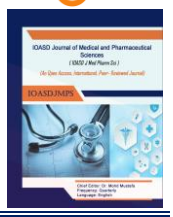
OPEN ACCESS

IOASD Journal of Medical and Pharmaceutical Sciences

IOASD J Med Pharm Sci, Vol-3, Iss-1, Jan-Mar., 2026
Frequency: Quarterly
ISSN: 3049-0294 (Online)
ISSN: 3049-3773 (Print)
Website: www.ioasdpublisher.com



Understanding the Pharmacokinetic Effect of Aspartame and Nateglinide Against Hydrolase: An Insilico Study

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ABSTRACT

This study is performed to understand the pharmacokinetic effect of aspartame over nateglinide by an *insilico* approach. Virtual screening was performed for the analogues of aspartame and nateglinide against the hydrolase enzyme (3BER) involved in the metabolism the drugs using AUTO DOCK/GOLD. Molecular docking was used to evaluate a competitive interaction study of analogues. The results reviled that the amino acids THR75, THR70 and TRP44 of the active site contributed for the hydrogen bond interaction with both analogous. Aspartame analogues m843_10 and nateglinide analogues m49_2 showed the highest binding energy generating the highest F-Score of -73.94 kcal/moland -54.59kcal/mol respectively. It can be concluded that interaction profile providea roadmap that analogues interact with the same binding site and act as a competitive inhibitor leading to less hypoglycemic effect and thus it's hypothesis that nateglinide should not be taken along with the artificial sweetener aspartame resulting in leading to low hypoglycemic activity.

Keywords: Aspartame. Nateglinide. Molecular docking. Hydrolase. Nateglinide.

Original Research Article

Article History

Received: 06-02-2026

Accepted: 14-03-2026

Published: 19-03-2026

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has turned out to be a one of the most alarming diseases to mankind across the globe. In the recent past, this disease posed even more a greater risk to humans of all age groups. T2DM is a disease that is initiated by a disorder called insulin resistance. This is a disease condition that occurs based on two important factors. Firstly, when the pancreatic cells lose their ability to utilize the insulin though they have the ability to produce insulin or when the function of the pancreatic beta-cells starts plummeting and secondly when the level of hyperglycaemia starts increasing alongside. Thus, improper functioning of the beta cells that occur early in individuals with impaired fasting and/or post-prandial glucose levels can be diagnosed. Among three types of DM, Type 2 DM associated with impaired insulin secretion and constituting 80%–90% of all reported diabetes cases. If left untreated, diabetes can cause many complications such as cardiovascular disease, stroke, chronickidney failure, foot ulcers, and diabetic retinopathy (Meng *et.al*,2011).Diverse treatment methods to cure diabetes are currently available and continuously emerging in the medical realm bearing in mind the safety and efficacy point of views as well as mechanisms of action to improve deranged glucose metabolism.

Asparatane is one of the important artificial sweeteners are advised as sugar alternative for T2DM individuals. The safety of aspartame in particular, has long been many controversies. Although it is such a controversial product, many clinicians recommend its use to T2DM patients, during a controlled diet and as part of an intervention strategy. Aspartame is 200 times sweeter than sugar and has a negligible effect on blood glucose levels, and it is suggested for use so that T2D can control carbohydrate intake and blood glucose levels. However, research suggests that aspartame intake may lead to an increased risk of weight gain rather than weight loss, and cause impaired blood glucose tolerance in T2D (Rycerz and Jaworska,2013; Choudhary,2018; Santos *et. al*,2018)

In this study we see the derivative of meglitinide, namely nateglinide. It promotes the

secretion of insulin but with a shorter half-life. Nateglinide possess both pharmacodynamics and pharmacokinetic properties which makes it an ideal compound for the treatment of T2D Malong with its proposed mode of action.

There are many drugs available to control hyperglycemic condition of T2DM, however in this study analysed nateglinide drug. It is a novel nonsulfonylurea oral antidiabetic agent that stimulates insulin secretion from the pancreas. It has a rapid onset and short duration of action, allowing administration before a meal to reduce postprandial hyperglycemia. Improvement in glycemic control with nateglinide immunotherapy has been demonstrated in patients not previously treated with antidiabetic medications. Greater improvement in glycemic control was observed when nateglinide was administered in combination with metformin.

Therefore, in this study is designed with the speculation of establishing the safe intake of aspartame, a sugar additive in such a manner that it does not affect patient's health and thus no interference with oral hypoglycemic drug nateglinide. The confounding factor here is an enzymehydrolase that is observed to be common for aspartame and nateglinide in their respective metabolism via cytochrome P 450 (CYP450). For the study, library consisting of 1595 analogues and 110 analogues for aspartame and nateglinide respectively were selected. Five docking runs were performed per structure.

METHODS

Protein Preparation and active site analysis

The crystal 3D structure of target protein was **screened** out from protein databank (PDB: 3BER) based on selection criterion as follows in the PDB (http://www.rcsb.org/structure/3BER)[initial search as a potassium channel (855), then search taxonomy as *homo sapiens* (human) were found (168 structures)by filtering then **selected** as enzyme classification as a hydrolases (17), taxonomy is only just *homo sapiens* (human)(14) and finally select as resolution is selected as 1.499 or less (2)]. The protein Human DEAD-box RNA-helicase DDX47 with protein Id 3BER is a hydrolase enzyme of *Homo.* It is an X-Ray diffraction solved structure with a resolution of 1.4 Å. The obtained protein was prepared by adding hydrogens to the structure.

Ligand Preparation

The analogous of aspartame and nateglinide were obtained from ligand database PubChem database) respectively got the 3370 and 150 molecules. The retrieved structures were prepared by adding hydrogens, charges and other required standardization. The prepared analogous were saved in specific formats (mol2 format).

Active Site analysis

The functional active site for the hydrolase enzyme with the hydrolase activity was predicted and the aminoacids involved in the active site are as THR75, THR 70, THR75, TRP44, GLY73, ASP174, LYS 74 and GLN111. This site was used for the receptor-ligand interactions.The predicted site is based on the ligand binding of the PDB structure of hydrolease enzyme. (Literature based binging pocket).

Molecular Docking

Docking was performed for the analogous of aspartame and nateglinide with DEAD-box RNA-helicase DDX47 using GOLD 4.1 software (Jones et.al, 1997). Setting default GOLD fitness function (VDW= 4.0, H-bonding = 2.5) and evolutionary parameters: population size = 100; selection pressure = 1.1; # operations = 100,000; # islands = 5; niche size = 2; migration = 10; mutation = 95; crossover = 95. Scoring function used for evaluation of different docking was "Goldscore".

Formula for GOLD Docking

Fitness = S (hbext) + 1.3750 ∗ S (vdwext) + S (hbint) + 1.0000 ∗S (vdwint)

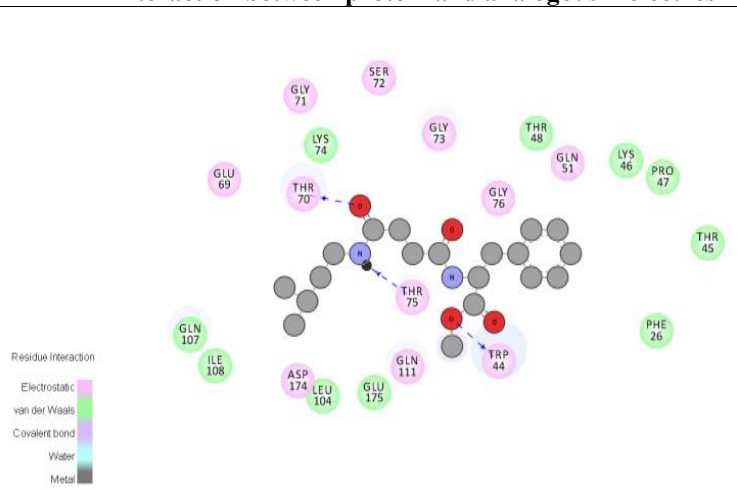
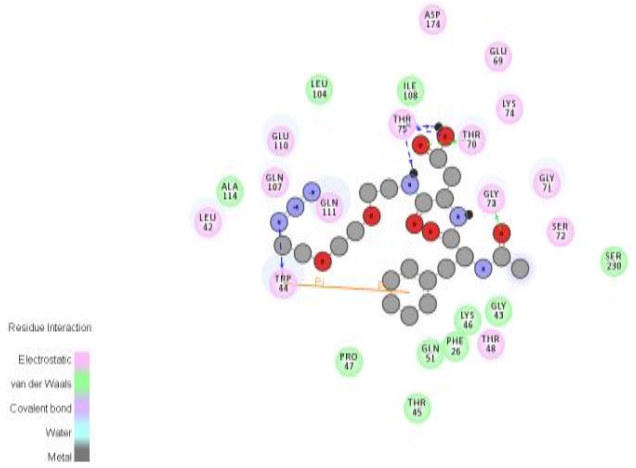
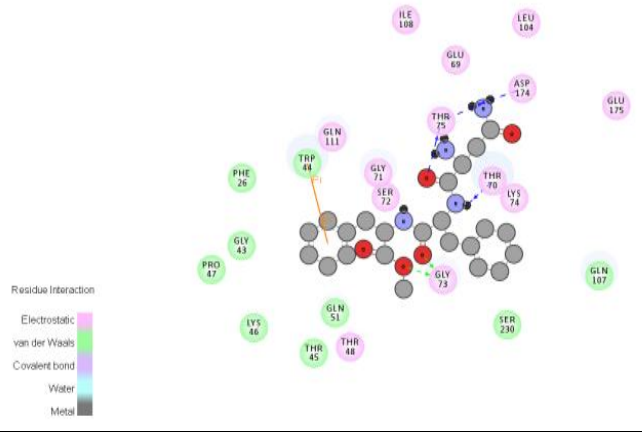
Five docking runs were performed per structure. If at any time 3 of the 10 poses were within 1.5A˚ RMSD of each other, the docking run for that structure was terminated and docking calculations began for the next structure. Best three poses and docking scores were outputted into a *.mol file and text file respectively. Among these poses, the most suitable docking mode with a highest docking score and a high fitness score from consensus functions was finally selected as a suitable ligand for controlling blood sugar level.

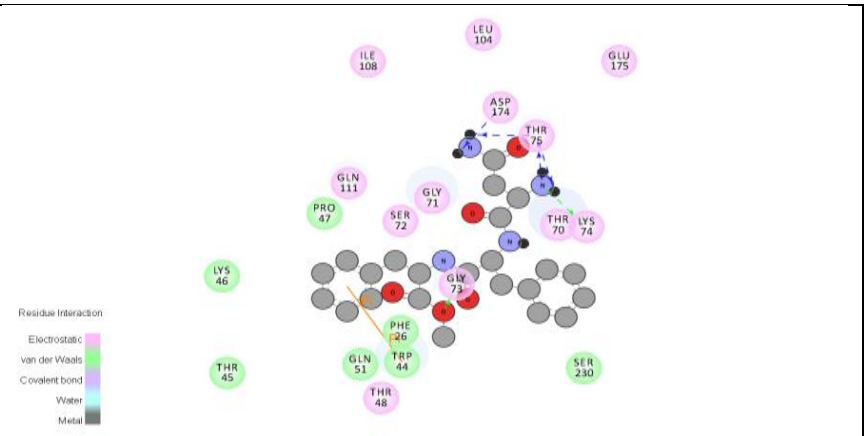
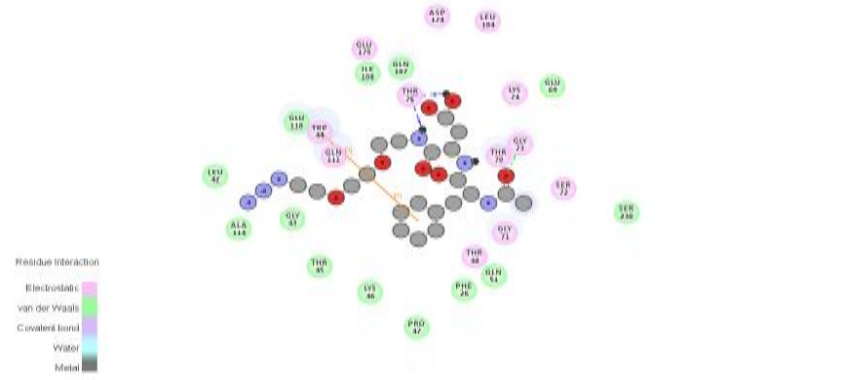
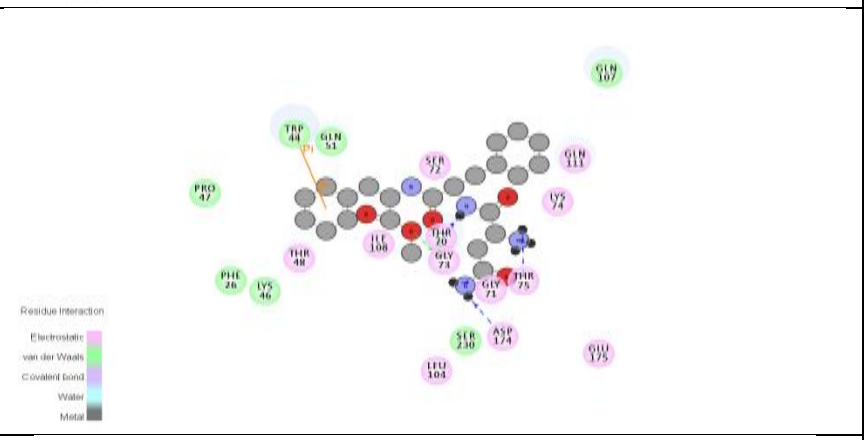
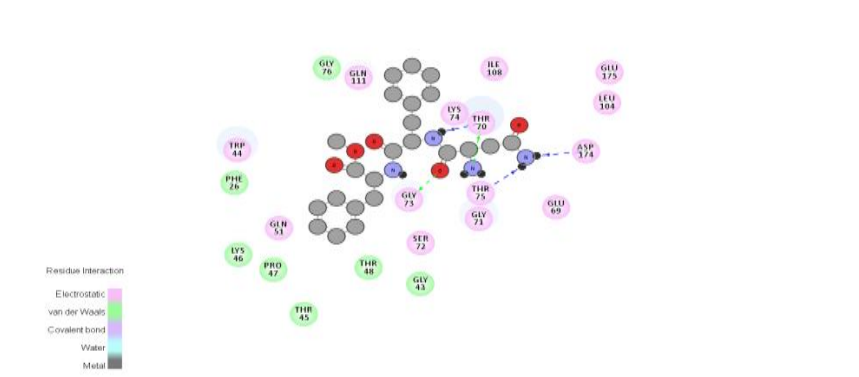
RESULTS AND DISCUSSION

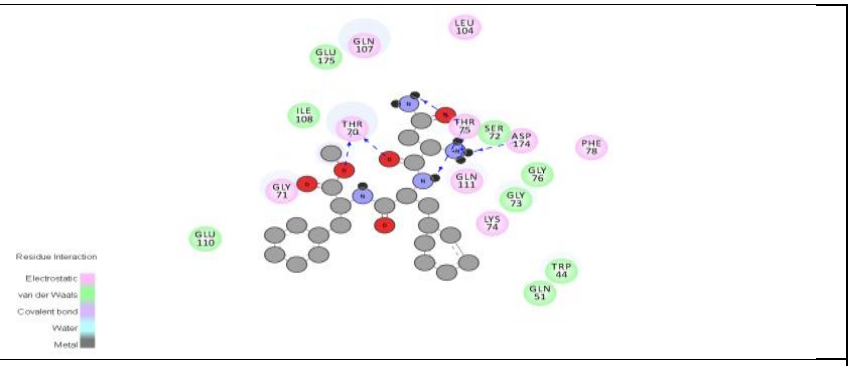
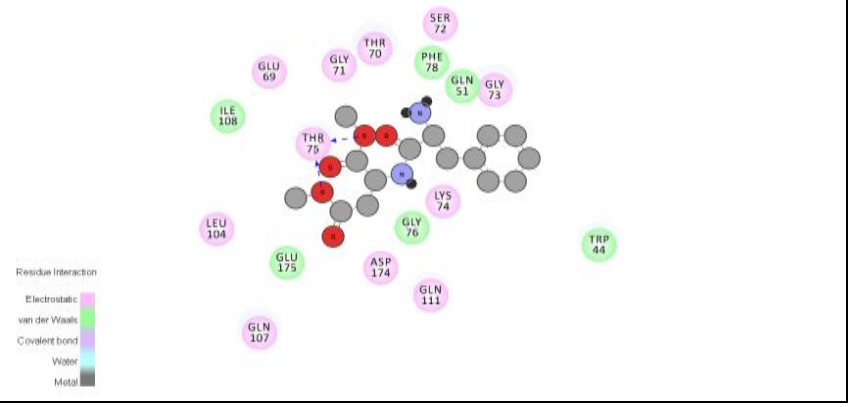
Diabetes mellitus is a physiological dysfunction characterized by hyperglycemia resulting in insulin resistance, inadequate insulin secretion, or excessive glucagon secretion. The analogous of ~~a~~spartame and nateglinide were retrieved from pubchem database and respectively got 3370 and 150 different analogous and ligand proparation were done in discovery studio (Visulizer). The active site for hydrolyse activity used in the study which contains aminoacids such as THR75, THR 70, THR75, TRP44, GLY73, ASP174, LYS 74 and GLN111.

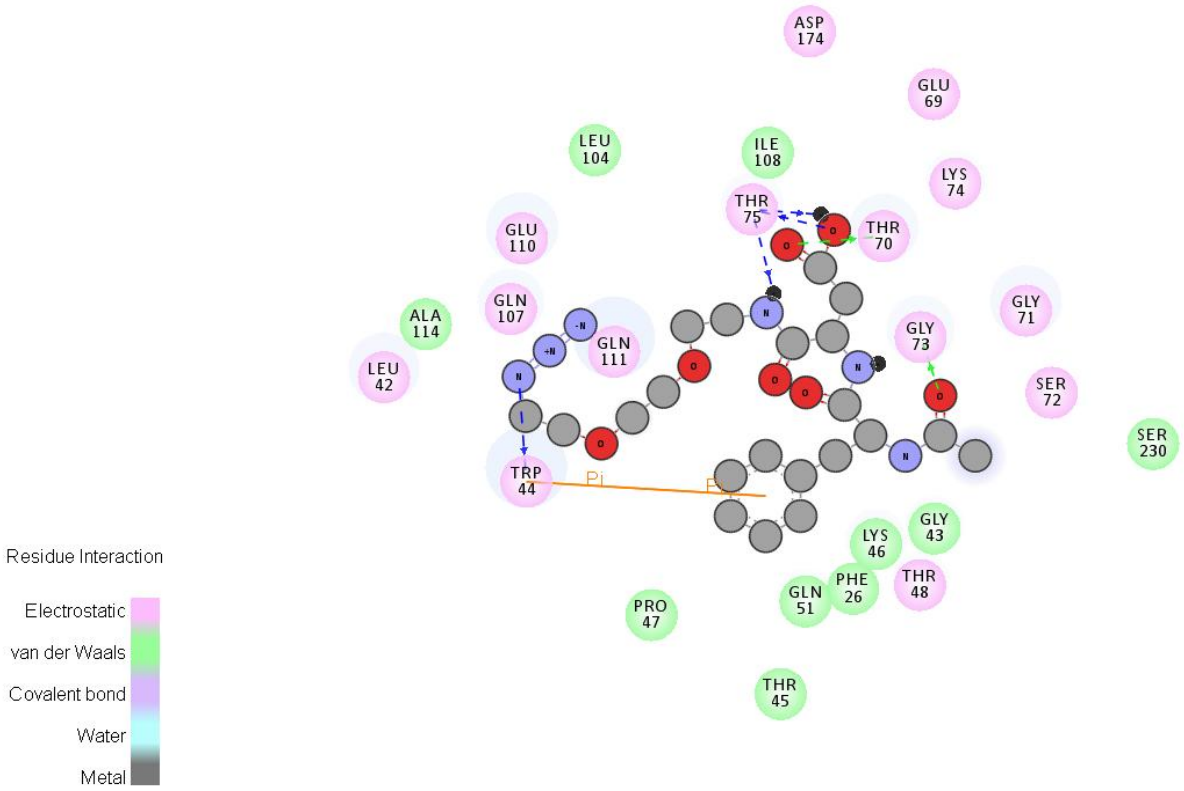
As the result of the docking study performed it was fortunate to note that both the analogous of aspartame and nateglinide showed equally effective binding energy score with a maximum binding energy of -73.94 KJ/mol and -54.59 KJ/mol against aspartame and nateglinide respectively the detailed interaction profile of the analogous of aspartame and nateglinide is given in the table 1 and figures 1 and 2.

Table 1: Illustrated interaction of protein and analogous molecules by docking studies

Sl. No	Molecule	F. Score	Interaction between protein and analogous molecules
1468	m1468_4.mol2	75.75	
843	m843_10.mol2	73.94	
996	m996_1.mol2	73.72	

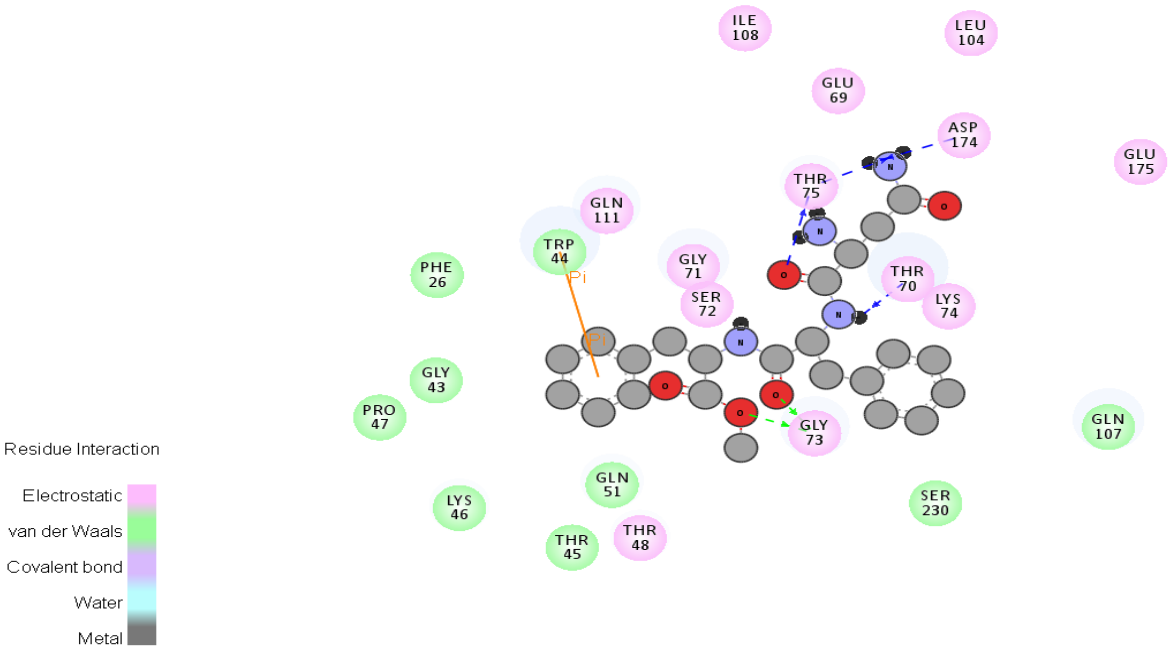
1465	m1465_5.mol2	73.72	
840	m840_3.mol2	73.41	
1470	m1470_2.mol2	73.02	
997	m997_4.mol2	72.8	

1466	m1466_8.mol2	72.02	
1001	m1001_1.mol2	72.01	



m843_10

Figure 1:2D interaction profile of Aspartame analogous against the metabolising hydrolyse protein 3BER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van der Waals
Covalent bond
Water
Metal
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LEU 104
GLU 69
ASP 174
GLU 175
THR 75
GLN 111
TRP 44
PHE 26
GLY 71
SER 72
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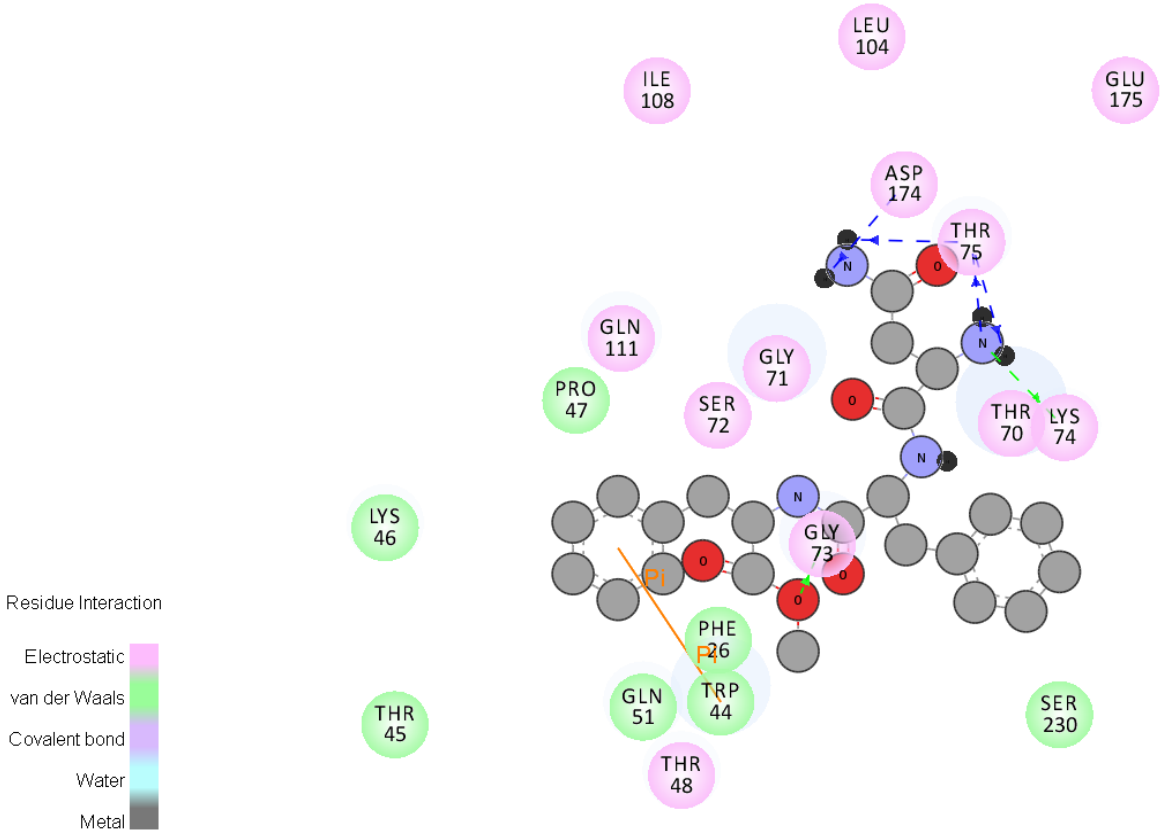
LYS 46
SER 230
THR 45
THR 48

m996_1


Residue Interaction
Electrostatic
van der Waals
Covalent bond
Water
Metal
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ILE 108
GLU 175
ASP 174
THR 75
GLN 111
GLY 71
PRO 47
SER 72
THR 70
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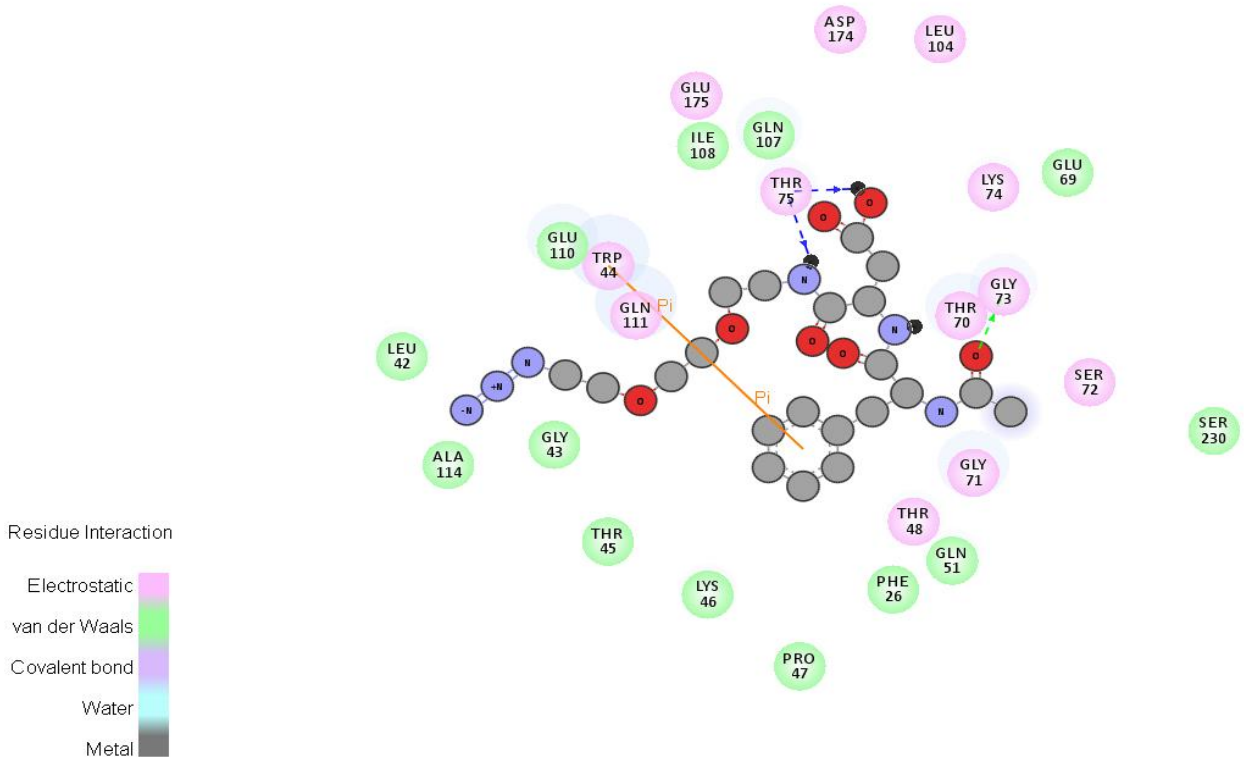
LYS 46
GLY 73
PHE 26
THR 45
GLN 51
TRP 44
SER 230
THR 48

m49_2



m48_2

Figure 2: 2D interaction profile of nateglinide analogous against the metabolising hydrolyse protein

Many studies have been performed to report the antidiabetic property of various inhibitors like (Khalaf *et.al*, 2018; Wang *et.al,* 2017; Bustanji *et.al*, 2009: Manimaran *et.al*, 2018) Vbut in this study we have tried to understand the pharmacokinetic property of anti-diabetic drug of nateglinide and artificial sweetener of aspartame. In the present study, we have found that both the compounds acts a competitive inhibitor against 3BER hydrolase and use of one would suppress the action of other. Since both target follow the same metabolic pathway and so both the compounds should not be taken together.

Regarding binding interactions of each analogues and target sites, the interaction profile of aspartame and nateglinide analogous were showed an interesting results that both share a similar pattern of hydrogen bonding. Especially the aspartame analogous m843_10 exhibited the highest interaction and fitness value was -73.94 KJ/mol. Analogues of nateglinide were showed very similar fitness value -53.4 and -54.59 and interaction parameters (Hydrogen bond/ Hydrophobic bond/ Pi P Bond) which shown in figures 1 and 2 (Table).

Table 2: Detailed interaction profile of analogs of aspartame and nateglinide against the target protein 3BER

S.No	Target Protein	Analogs of aspartame and nateglinide	F_ Score	Interaction profile		
				Hydrogen bond	Hydrophobic bond	Pi P Bond
1	3BER	m843_10 _ aspartame	-73.94	GLY73,THR70	THR75,TRP44	TRP44
2	3BER	m996_1_ aspartame	-73.72	GLY73	THR75,ASP174,THR70	TRP44
3	3BER	m49_2_ nateglinide	-54.59	GLY73,LYS74	ASP174,THR75	TRP44
4	3BER	m48_2_nateglinide	-53.4	GLY73	THR75	TRP44

Both the compounds are being metabolised by the metabolizing enzyme (hydrolase enzyme that is ATP-dependent potassium channels in the membrane of the β cells and other isheterodimer G-protein coupled receptor also group under hydrolase enzyme). The nateglinide is the rapidly (~90%) absorbed drug, with peak blood and plasma concentrations at ~1 h post dose and it is believed to have the bioavailability of 72% (Weaver et.al,2007). Aspartame, a widely used sweetener in many food products. Aspartame was discovered in 1965, is a polypepetide compound [2] and it developing harmful metabolite that affects the central nervous system.

Mechanism of action of two drugs

Nateglinide lowers blood glucose by stimulating the release of insulin from the pancreas. It achieves this by closing ATP-dependent potassium channels in the membrane of the β cells. This depolarizes the β cells and causes voltage-gated calcium channels to open. The resulting calcium influx induces fusion of insulin-containing vesicles with the cell membrane, and insulin secretion occurs. The perceived sweetness of aspartame (and other sweet substances like acesulfame K) in humans is due to its binding of the heterodimer G-protein coupled receptor formed by the proteins TAS1R2 and TAS1R3.

The competitive inhibition of the compounds suggests that the activity of one compound would alter the activity of the other. It can be hypothesizes that the pharmacokinetic activity would be altered when administered both aspartame and nateglinide together. However, the present study findings need further *in vivo* validation studies to confirm theses effects.

CONCLUSION

This study is a different perceptive to identify the pharmacokinetic property of two compounds of hypoglycemic drug nateglinide and artificial sweetener of aspartame which bind to specific site of enzymes by different interacting amino acids (THR75, THR 70, THR75, TRP44, GLY73, ASP174, LYS 74 and GLN111).

Conflict of interest

The authors have declared having no conflict of interest concerning this article.

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