansion of structural, chemical, and biological data pertaining to a wide range of therapeutic targets and the most recent advancements in computer technology.

Over the past few decades, the utilization of artificial intelligence (AI), molecular modelling, and cheminformatics methodologies has increased significantly [2–6]. Presently, in silico methodologies enable the expeditious virtual screening of a substantial quantity of compounds, thereby reducing the initial expenditures associated with the identification of potential drug candidates and augmenting the likelihood of discovering the necessary medications. Presently, a plethora of molecular modelling techniques exist to aid in the progress of drug development. The vast majority of these techniques can be classified into one of two categories: ligand-based or structure-based methodologies

Structure-based approaches enable the prioritization of molecule databases based on the structural and electrical compatibility of ligands with targets [7]. These approaches operate under the assumption that one possesses knowledge of the three-dimensional structure of an intriguing target. In this regard, molecular docking [7] is one of the most well-known and efficient structure-based in silico methods for predicting the interactions that occur between molecules and biological targets. A scoring function is commonly employed to estimate the complementarity of a ligand with a receptor subsequent to predicting its molecular orientation [7]; this is the means by which the procedure is concluded.

Since its inception in the mid-1970s, the docking procedure has demonstrated its utility in elucidating the interactions between chemical compounds and their molecular targets, in addition to facilitating the discovery and development of novel pharmaceuticals. In reality, an increasing number of studies are employing molecular docking to identify the crucial structural elements necessary for ligands to interact effectively with receptors [7–21]. Furthermore, the development of docking techniques that are more precise is underway. In the early 1980s, Kuntz et al. conducted one of the pioneering and most significant investigations in the fields of drug discovery and biology by employing a computer technique to analyze docking. The geometric feasibility of ligand and receptor alignments for the home-myoglobin/metmyoglobin and thyroxine/prealbumin structures was investigated in this study [13]. While not the initial study to employ docking to predict potential molecular complex configurations [9], it was the first to present a more straightforward function for characterizing protein-ligand interactions, consisting solely of "hard sphere repulsions" and "hydrogen bonding" [9,11,12,22]. The authors' conceptualization of the receptor as a rigid body featuring "pockets" at the site of binding also represented a novel approach. It is worth noting that the methodology employed in this study successfully identified protein conformations that hold promise for future energy refinement and design. Additionally, the predicted structures closely resembled those of X-ray complexes that have been previously published. Ligands that are novel [13]. Subsequent to its inception, molecular docking has witnessed substantial progress, including the implementation of flexible computation algorithms [21, 23–26]. Furthermore, it was progressively implemented in the advancement and refinement of molecules that held promise for therapeutic uses. An example of this can be observed in the research conducted by Ring et al. [27], wherein they utilized docking and other structure-based drug design methods to identify novel non-peptidic inhibitors of cysteine and serine protease enzymes.

The results of this research provided additional evidence for the utility of computer-aided methods in drug design that utilize molecular structures to generate lead compounds [27].

Due to the potential of this methodology, additional endeavours are being undertaken to improve docking algorithms and overcome their intrinsic limitations [28–30]. Significant limitations associated with docking methods encompass the reliance on estimated scoring functions, which may produce results that fail to correspond with true binding affinities, as well as a restricted sample size for pose prediction encompassing both ligand and receptor conformations [31, 32]. When designing medications, docking can only be applied to biological targets whose crystal structures are known. There have been numerous approaches taken to resolve this latter constraint. In the absence of three-dimensional structures, homology models can be constructed using structural templates that possess sequences that are extremely similar. Moreover, in order to validate and enhance the in silico simulated complexes, it is possible to combine these methods with molecular dynamics (MD) [33–35].

Nevertheless, the current progress in crystal structure determination and structural biology will undoubtedly mitigate this issue by consistently increasing the availability of ligand-target complexes generated experimentally [36–39]. Utilising in silico methods, including molecular dynamics, the conformational space of the targets, ligands, and ligand-target combinations under investigation has also been exhaustively investigated.

Stricter virtual screening procedures and the fine-tuning of docking results are more sophisticated approaches that more accurately represent the dynamic behaviour of ligand-target complexes and enhance docking results. These post-docking refining and rescoring techniques are highly advantageous in the field of drug discovery due to the fact that they typically increase the success rate of virtual screening campaigns and establish more robust connections with experimental data. There have been numerous publications that examine the function and

applications of docking in the discovery and design of new medications. It is essential to keep in mind that since the invention of docking, its applications and purposes have evolved. Initially developed to investigate molecular recognition between large and small compounds, docking is now applied to a vast array of pharmacological applications.

Moreover, docking facilitates the comprehension of the interrelationships among multiple molecular targets associated with a specific disease, a critical aspect of modern drug development and polypharmacology at large.

As a result of advancements in docking algorithms and the accessibility of publicly available ligand and target data, the application of this methodology has expanded to facilitate the discovery of new drugs. An illustration of this can be seen in the ease with which large-scale screening protocols can now incorporate docking due to its enhanced speed and predictive capability. These protocols aim to identify various factors, such as potential negative drug reactions, ligands with unique chemical structures that exhibit activity against specific targets or desired sets of targets, and protein binding sites for putative ligand binding. This analysis will examine the contribution that docking techniques make to drug discovery initiatives. Innovative drug design strategies, including target identification, polypharmacology, drug repurposing, and adverse drug response prediction, will be highlighted in particular.

It has been established that current docking-based rational design techniques hold great promise for drug discovery [3,5,7,18,47,49,50,63]. As previously stated, anchoring is subject to inherent limitations that restrict its capacity for prediction. Docking, which was previously employed as an independent approach in drug design, is now frequently incorporated into pipelines alongside ligand-based, structure-based, and artificial intelligence (AI) methodologies (Figure 2) [50, 64]. An important limitation of the structure-based approach is mitigated through the implementation of this integration.

As its initial purpose envisaged, docking is utilized in the drug development environment to validate ligand activity towards a specific target and to conduct structure-based virtual screening campaigns. In addition, target complementarity groups can potentially be identified through the utilization of docking techniques, which involve target fishing and profiling. A subset of these groups might be associated with unforeseen adverse effects of medications (off-targets prediction). Moreover, docking is currently being employed to identify ligands that can simultaneously bind to multiple receptors (polypharmacology) and to discover novel applications for compounds whose safety profiles are well-established (drug repositioning).

Advancements in docking algorithms and the accessibility of publicly available ligand and target data have significantly expanded the potential applications of docking methods in the field of pharmaceutical development. As an illustration, mooring has been integrated into screening protocols for large-scale operations due to its enhanced speed and predictive capabilities. The purpose of these protocols is to identify potential adverse drug reactions (ADRs) [62], novel molecular targets of known ligands [54], protein binding sites suitable for ligand binding [61], ligands with novel chemotypes that exhibit activity against a specific target or a desired set of targets [55], and potential ligands that bind to novel adversity [62].

In this study, we will investigate the potential utility of docking techniques in drug discovery tasks, focusing on novel approaches to drug design including polypharmacology, target identification, drug repurposing, and prediction of adverse drug reactions.

For computer-aided structure-based drug design, it is critical to comprehend the targeted protein structure in order to calculate the interaction energies between various compounds [43–46]. Utilizing a structural database comprising crystallised target proteins can serve as a fundamental basis for the development of energy-efficient and selective compounds that bound to the target [47–57]. A more comprehensive term to describe this approach is Virtual High-Throughput Screening [58–65]. It involves the utilisation of computer-based screening methods to evaluate a substantial collection of chemically similar compounds for a specific biological activity. Virtual high-throughput screening may manifest in various forms, including strategies and techniques based on chemicals.

The lead optimization process during pharmaceutical development necessitates the utilization of computational tools, which offer significant cost advantages. This includes techniques such as similarity search, which selects compounds based on anticipated biological activity using models such as pharmacophore mapping or

Quantitative Structure-Activity Relationship (QSAR). In addition, virtual docking is employed to transfer compounds to a specific protein target. The utilization of computational techniques during the hit-to-lead optimization phase aids in the reduction of the quantity of compounds that need to be produced and assessed in vitro [66-74].[75-79].

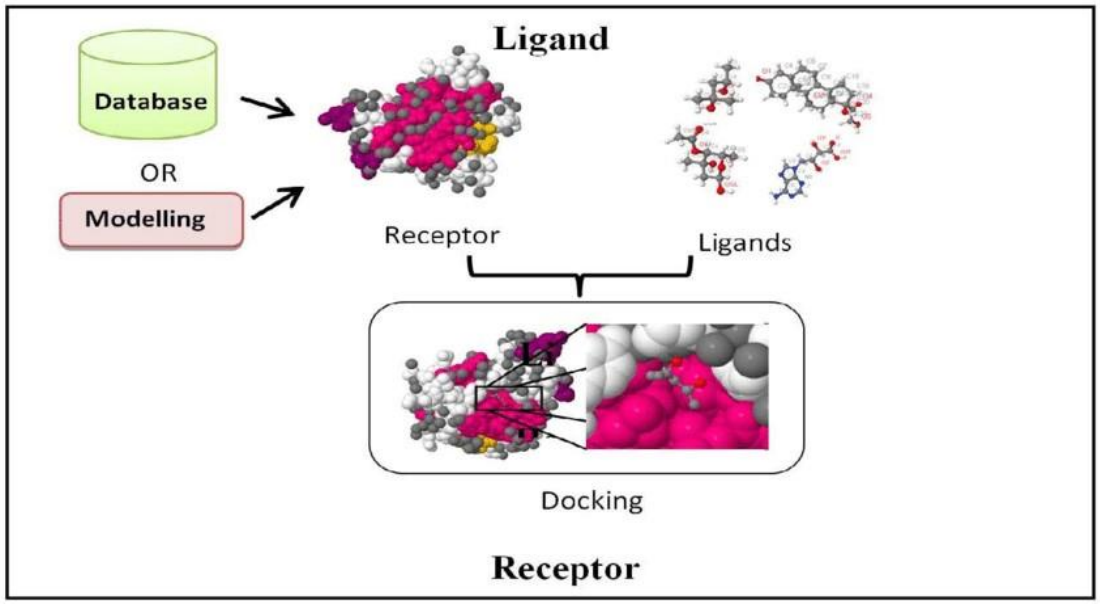


Fig. 1. Computer aided drug design model (CADD)

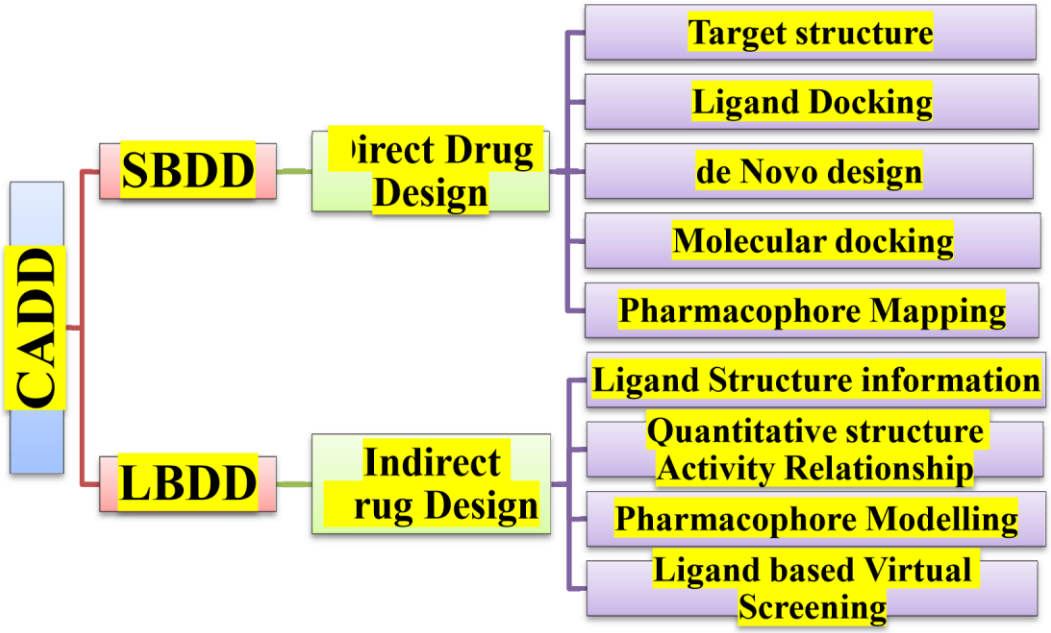


Fig. 2. Drug design structure

Structure - Based Drug Design (SBDD)

Ligand - Based Drug Design (LBDD)

THE PREVALENCE AND INCIDENCE OF THYROID DYSFUNCTION IN PATIENTS WITH DIABETES

Background

Thyroid disorders are generally acknowledged within the populace [1]. 2.8% of men and 7.5% of women of all ages had abnormally high levels of thyroid stimulating hormone (TSH), according to a study conducted in Whickham, United Kingdom [2]. A similar pattern was observed at a statewide health fair, where aberrant TSH levels were detected in 11.7% of attendees, per the Colorado Thyroid Disease Prevalence Study [3]. An increased risk of thyroid dysfunction is associated with advancing age [4–8]. Over the course of two decades, the Whickham study discovered that the mean annual occurrence of idiopathic hypothyroidism was 4%. Conversely, cases of thyroid antibodies were 27% more prevalent annually among women [2]. Additionally, there may be ethnic variations in prevalence, with Indians exhibiting 15–30% higher rates.
Thyroid abnormalities, the most prevalent autoimmune disorders among individuals with diabetes, affect twelve to twenty-four percent of patients diagnosed with type 1 diabetes (T1DM) and three to six percent of patients diagnosed with type 2 diabetes (T2DM) [13–16]. Regular thyroid dysfunction screening is recommended in light of the data suggesting a greater incidence of thyroid dysfunction among individuals with type (1) diabetes mellitus and type (2) diabetes mellitus [13, 14].
Nonetheless, prevalence statistics were utilized in the formulation of thyroid screening guidelines. A prospective study found that the annual incidence of patients with abnormal thyroid function was a mere 1%.
Illness of the 2nd type of diabetes mellitus (T2DM) is a chronic metabolic disorder caused by dysfunctional pancreatic beta cells and peripheral insulin resistance. It is estimated that 9.1% of the global population, or 415 million individuals, are afflicted with this disease. Both genetic and lifestyle factors contribute to the development of type 2 diabetes, a complex disease. Recent research suggests that individuals with prediabetes or low thyroid hormone levels, even when they fall within the normal reference range, may have an increased susceptibility to type 2 diabetes.
Similar to diabetes, thyroid dysfunction arises from disturbances in the secretion of hormones. The Colorado Thyroid Disease Prevalence study revealed that 2.2% of the participants exhibited hypothyroid-stimulating hormone (TSH) levels, whereas 9.5% of the individuals tested positive for excessive TSH. The thyroid hormone axis consists of thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH); all three are vital for maintaining thyroid function. Potential consequences of these hormonal imbalances include hyperactivity (hyperthyroidism) or metabolic underactivity.
Hypothyroidism, in other words. Subclinical or clinical classifications are assigned to the disorder, clinical being the more common, contingent upon the severity of the imbalance. TSH levels that deviate from the norm (normal T4 concentration) are frequent indicators of subclinical thyroid disease. There is not always a correlation between T4 levels and the presence or absence of symptoms. Despite its benign manifestation, subclinical thyroid dysfunction has been shown to have significant clinical implications.
associated with a variety of complications, including cardiovascular disease (CVD) [25, 27], type 1 diabetes in adolescents [27], and chronic renal disease [26].
A multitude of studies have established a correlation between type 2 diabetes and thyroid dysfunction [28–29]. Research suggests that there might be a reciprocal relationship between thyroid issues and diabetes [30, 31]. The Third National Health and Nutrition Examination Survey (NHANES III), a significant cross-sectional survey, revealed that 1.3% of 17,353 individuals in the United States had hyperthyroidism and 4.6% had hypothyroidism [32]. In addition, NHANES III identified a greater

Those diagnosed with diabetes had a higher incidence of thyroid dysfunction compared to those without the condition.
Research has demonstrated that thyroid hormone regulates both the function of the pancreas and the carbohydrate metabolism [33].
However, diabetes has the potential to impact thyroid function in a variety of ways.
For example, research has shown that diabetes can impact the manner in which thyrotropin-releasing hormone

(TSH) reacts with TSH; this can lead to hypothyroidism and a subsequent reduction in T3 levels [34]. Lower T3 concentrations have been suggested as the result of a reduced quantity of Extensive research has been conducted on the correlation between hyperglycemia-induced reversible deiodinase activity reduction and hepatic thyroxine levels and the conversion of T4 to T3 in diabetes [35]. A short-term excess of T3 may induce insulin resistance, which may subsequently contribute to the development of T2DM, according to some studies [36, 37]. However, the relationship between thyroid hormone levels and the risk of type 2 diabetes remains controversial due to inconclusive findings in human studies. While certain studies have failed to establish a statistically significant correlation, others have posited that elevated levels of thyroid-stimulating hormone (TSH) and decreased levels of free thyroxine exert a positive impact on insulin resistance and hyperglycemia [38–39, 40]. As a result, it is evident that a comprehensive assessment of the correlation among TSH, free thyroxine, and T2DM is necessary. In addition, the dose-response relationship between thyroid hormone levels and the risk of developing type 2 diabetes mellitus has been the subject of few studies [41–42]. To date, the majority of analyses have focused on determining the effects of baseline TSH and free thyroxine levels on the risk of developing T2DM.

RESULTS AND DISCUSSION

Docking Analysis, the docking scores were obtained from compounds
withe against (insulin Hormone) receptor. The yield of all ligands was given by energy values in kcal/mole as appeared in Table 1. Some ligands show great docking scores. Docking score of the compounds targeted was compared with the score of the drug (metformin and pioglitazone) which is used as a potent drug for the treatment of diabetes show higher docking scores. The interactions were the strength of the association of vehicles

The interactions were the strength of the association of vehicles with the future is strong and close The results showed in Tables (1) and (2) that the best correlation with protein and separated from was that the strongest correlation of the compound (1),(2), with the protein was found to be strongly linked with amino acidity (LYS 75,PHE 106,LYS 40, ARG 67) and (NH1 ARG 18)was associated with the functional group (Amin, hydroxide,) H-donor And pi-H of H-acceptor, pi-cation

Then followed by the compound (1) is strongly bound with the amino acid and then the bonding strength of the compound (2) comes less than the previous compound and at the same time they have a good correlation with the drug compound (1,2) and how the images of these compounds are shown through the forms taken from the program MOE Which shows its association with (ligand) in the figures.

Table (1) compounds (1,2)

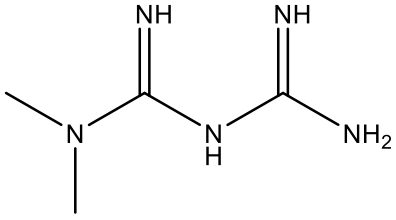
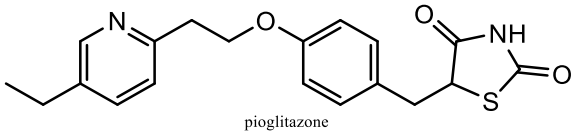
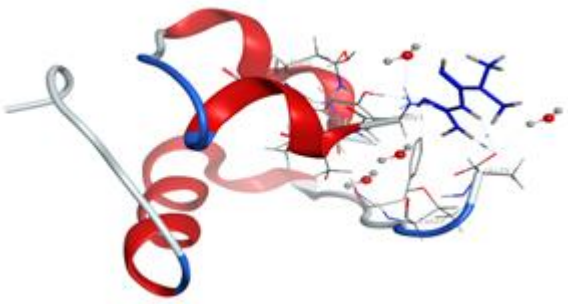
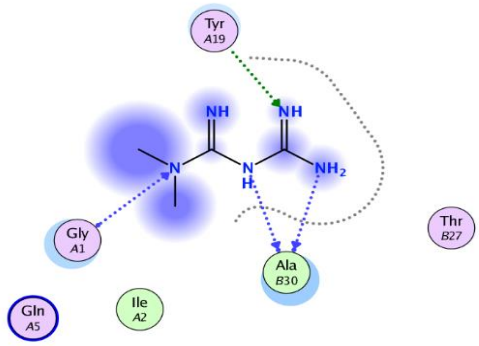
NO.	Name of the compounds	structure
1	metformin	
2	pioglitazone	

Table (2) Calculate the energies 1,2 and (insulin) with protein.

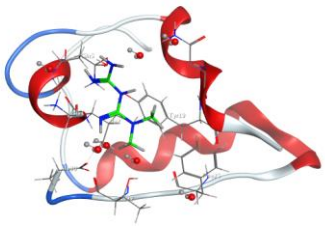
Compound	Docking Score E (Kcal/ mole)	Amino acid interaction	function group interaction
1	-4.504	LYS 75,PHE 106, LYS 40, ARG 67	Amine, hydroxide
2	-10.223	NH1 ARG 18	Amine, hydroxide



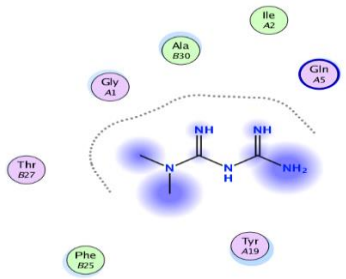
connucation of insulin with metformin more stabile



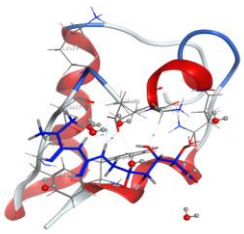
Intraction the metformin with insulin more stable



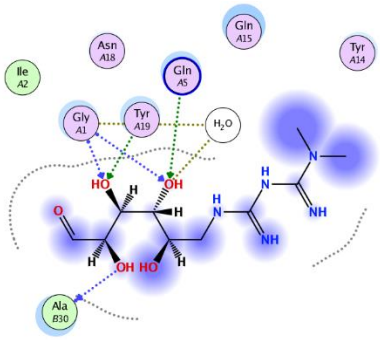
connucation of insulin with metformin less stabile

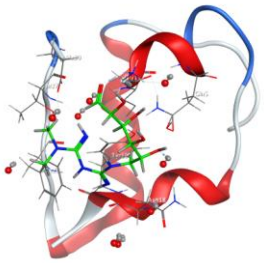


Intraction the metformin with insulin less stable

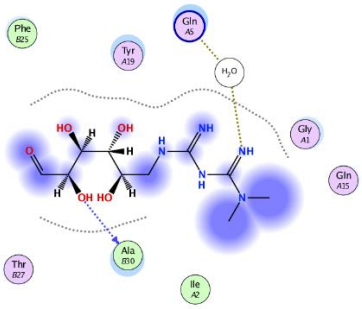


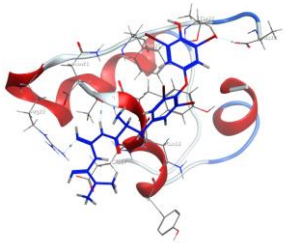
connucation of insulin with metformin and glucose more stabile



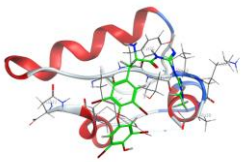


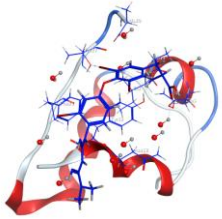
Intraction of insulin with metformin and glucose more stabile connucation of insulin with metformin and glucose less stabile



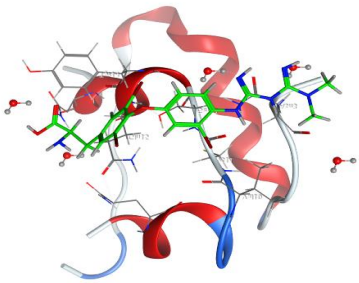


Intraction of insulin with metformin and glucose less stabile connucation of insulin with metformin-thyroxin more stabile

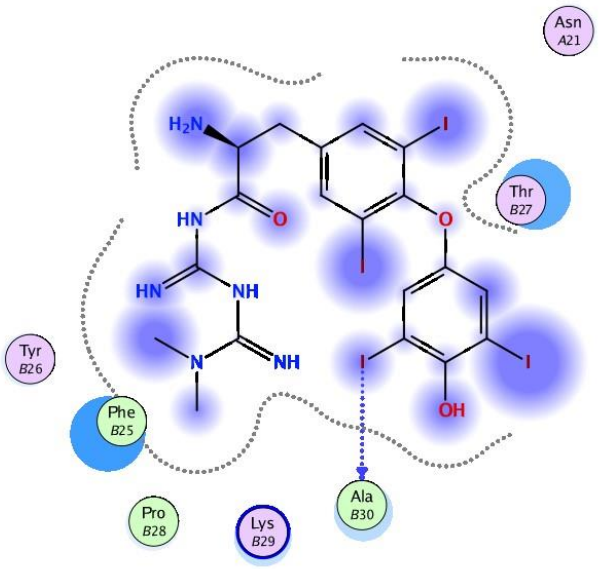




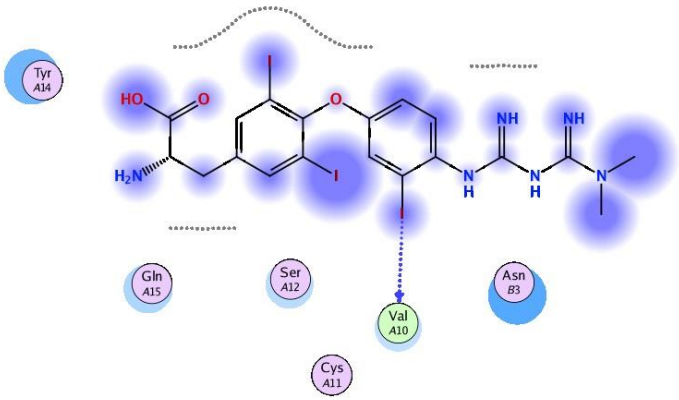
connucation of insulin with metformin-thyroxin less stabile connucation of insulin with metformin-thyroxin more stabile



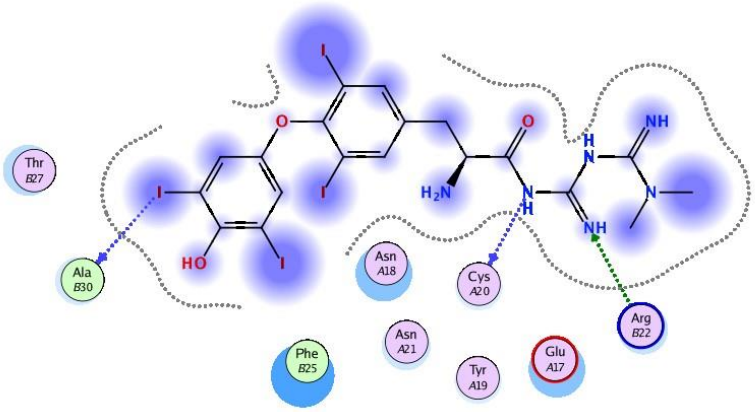
connucation of insulin with metformin-ttiiodinthroxin more stabile



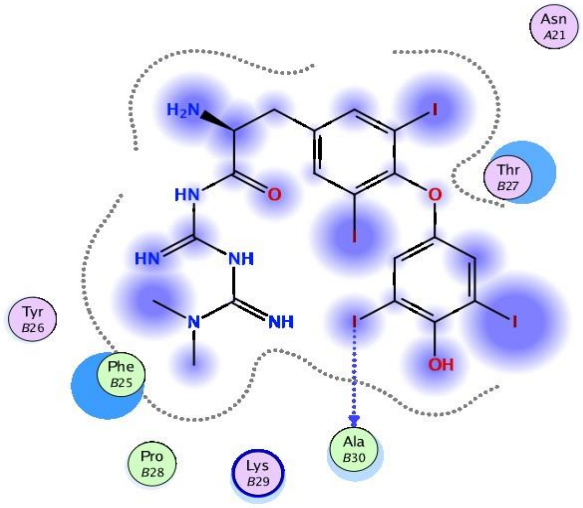
Intraction metformin-thyroxin less more stable



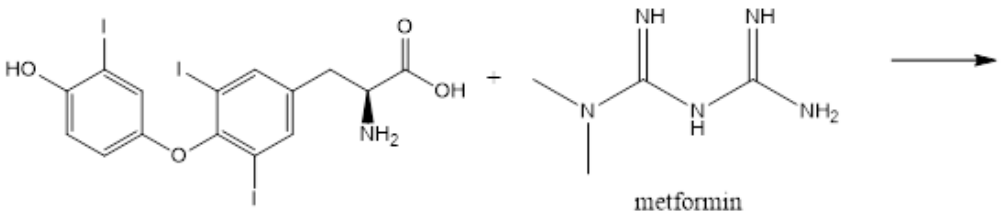
Intraction metformin-triiodothyronine less stable



Intraction metformin-thyroxin more stable

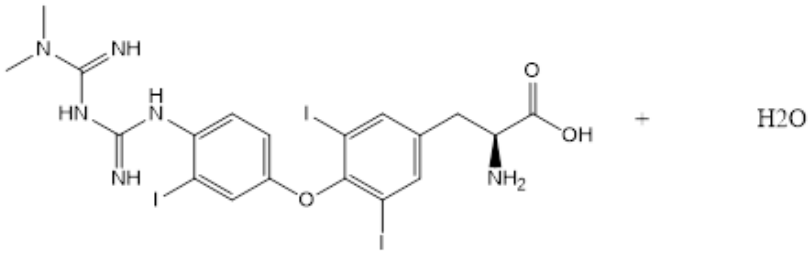


intrction metformin-thyroxin less stable



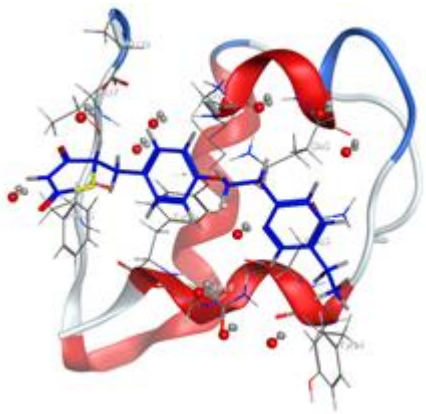
Triiodothyronine

metformin

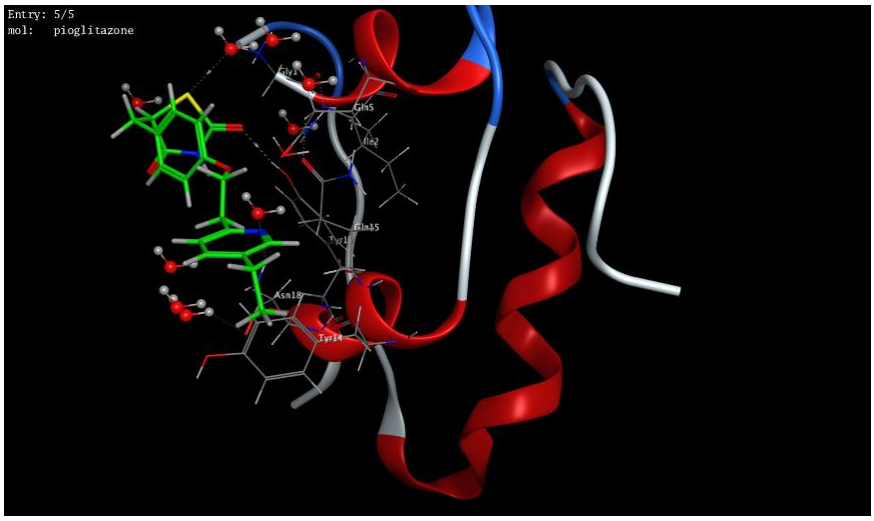


(*S*)-2-amino-3-(4-(4-(3-(*N*,*N*-dimethylcarbamimidoyl)guanidino)-3-iodophenoxy)-3,5-diiodophenyl)propanoic acid

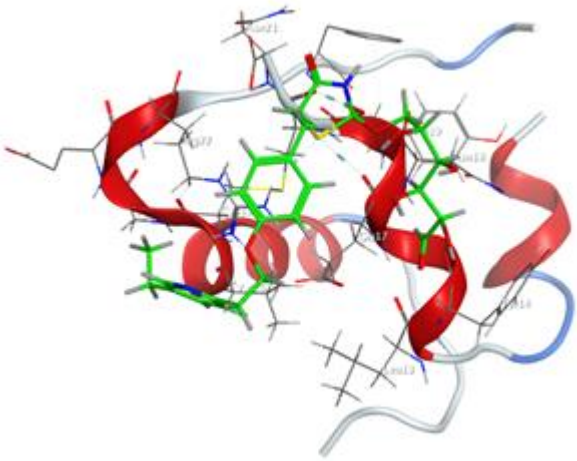
H2O



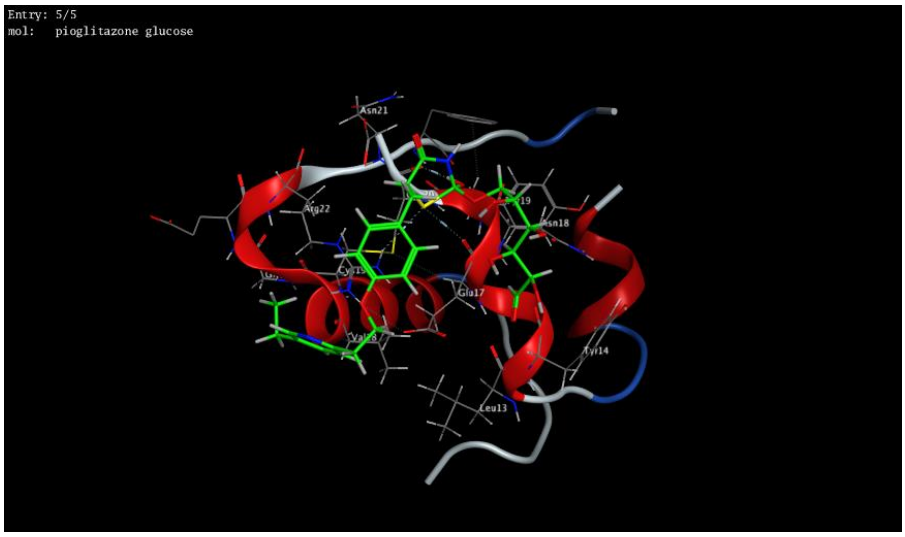
connucation of insulin with pioglitazone more stabile



connucation of insulin with pioglitazone less stabile

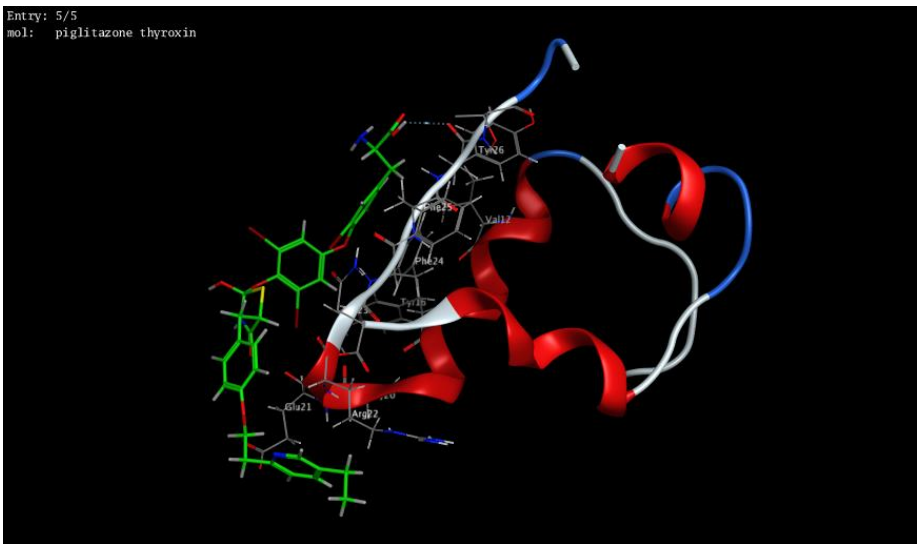


connucation of insulin with pioglitazone -glucose more stabile

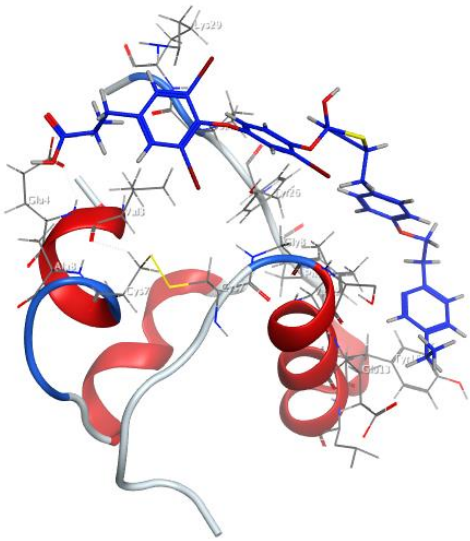


connucation of insulin with pioglitazone -glucose less stabile

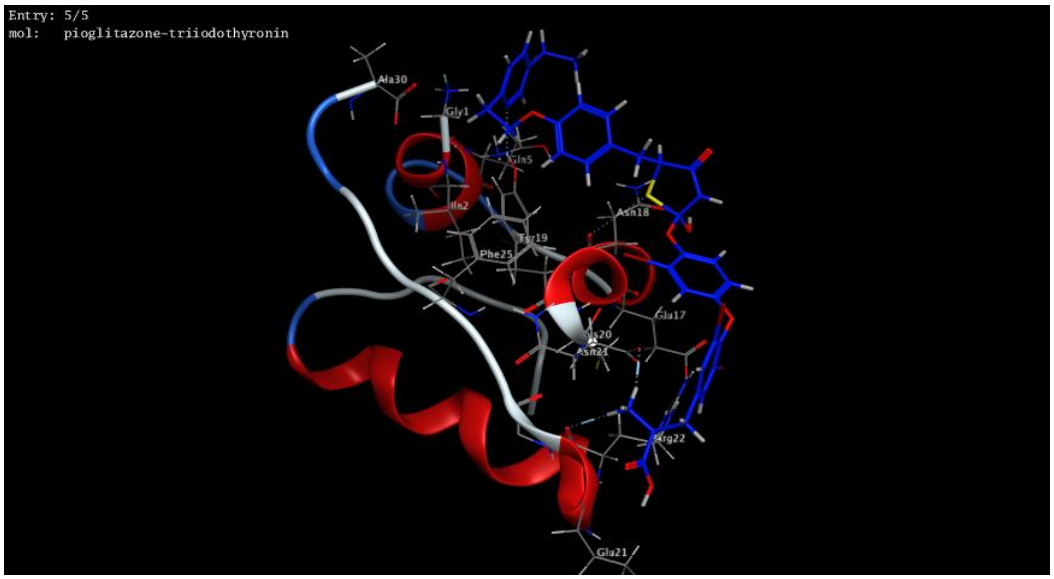
connucation of insulin with pioglitazone -thyroxin more stabile



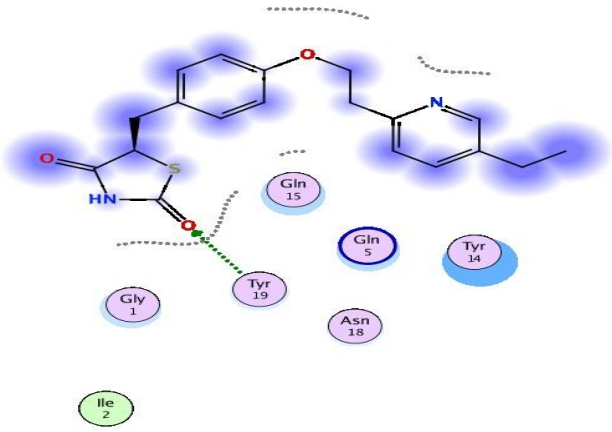
connucation of insulin with pioglitazone -thyroxin less stabile



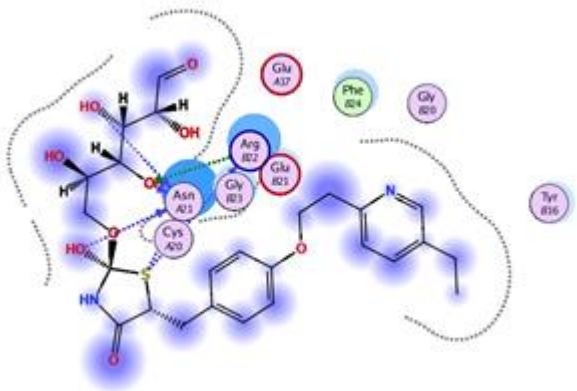
connucation of insulin with pioglitazone -triiodothyronine more stabile



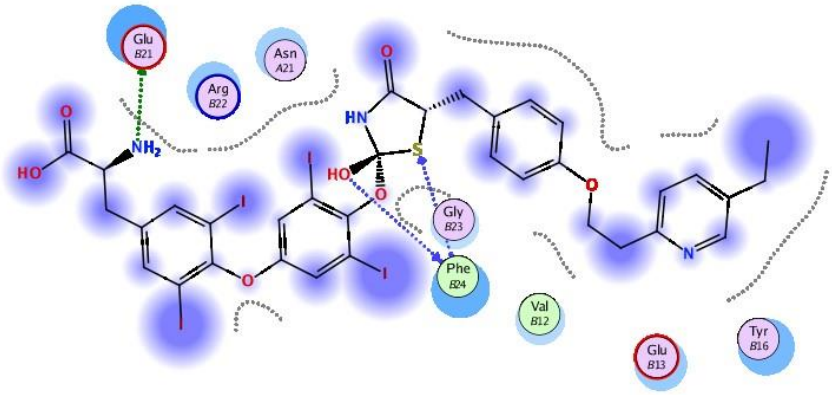
connucation of insulin with pioglitazone -triiodothyronine more stabile



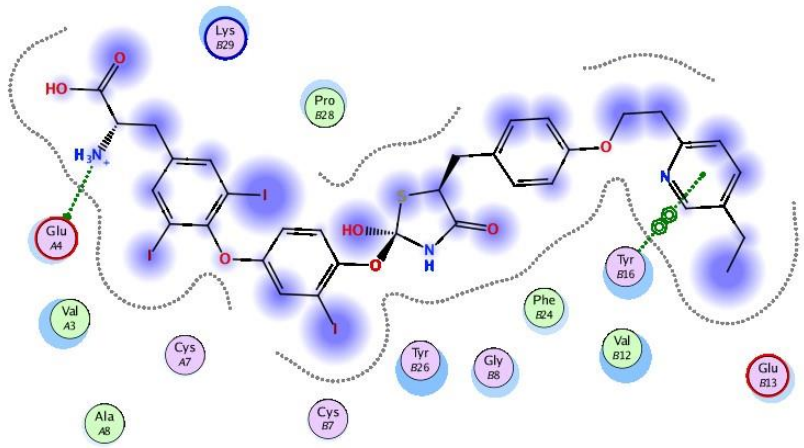
Intraction pioglitazone of the insulin



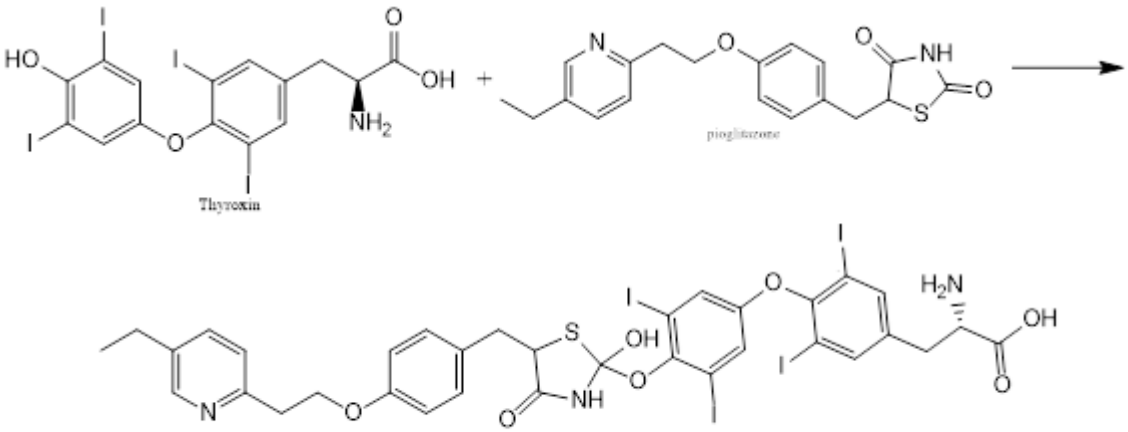
Intraction pioglitazone-glucose more stable



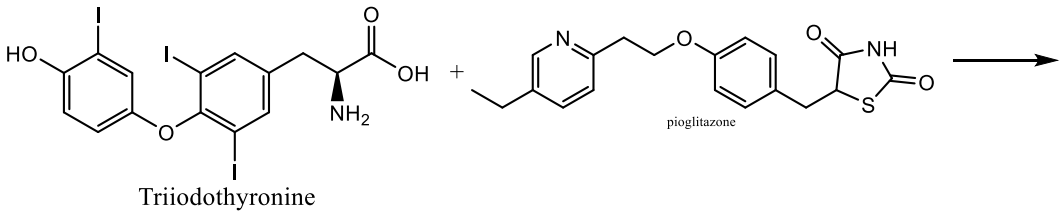
Intraction pioglitazone-thyroxin more stable

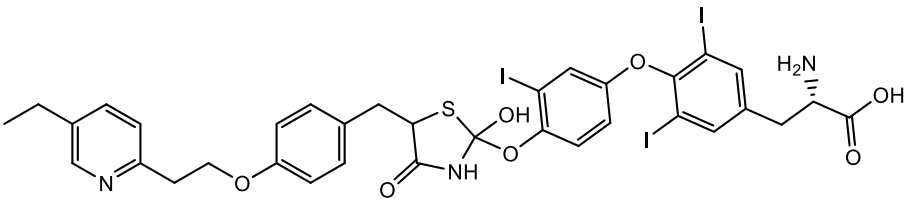


Intraction pioglitazone-triiodothyronine more stable



(2*S*)-2-amino-3-(4-(4-((5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2-hydroxy-4-oxothiazolidin-2-yl)oxy)-3,5-diiodophenoxy)-3,5-diiodophenyl)propanoic acid





(2*S*)-2-amino-3-(4-(4-((5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2-hydroxy-4-oxothiazolidin-2-yl)oxy)-3-iodophenoxy)-3,5-diiodophenyl)propanoic acid

Table (3) :The results and study from docking of Drugs with Insulin hormone.

Drugs	S score Kcal/mole	RMSD	Atom of compound	Atom of receptor	Involved Receptor residues	Type of interaction bond	Distance (A)	E(kcal/mole)
metformin	-5.07	2.08	N-2 N-6	OE1 OE1	GLU 21 GLU 21	H-donor H-donor	3.331 3.04	-1.4 -4.5
Pioglitazone	6.52	2.53	S-31 6-ring	O 6-ring	LEU 17 TYR 16	H-donor Pi-pi	11.01 5.43	-0.6 -0.0
Pioglitazone and glucose	7.15	2.21	N-1 NE2 14 NE2 14 OE1 17	O OE1 OD1 OH	ILE 2 GLN 15 ASN 18 TYR 19	H-donor H-donor H-donor H-acceptor	3.00 2.85 2.95 2.66 2.92 2.93	-1.2 -3.4 -1.6 -3.3 -2.6 -1.0
Metformin and glucose	5.39	2.22	O-29 O-33	O O	TYR 26 TYR 26	H-donor H-donor		

Table (4) :The results and study from docking of Drugs and Thyroid hormones with Insulin hormone.

Drugs	S score Kcal/mole	RMSD	Atom of compound	Atom of receptor	Involved Receptor residues	Type of interaction bond	Distance (A)	E(kcal/mole)
Metformin and thyroxin	-6.03	2.35	N-16 I-40 N-18	O O NH2	CYS ALA ARG	H-donor H-donor H-acceptor	2.99 3.84 3.30	-2.4 -1.1 -2.4

			S-31	O	LEU 17	H-donor	11.01	-0.6
			6-ring	6-ring	TYR 16	Pi-pi	5.43	-0.0
Metformin	-6.32	2.24					3.75	-0.7
and			I-31	OG1	THR	H-donor	2.94	-0.4
triiodothyronine			N-21	OH	TYR	H-acceptor		
							2.66	-3.3
							3.20	-0.9
Pioglitazone and	-6.69	2.32	N-46	OE2	GLU 21	H-donor	3.22	-1.4
thyroxin			O-79	O	PHE 24	H-donor	3.42	-2.6
			S-31	N	PHE 24	H-acceptor		
							3.01	-5.9
Pioglitazone and		2.53	N-46	OE2	GLU	H-donor	3.01	-4.4
triiodothyronine			N-46	OE2	GLU	Ionic	3.99	-0.0
	-6.97		6-ring	6-ring	TYR	Pi-pi		

CONCLUSIONS

In this research, the Docking process was performed to computer-reveal the strength of the association between compounds and proteins using the (MOE) program. The theoretical association process was performed for the compounds listed in the table. Two compounds from the literature that previously showed effectiveness as a treatment for diabetes were studied to find out the best compound from them in terms of binding to the amino acids of the insulin hormone, and thus nominate the best activator to insulin and increase its sensitivity to enter the cells. The results showed that (Metformin and Blackraz) have effectiveness and preference through their binding energy with insulin. The amino acids that were linked to the mentioned drugs are responsible for increasing the effectiveness of these compounds, as the best compounds showed strong binding with these acids. Through this study, we show the mechanism of the effectiveness of these drugs in terms of their binding and increasing the sensitivity of both compounds.

REFERENCES

1. Wang C, Crapo LM (1997) The epidemiology of thyroid disease and implications for screening. EndocrinolMetab ClinNAm26(1):189–218
2. Tunbridge WM, Evered DC, Hall R et al (1977) The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol 7(6):481–493
3. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. Arch Intern Med 160(4):526–534
4. Eggertsen R, Petersen K, Lundberg PA, Nystrom E, Lindstedt G (1988) Screening for thyroid disease in a primary care unit with a thyroid stimulating hormone assay with a low detection limit. BMJ297(6663):1586–1592
5. Cooper DS (1998) Subclinical thyroid disease: a clinician's perspective. Ann Intern Med 129(2):135–138
6. Sawin CT, Chopra D, Azizi F, Mannix JE, Bacharach P (1979) The aging thyroid. Increased prevalence of elevated serum thyrotropin levels in the elderly. JAMA 242(3):247–250
7. Vanderpump MP, Tunbridge WM, French JM et al (1995) The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. Clin Endocrinol 43(1):55–68

8. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC (1991) Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations n the elderly in the United Kingdom. Clin Endocrinol 34(1):77–83
9. Nair A, Jayakumari C, Jabbar PK, Jayakumar RV, Raizada N, Gopi George GS, Seena TP (2018) Prevalence and associations of hypothyroidism in Indian patients with type 2 diabetes mellitus. J Thyroid Res 2018:5386129. https://doi.org/10.1155/2018/5386129
10. Chutia H, Bhattacharyya H, Ruram AA, Bora K, Chakraborty M (2018) Evaluation of thyroid function in type 2 diabetes in northeastern part of India: a hospital-based study. J Family Med Prim Care 7(4):752–755. https://doi.org/10.4103/jfmpc.jfmpc_292_17
11. Barmpari ME, Kokkorou M, Micheli A, Alexiou I, Spanou E, Noutsou M, Thanopoulou A (2017) Thyroid dysfunction among Greek patients with type 1 and type 2 diabetes mellitus as a disregarded comorbidity. J Diabetes Res 2017:6505814. https:// doi.org/10.1155/2017/6505814
12. Han C, He X, Xia X, Li Y, Shi X, Shan Z, Teng W (2015) Subclinical hypothyroidism and type 2 diabetes: a systematic review and meta-analysis. PLoS One 10(8):e0135233. https://doi. org/10.1371/journal.pone.0135233
13. Riley WJ, Maclaren NK, Lezotte DC, Spillar RP, Rosenbloom AL (1981) Thyroid autoimmunity in insulin-dependent diabetes mellitus: the case for routine screening. J Pediatr 99(3):350–354
14. Perros P, McCrimmon RJ, Shaw G et al (1995) Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabet Med 12(7):622–627
15. Gray RS, Irvine WJ, Clarke BF (1979) Screening for thyroid dysfunction in diabetics. Br Med J 2(6202):1439
16. Feely J, Isles TE (1979) Screening for thyroid dysfunction in diabetics. Br Med J 1(6179):1678
17. Nerup J, Binder C (1973) Thyroid, gastric and adrenal autoimmunity in diabetes mellitus. Acta Endocrinol 72(2):279–286
18. Warren RE, Perros P, Nyirenda MJ, Frier BM (2004) Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid 14(10):853–857. https:// doi.org/10.1089/thy.2004.14.853
19. Hu C, Jia W. Diabetes in China: epidemiology and genetic risk factors and their clinical utility in personalized medication. Diabetes. 2018;67(1):3–11.
20. Gronich N, Deftereos SN, Lavi I, Persidis AS, Abernethy DR, Rennert G. Hypothyroidism is a risk factor for new-onset diabetes: a cohort study. Diabetes Care. 2015;38(9):1657–64.
21. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526–34. Fig. 6 Meta-analysis for associations of serum TSH levels (high TSH levels and low TSH levels) with CVD events and all-cause deaths among T2DM patients Rong et al. BMC Medicine (2021) 19:257 Page 11 of 13
22. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821): 1142–54.
23. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291(2):228–38.
24. Razvi S, Weaver JU, Pearce SH. Subclinical thyroid disorders: significance and clinical impact. J Clin Pathol. 2010;63(5):379–86. 25. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med. 2012;172(10):799–809.
26. Chuang MH, Liao KM, Hung YM, Wang PY, Chou YC, Chou P. Abnormal thyroid-stimulating hormone and chronic kidney disease in elderly adults in Taipei City. J Am Geriatr Soc. 2016;64(6):1267–73.
27. Bellastella G, Maiorino MI, Scappaticcio L, Casciano O, Petrizzo M, Caputo M, et al. TSH oscillations in young patients with type 1 diabetes may be due to glycemic variability. J Endocrinol Invest. 2018;41(4):389–93.
28. Feely J, Isles TE. Screening for thyroid dysfunction in diabetics. Br Med J. 1979;1(6179):1678.
29. Ghazali SM, Abbiyesuku FM. Thyroid dysfunction in type 2 diabetics seen atthe University College Hospital, Ibadan, Nigeria. Niger J Physiol Sci. 2010;25(2):173–9.

30. Blanc E, Ponce C, Brodschi D, Nepote A, Barreto A, Schnitman M, et al. Association between worse metabolic control and increased thyroid volume and nodular disease in elderly adults with metabolic syndrome. Metab Syndr Relat Disord. 2015;13(5):221–6.
31. Gray RS, Irvine WJ, Clarke BF. Screening for thyroid dysfunction in diabetics. Br Med J. 1979;2(6202):1439.
32. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489–99.
33. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014;94(2):355–82.
34. TE Gursoy NT. The relationship between the glycaemic control and hypothalamus-pituitary-thyroid axis in diabetic patients. Turkish J Endocrinol Metab. 1999;12:163–8.
35. Hage M, Zantout MS, Azar ST. Thyroid disorders and diabetes mellitus. J Thyroid Res. 2011;2011:439463.
36. Dimitriadis G, Baker B, Marsh H, Mandarino L, Rizza R, Bergman R, et al. Effect of thyroid hormone excess on action, secretion, and metabolism of insulin in humans. Am J Physiol. 1985;248(5 Pt 1):E593–601.
37. Solá E, Morillas C, Garzón S, Gómez-Balaguer M, Hernández-Mijares A. Association between diabetic ketoacidosis and thyrotoxicosis. Acta Diabetol. 2002;39(4):235–7.
38. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007;92(2):491–6.
39. Mehran L, Amouzegar A, Tohidi M, Moayedi M, Azizi F. Serum free thyroxine concentration is associated with metabolic syndrome in euthyroid subjects. Thyroid. 2014;24(11):1566–74.
40. Luna-Vazquez F, Cruz-Lumbreras R, Rodríguez-Castelán J, Cervantes-Rodríguez M, Rodríguez-Antolín J, Arroyo-Helguera O, et al. Association between the serum concentration of triiodothyronine with components of metabolic syndrome, cardiovascular risk, and diet in euthyroid post-menopausal women without and with metabolic syndrome. Springerplus. 2014;3:266.
41. De Pergola G, Ciampolillo A, Alò D, Sciaraffia M, Guida P. Free triiodothyronine is associated with smoking habit, independently of obesity, body fat distribution, insulin, and metabolic parameters. J Endocrinol Invest. 2010;33(11):815–8.
42. Bakiner O, Bozkirli E, Cavlak G, Ozsahin K, Ertorer E. are plasma thyroid stimulating hormone levels associated with degree of obesity and metabolic syndrome in euthyroid obese patients? A Turkish cohort study.ISRN Endocrinol. 2014; 2014:803028.
43. Jun JE, Jee JH, Bae JC, Jin SM, Hur KY, Lee MK, et al. Association between changes in thyroid hormones and incident type 2 diabetes: a seven-year longitudinal study. Thyroid. 2017;27(1):29–38.
26. de Vries TI, Kappelle LJ, van der Graaf Y, de Valk HW, de Borst GJ, Nathoe HM, et al. Thyroid-stimulating hormone levels in the normal range and incident type 2 diabetes mellitus. Acta Diabetol. 2019;56(4):431–40.
44. Chang CH, Yeh YC, Shih SR, Lin JW, Chuang LM, Caffrey JL, et al. Association between thyroid dysfunction and dysglycaemia: a prospective cohort study. Diabet Med. 2017;34(11):1584–90.