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AN EXPLAINING THEORY FOR DIURETIC-INDUCED-DIABETES INCIDENCES

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ABSTRACT

Many patients with hypertension are also suffering from Type II Diabetes Mellitus (TIIDM). Different studies argued the fact that if these patients can use Hydrochlorothiazide (HCTZ) group or not to treat hypertension as these diuretics are accused of with diuretic-induced diabetes especially Chlorthalidone and Bendroflumethiazide. As nothing is definite yet; in this paper, we are jotting down a new theory. In other words, we are seeking to study HCTZ interactions with sulfonylurea receptor Kir 6.2\SUR1 considering the chemical fact that HCTZ is also sulfonamide derivates like sulfonylurea drugs which are hypoglycemic agents used in the treatment of TIIDM. Therefore, we have studied in-silico 12 HCTZ compounds' interactions with the binding site of sulfonylurea in its receptor Kir6.2\SUR1. Then, we compared the results to the interactions of Glibenclamide (GBM); a sulfonylurea agent, with the named receptor. As a result, three compounds of this family (Chlorthalidone 1-1, Bendroflumethiazide 4-1, Metolazone 6-1) had bound to Kir6.2\SUR1 receptor in the same binding site of GBM. The rest members were almost close to the GBM binding site. These findings may explain the adverse effect that chlorthalidone and Bendroflumethiazide are accused of with. We suggest that they are agonists for Kir6.1\SUR1 receptor, which results in decreasing insulin secretion from the pancreas which consequences with hyper-glycemia. On the other hand, our results confirm that developing new anti-hyperglycemia agents from HCTZ as a lead compound is also possible and promising.

KEYWORDS: ***Thiazides, hypertension, hypoglycemic activity, Type II Diabetes Mellitus, Docking, Kir6.2\SUR1.***

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INTRODUCTION

Many patients with hypertension are also suffering from Type II Diabetes Mellitus (TIIDM). Different studies argued the fact if these patients can use Hydrochlorothiazide (HCTZ) group or not treat hypertension as these diuretics are accused of with the adverse effect diuretic-induced diabetes.[1] However, this effect is not definite yet as different factors play a role in it.[1-2] Researchers have resulted with those patients taking HCTZ who have Angiotensin Converter Enzyme ACE 4656 GG genotype will not suffer from diabetes, whereas patients with ACE 4565 hetero-type will.[1] Other studies have found a correlation between Hypokalemia and Hypoglycemia induced by HCTZ. Yet, other study casts doubt on it.[3] In addition, though HCTZs play an effective role in hypertension treatment, [4] and there are many pharmaceutical combinations between them and other anti-hypertension agents[5]; however, other papers confirmed that HCTZ initiate the onset of diabetes independently from B-blockers, or other anti hypertension agents.[6] On the other hand, there are recommendations to use HCTZ with diabetic patients but in low dose to treat hypertension in these cases.[7] However, another study proved that people taking HCTZs to avoid kidney stones incidences did not suffer from diabetes.[8] As none of these perspectives is definite yet, and diuretic-induced diabetes effect is still in debates; in this paper, we are suggesting a new theory for this adverse effect. This theory is based on in-silico detecting for HCTZ compounds and their interactions with sulfonylurea receptor Kir6.2\SUR1 considering the chemical fact that HCTZ is also sulfonamide derivates, Fig. 1, like the anti-hyperglycemia sulfonylurea drugs.[9]

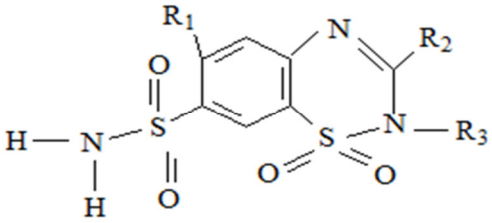
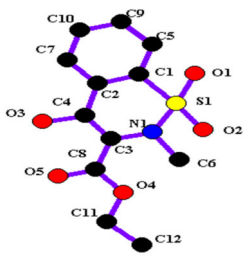


Figure 1
Thiazide diuretics general structure

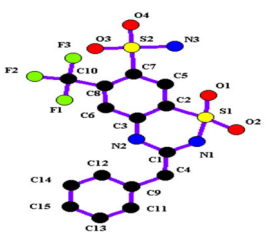
METHODS

Thiazide compounds' structures were obtained from Pubchem.com database. (Fig 2) Kir 6.2\SUR1 PDB ID used in this research was 6BAA. It was uploaded from Protein Data Bank database. [10-11] Autodock 4.2.1 software was used for the rigid docking process in default settings. PyMol, Chimera, PLIP and LigPlot+ were used for virtual screening and interactions' analyzing. Validation of the software was done by re-docking in the rigid mode the isolated GBM from its crystal structure with its receptor. As four Glibenclamide (GBM) molecules located in the chains (E-H) of the receptor Kir6.2\SUR1, we have worked only on chain F. The binding site residues were obtained from PDB database.[10] And,each compound of HCTZ was docked with the binding site in the named chain. Scoring function used was binding energy in addition to the study of the binding sites' interactions and the number of complexes indicated in the same pockets out of 10 for each molecule.

Benzthiazide



Bindroflumethiazide



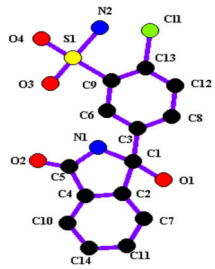
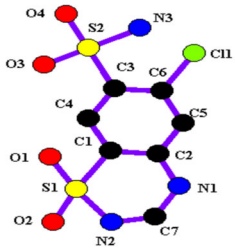
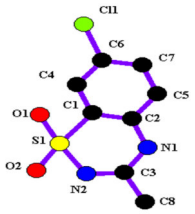
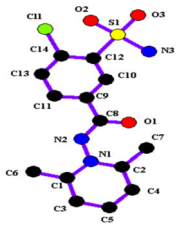
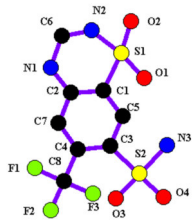
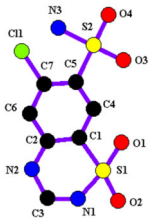
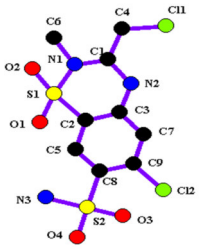
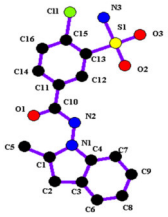
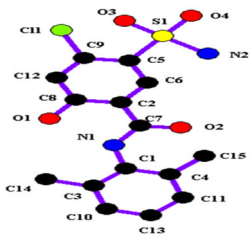
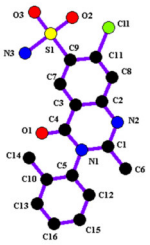
Chlorthalidone		**Chlorothiazide**	
Diazoxide		**Clopamide**	
Hydroflumethiazide		**Hydrochlorthiazide**	
Methichlothiazide		**Indapamide**	
Xepamide		**Metholazone**	

Figure 2
HCTZ chemical structures.

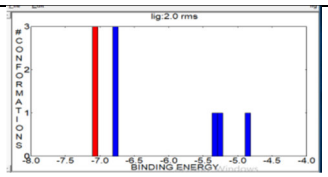
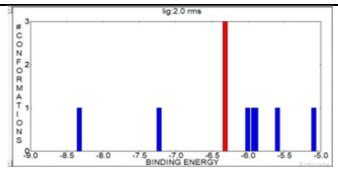
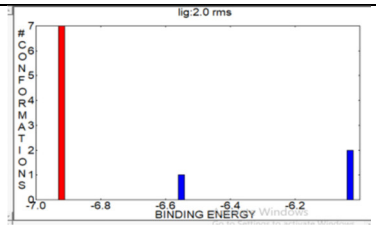
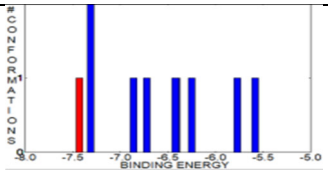
RESULTS AND DISCUSSION

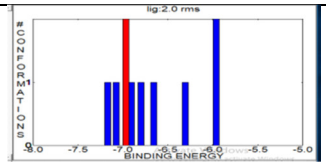
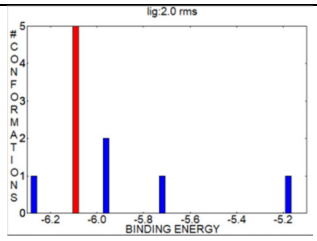
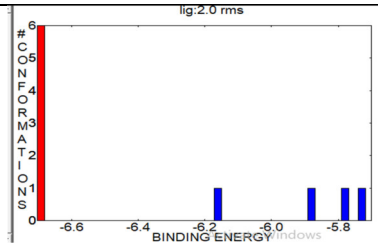
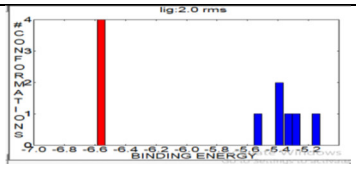
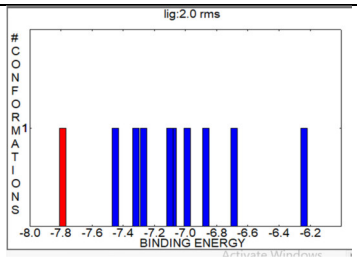
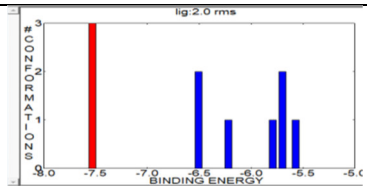
As researchers can see in Table 1, we have studied the twelve HCTZ compounds' interactions with Glibenclamide (GBM) binding site in the sulfonylurea receptor Kir 6.2\SUR1. Table 2 presents these findings in short. It is clear that Chlorthalidone, Bendroflumethiazide, Metholazone with their complex conformations 1-1, 4-1, 6-1 respectively bind to Kir6.2\SUR1 in the same pocket as Glibenclamide by conforming H-bonds and hydrophobic bonds. The common bounded residues are ARG 1246, SER 1238, TRP 430, THRE 1242, ASN 1245 and PHE 433 shown in Table 3. This may explain the reason behind being these drugs especially the first two are not very recommended for diabetic patients with hypertension. The new theory that we suggest is that probably these compounds work as agonists for Kir6.2\SUR1 receptor. This results in decreasing Insulin secretion from pancreatic cells which causes hyperglycemia as a consequence. However, we

hope this suggestion be undergoing biological investigations. On the other hand, the rest members have another preferable binding site than GBM one. This new binding site is somehow close to GBM pocket. It includes the residues ILE 585, GLN 444, GLN 369, ASP 310, ARG 370 and ASN 1293 (Table 3). Superimposing the interacted complexes for the rest 9 compounds' conformations with Kir6.2\SUR1 is presented in Fig 3. There are 8 compounds in one pocket, and the last member which is Clopamide locates in the different site. These differences between GBM and HCTZs bindings are probably because of the thiazide group which is responsible for the affinity to other residues than the ones that GBM binds to (Fig 4). Therefore, The last presented findings in Fig 4 can be a cornerstone for developers in drug discovery to use HCTZs as lead compounds to discover new anti-hyperglycemia agents by applying chemical modifications like lengthening R moieties from sulfonylurea group or thiazide group as the pocket they bind to is too close to GBM one (Fig 5).

Table 1

HCTZ family members' docking results with Kir6.2\SUR1.

Compound Name	Complex: conformations	Binding energy	Notes	Complexes binding energy and conformation chart	Interaction with the binding site
Benzthiazide	**Complex1:**		**Best**		**Close**
	1-1	**-7.07**	**docked**		**closer**
	1-2	**-6.83**	**and**		
	1-3	**-6.76**	**best**		
	Complex2:		**clustered**		**close**
	2-1	**-6.77**			
	2-2	**-6.75**			
	2-3	**-6.77**			
Bindroflumethiazide	**Complex1:**		**Best**		**No**
	1-1	**-8.33**	**docked**		
	Complex3:				
	3-1	**-6.32**	**Best**		**No**
	3-2	**-6.29**	**clustered**		
	3-3	**-6.27**			
	Complex4:				**Yes**
	4-1	**-6.01**			
Chlorothiazide	**Complex1:**		**Best**		**No**
	1-1	**-6.92**	**docked**		
	1-2	**-6.91**	**and**		
	1-3	**-6.91**	**best**		
	1-4	**-6.72**	**clustered**		
	1-5	**-6.70**			
	1-6	**-6.68**			
	1-7	**-6.65**			
	Complex2:				
	2-1	**-6.55**			**Close**
Chlorthalidone	**Complex1:**		**Best**		**yes**
	1-1	**-7.43**	**docked**		
					Close
	Complex2:		**Best**		
	2-1	**-7.31**	**clustered**		**Close**
	2-2	**-7.23**			
	Complex3:				**Close**
	1-1	**-6.86**			

Clopamide	**Complex1:**		**Best**		
	1-1	**-7.17**	**docked**		**Close**
	Complex2:				
	2-1	**-7.08**			**Yes**
	Complex3:		**Best**		
	3-1	**-6.97**	**cluster**		**No**
	3-2	**-6.94**	**ed**		
	Complex8:				**No**
	8-1	**-5.96**	**Best**		
	8-2	**-5.76**	**cluster**		
			ed		
Diazoxide	**Complex1:**		**Best**		**No**
	1-1	**-6.27**	**docked**		
			Best		
	Complex2:	**-6.09**	**cluster**		**No**
	2-1	**-6.09**	**ed**		
	2-2	**-6.09**			
	2-3	**-6.07**			
	2-4	**-6.05**			
	2-5				
	Complex3:				**Close**
	3-1	**-5.96**			
	3-2	**-5.96**			
Hydrochlorothiazide	**Complex 1:**				
	1-1	**-6.69**	**Best**		**No**
	1-2	**-6.69**	**docked**		
	1-3	**-6.69**	**and**		
	1-4	**6.53**	**best**		
	1-5	**-6.18**	**cluster**		
	1-6	**-6.18**	**ed**		
Hydroflumethiazide	**Complex1:**	**Best**			**No**
	1-1	**docked**	**-6.56**		
	1-2	**and**	**-6.52**		
	1-3	**best**	**-6.48**		
	1-4	**cluster**	**-6.01**		
		ed			
Indapamide	**Complex1:**	**Best**			
	1-1	**docked**	**-7.79**		**Close**
		and			
	Complex4:	**best**			
	4-1	**cluster**	**-7.27**		**Close**
		ed			
	Complex6:				
	6-1		**-7.08**		**Close**
Methychlothiazide	**Complex1:**	**Best**			
	1-1	**docked**	**-7.53**		**Close**
	1-2	**and**	**-7.53**		
	1-3	**best**	**-7.19**		
		cluster			
	Complex5:	**ed**			
	5-1		**-5.7**		**Close**
	5-2		**-5.33**		

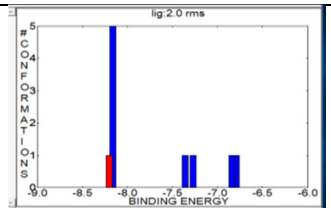
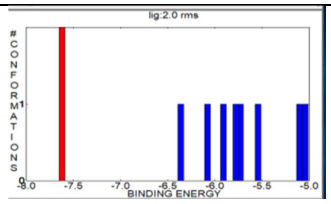
Metolazone	**Complex1: 1-1**	**Best docked**	**-8.20**		**Close**
	Complex2: 2-1	**Best cluster**	**-8.16**		**Close**
	2-2	**ed**	**-8.01**		
	2-3		**-7.94**		
	2-4		**-7.93**		
	2-5		**-7.67**		
	Complex3: 3-1		**-7.36**		**Close**
	Complex4: 4-1		**-7.27**		**Close**
	Complex6: 6-1		**-6.79**		**Yes**
Xipamide	**Complex1: 1-1**	**Best**	**-7.62**		**Close**
	1-2	**docked and best cluster**	**-7.30**		
	Complex9: 9-1	**ed**	**-5.04**		**Close**

Table 2

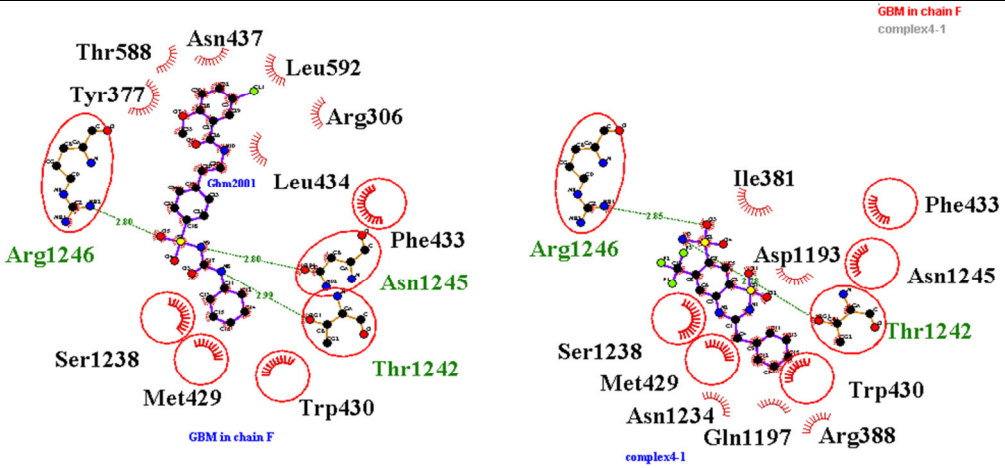
HCTZ family members' scoring function

Number	Compound name	Scoring function	Notes
1	Indapamide 1-1	-7.79	Close+
2	Xipamide	-7.62	Close
3	Methyclothiazide 1-1	-7.53	close
4	Chlorthalidone 1-1	-7.43	In*
5	Clopamide 2-1	-7.08	close
6	Benzthiazide 1-2	-6.83	close
7	Metolazone 6-1	-6.79	In
8	Hydrochlorothiazide 1-1	-6.69	close
9	Hydromethiaizde 1-1	-6.56	close
10	Chlorothiazide 2-1	-6.55	close
11	Bendroflumethiazide 4-1	-6.01	In
12	Diazoxide 3-1	-5.96	close

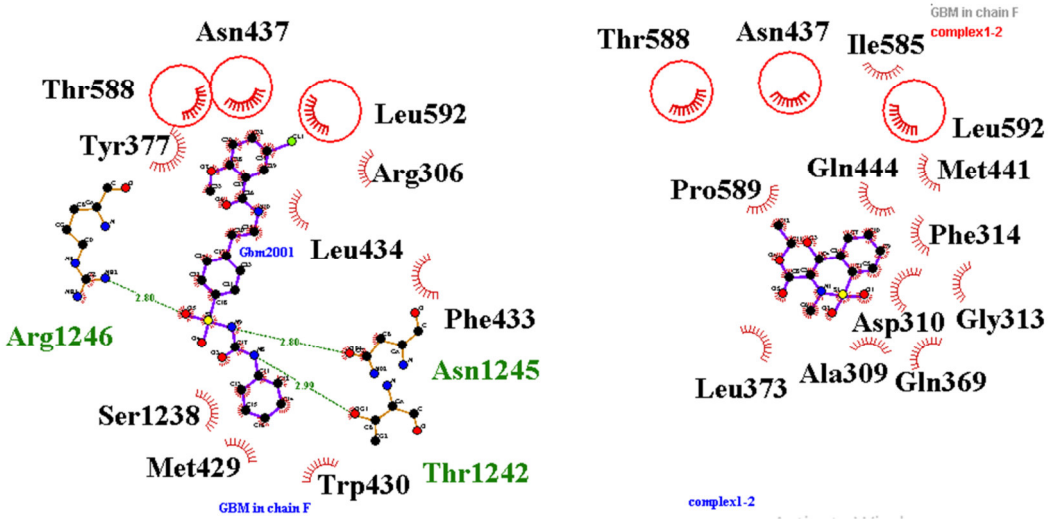
**: In: in the binding site. +: close: close to the binding site.*

Table 3

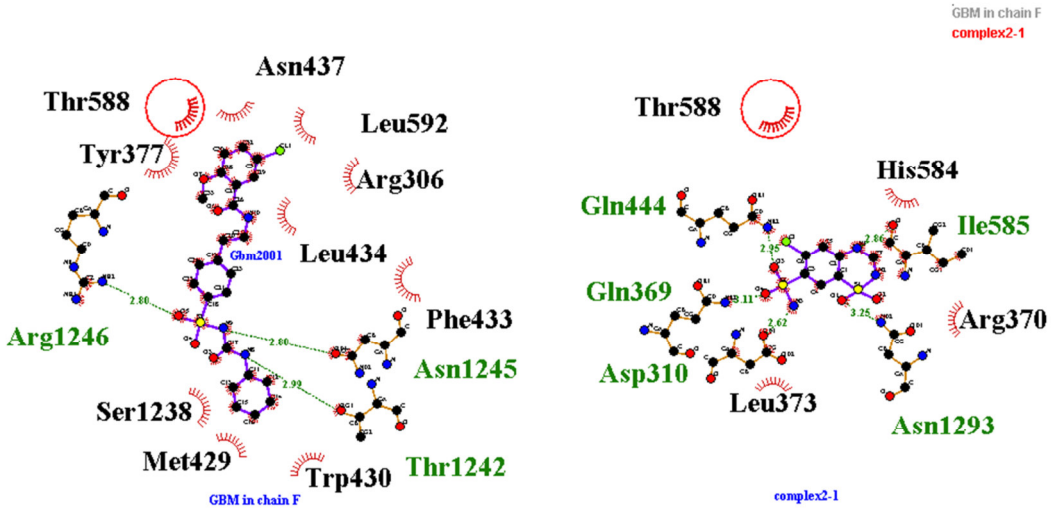
HCTZ compounds' interactions with the named GBM binding site study



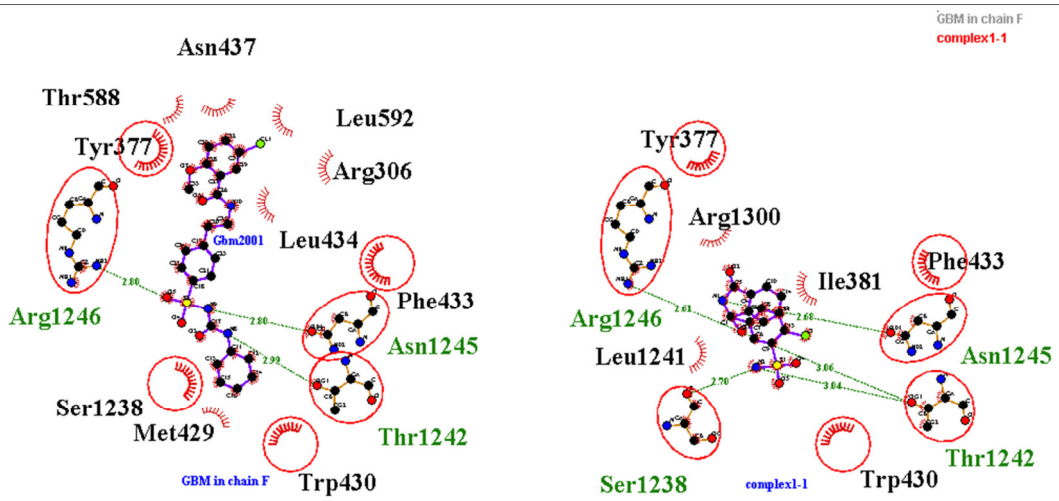
Bendroflumethiazide



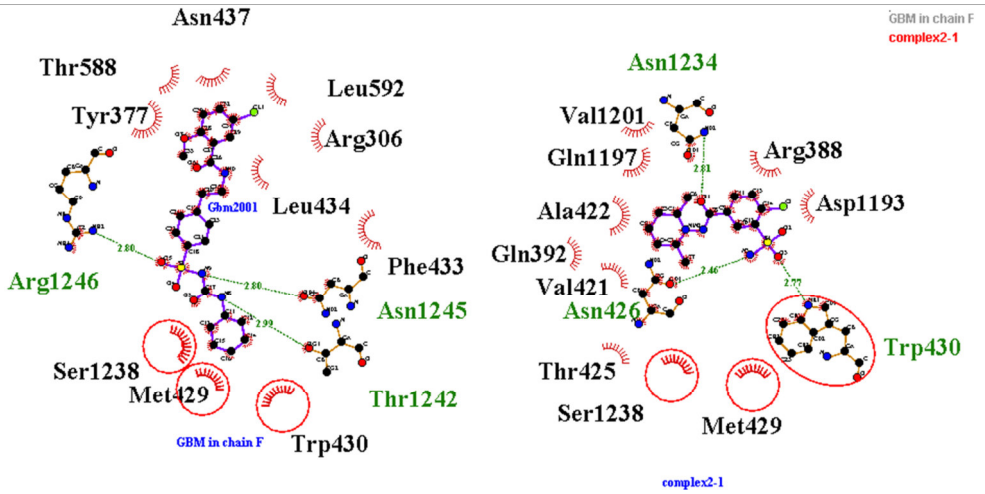
Benzthiazide



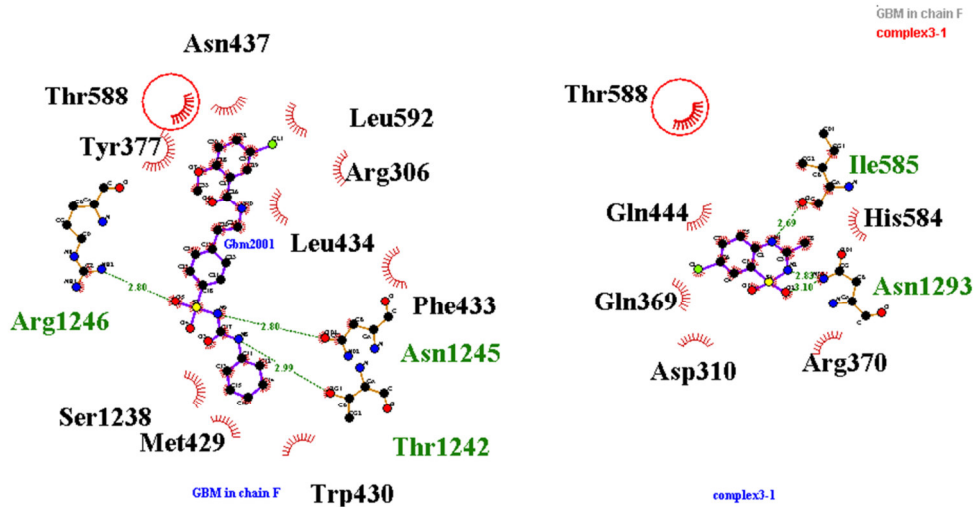
Chlorothiazide



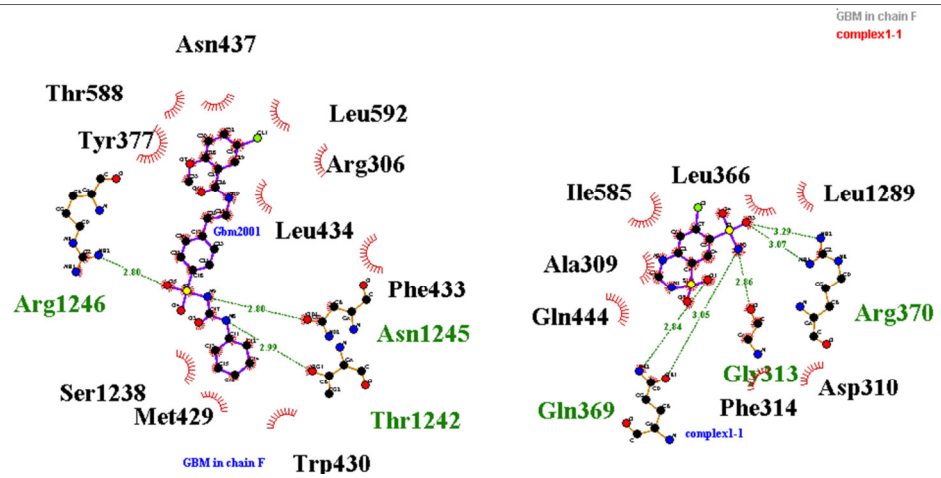
Chlorthalidone



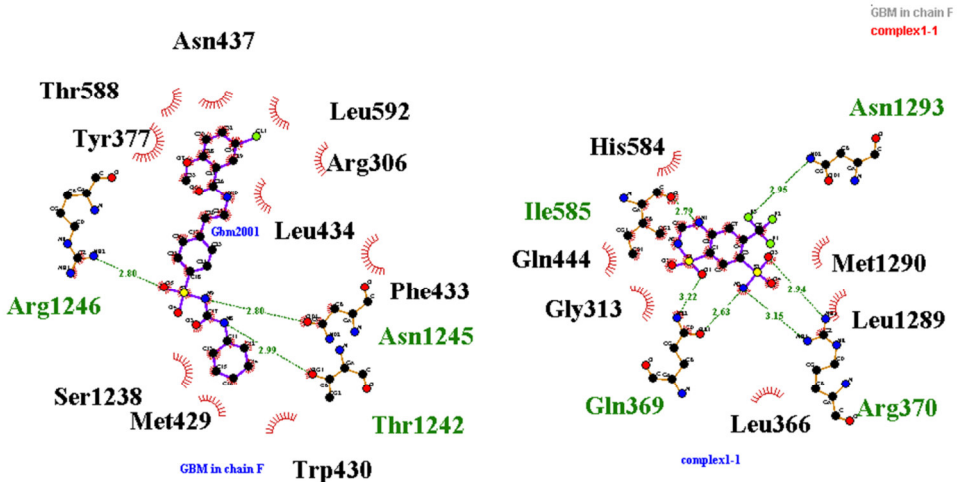
Clopamide



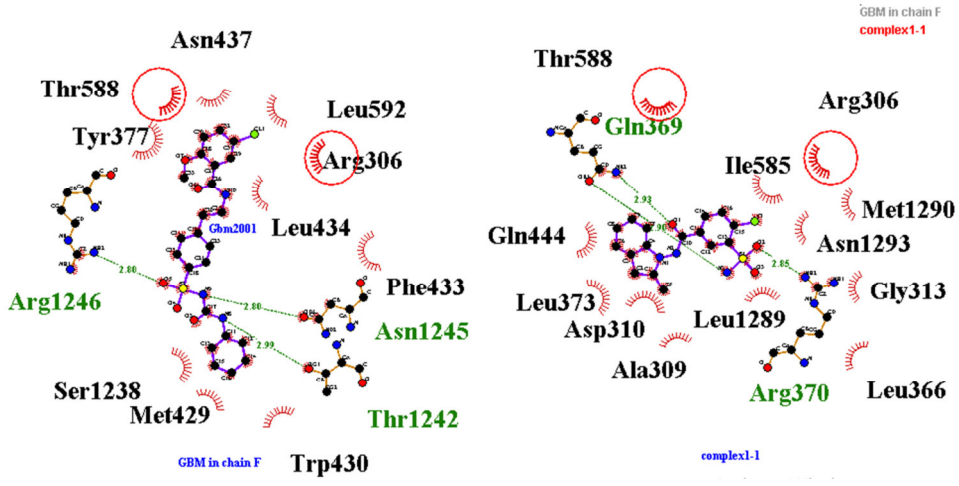
Diazoxide



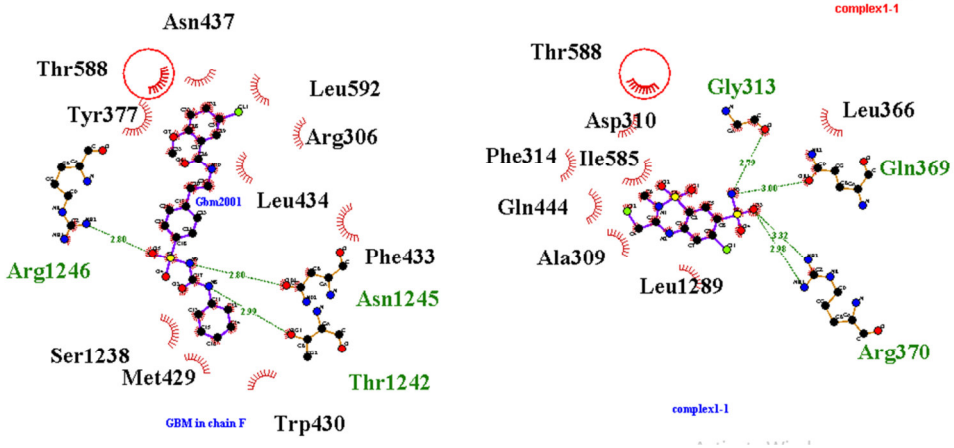
Hydrochlorthiazde



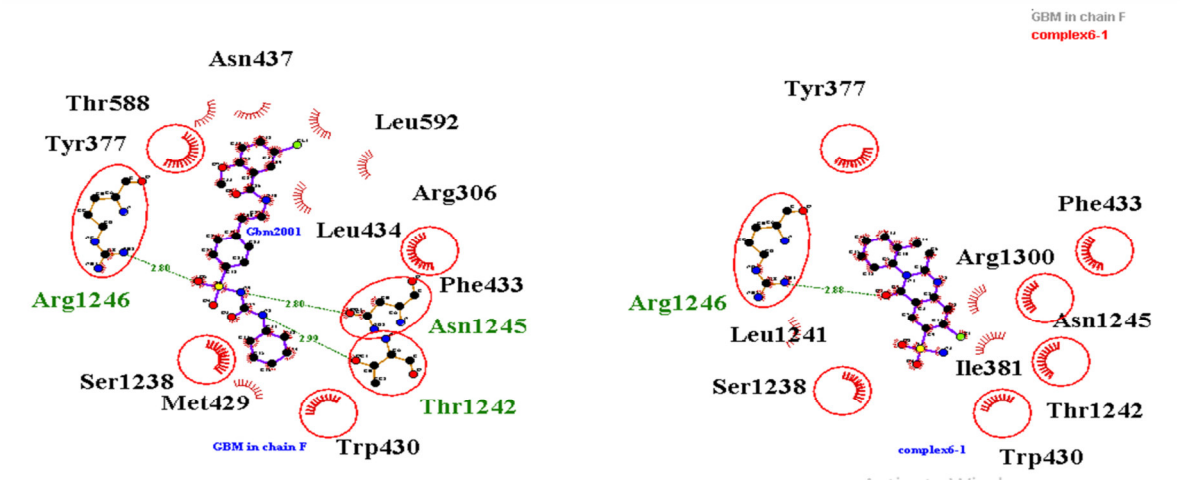
Hydroflumethiazde



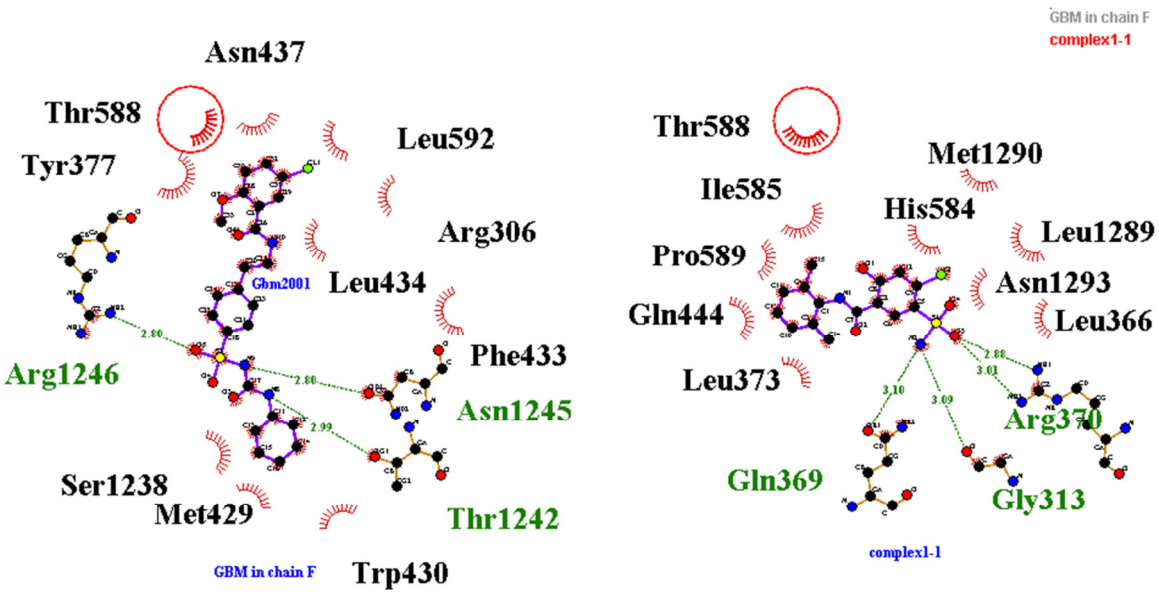
Indapamide



Methychlothiazide



Metolazone



Xipamide

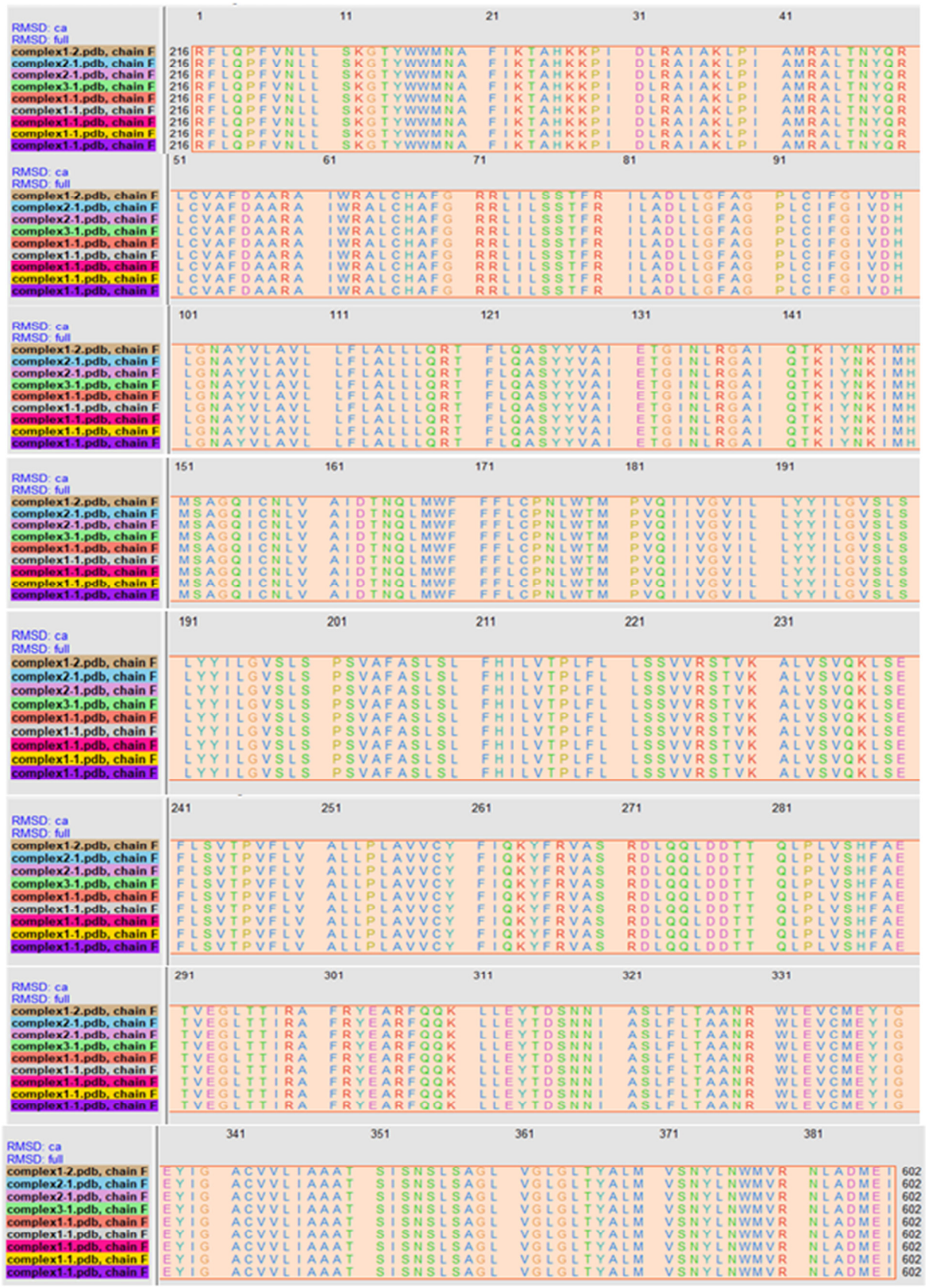


Figure 3
Sequence alignment for 9 HCTZ compounds

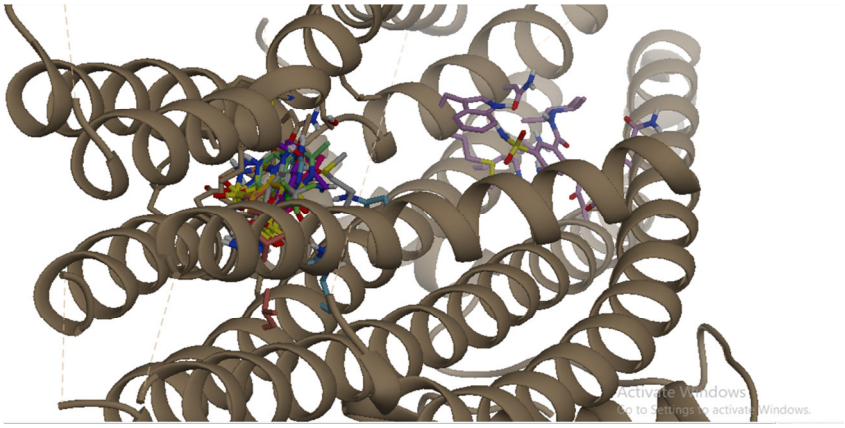


Figure 4
Superimposing for 9 HCTZ compounds.

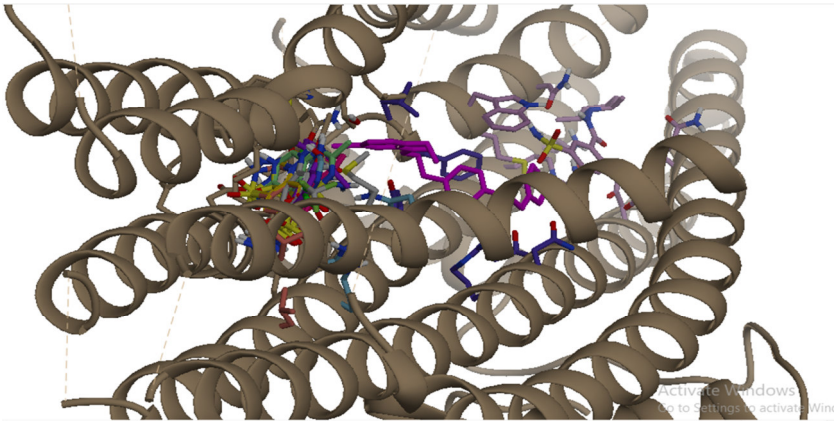


Figure 5
Superimposing between GBM pocket and the 9 HCTZ pockets. GBM is in magenta colour.

CONCLUSION

To encourage developing new HCTZ derivatives treat not only hypertension but also TIIDM in patients who are suffering from the two diseases, we have proved in this manuscript the interaction of 12 HCTZs with Glibenclamide (GBM) receptor Kir6.2\SUR1. Chlorthalidone, Bendroflumethiazide, and Metolazone bind to the same pocket as GBM, while the other members bind to a close binding site to GBM pocket. These results add a new explanation of why these Chlorthalidone and Bendroflumethiazide are most accused of diuretic-induced-diabetes adverse effect among HCTZs medications. On the other hand, we have discovered a new preferable binding site for HCTZs that may be a cornerstone for developing new anti-hyperglycemia agents starting with HCTZs as lead compounds.

AUTHORS CONTRIBUTION STATEMENT

Farah Yousef is the main author. he has done and written this research paper. Oussama Mansour is the Co-Supervisor for this research, and Jehad Herbali: Main Supervisor for this research. All authors discussed the methodology and results and contributed to the final manuscript.

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CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Carter BL, Ernst ME. Thiazide-Induced Hyperglycemia: Can It Be Prevented? Am J Hypertens. 2009 May 1;22(5):473–473. DOI:10.1038/ajh.2009.48
2. Bozkurt O, de Boer A, Grobbee DE, de Leeuw PW, Kroon AA, Schiffers P. Variation in Renin-Angiotensin System and Salt-Sensitivity Genes and the Risk of Diabetes Mellitus Associated With the Use of Thiazide Diuretics. Am J Hypertens. 2009;22(5):545-51. DOI: 10.1038/ajh.2009.38
3. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide Diuretics, Potassium, and the Development of Diabetes. Hypertension. 2006;48(2):219–24. DOI: 10.1161/01.hyp.0000231552.10054.aa
4. Smith HD. a review for the pharmacist. South Afr Pharm J. 2014;81(7):18021. Available from:http://www.sapj.co.za/index.php/SAPJ/article/view/1831
5. Collins R, Peto R, MacMahon S, Godwin J, Qizilbash N, Collins R. Blood pressure, stroke, and coronary heart disease. Lancet. 1990;335(8693):827–38. DOI: 10.1016/0140-6736(90)90944-z
6. Taylor EN. Antihypertensive Medications and the Risk of Incident Type 2 Diabetes. Diabetes Care. 2006;29(5):1065–70. DOI: 10.2337/diacare.2951065
7. Ueda S, Morimoto T, Ando S -i., Takishita S -i., Kawano Y, Shimamoto K. A randomised controlled trial for the evaluation of risk for type 2 diabetes in hypertensive patients receiving thiazide diuretics: Diuretics In the Management of Essential hypertension (DIME) study. BMJ Open. 2014; 4(7): e004576–e004576. DOI:10.1136/bmjopen-2013-004576
8. Singh P, Knoedler JJ, Krambeck AE, Lieske JC, Bergstralh EJ, Rule AD. Thiazide Diuretic Prophylaxis for Kidney Stones and the Risk of Diabetes Mellitus. J Urol. 2014; 192(6):1700–4. DOI: 10.1016/j.juro.2014.06.078
9. Yousef F Mohj. Sulfonamides: Historical Discovery Development (Structure-Activity Relationship Notes). In-vitro In-vivo In-silico J. 2018; 1(1):1–15. Available from: https://openaccesspub.org/iiij/article/749
10. Martin GM, Yoshioka C, Shyng SL. Cryo-EM structure of the pancreatic beta-cell KATP channel bound to ATP and glibenclamide. Protein Data Bank, Rutgers University; 2017. DOI: 10.2210/pdb6baa/pdb
11. PubChem BioAssay Tools to be replaced.. Pubchem blog. 2018 [cited 1BC Apr 4]. Available from: https://pubchemblog.ncbi.nlm.nih.gov/2018/04/