" Pharmacokinetic profiling of Anti-diabetic agents with changes in pharmacophore using Computer aided drug design approach."

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

BACHELOR OF PHARMACY

BY

DEVYANI THAKOR (16BPH014)

B. Pharm. Semester VIII

UNDER THE GUIDANCE OF

GUIDE

DR. PRITI . J. MEHTA

Co-Guide

DR. VIVEK .K. VYAS

INSTITUTE OF PHARMACY

NIRMA UNIVERSITY

SARKHEJ-GANDHINAGAR HIGHWAY

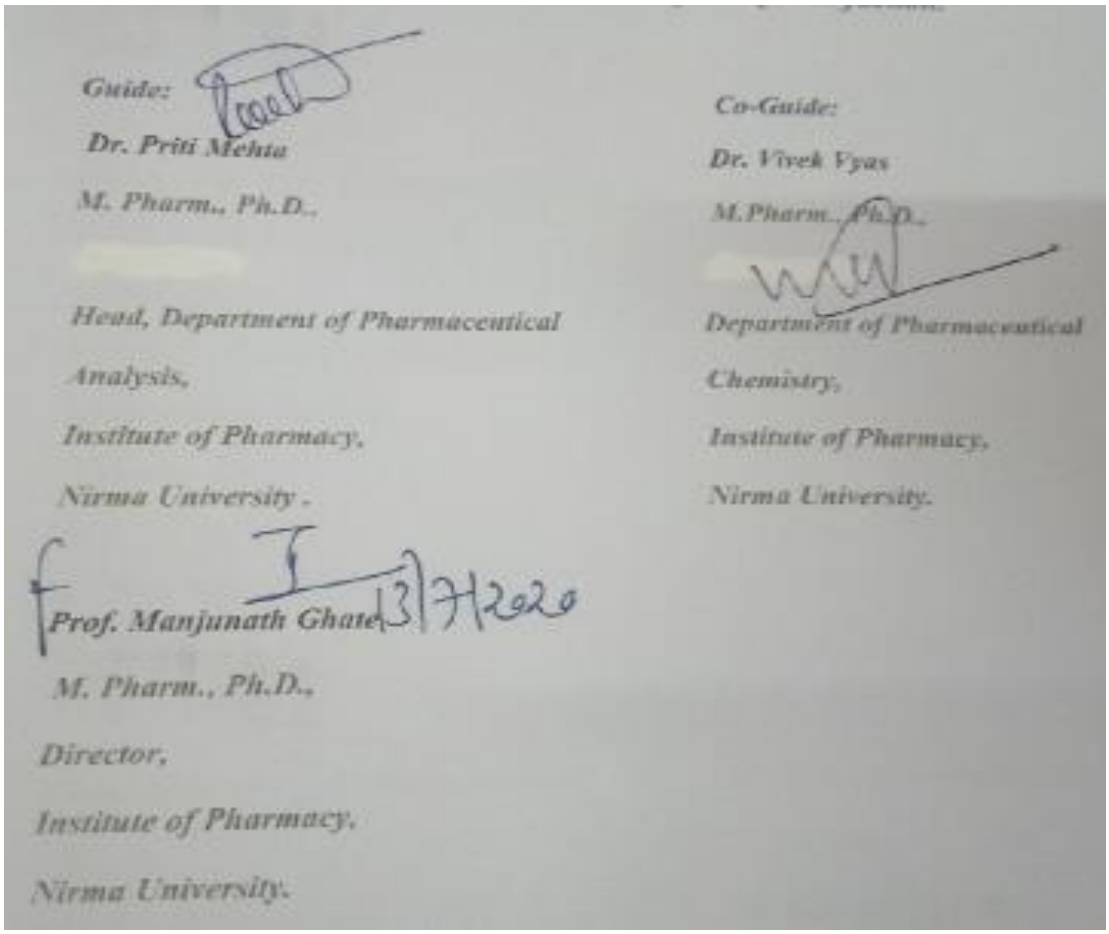
AHMEDABAD-382481

GUJARAT, INDIA

MAY 2020

CERTIFICATE

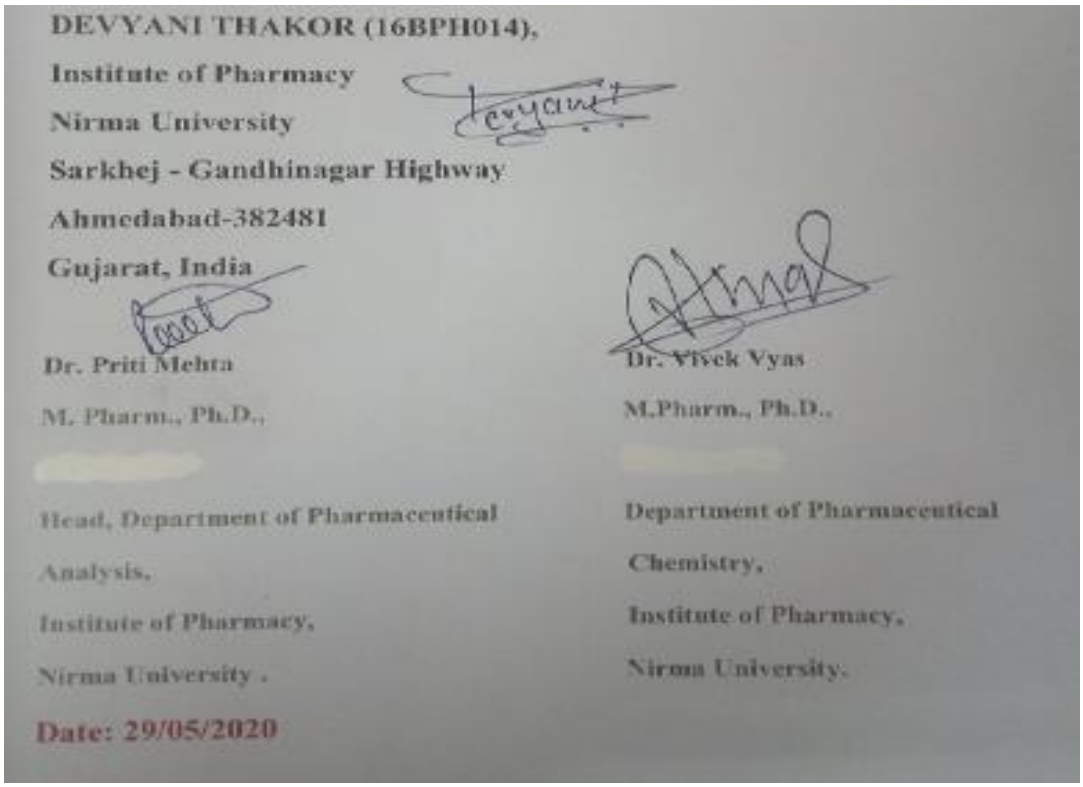
This is to certify that ***"Pharmacokinetic profiling of Anti-diabetic agents with changes in pharmacophore using Computer aided drug design approach."*** *is the bonafide work carried out by* ***DEVYANI THAKOR (16BPH014),*** *B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.*



Date: 29/05/2020

CERTIFICATE FOR SIMILARITY WORK

*This is to undertake that the B.Pharm. Project work entitled "**Pharmacokinetic profiling of Anti-diabetic agents with changes in pharmacophore using Computer aided drug design approach**" submitted by **DEVYANI THAKOR (16BPH014**), B.Pharm. Semester VIII is a bonafide review/research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of "Dr.Priti Mehta and Dr.Vivek Vyas". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by me is not reported anywhere as per best of my Knowledge.*



DEVYANI THAKOR (16BPH014),
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Dr. Priti Mehta
M. Pharm., Ph.D.,

Head, Department of Pharmaceutical Analysis,
Institute of Pharmacy,
Nirma University .

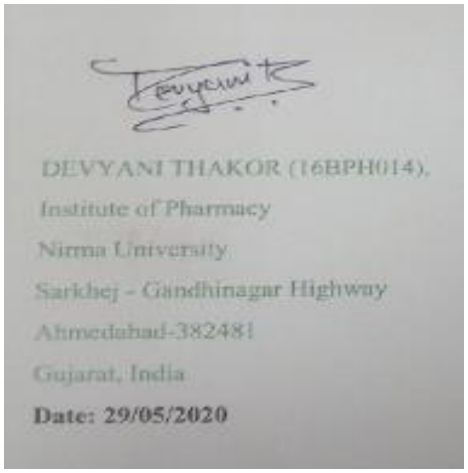
Dr. Vivek Vyas
M.Pharm., Ph.D.,

Department of Pharmaceutical Chemistry,
Institute of Pharmacy,
Nirma University.

Date: 29/05/2020

DECLARATION

I, DEVYANI THAKOR, student of Semester of VIII of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project work entitled "Pharmacokinetic profiling of Anti-diabetic agents with changes in pharmacophore using Computer aided drug design approach" is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. This bonafide review/research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of "Dr.Priti Mehta and Dr.Vivek Vyas". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad.



ACKNOWLEDGEMENTS

During the period of my work, I have been supported by guidance and suggestion from many people in different way.

First, I am grateful to God and my parents for making me whatever I am and always supporting me and guiding me through my venture. I would like to take this opportunity to express my gratitude and heartily thanks to my guide DR. PRITI MEHTA for sharing her guidelines with me. I would like to thanks also my co-guide DR.VIVEK VYAS. I would always be thankful for knowledge and support.

I am thankful to my friends HARSHVI, ANANYA, PRIYANSHI and DEEP for providing their help whenever I needed.

Last but not the least, I am sincerely grateful to Nirma University for giving me this opportunity to venture out, learn and delve into various interdisciplinary topics and enhance my education through the medium of this project. Thank you one and all.

TABLE OF CONTENTS

Introduction: Diabetes is a kind of a chronic disease. when very high level of sugar is suspected in blood this condition is more likely to happen. It is also termed as adult onset diabetes. But in the modern world its prevalence is widely seen, even the infants and adolescents are having this disease.

Digestion is a basic process which is in which the food is converted into very basic molecules. These basic molecules such as Carbohydrates, proteins and others. Mainly Carbohydrates are converted in simplest form of sugar (Glucose). Glucose is prime component which servers energy to all the cells of the body. In order to do so glucose penetrates into the cells by leaving blood.

This signaling to the cells to absorb glucose is done by Insulin. Insulin is primarily produced by pancreas. Usually when the glucose level increases in the blood more insulin is secreted through pancreas.

Primary hormone controlling metabolism in human body is Insulin. Main function of this hormone is to control the blood glucose level. Lower or stopped secretion of insulin causes Diabetes mellitus. Resistance of Insulin causes Obesity. Diabetes mellitus, recognized since ancient times, is named for the production of sugary urine in copious volume ,and its consequences are dire – especially chronic atherosclerosis, failure of kidney, neuropathy and blindness.

There are two types of diabetes :

(1) Type 1 : It is associated with people who cannot produce insulin in required amount .

(2)Type 2 : This type of diabetes is occurred when cells of body resist insulin.

The diagnosis of diabetes can be done by anyone of the plasma glucose criteria :

(1) when level of plasma glucose is more than 126 mg/dL it is known as fasting plasma glucose .

(2) By checking Plasma glucose level after 2 hours during 75 gram oral glucose tolerance test which can be detected by elevated level i.e. more than 200 mg/dL .

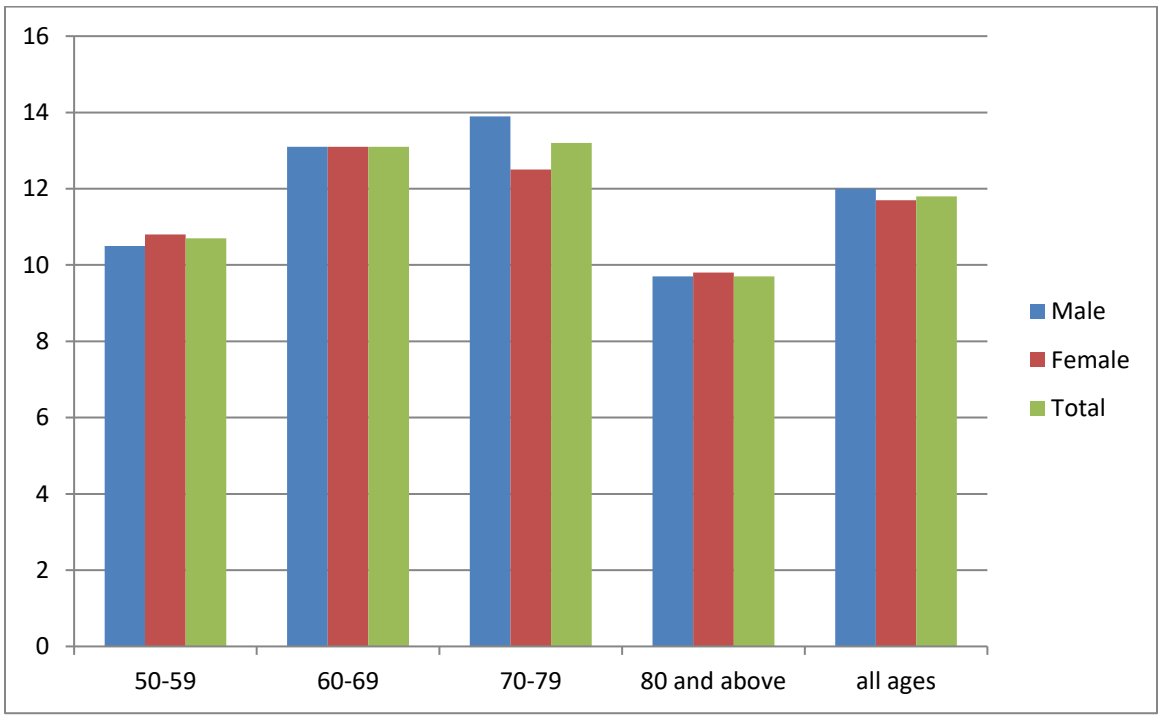
(3) when the plasma glucose level is more than 200 mg/dL with additional sign of hyperglycemia.

(4) when the hemoglobin A1C level is above 6.5%.

Treatment for type 1 Diabetes is following insulin regimen daily , it can be continuous subcutaneous administration by insulin pump. Insulin dose requirement is estimated by considering individuals weight which usually ranges from 0.4 to 1.0 units/kg/day .

First line Treatment for Type 2 Diabetes mellitus is Metformin and it should be continued by patient as long as it is tolerated other agents such as insulin should be added to regular regimen.

Mortality rate of Diabetes in India: Diabetes is a prime epidemic disease in India. Around, 62 million citizens are giving positive symptoms for diabetes in India. India has been seen to have most of the diabetes cases in the world, in 2002 number of individuals having diabetes were highest in India as compared to china (second) and United states (third) the figures were 31.7 million, 20.8 million and 17.7 million respectively. It has been estimated that these figures in upcoming future i.e. 2030 will upsurge to 79.4 million, 42.3 million and 30.3 million respectively.



This is graph showing diabetes prevalence in India for the year 2019.

x axis is showing age groups.

y axis is showing percentage of population affected.

Currently available drugs for Type 2 Diabetes:

(a)Oral agents:

(1) Biguanide: Metformin

(2)Sulfonylureas :Glipizide, Glyburide, Glimepride , Gliclazide

(3)Meglitinides: Repaglinide, Nateglinide

(4)Thiazolidinediones: Rosiglitazone, Pioglitazone

(5)Alpha- glycosidase inhibitors :Acarbose, Miglitol

(6)Dipeptidyl- peptidase 4 inhibitors: Sitagliptin, Linagliptin , Saxagliptin, Alogliptin

(7)Sodium- glucose co-transporter 2: Canagliflozin, Dapagliflozin

(8)Bile acid resin: Colesevelam

(9)Dopamine agonist : Bromocriptine

(b)Injectable agents:

(1)Amylin analog

(2)Incretin mimetics

(3)Insulin

There are 5 proteins in body which acts as drug target by various anti diabetic agents :

(1) Dipeptidylpeptidase 4 (DPP 4) (enzyme).

(2) Cyclooxygenase 1 and 2 (COX1 and COX2) (enzyme).

(3) Angiotensin-Converting Enzyme (ACE) (enzyme).

(4) Serotonin Transporter (SERT) (Transporters / Channels).

(5) GLP1 Receptor (G-Protein Coupled Receptor).

<u>Different drug targets :</u>

(1) Dipeptidylpeptidase 4 (DPP 4) : Type of a multi-functional protein which potentiates activation of T cell with the help of ADA(adenosine deaminase) , caveolin-1,CD45 and many other growth factors.

Bioactivity related to chemokines is modulates by proline specific Dipeptidyl peptidase. While, many enzymes illustrates either same as DPP4-like activities or depicts homologues structural presentation to as DPP4 activity.

Other than DPP4,several proteins are involved in activation of fibroblast for instance : DASH proteins , Alpha proteins , DPP8 protein , DPP9 protein , DPP4-like protein 1 ,

DPP4-like protein 2 such as DPL2, DPP10 from the DPP4-gene family S9b and structurally unrelated enzyme DPP2, displaying DPP4-like activity.

On the other hand , proteins such as DPP6 and DPP10 does not show activity same as DPP4. All of these DASH proteins have crucial role for providing immunity such as cell proliferation, antigen-presenting , signal transduction ,T cell activation , differentiation as well as tissue remodeling.

Being a potential biomarker it is involves in numerous pathophysiological processes along with this it can act as drug target in inflammatory diseases as well as cancer. Despite of having many advances there is challenging fact about DASH members regarding their drug selectivity for betterment of efficacy along with unwanted serious side effects

(2) Cyclooxygenase 1 and 2 (COX1 and COX2): COX enzymes catalyze formation of thromboxane, prostaglandins and levuloglandins. Prostaglandins are kind of a autocoid mediators which affect all the physiological as well as pathological pathways , they attach reversibly with G-protein coupled membrane receptors.

In contrast to that levuloglandins are newer class of product which attach irreversibly to number of the proteins. COX enzymes are inhibits by aspirin and other NSAIDS and that is the reason they as clinically important. This inhibition will result into positive signs for relief from thrombotic, oncological maladies, neurodegenerative , pyretic and inflammatory disorders.

Due recent advances of designing and synthesis of COX-2 selective inhibitors it has reduced the GI irritation caused due to aspirin.

(3) Angiotensin-Converting Enzyme (ACE) : Angiotensin- converting enzymes are concentrated in the endothelial lining of the blood vessels mainly in the pulmonary circulation. This enzymes have control on systemic vascular tone due to the Angiotensin II .

Nowadays, numerous agents are available which can inhibit the converting enzyme activity and results into reduction of blood pressure(BP). Sarcoidosis(active) along with Macrophages are a rich source of ACE activity. Increase in activities have reported inn numerous other conditions such as hyperthyroidism and diabetes mellitus.

It has been indicated in the recent studies that most of the diabetic complications such as hypertension and nephropathy are vascular originated. ACE activity level changes with involvement of Renin angiotensin and also a important factor since ACE converts

Angiotensin I to Angiotensin II , Angiotensin II is a crucial vasoconstrictor which is essential in blood pressure regulation.

(4) Serotonin Transporter (SERT): Main and important function of SERTs is to take back serotonin to the presynaptic terminal after release. Besides this they have to produce currents large enough for physiological changes.

Alternating access model is the standard model for electrogenic transport in this transport of serotonin with a predetermined ratio of co-transported ions which consequently generates net charge per cycle. But, this alternate access cannot account all the currents of SERT.

(5) GLP1 Receptor: GLP1 also known as Glucagon -like peptide -1 receptor for the most potent gastrointestinal hormone , endogenous incretin that stimulates secretion of insulin in glucose dependant manner. GLP-1 , incretins as well as glucose-dependant insulinotropic polypeptide are believed to be responsible for more than 70 percent meal stimulated insulin response.

Ultimately , the effect of GLP-1 was retained largely , on the other hand effect of GIP was reduced a lot.

Objective of my work: In modern world, the prevalence of diabetes is increasing at a tremendous pace and as many of the drug molecules are losing their activity being resistant to work on human body maybe due to overdose or false use of medication. This work will try to modify currently available drugs for diabetes in market and will try to predict their activity in the human body simultaneously using various software.

The proposed methodology (Computer aided drug design) : Computer aided drug design is an advanced technique as compared to High throughput screening because it doesn't require more knowledge about design of compound prior its designing. whereas it can lead to many hit compounds which as are best suited as promising candidate for drug designing process.

The main role of CADD is to screen out enormous range of compound libraries into small clusters with predicted active compounds and also helps in improving biological properties of lead compounds such as ADMET and affinity properties. With the help of computational tools it is easy to elaborate and define strength between the interactions of ligands and targets, and it is also necessary for the identification of lead molecules .

As compared to another conventional methods such as HTS, CADD is more targeted and elegant approach for the generation of "hits". It also enables the elucidation of compounds as well as therapeutic activities of all possible derivatives , it also suggests

variables to be applied for improving a drug compound. This method is also cost effective as well as less time consuming.

It can be applied in different stages of drug discovery such as : Identification of target, Target validation , Designing of molecule also the interaction of drug candidates with the targets. CADD can be ligand based and can also be structure based. Generally, CADD is best suited when minimal information about the structure is available. And this case is normally seen with membrane protein targets.

Software used for this work:

- Chimera: It is a software used for molecular docking. The suitable protein is selected and then the desired molecule is docked inside it. The specific pocket is selected in the receptor for a specific drug, after docking scores are interpreted for every possible position the best conformer is selected comparing it with a drug having great bioavailability.
- ADMET predictor : It will give idea about the pka, solubility bioavailability , molecular weight, Tmax, Cmax and other properties of the molecule.
- GASTRO plus simulator: The Plasma concentration curve , Solubility curve can be obtained using this software.
- Osiris Property Explorer: Various Toxicity risks for the desired molecule can be predicted using this software.
- Swiss ADME: Pharmacokinetics of molecule can be predicted using this molecule
- Molinspiration: This software is used to know the bioactivity of the molecules.

Results and discussion: all the results of silico work

(A)Gliclazide analogues:

***Molecular docking of Gliclazide analogue by adding Iodine to 3,4,5 position of parent Gliclazide molecule using chimera*:**

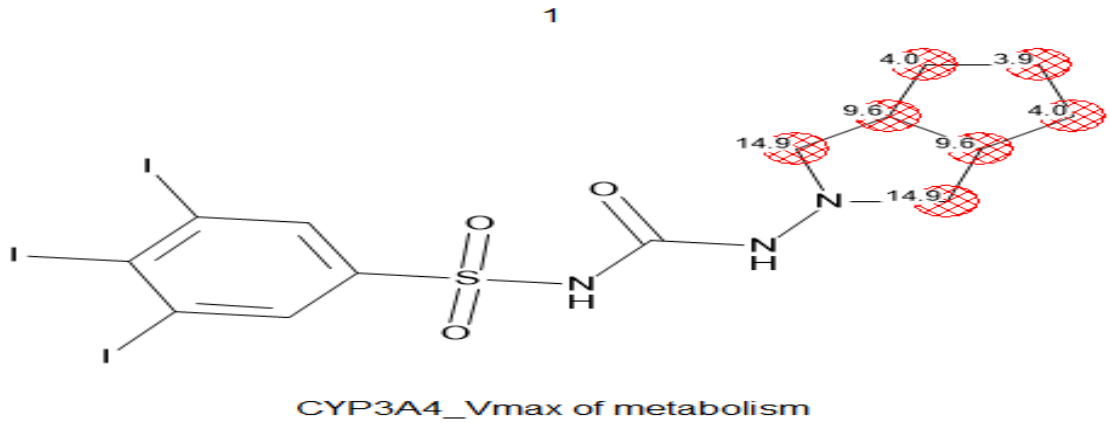


Figure 1.1: 3,4,5 triiodo- Gliclazide

Solubility (mg/L)	pka	Log P	T1/2	F	Dose	Cmax	Tmax	AUC	Metabolic Sites/ Pathway
22.8	6.31	4.82	19.23 hours	99.06	80 mg/daily	3.63	10.96	76.69	2C9->C6.7.8.9.10 3A4->C4.6.7.8.9.10

Table 1: Various properties of 3,4,5 triiodo-Gliclazide predicted using Gastro plus and ADMET predictor

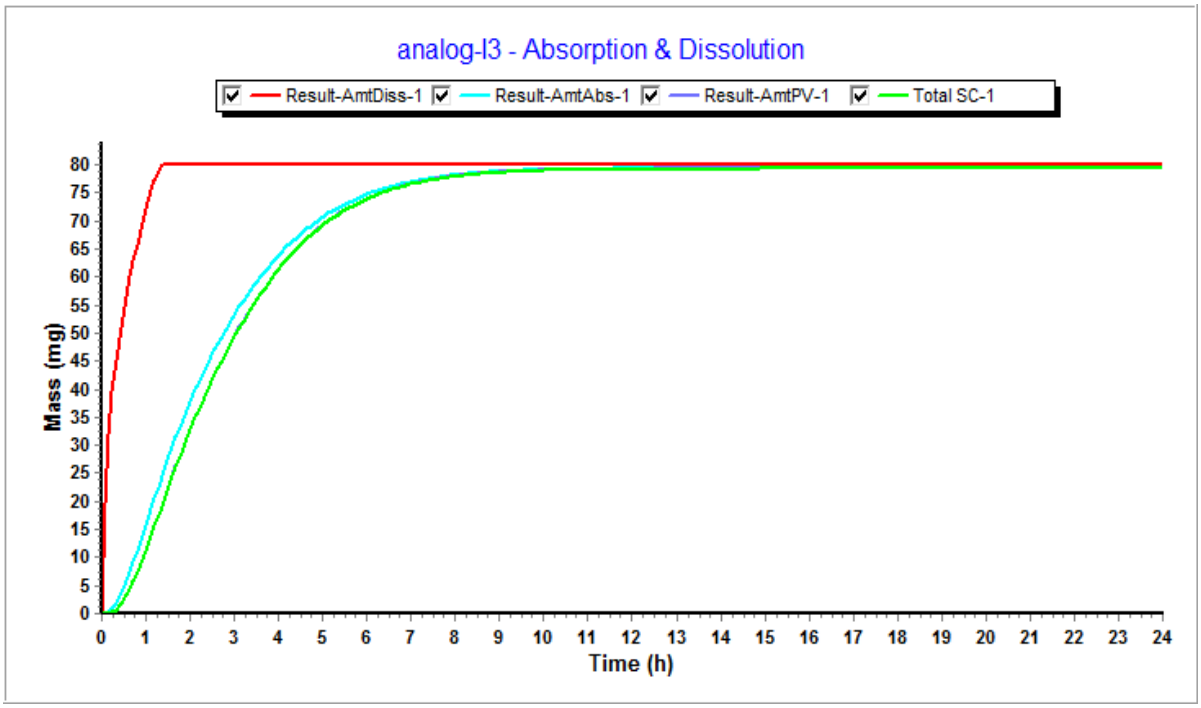


Figure 1.2: Absorption and Dissolution curve of 3,4,5 triiodo-Gliclazide

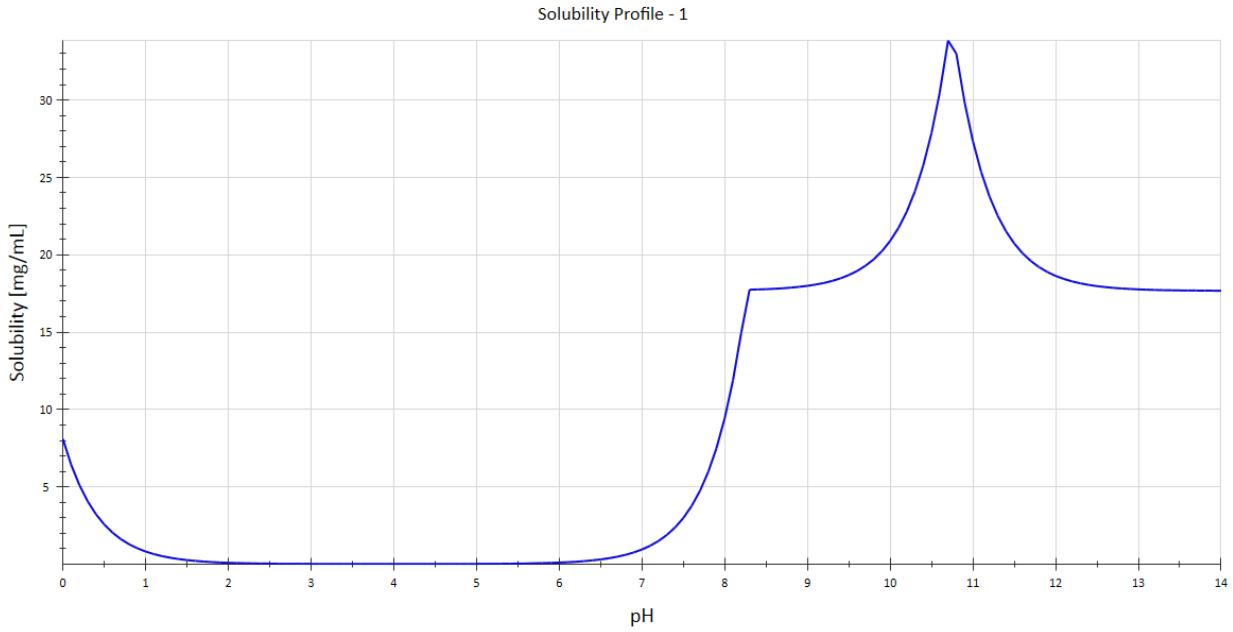


Figure 1.3: Solubility curve of 3,4,5 triiodo-Gliclazide

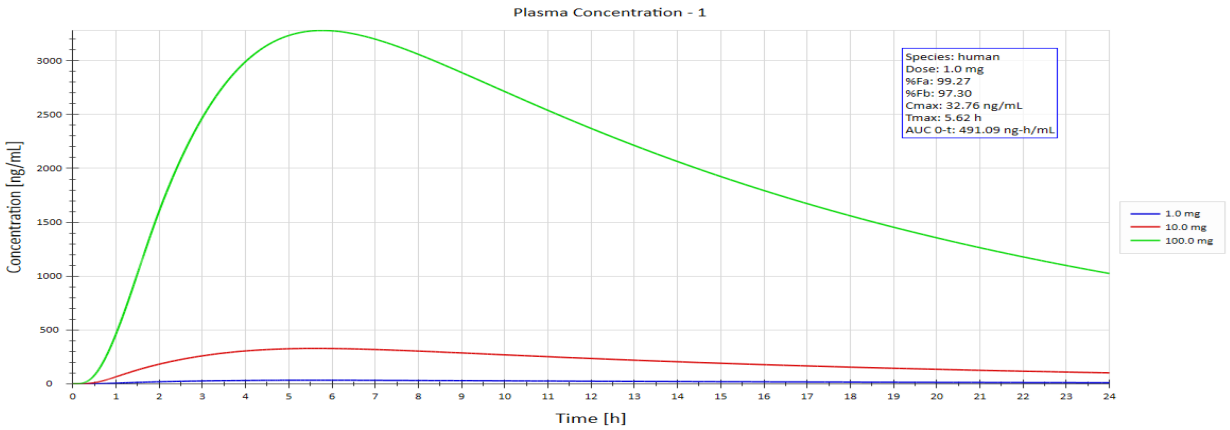


Figure 1.4: Plasma concentration curve of 3,4,5 triiodo-Gliclazide

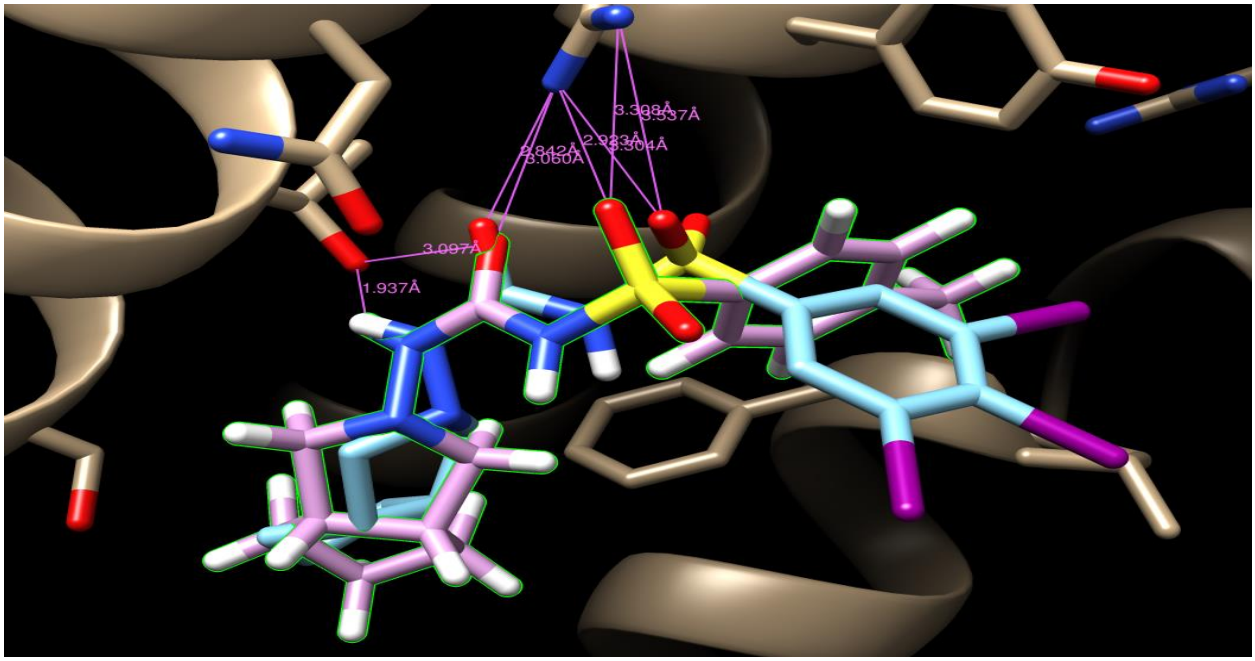
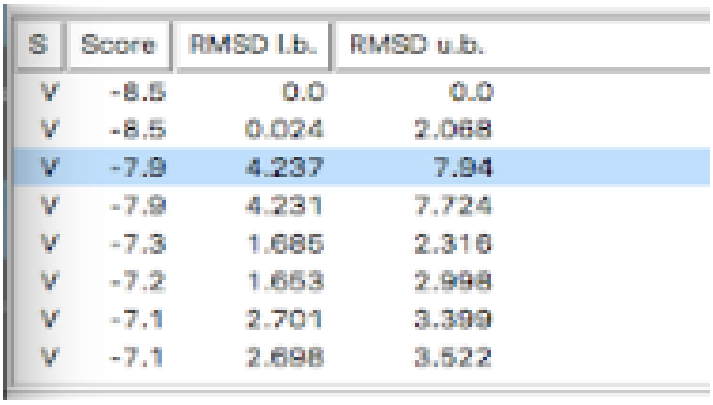


Figure 1.5: Best suited position of 3,4,5 triiodo-Gliclazide compared to GBM



S	Score	RMSD l.b.	RMSD u.b.
V	-8.5	0.0	0.0
V	-8.5	0.024	2.068
V	-7.9	4.237	7.94
V	-7.9	4.231	7.724
V	-7.3	1.685	2.316
V	-7.2	1.653	2.998
V	-7.1	2.701	3.399
V	-7.1	2.698	3.522

Figure 1.6: Scores of 3,4,5 triiodo-Gliclazide when docked with GBM

Interpretation of properties from above data:

Increase in logP value from 1.32 to 4.82. Here the pka value also increases from 5.5 to 6.31 that means the modified molecule will be less acidic as compared to the parent molecule so it's solubility will also decrease .

Half life of the drug also increases from 18 hours to 19.23 that means elimination rate of the analogue will be slower as compared to parent molecule .

Bioavailability significantly increases from 78.18 to 99.06.

Accordingly the Cmax and Tmax of modified molecule also increases a slight which is 3.63 and 10.96 respectively .

AUC increases from 15.74 to 76.69 .

The sites for metabolism are c2 and others are c 678910 .

Due to increase in the pka value the solubility of the drug decreases but it shows highest solubility around pH 11 .

Plasma concentration of drug increases at about 6-7 hours in the body .

After docking the modified molecule with GBM the most similar docking was seen for the molecule with score of -7.9.

we can see distance for the same docked molecule from zinc is 9.58 Armstrong which is lowest among all the docked possibilities so the clearance of this position will be highest.

There is no risks related to Mutagenic , Tumorigenic, Irritation effect but a moderate possibility of Reproductive effects for the modified molecule.

It show good activity towards GPCR ligand.

Its GI absorption is high.

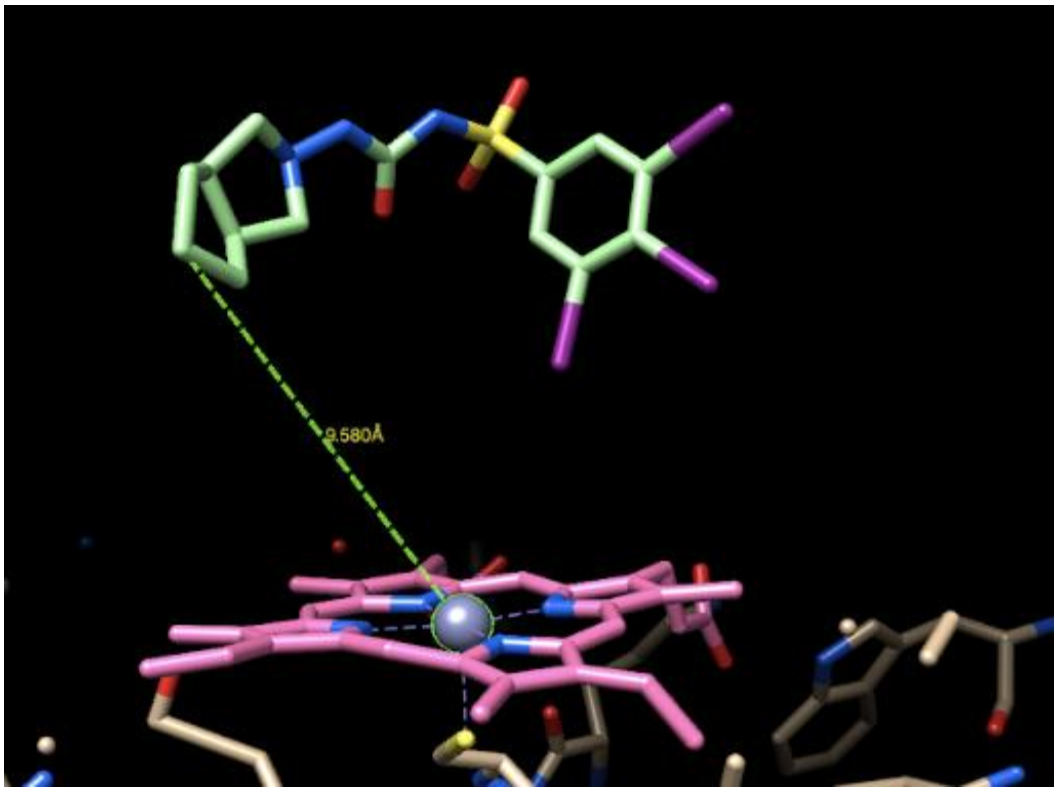


Figure 1.7: Distance of 3,4,5 triiodo-Gliclazide from zinc molecule

***Molecular docking of Gliclazide analogue by adding chlorine to 3,5 position of parent Gliclazide molecule using chimera*:**

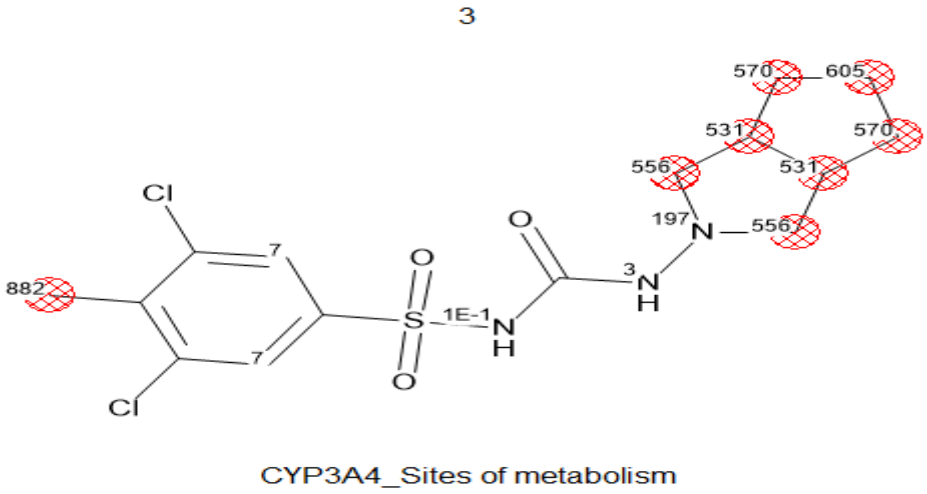


Figure 2.1: 3,5 dichloro- Gliclazide

Solubility (mg/L)	pka	Log P	T1/2	F	Dose	Cmax	Tmax	AUC	Metabolic Sites/ Pathway
3.3	5.95	1.89	22.79 hours	95.38	80 mg/daily	3.63	16.246	71.57	**3A4->C15~21. C2.3.5.22.23**

Table 2 : Various properties of 3,5 dichloro-Gliclazide predicted using Gastro plus and ADMET predictor

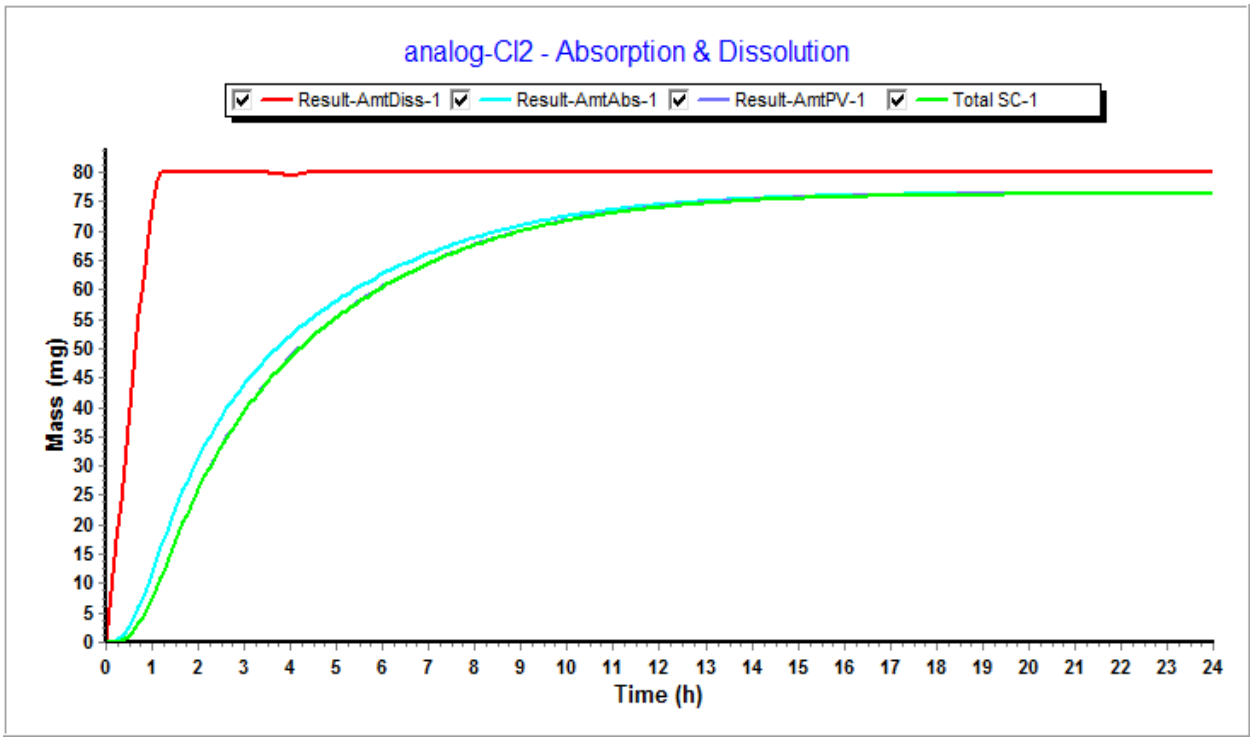


Figure 2.2: Absorption and Dissolution curve of 3,5 dichloro-Gliclazide

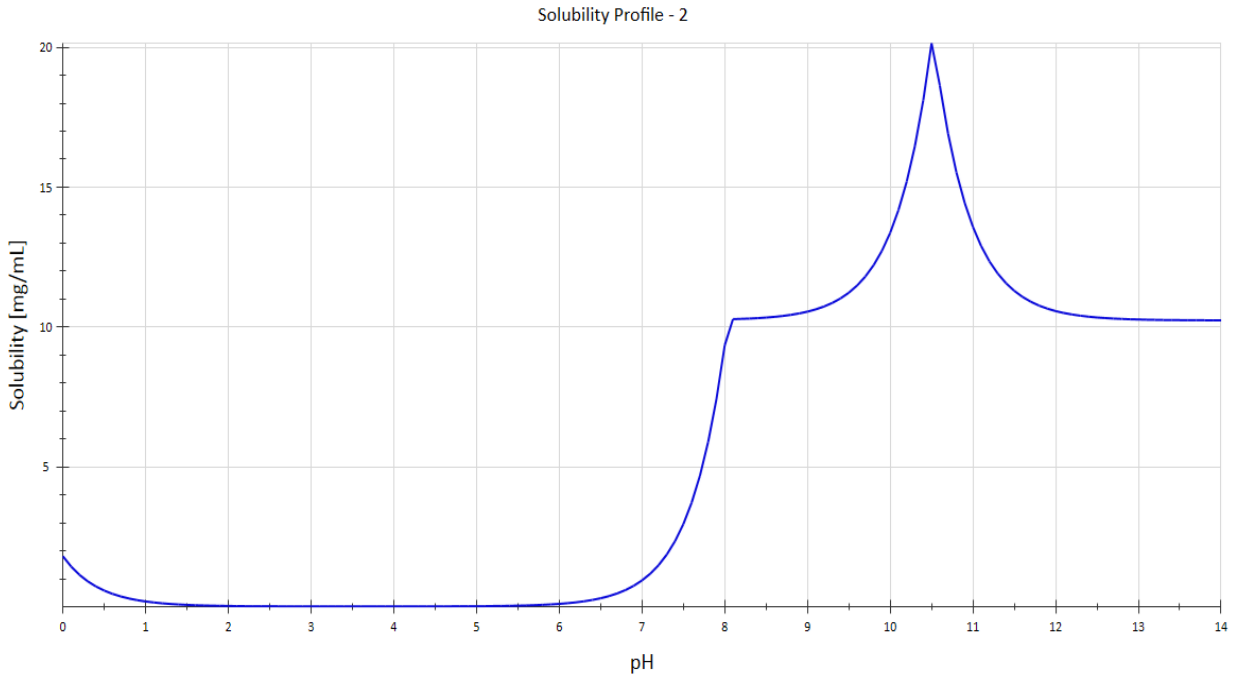


Figure 2.3: Solubility curve of 3,5 dichloro-Gliclazide

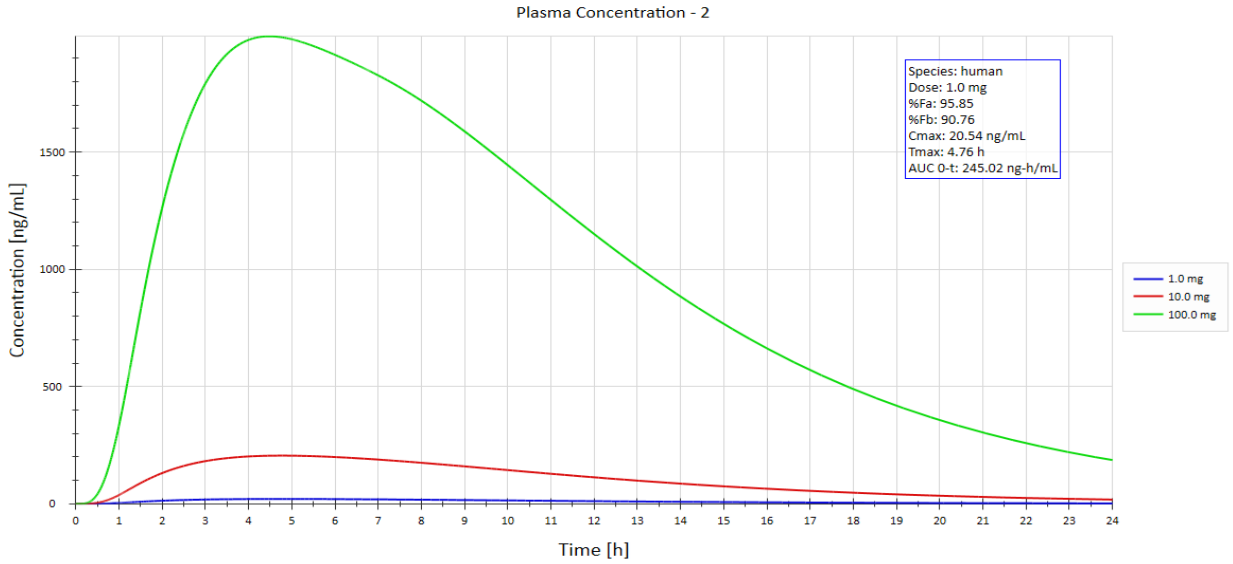


Figure 2.4: Plasma concentration curve of 3,5 dichloro-Gliclazide

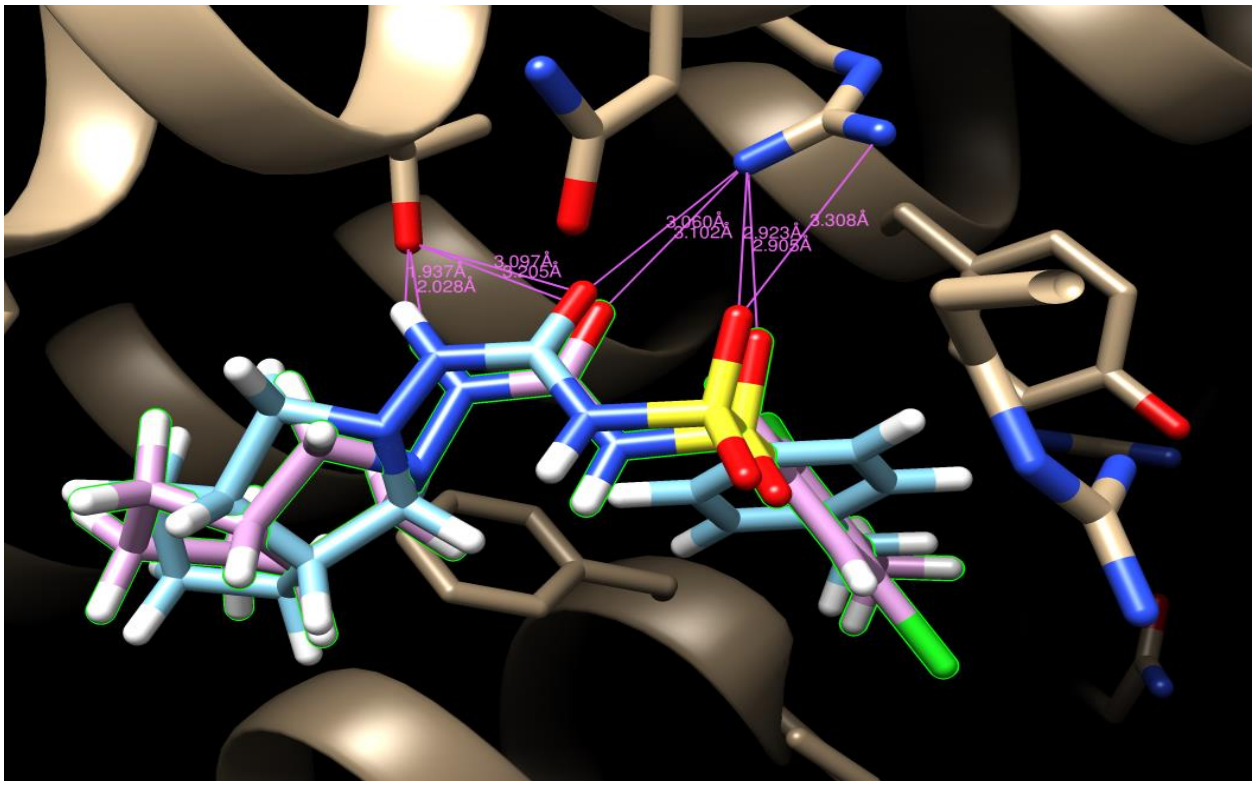


Figure 2.5: Best suited position of 3,5 dichloro-Gliclazide compared to GBM

S	Score	RMSD l.b.	RMSD u.b.
V	-8.5	0.0	0.0
V	-8.4	3.524	7.613
V	-8.4	3.518	7.73
V	-8.4	2.714	3.809
V	-8.4	2.714	3.538
V	-8.4	1.874	3.053
V	-8.2	0.05	1.841
V	-8.2	4.063	5.61

Chimera Model #3.5

```
REMARK VINA RESULT:      -8.4      2.714      3.538
REMARK   4 active torsions:
REMARK   status: ('A' for Active; 'I' for Inactive)
REMARK     1  A    between atoms: C1_1  and  C2_2
REMARK     2  A    between atoms: C5_6  and  S1_7
REMARK     3  A    between atoms: N1_10  and  S1_7
REMARK        I    between atoms: C6_11  and  N1_10
REMARK        I    between atoms: C6_11  and  N2_13
REMARK     4  A    between atoms: N2_13  and  N3_14
```

Change Compound State

Figure 2.6: Scores of 3,5 dichloro-Gliclazide when docked with GBM

Interpretation of properties from above data:

Slight increase in logP value from 1.32 to 1.89. Here the pka value also increases from 5.5 to 5.95 that means the modified molecule will be less acidic as compared to the parent molecule so it's solubility will also decrease .

Half life of the drug also increases from 18 hours to 22.79 hours that means elimination rate of the analogue will be slower as compared to parent molecule.

Bioavailability significantly increases from 78.18 to 95.38.

Accordingly the Cmax and Tmax of modified molecule also increases a slight which is 3.63 and 16.24 respectively .

AUC increases from 15.74 to 71.57.

The sites for metabolism are 3A4>C15-21 and others are c2.3.5.22.23 .

Due to increase in the pka value the solubility of the drug decreases but it shows highest solubility around pH 11 .

Plasma concentration of drug increases at about 4-5 hours in the body .

After docking the modified molecule with GBM the most similar docking was seen for the molecule with score of -8.4.

we can see distance for the same docked molecule from zinc is 10.532 Armstrong which is lowest among all the docked possibilities so the clearance of this position will be highest.

There is high risk related to Mutagenic , Irritation and moderate possibility of Reproductive effects for the modified molecule , on the other hand there is no chance of molecule being Tumorigenic

Its GI absorption is high.

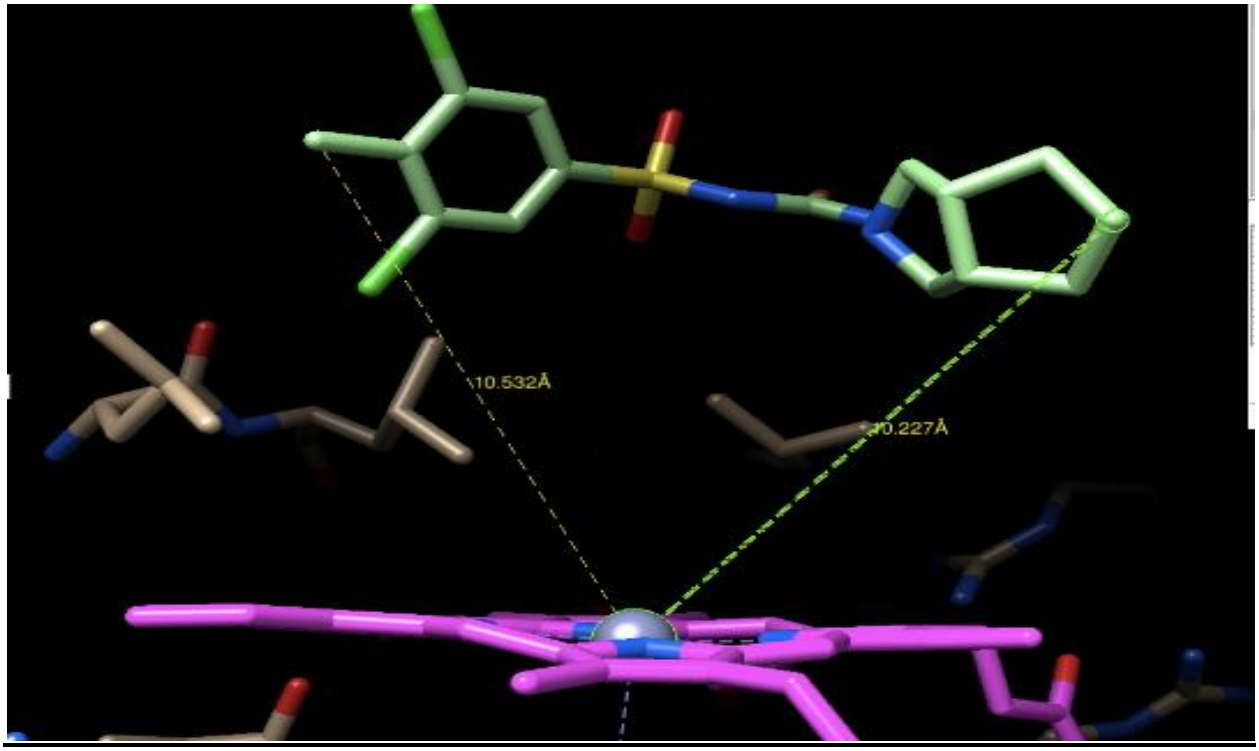


Figure 2.7: Distance of 3,5 dichloro-Gliclazide from zinc molecule

***Molecular docking of Gliclazide analogue by adding CF3 to parent Gliclazide molecule using chimera*:**

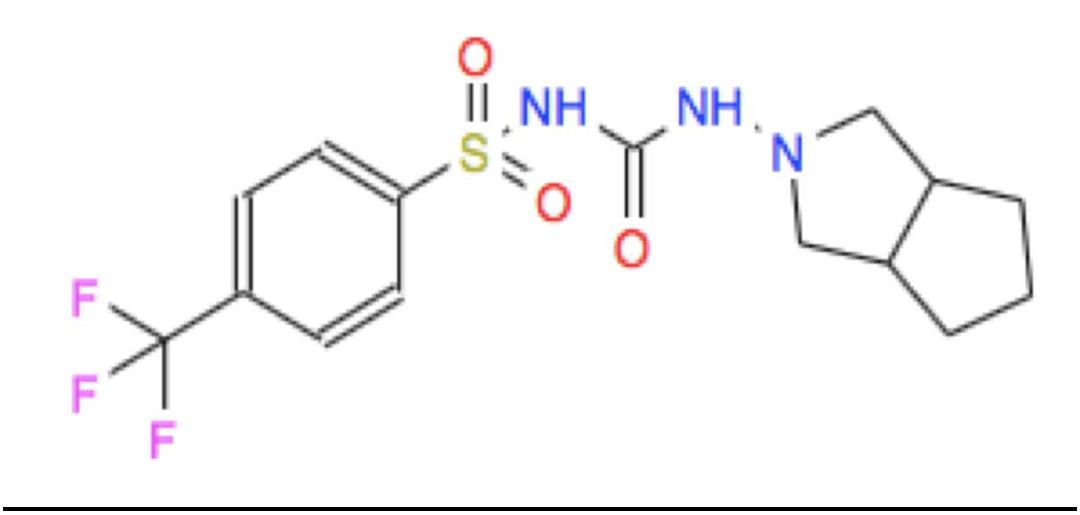


Figure 3.1: CF3- Gliclazide

Solubility (mg/L)	pka	LogP	T1/2	F	Dose	Cmax	Tmax	AUC	Metabolic Sites/ Pathway
35.3	5.12	2.26	163.44 Hours	91.37	80 mg/daily	1.85	18.16	37.51	3A4->C5~11

Table 3: Various properties of CF3-Gliclazide predicted using Gastro plus and ADMET predictor

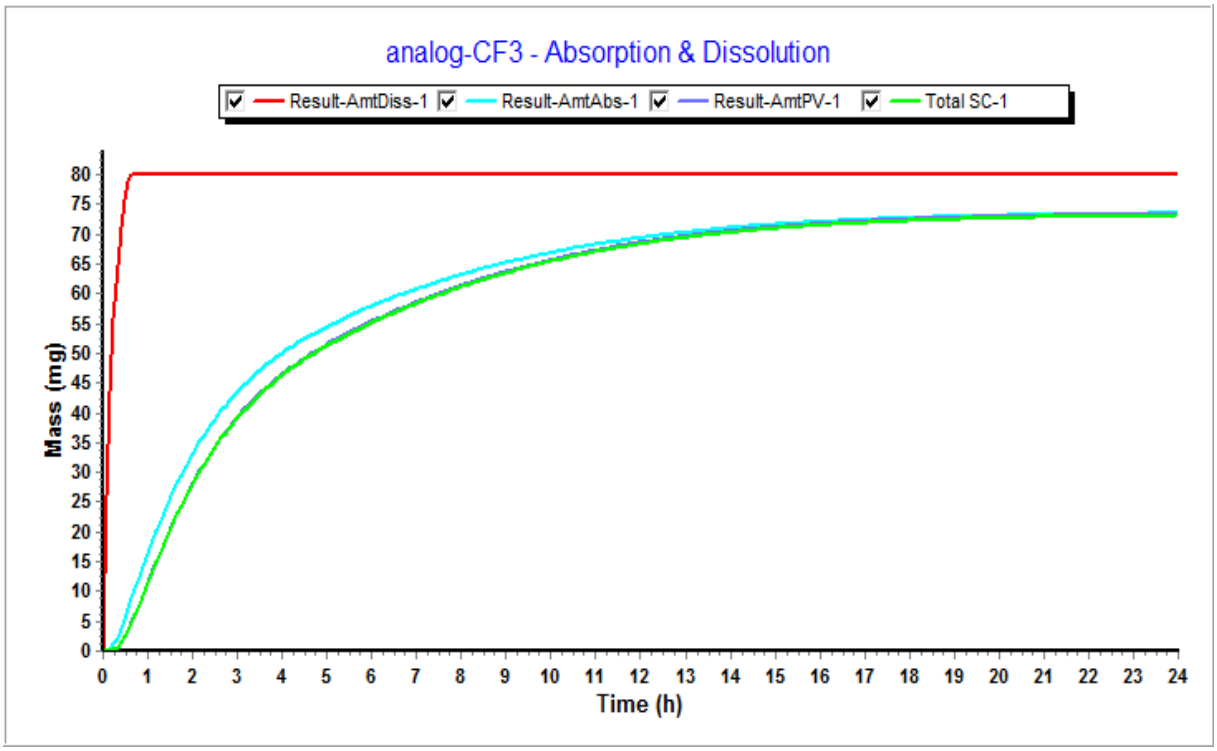


Figure 3.2: Absorption and Dissolution curve of CF3-Gliclazide

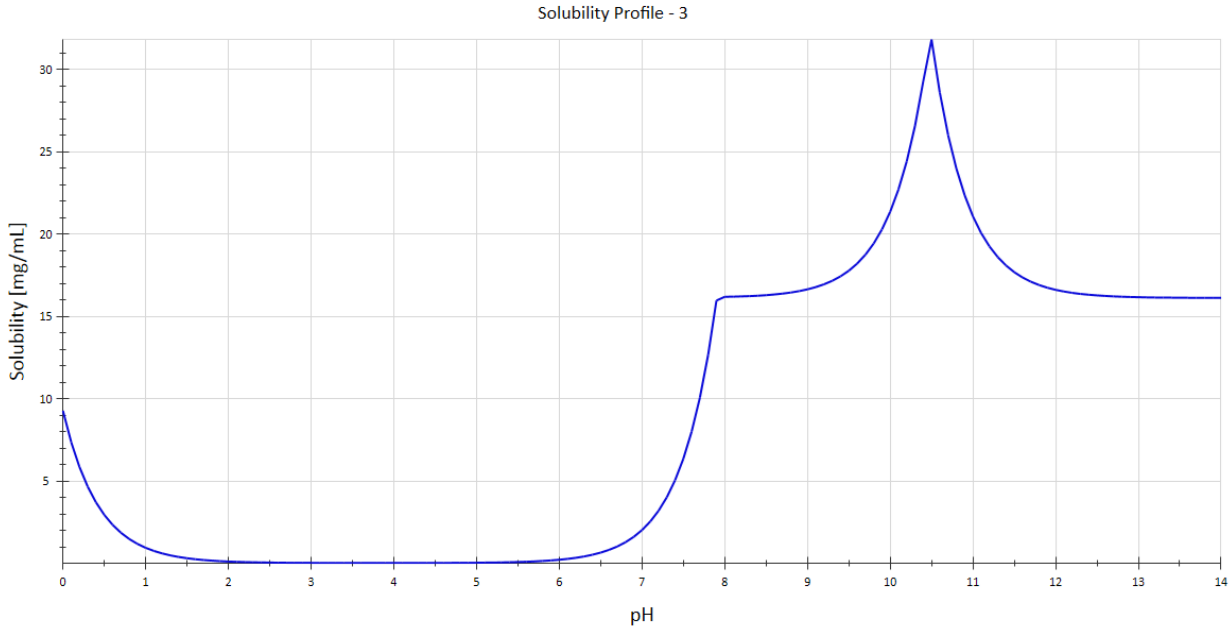


Figure 3.3: Solubility curve of CF3-Gliclazide

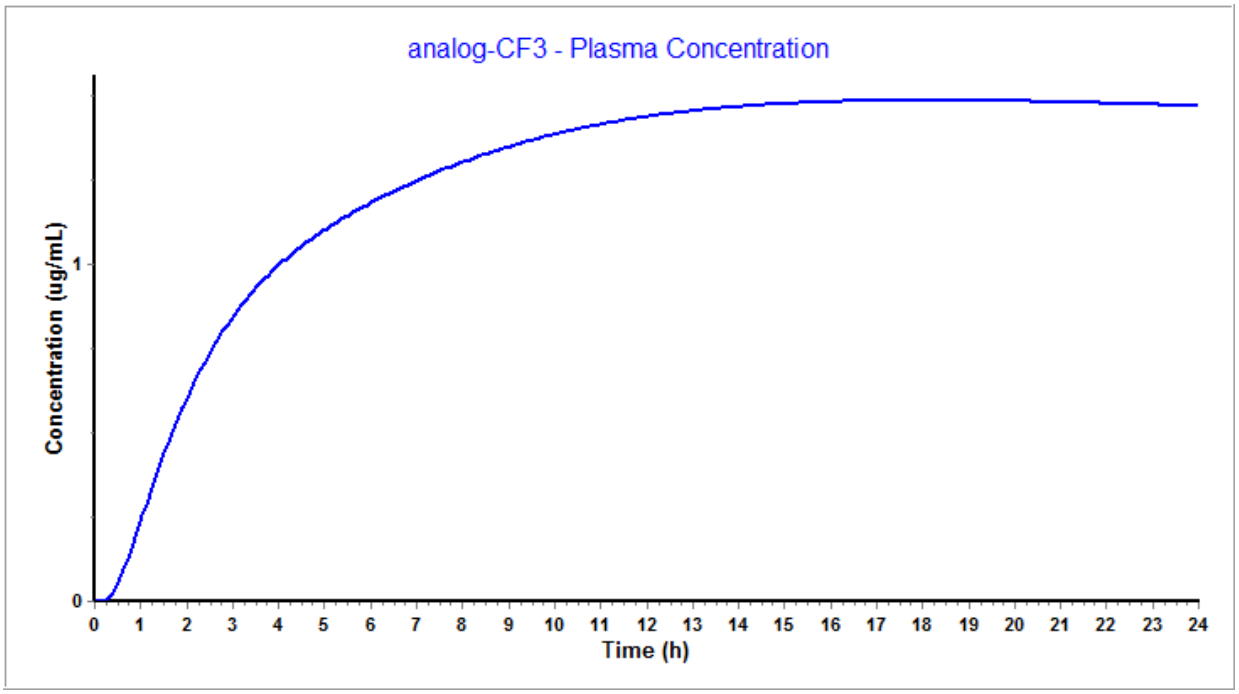


Figure 3.4: Plasma concentration curve of CF3-Gliclazide

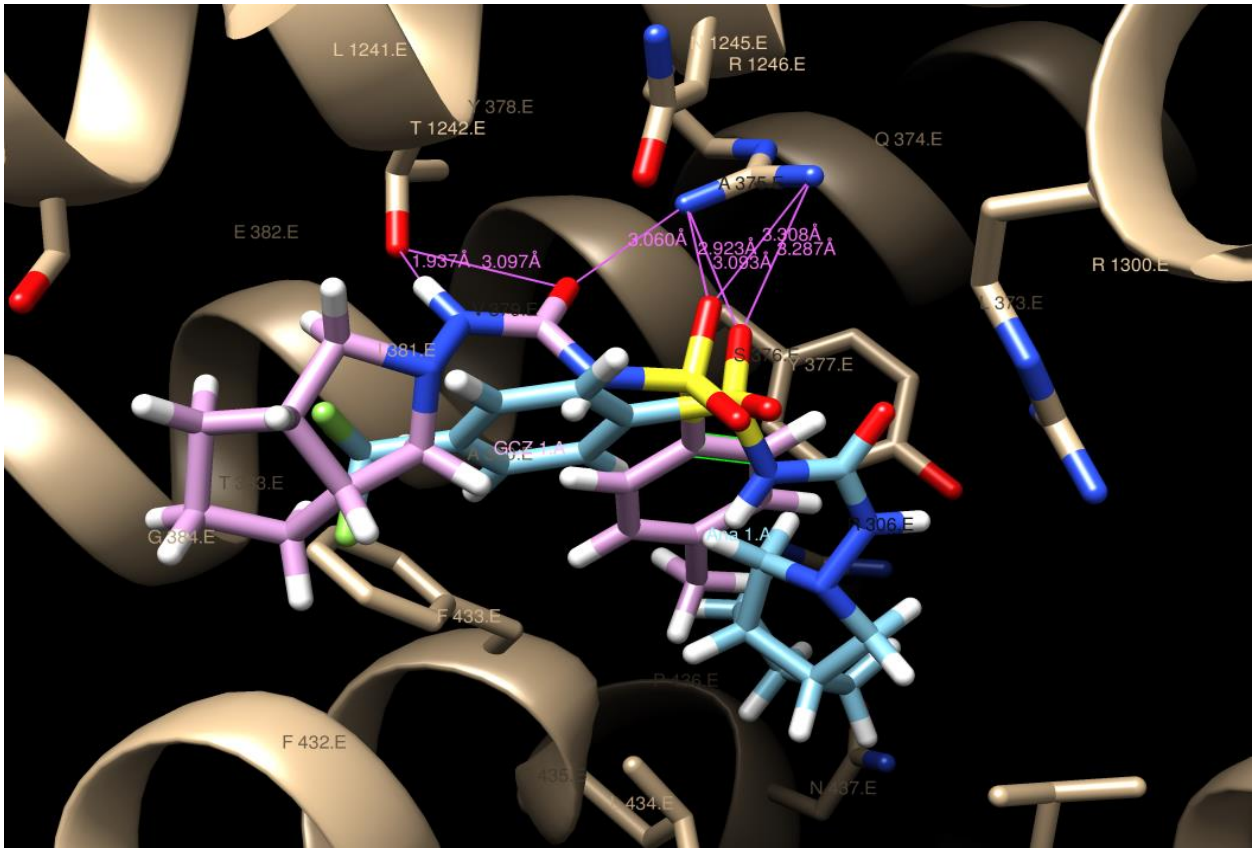


Figure 3.5: Best suited position of CF3-Gliclazide compared to GBM

File Compounds Column Selection Chimera HBonds Movie

S	Score	RMSD l.b.	RMSD u.b.
V	-8.9	1.452	2.157
V	-8.8	4.263	8.237
V	-8.5	1.16	1.954
V	-8.4	4.915	8.394
V	-8.2	2.442	3.3
V	-8.2	2.827	3.727
V	-8.2	4.116	8.048
V	-8.2	1.776	2.362

Figure 3.6: Scores of CF3-Gliclazide when docked with GBM

Interpretation of properties from above data:

Increase in logP value from 1.32 to 2.26. Here the pka decreases from 5.5 to 5.12 that means the modified molecule will be less acidic as compared to the parent molecule so it's solubility will also decrease .

Half life of the drug also increases from 18 hours to 163.44 hours that means elimination rate of the analogue will be slower as compared to parent molecule .

Bioavailability significantly increases from 78.18 to 91.37.

Accordingly the Cmax and Tmax of modified molecule is 1.85 and 18.16 respectively .

AUC increases from 15.74 to 37.51 .

The sites for metabolism are 3A4->C5-11 .

Plasma concentration of drug increases at about 10 hours in the body .

After docking the modified molecule with GBM the most similar docking was seen for the molecule with score of -8.2.

we can see distance for the same docked molecule from zinc is 10.262 Armstrong which is lowest among all the docked possibilities so the clearance of this position will be highest.

There is no risks related to Mutagenic , Tumorigenic , Irritation effects while it is having moderate chances to develop Reproductive system toxicity.

It show bioactivity towards GPCR ligand as well as Protease inhibitor.

Its GI absorption is high.

Ideally this analogue have no practical value due to its very high half life.

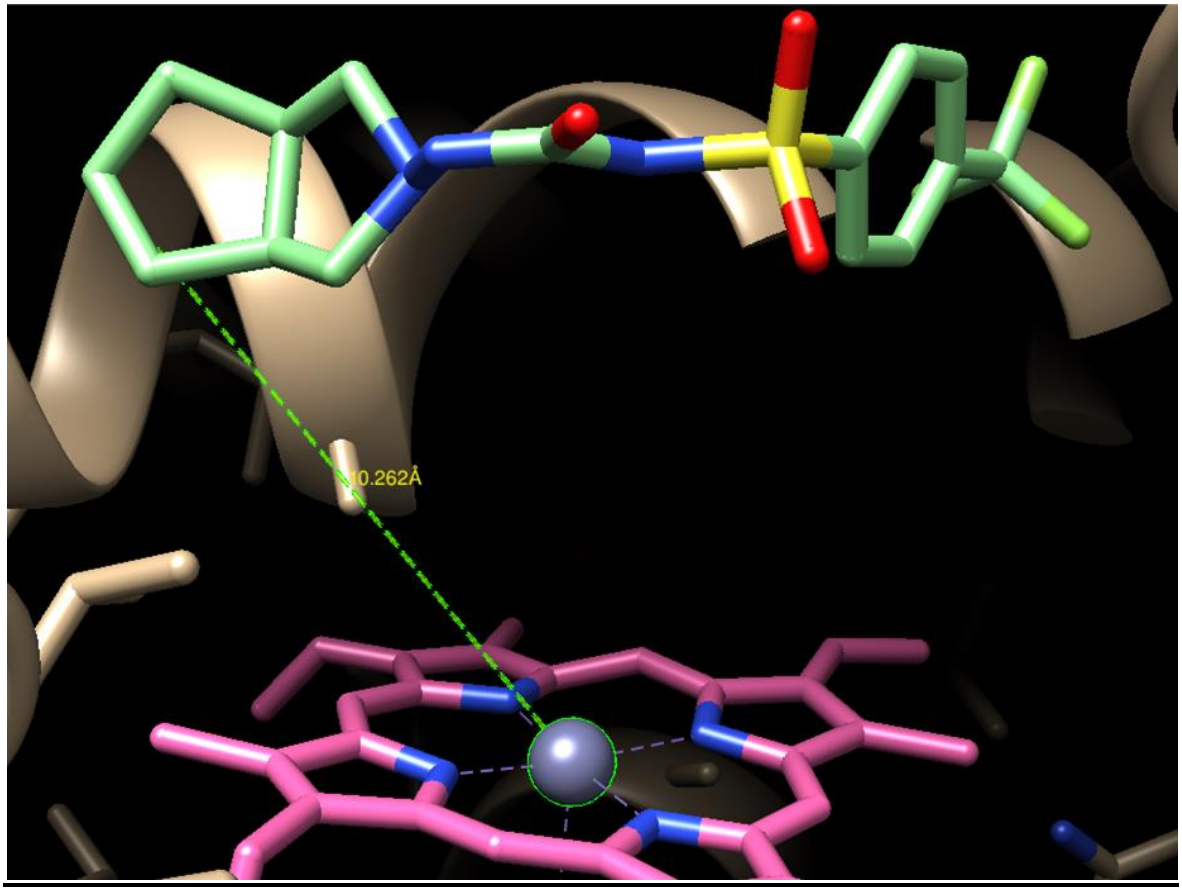


Figure 3.7: Distance of CF3-Gliclazide from zinc molecule

***Molecular docking of Gliclazide analogue by adding CH3 to parent Gliclazide molecule using chimera*:**

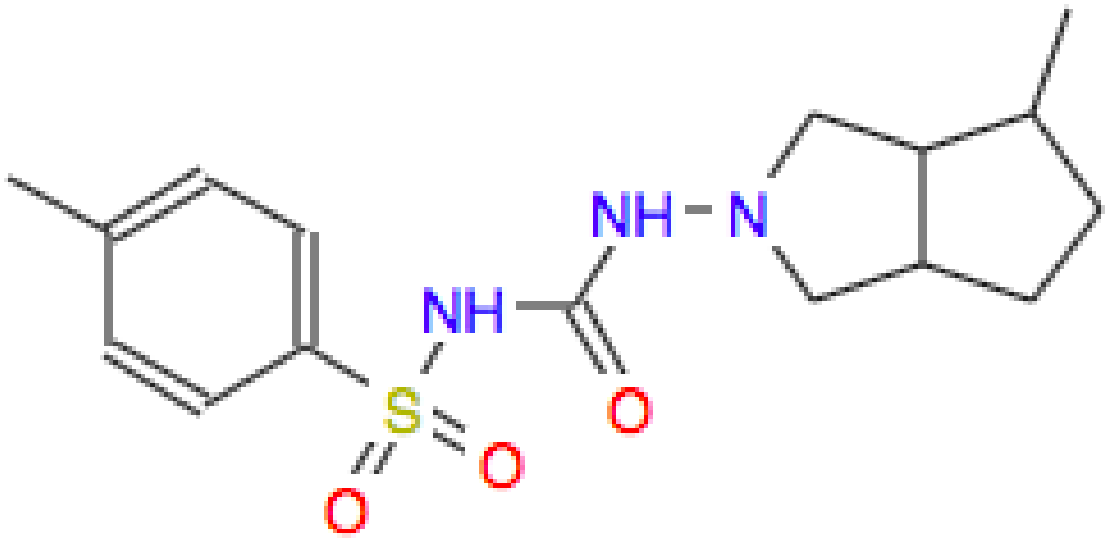


Figure 4.1: CH3- Gliclazide

Solubility (mg/L)	pka	LogP	T1/2	F	Dose	Cmax	Tmax	AUC	Metabolic Sites/ Pathway
54	5.53	1.6	2.88 Hours	76.72	80 mg/daily	0.48	3.28	12.15	2C9->C18～21.C16, 23, 10 2C19->C10,20

Table 4: Various properties of CH3-Gliclazide predicted using Gastro plus and ADMET predictor

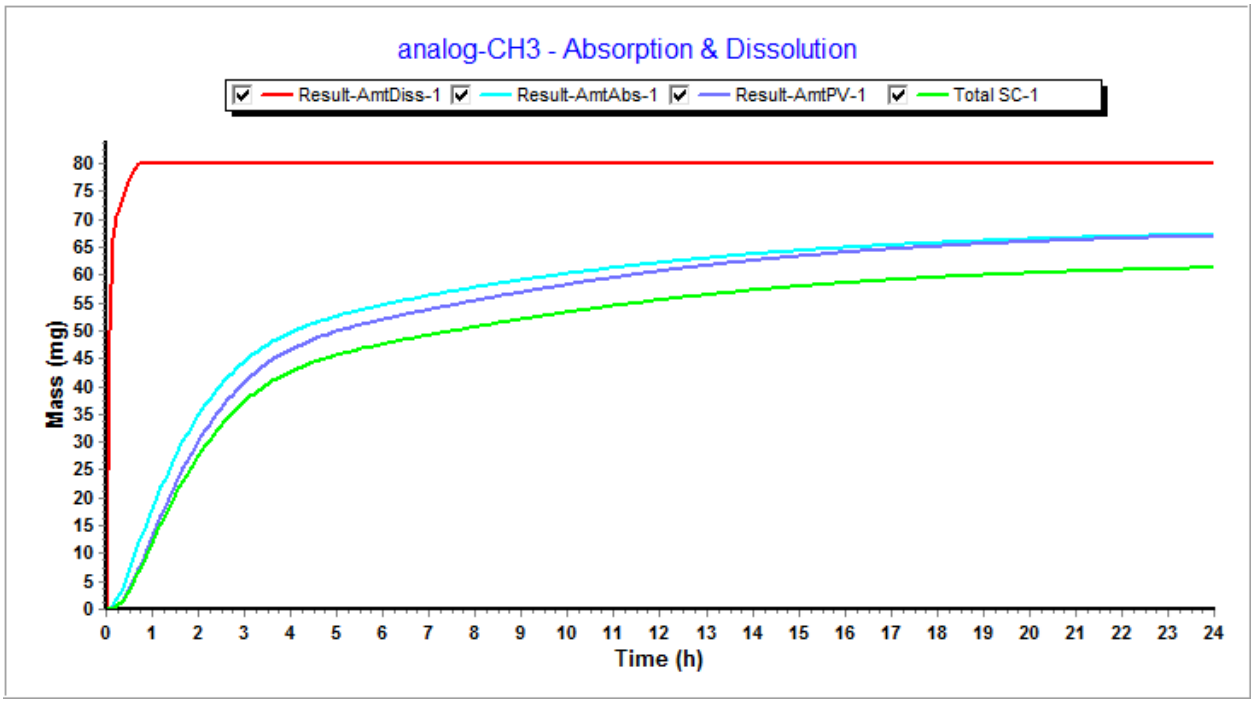


Figure 4.2: Absorption and Dissolution curve of CH3-Gliclazide

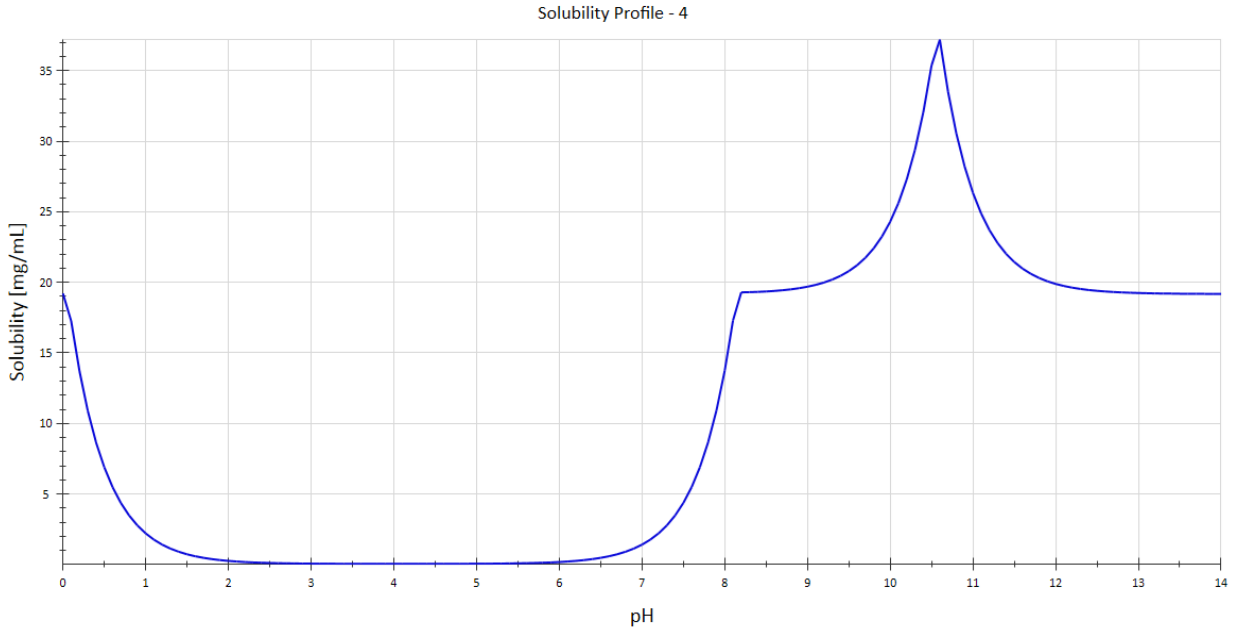


Figure 4.3: Solubility curve of CH3-Gliclazide

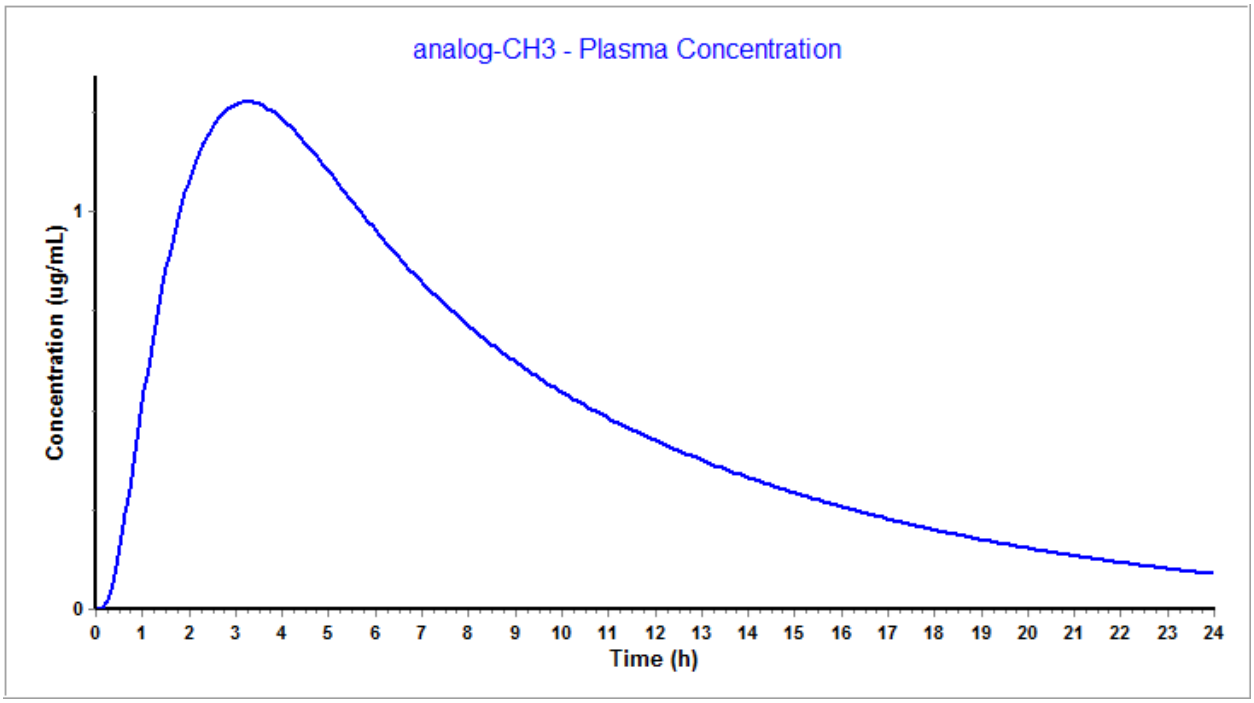


Figure 4.4: Plasma concentration curve of CH3-Gliclazide

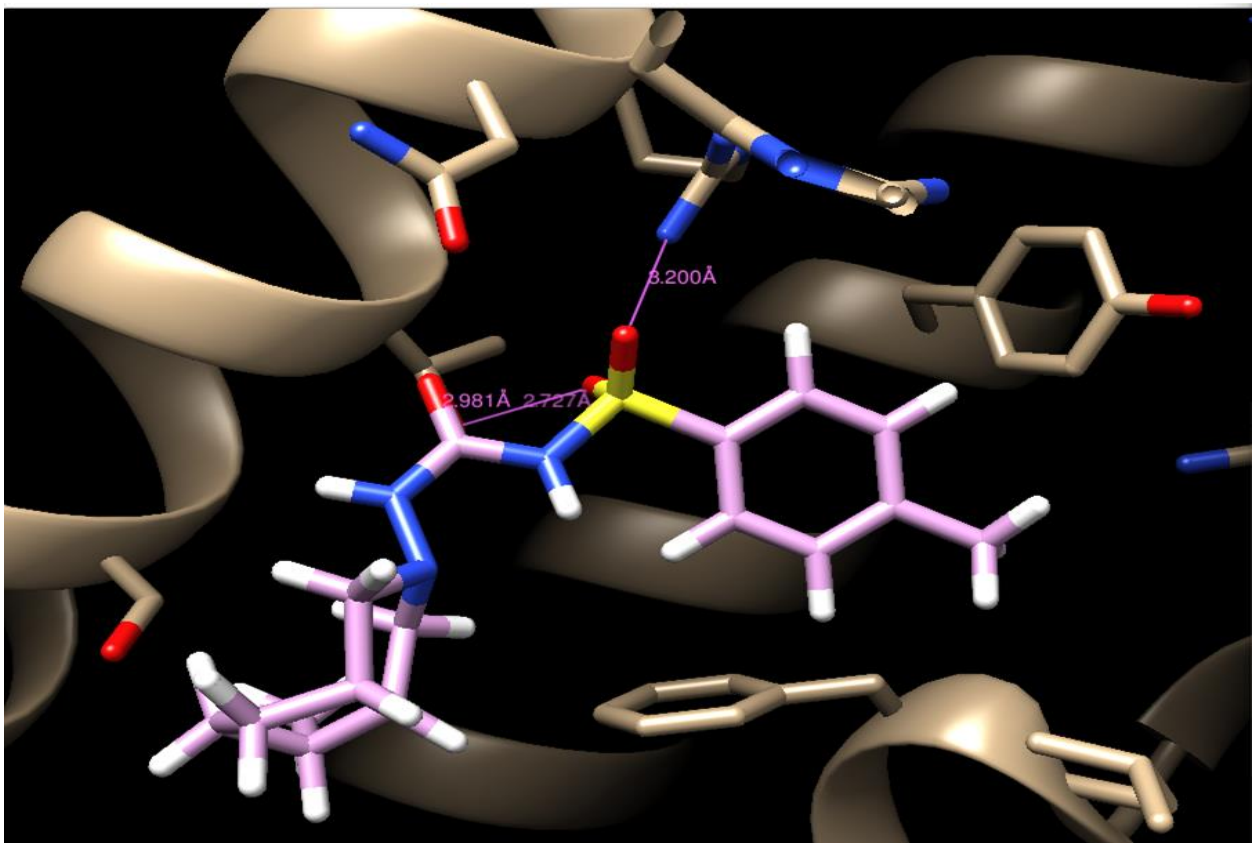


Figure 4.5: Best suited position of CH3-Gliclazide compared to GBM

Interpretation of properties from above data:

Slight increase in logP value from 1.32 to 1.6.

Here the pka value also increases with no significant difference , that means the modified molecule will have same solubility as the parent molecule.

Half life of the drug decreases from 18 hours to 2.88 hours that means elimination rate of the analogue will be faster as compared to parent molecule .

Bioavailability is nearly same as compared to parent molecule.

Accordingly the Cmax and Tmax of modified molecule is 0.48 and 3.28 respectively .

AUC is 12.15

The sites for metabolism are c2 and others are c 678910 .

Plasma concentration of drug increases at about 2-4 hours in the body .

we can see distance for the same docked molecule from zinc is 10.83 Armstrong which is lowest among all the docked possibilities so the clearance of this position will be highest.

If fast action is needed then this analogue should be used as it reaches its highest plasma concentration within 2-3 hours only.

There is no risks related to Mutagenic , Tumorigenic , Irritation effect, where as this molecule is more likely to develop toxicity related to Reproductive system..

Its GI absorption is high.

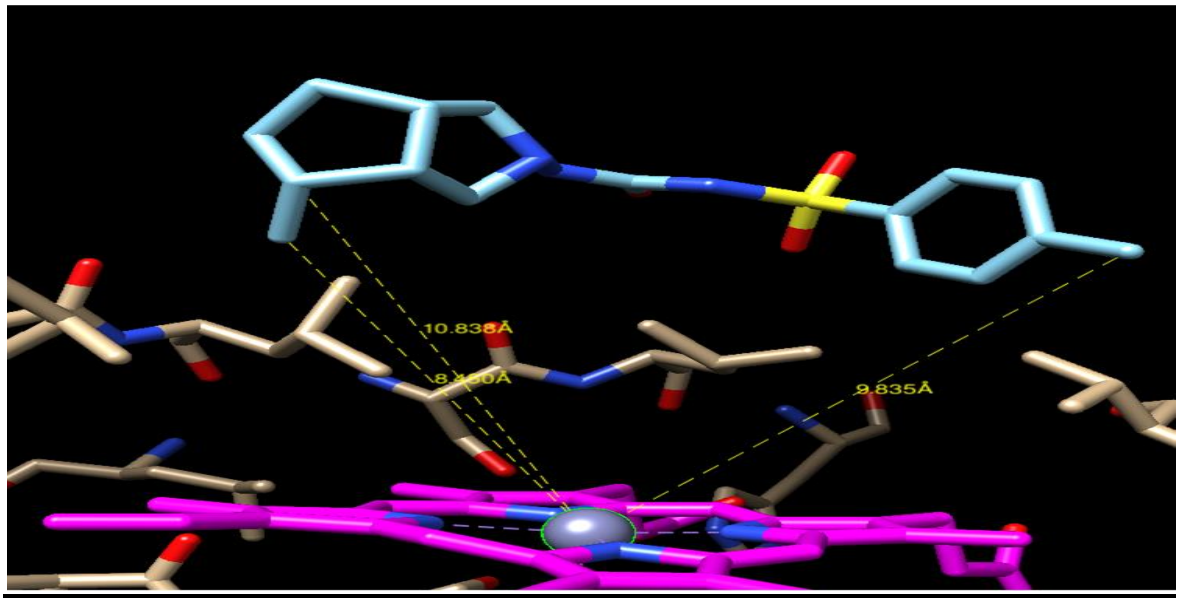
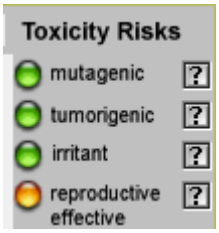
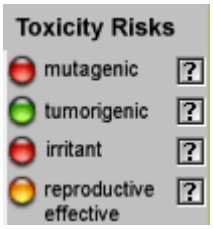
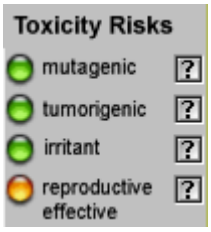
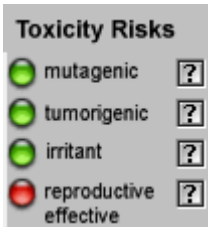


Figure 4.6: Distance of CH3-Gliclazide from zinc molecule

Toxicity Comparison of all four molecules:

 **3,4,5 triiodo- Gliclazide**	 **3,5 dichloro-Gliclazide**
 **CF3-Gliclazide**	 **CH3-Gliclazide**

Bioactivity of all four molecules in scores:

	3,4,5 triiodo-Gliclazide	3,5 dichloro-Gliclazide	CF3-Gliclazide	CH3-Gliclazide
GPCR ligand	0.25	0.15	0.30	0.10
Ion Channel modulator	-0.26	-0.38	-0.15	-0.34
Kinase Inhibitor	-0.28	-0.36	-0.18	-0.40
Nuclear receptor ligand	-0.29	-0.36	-0.13	-0.27
Protease inhibitor	0.16	0.08	0.28	0.14
Enzyme inhibitor	0.08	-0.08	0.07	-0.07

Pharmacokinetics of all four molecules:

GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.26 cm/s

3,4,5 triiodo- Gliclazide

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.70 cm/s

3,5 dichloro-Gliclazide

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.13 cm/s

CF3-Gliclazide

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.94 cm/s

CH3-Gliclazide

Comparison of Lipinski Rule of 5 for all molecules of Gliclazide:

Molecules	Molecular weight (gm/mol)	H bond Acceptor	H bond donor	LogP
3,4,5 triiodo-Gliclazide	687.07	4	2	4.82
3,5 dichloro-Gliclazide	392.30	4	2	2.24
CF3-Gliclazide	377.38	7	2	2.08
CH3-Gliclazide	337.44	4	2	1.63

(B)Pioglitazone Analogues:

***Molecular docking of Pioglitazone analogue by adding Ethoxy to Pioglitazone molecule using chimera*:**

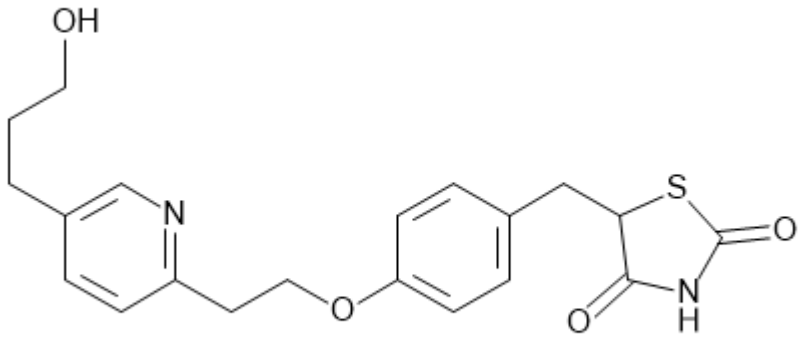


Figure 5.1: Ethoxy-Pioglitazone

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
400.49	28	12	10	5	1	112.86	102.86	3.17

Table 5: Various properties of Ethoxy-Pioglitazone predicted using Swiss ADME

Log *S* (ESOL)	-4.13
Solubility	2.94e-02 mg/ml ; 7.33e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.26
Solubility	2.20e-03 mg/ml ; 5.50e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.30
Solubility	2.01e-05 mg/ml ; 5.01e-08 mol/l
Class	Poorly soluble

Figure 5.2: Water Solubility of Ethoxy-Piogitazone predicted using Swiss ADME

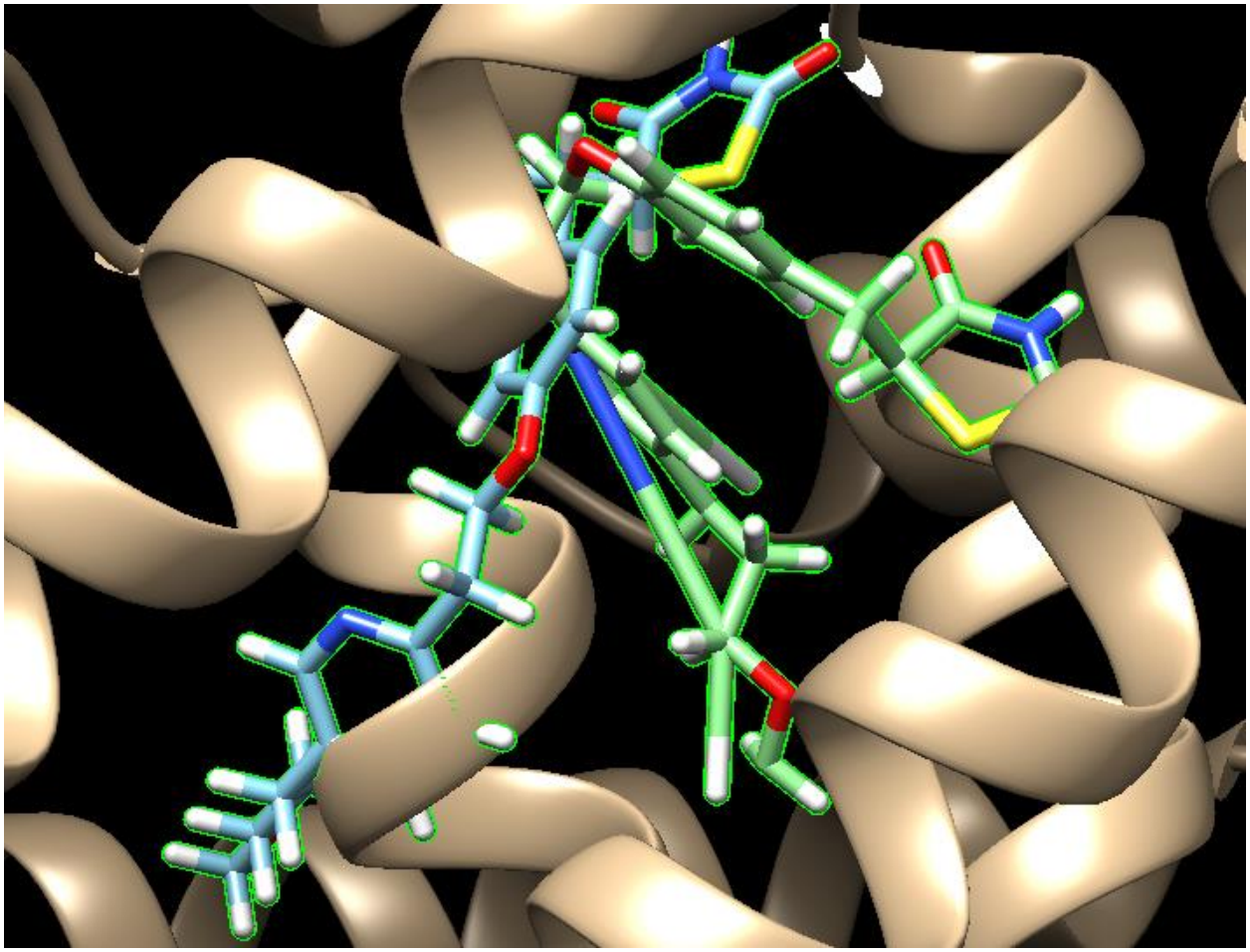


Figure 5.3: Best suited position of Ethoxy-Pioglitazone

S	Score	RMSD l.b.	RMSD u.b.
V	36.1	0.0	0.0
V	37.6	1.552	2.718
V	37.7	2.267	5.025
V	38.1	2.974	6.124
V	38.9	2.601	5.548

Figure 5.4: Scores of Ethoxy-Pioglitazone

Interpretation of properties from above data:

Increase in logP value from 2.72 to 3.17. Here the pka value also increases from 5.5 to 6.31 that means the modified molecule will be less acidic as compared to the parent molecule so it's solubility in water will also decrease .

After docking the modified molecule with Rosiglitazone the most similar docking was seen for the molecule with score of 37.7.

The Modified molecule follows the Lipinski rule of 5.

There is no risks related to Mutagenic , Tumorigenic , Irritation and Reproductive effects for the modified molecule.

It show good activity towards GPCR ligand and great bioactivity towards Nuclear receptor ligand.

Its GI absorption is high.

***Molecular docking of Pioglitazone analogue by adding Iodine and Chlorine to Pioglitazone molecule using chimera*:**

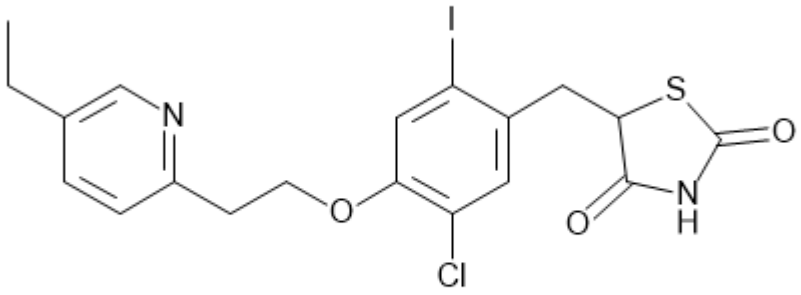


Figure 6.1: Chloro-Iodo-Pioglitazone

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
516.78	27	12	7	4	1	119.89	93.59	2.92

Table 6: Various properties of Chloro-Iodo Pioglitazone predicted using Swiss ADME

Log *S* (ESOL)	-6.08
Solubility	4.30e-04 mg/ml ; 8.32e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-6.74
Solubility	9.49e-05 mg/ml ; 1.84e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.20
Solubility	3.29e-06 mg/ml ; 6.37e-09 mol/l
Class	Poorly soluble

Figure 6.2: Water Solubility of Chloro-Iodo-Pioglitazone predicted using Swiss ADME

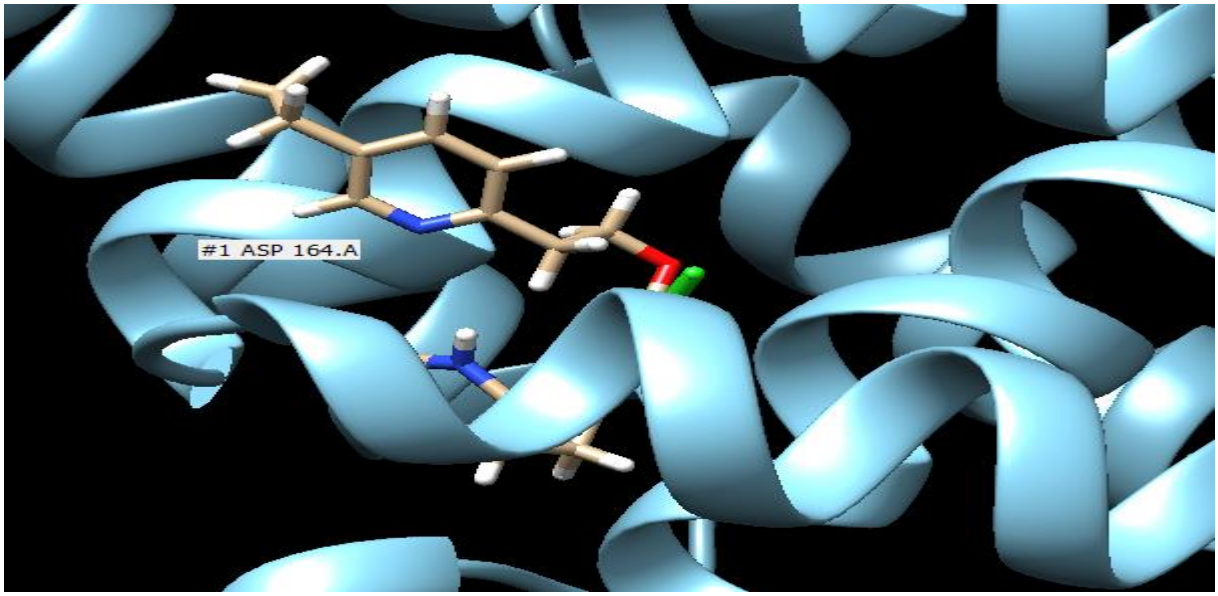


Figure 6.3: Best suited position of Chloro-Iodo-Pioglitazone

S	Score	RMSD l.b.	RMSD u.b.
V	44.3	0.0	0.0
V	45.3	4.741	6.498
V	45.8	3.077	3.84
V	46.6	3.463	7.782
V	46.7	4.43	7.811

Figure 6.4: Scores of 3,5 Chloro-Iodo-Pioglitazone

Interpretation of properties from above data:

Increase in logP value from 2.72 to 2.92 so there will be no significant change in solubility of the molecule.

After docking the modified molecule with Rosiglitazone the most similar docking was seen for the molecule with score of 45.8.

The Modified molecule shows Lipinski rule of 5 violation, as the molecular weight is 516.78 mg/mole

There is no risks related to Mutagenic , Tumorigenic , Irritation and Reproductive effects for the modified molecule.

It show good activity towards GPCR ligand and great bioactivity towards Nuclear receptor ligand.

Its GI absorption is high.

***Molecular docking of Pioglitazone analogue by adding Fluorine and Dimethyl to Pioglitazone- molecule using chimera*:**

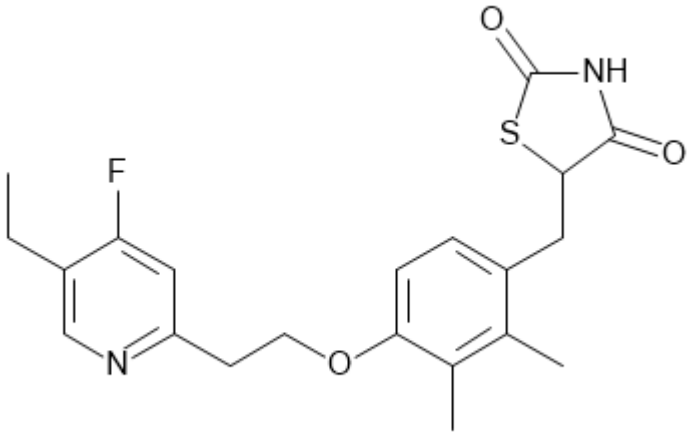


Figure 7.1: Fluoro-Dimethyl-Pioglitazone

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
402.48	28	12	7	5	1	112.06	93.59	3.28

Table 7: Various properties of Fluoro-Dimethyl-Pioglitazone predicted using Swiss ADME

Log *S* (ESOL)	-5.08
Solubility	3.38e-03 mg/ml ; 8.40e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.27
Solubility	2.17e-04 mg/ml ; 5.38e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.80
Solubility	6.35e-06 mg/ml ; 1.58e-08 mol/l
Class	Poorly soluble

Figure 7.2: Water Solubility of Fluoro-Dimethyl-Pioglitazone predicted using Swiss ADME

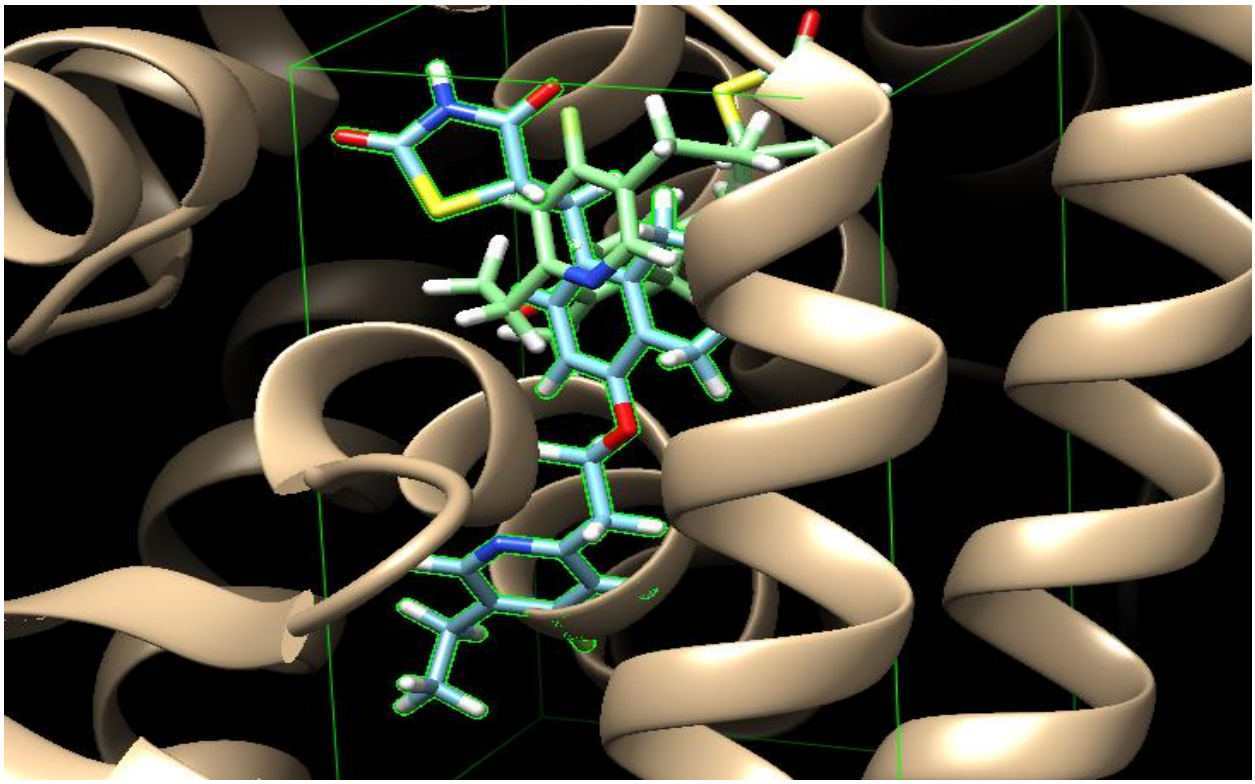


Figure 7.3: Best suited position of Fluoro-Dimethyl-Pioglitazone

S	Score	RMSD l.b.	RMSD u.b.
V	36.4	0.0	0.0

Figure 7.4: Scores of Fluoro-Dimethyl-Pioglitazone

Interpretation of properties from above data:

Increase in logP value from 2.72 to 3.28 that means the modified molecule will be less acidic as compared to the parent molecule so it's solubility in water will moderately decrease .

After docking the modified molecule with Rosiglitazone only one docking possibility was seen for the molecule with score of 36.4.

The Modified molecule follows the Lipinski rule of 5.

There is no risks related to Mutagenic , Irritation and Reproductive effects . But there are great chances for this molecule to produce Tumorigenic toxicity risks .

It show great bioactivity towards Nuclear receptor ligand.

Its GI absorption is high.

***Molecular docking of Pioglitazone analogue by adding tetrahydroxy to parent Pioglitazone molecule using chimera*:**

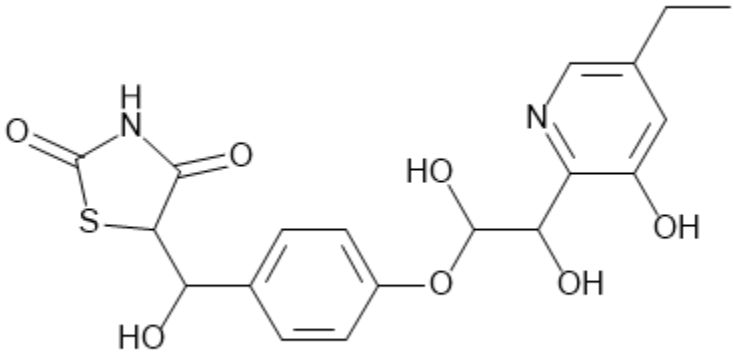


Figure 8.1:Tetrahydroxy-Pioglitazone

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
420.44	29	12	7	8	5	107.67	174.51	1.31

Table 8: Various properties of Tetrahydroxy-Pioglitazone predicted using Swiss ADME

Log *S* (ESOL)	-3.40
Solubility	1.67e-01 mg/ml ; 3.98e-04 mol/l
Class	Soluble
Log *S* (Ali)	-5.04
Solubility	3.81e-03 mg/ml ; 9.07e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-3.36
Solubility	1.82e-01 mg/ml ; 4.33e-04 mol/l
Class	Soluble

Figure 8.2: Water Solubility of Tetrahydroxy-Pioglitazone predicted using Swiss ADME

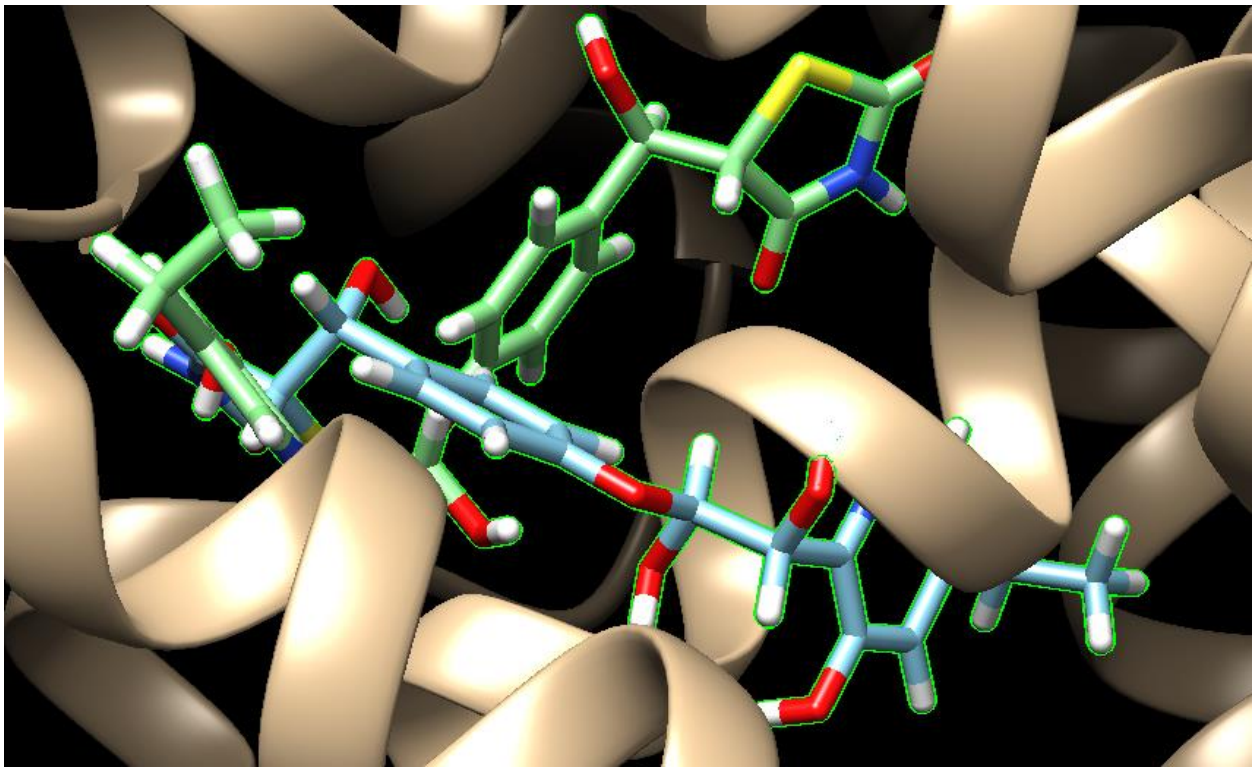


Figure 8.3: Best suited position of Tetrahydroxy-Pioglitazone

S	Score	RMSD l.b.	RMSD u.b.
V	38.1	0.0	0.0
V	39.3	3.613	5.093
V	39.7	1.18	1.554
V	40.2	1.811	4.174

Figure 8.4: Scores of Fluoro-Dimethyl-Pioglitazone

Interpretation of properties from above data:

This molecule shows decrease in logP value from 2.72 to 1.31 as a result the solubility of molecule will increase as compared to the parent molecule .

After docking the modified molecule with Rosiglitazone best ineraction with receptor was seen for the molecule with score of 39.3.

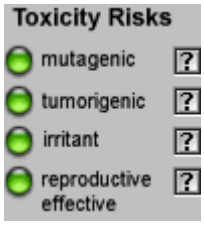
The Modified molecule follows the Lipinski rule of 5.

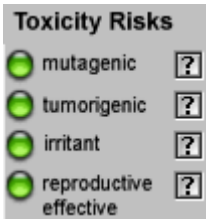
There is no risks related to Mutagenic , Tumorigenic, Irritation and Reproductive effects ..

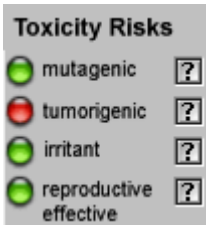
It show good bioactivity towards Nuclear receptor ligand.

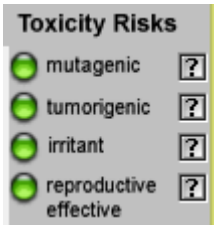
Its GI absorption is low.

Toxicity Comparison of all four molecules:

<table>
<tr>
<td> 

Ethoxy-Pioglitazone</td>
<td> 

Chloro-Iodo-Pioglitazone</td>
</tr>
<tr>
<td> 

Fluoro-Dimethyl-Pioglitazone</td>
<td> 

Tetrahydroxy-Pioglitazone</td>
</tr>
</table>

Bioactivity of all four molecules in scores:

	Ethoxy-Pioglitazone	Chloro-Iodo-Pioglitazone	Fluoro-Dimethyl-Pioglitazone	Tetrahydroxy-Pioglitazone
GPCR ligand	0.27	0.21	0.15	0.17
Ion Channel modulator	-0.47	-0.50	-0.68	-0.43
Kinase Inhibitor	-0.60	-0.71	-0.74	-0.62
Nuclear receptor ligand	0.57	0.63	0.55	0.38
Protease inhibitor	-0.01	-0.32	-0.21	-0.08
Enzyme inhibitor	0.07	-0.09	-0.05	0.07

Pharmacokinetics of all four molecules:

GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.31 cm/s

Ethoxy-Pioglitazone

GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.88 cm/s

Chloro-Iodo-Pioglitazone

GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.50 cm/s

Fluoro-Dimethyl-Pioglitazone

GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.62 cm/s

Tetrahydroxy-Pioglitazone

Comparison of Lipinski Rule of 5 for all molecules of Pioglitazone:

Molecules	Molecular weight (gm/mol)	H bond Acceptor	H bond donor	LogP
Ethoxy-Pioglitazone	400.49	5	1	3.17
Chloro-Iodo-Pioglitazone	516.78	4	1	2.92
Fluoro-Dimethyl-Pioglitazone	402.48	5	1	3.28
Tetrahydroxy-Pioglitazone	420.44	8	5	1.31

(C)Saxagliptin Analogues:

***Molecular docking of Saxagliptin analogue by adding chloro-dimethyl to Saxagliptin molecule using chimera*:**

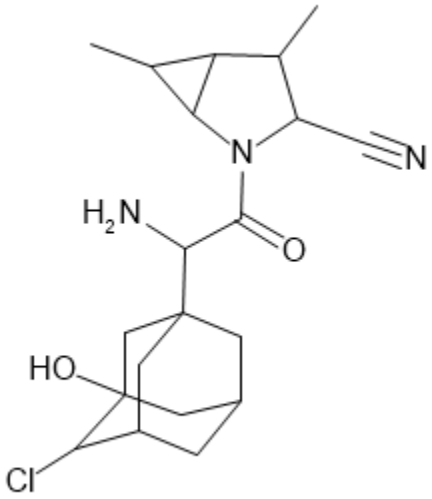


Figure 9.1: Chloro-Dimethyl-saxagliptin

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
377.91	26	0	3	4	2	102.89	90.35	1.95

Table 9: Various properties of Chloro-dimethyl-saxagliptin predicted using Swiss ADME

Log *S* (ESOL)	-3.07
Solubility	3.23e-01 mg/ml ; 8.54e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.23
Solubility	2.21e-01 mg/ml ; 5.84e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-1.98
Solubility	3.96e+00 mg/ml ; 1.05e-02 mol/l
Class	Soluble

Figure 9.2: Water Solubility of Chloro-dimethyl-saxagliptin predicted using Swiss ADME

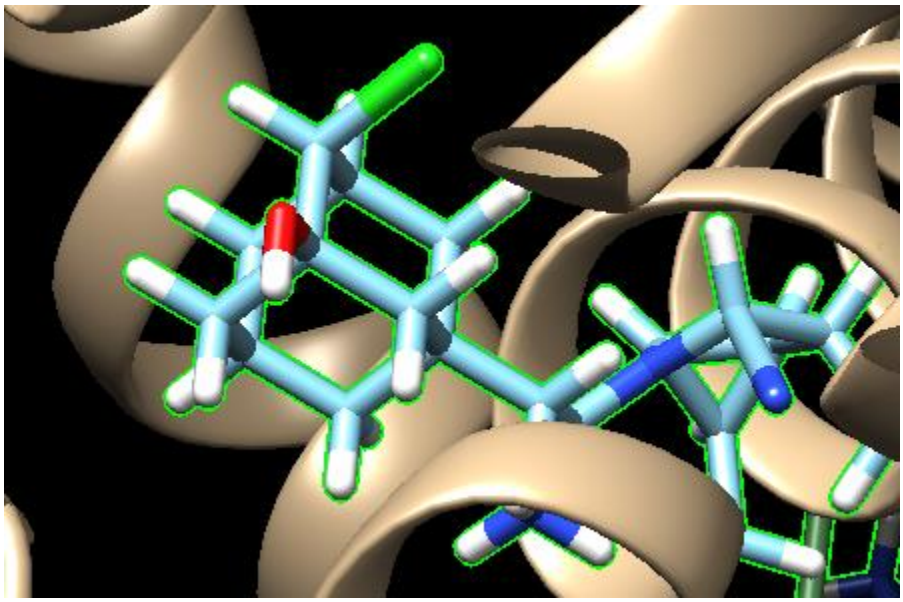


Figure 9.3: Best suited position of Chloro-dimethyl-saxagliptin

S	Score	RMSD l.b.	RMSD u.b.
V	-4.2	0.0	0.0
V	-4.0	2.824	5.706
V	-3.8	2.49	4.23
V	-3.8	4.691	6.374
V	-3.8	2.303	3.026

Figure 9.4: Scores of Chloro-dimethyl-saxagliptin

Interpretation of properties from above data:

The molecule shows slight decrease in logP value from 1.99 to 1.95 so there will be no significant change in solubility of the molecule.

After docking the modified molecule with Alogliptin the most similar docking was seen for the molecule with score of -3.8.

The Modified molecule follows the Lipinski rule of 5.

There is no risks related to Mutagenic , Tumorigenic , Irritation, but its high chances to develop Reproductive risks for the modified molecule.

It show good activity towards GPCR ligand and great bioactivity towards Nuclear receptor ligand.

Its GI absorption is high.

***Molecular docking of Saxagliptin analogue by adding fluorine, hydoxy and methyl to Saxagliptin molecule using chimera*:**

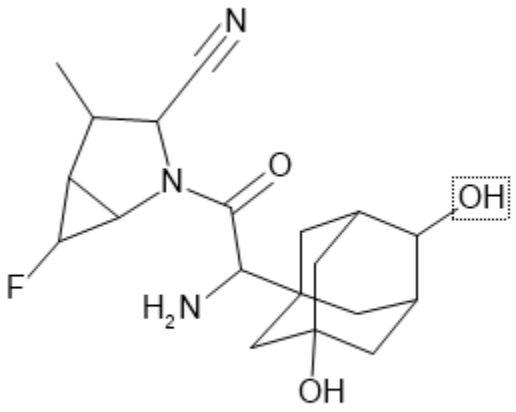


Figure 10.1: Fluoro-hydroxy-methyl-Saxagliptin

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
363.43	26	0	3	6	3	94.5	110.58	1.94

Table 10: Various properties of Fluoro-hydroxy-methyl-Saxagliptin predicted using Swiss ADME

Log *S* (ESOL)	-1.94
Solubility	4.18e+00 mg/ml ; 1.15e-02 mol/l
Class	Very soluble
Log *S* (Ali)	-1.95
Solubility	4.12e+00 mg/ml ; 1.13e-02 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-0.69
Solubility	7.39e+01 mg/ml ; 2.03e-01 mol/l
Class	Soluble

Figure 10.2: Water Solubility of Fluoro-hydroxy-methyl-Saxagliptin predicted using Swiss ADME

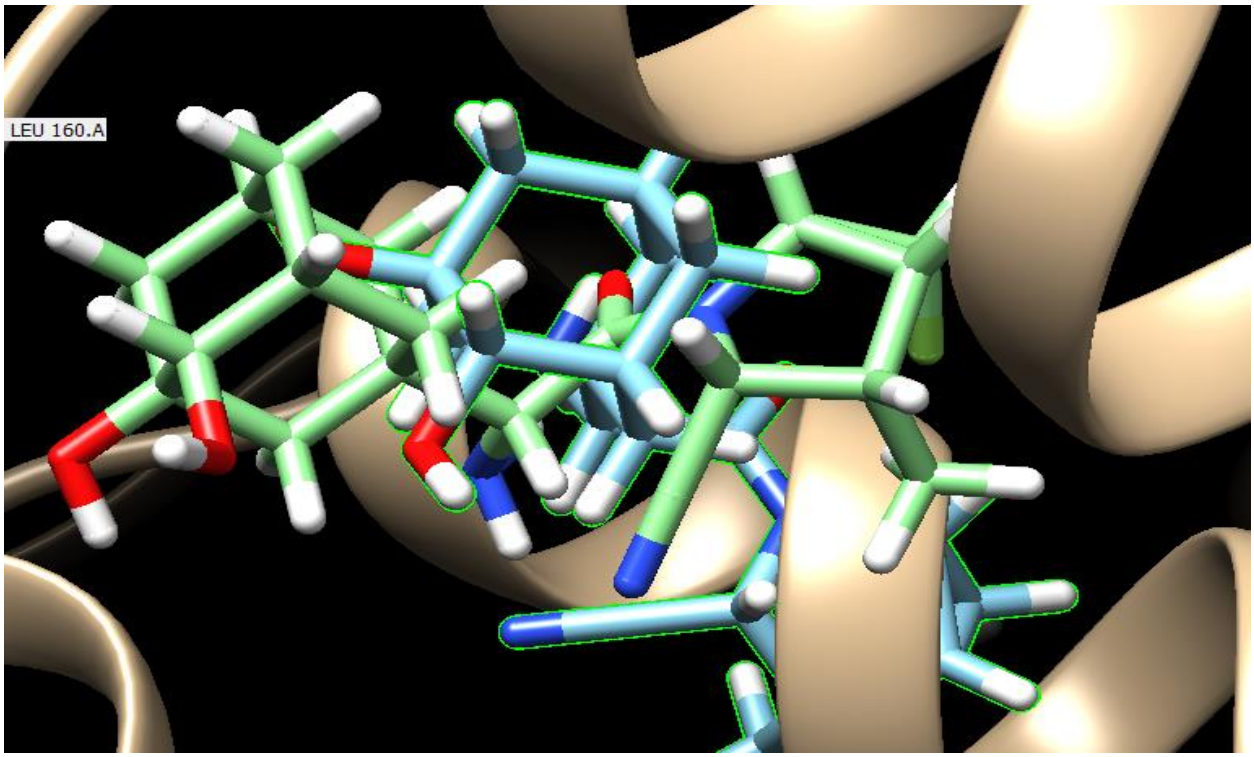


Figure 10.3: Best suited position of Fluoro-hydroxy-methyl-Saxagliptin

S	Score	RMSD l.b.	RMSD u.b.
V	61.5	0.0	0.0
V	62.3	2.103	3.594

Figure 10.4: Scores of Fluoro-hydroxy-methyl-Saxagliptin

Interpretation of properties from above data:

The molecule shows slight decrease in logP value from 1.99 to 1.94 so there will be no significant change in solubility of the molecule.

After docking the modified molecule with Alogliptin the most similar docking was seen for the molecule with score of -3.8.

The Modified molecule follows the Lipinski rule of 5.

There is no risks related to Mutagenic , Tumorigenic , Irritation as well as Reproductive risks for the modified molecule.

It show good activity towards GPCR ligand and great bioactivity towards Nuclear receptor ligand. This may be a Enzyme inhibitor.

Its GI absorption is high.

***Molecular docking of saxagliptin analogue by adding dihydroxy and iodo to Saxagliptin molecule using chimera*:**

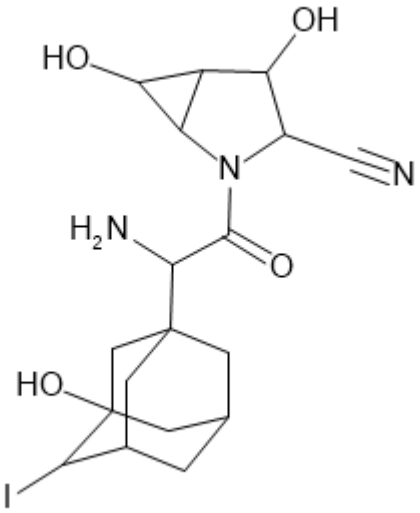


Figure 11.1: Dihdroxy-iodo-Saxagliptin

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
473.31	26	0	3	6	4	103.76	130.81	1.45

Table 11: Various properties of Dihdroxy-iodo-Saxagliptin predicted using Swiss ADME

Log *S* (ESOL)	-2.56
Solubility	1.29e+00 mg/ml ; 2.73e-03 mol/l
Class	Soluble
Log *S* (Ali)	-2.28
Solubility	2.50e+00 mg/ml ; 5.28e-03 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-0.30
Solubility	2.37e+02 mg/ml ; 5.01e-01 mol/l
Class	Soluble

Figure 11.2: Water Solubility of Dihdroxy-iodo-Saxagliptin predicted using Swiss ADME

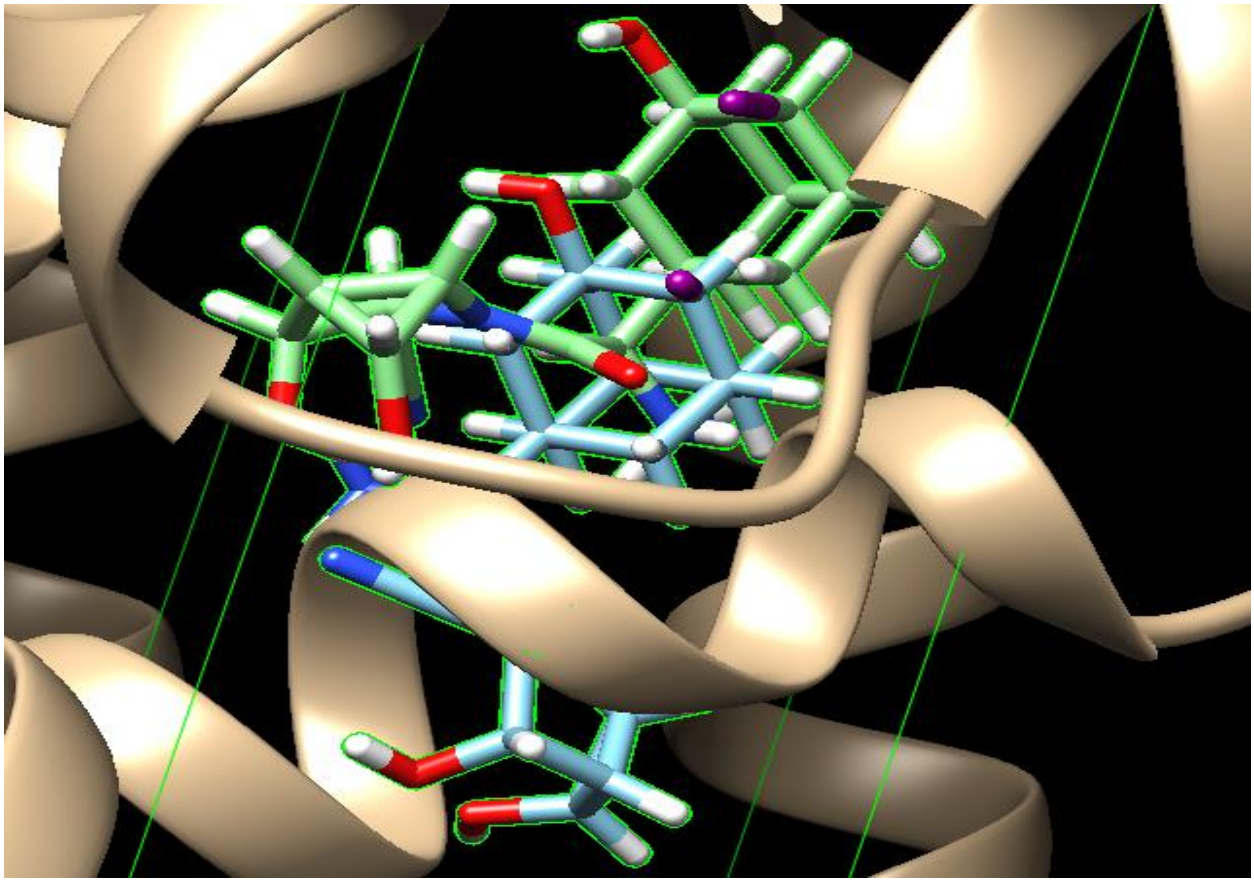
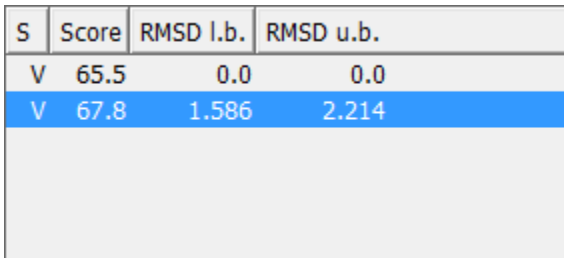


Figure 11.3: Best suited position of Dihdroxy-iodo-Saxagliptin



S	Score	RMSD l.b.	RMSD u.b.
V	65.5	0.0	0.0
V	67.8	1.586	2.214

Figure 11.4: Scores of Dihdroxy-iodo-Saxagliptin

Interpretation of properties from above data:

The molecule shows decrease in logP value from 1.99 to 1.45 so there will be increase in the solubility of molecule.

After docking the modified molecule with Alogliptin the most similar docking was seen for the molecule with score of 67.8.

The Modified molecule follows the Lipinski rule of 5.

There is no risks related to Mutagenic , Tumorigenic , Irritation as well as Reproductive risks for the modified molecule.

It show good activity towards GPCR ligand and great bioactivity towards Nuclear receptor ligand. This may be a Enzyme inhibitor.

Its GI absorption is high.

***Molecular docking of Saxagliptin analogue by adding Bromine, Fluorine and Methyl to parent Saxagliptin molecule using chimera*:**

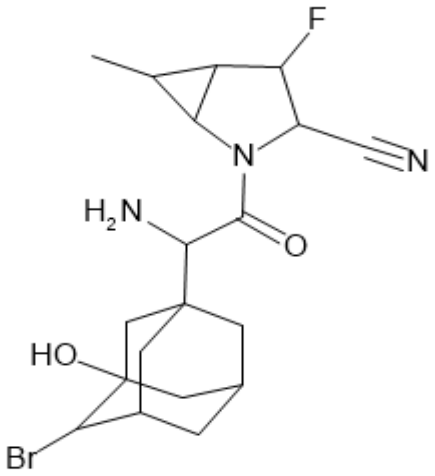


Figure 12.1:Bromo-fluoro-methyl-saxagliptin

Molecular weight (g/mol)	Number of Heavy Atoms	Number of Aromatic Heavy Atoms	Number of Rotatable Bonds	Number of H bond acceptors	Number of H bond donors	Molar Refractivity	TPSA (Armstrong)	LogP
426.32	26	0	3	5	2	101.21	90.35	2.21

Table 12: Various properties of Bromo-fluoro-methyl-saxagliptin predicted using Swiss ADME

Log *S* (ESOL)	-3.24
Solubility	2.47e-01 mg/ml ; 5.80e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.02
Solubility	4.11e-01 mg/ml ; 9.65e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-2.07
Solubility	3.66e+00 mg/ml ; 8.59e-03 mol/l
Class	Soluble

Figure 12.2: Water Solubility of Bromo-fluoro-methyl-saxagliptin predicted using Swiss ADME

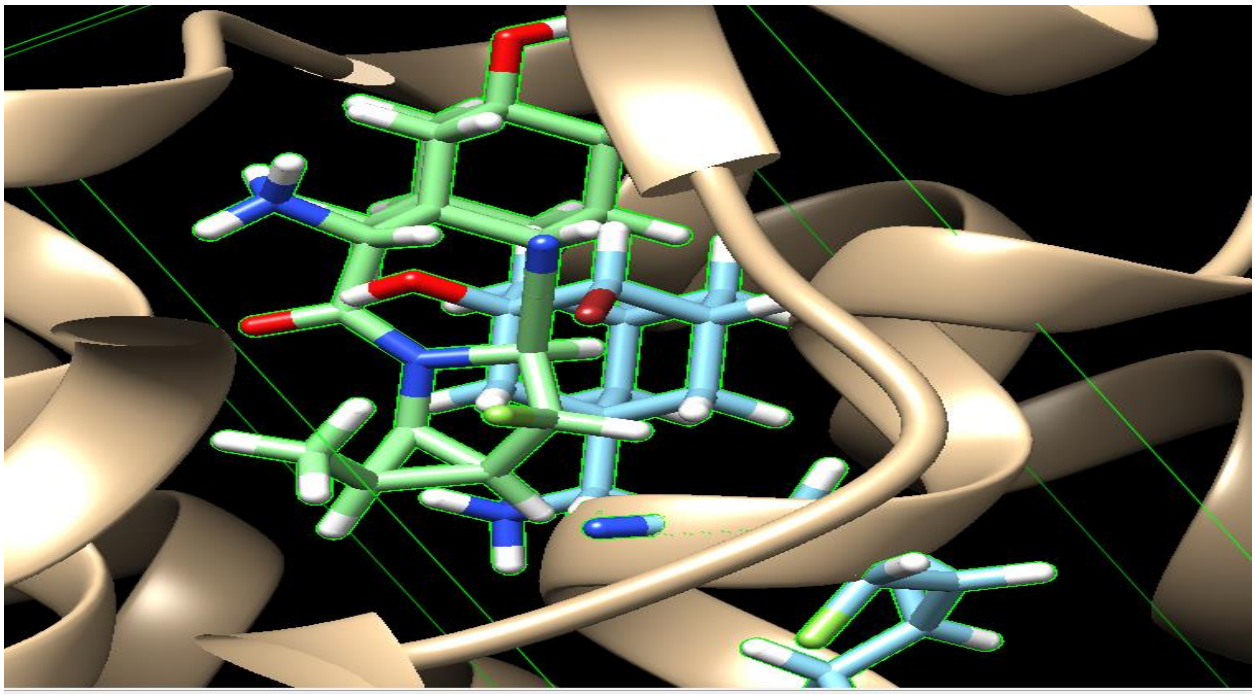


Figure 12.3: Best suited position of Bromo-fluoro-methyl-saxagliptin

S	Score	RMSD l.b.	RMSD u.b.
V	66.8	0.0	0.0
V	68.1	2.156	3.234
V	68.7	2.199	3.431
V	69.7	2.184	3.172

Figure 12.4: Scores of Bromo-fluoro-methyl-saxagliptin

Interpretation of properties from above data:

Slight increase in logP value from 1.99 to 2.21 that means the modified molecule will have moderately less solubility as the parent molecule.

After docking the modified molecule with Alogliptin the most similar docking was seen for the molecule with score of 66.8.

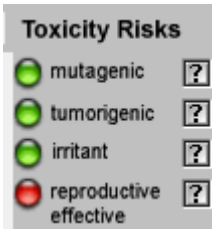
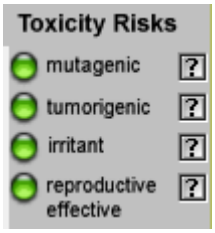
The Modified molecule follows the Lipinski rule of 5.

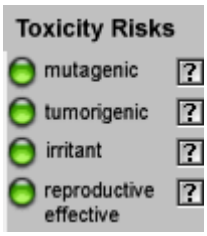
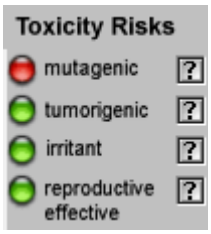
There is no risks related to Tumorigenic , Irritation as well as Reproductive risks for the modified molecule. But high risk for the molecule to be mutagenic.

It show good activity towards GPCR ligand and great bioactivity towards Nuclear receptor ligand.

Its GI absorption is high

Toxicity Comparison of all four molecules:

	
Chloro-Dimethyl-saxagliptin	**Fluoro-hydroxy-methyl-Saxagliptin**

 **Dihdroxy-iodo-Saxagliptin**	 **Bromo-fluoro-methyl-saxagliptin**

Bioactivity of all four molecules in scores:

	Chloro-Dimethyl-saxagliptin	**Fluoro-hydroxy-methyl-Saxagliptin**	**Dihdroxy-iodo-Saxagliptin**	**Bromo-fluoro-methyl-saxagliptin**
GPCR ligand	0.25	0.36	0.32	0.29
Ion Channel modulator	-0.19	0.04	0.02	-0.23
Kinase Inhibitor	-0.32	-0.24	-0.31	-0.34
Nuclear receptor ligand	-0.14	0.18	-0.01	0.13
Protease inhibitor	0.84	0.92	0.89	0.94
Enzyme inhibitor	0.01	0.37	0.28	0.17

Pharmacokinetics of all four molecules:

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.38 cm/s

Chloro-Dimethyl-saxagliptin

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.47 cm/s

Fluoro-hydroxy-methyl-Saxagliptin

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-9.20 cm/s

Dihdroxy-Iodo-Saxagliptin

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.83 cm/s

Bromo-fluoro-methyl-saxagliptin

Comparison of Lipinski Rule of 5 for all molecules of Saxagliptin:

Molecules	Molecular weight (gm/mol)	H bond Acceptor	H bond donor	LogP
Chloro-Dimethyl-saxagliptin	377.91	4	2	1.95
Fluoro-hydroxy-methyl-Saxagliptin	363.43	6	3	1.94
Dihdroxy-iodo-Saxagliptin	473.31	6	4	1.45
Bromo-fluoro-methyl-saxagliptin	426.32	5	2	2.21

Summary and conclusion :

For Gliclazide molecule, 3,4,5 triiodo-Gliclazide and 3,5 dichloro Gliclazide both seems to be promising as the bioavailability has increased dramatically for both the molecules. On the other hand, for CF3-Gliclazide half life is too high so it's of less importance. CH3-Gliclazide is having Bioavailability less as compared to parent Gliclazide molecule so it is not a promising one. Among 3,4,5 triiodo-Gliclazide and 3,5 dichloro Gliclazide , 3,5 dichloro Gliclazide seems to be the best one as it doesn't show any violation of Lipinski rule of 5 as 3,4,5 triiodo-Gliclazide.

For Pioglitazone molecule, Chloro-Iodo-Pioglitazone is not considered as promising modified molecule as it doesn't follow Lipinski rule of 5 . Fluoro-Dimethyl-Pioglitazone is more likely to show Tumorigenic risks so that one is also not the promising one. On the other hand Ethoxy-Pioglitazone and Tetrahydroxy-Pioglitazone both seems to be ideal as they follow Lipinski rule as well as no risks for toxicity , Tetrahydroxy-Pioglitazone seems to be most promising among all the modified molecules as it shows increase in the solubility of the drug.

For Saxagliptin, Chloro-Dimethyl-saxagliptin and Bromo-fluoro-methyl-saxagliptin are not ideal modifications as they have risks related to reproductive system and mutagenic respectively. Among Fluoro-hydroxy-methyl-Saxagliptin and Dihdroxy-Iodo-Saxagliptin, Dihdroxy-Iodo-Saxagliptin seems to be most promising as it shows increase in solubility as compared to parent molecule while Fluoro-hydroxy-methyl-Saxagliptin shows no significant change in solubility**.**

References:

1. Peters A, Laffel L (Eds.). American Diabetes Association/JDRF Type 1 Diabetes Sourcebook. Alexandria, VA, American Diabetes Association, 2013.

2. Chiang JL, Kirkman MS, Laffel LMB, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2034–2054 .

3. Wolpert HA, Atakov-Castillo A, Smith SA, Steil GM. Dietary fat acutely increases glucose concentrations and insulin requirements in patients with type 1 diabetes: implications for carbohydrate-based bolus dose calculation and intensive diabetes management. Diabetes Care 2013;36:810–816

4. Bell KJ, Toschi E, Steil GM, Wolpert HA. Optimized mealtime insulin dosing for fat and protein in type 1 diabetes: application of a model- based approach to derive insulin doses for open- loopdiabetesmanagement.DiabetesCare2016; 39:1631–1634

5. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type1diabetes :implications for intensive diabetes management in the continuous glucose monitoring era. Diabetes Care 2015;38:1008–1015

6. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta- analysis. Ann Intern Med 2012;157:336–347

7. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta- analysis.JDiabetesSciTechnol2013;7:1567– 1574

8. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232

9. Buckingham BA, Raghinaru D, Cameron F, et al.; In Home Closed Loop Study Group. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. Diabetes Care 2015; 38:1197–1204

10. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408

11. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155–163

12. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardio- vascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653

13. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications(EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC

14. Tricco AC, Ashoor HM , AntonyJ,etal.Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic re- view and network meta-analysis. BMJ 2014;349: g5459

15. Scanlan MJ, Raj BK, Calvo B *et al* Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci USA 1994; 91:5657–61.

16. Abbott CA, Yu DM, Woollatt E, Sutherland GR, McCaughan GW, Gorrell MD. Cloning, expression and chromosomal localization of a novel human Dipeptidyl peptidase (DPP) IV homolog, DPP8. Eur J Biochem 2000; 267:6140–50.

17. Olsen C, Wagtmann N. Identification and characterization of human DPP9, a novel homologue of Dipeptidyl peptidase IV. Gene 2002; 299:185–93.

18. Wada K, Yokotani N, Hunter C, Doi K, Wenthold RJ, Shimasaki S. Differential expression of two distinct forms of mRNA encoding members of a Dipeptidyl amino peptidase family. Proc Natl Acad Sci USA 1992; 89:197–201.

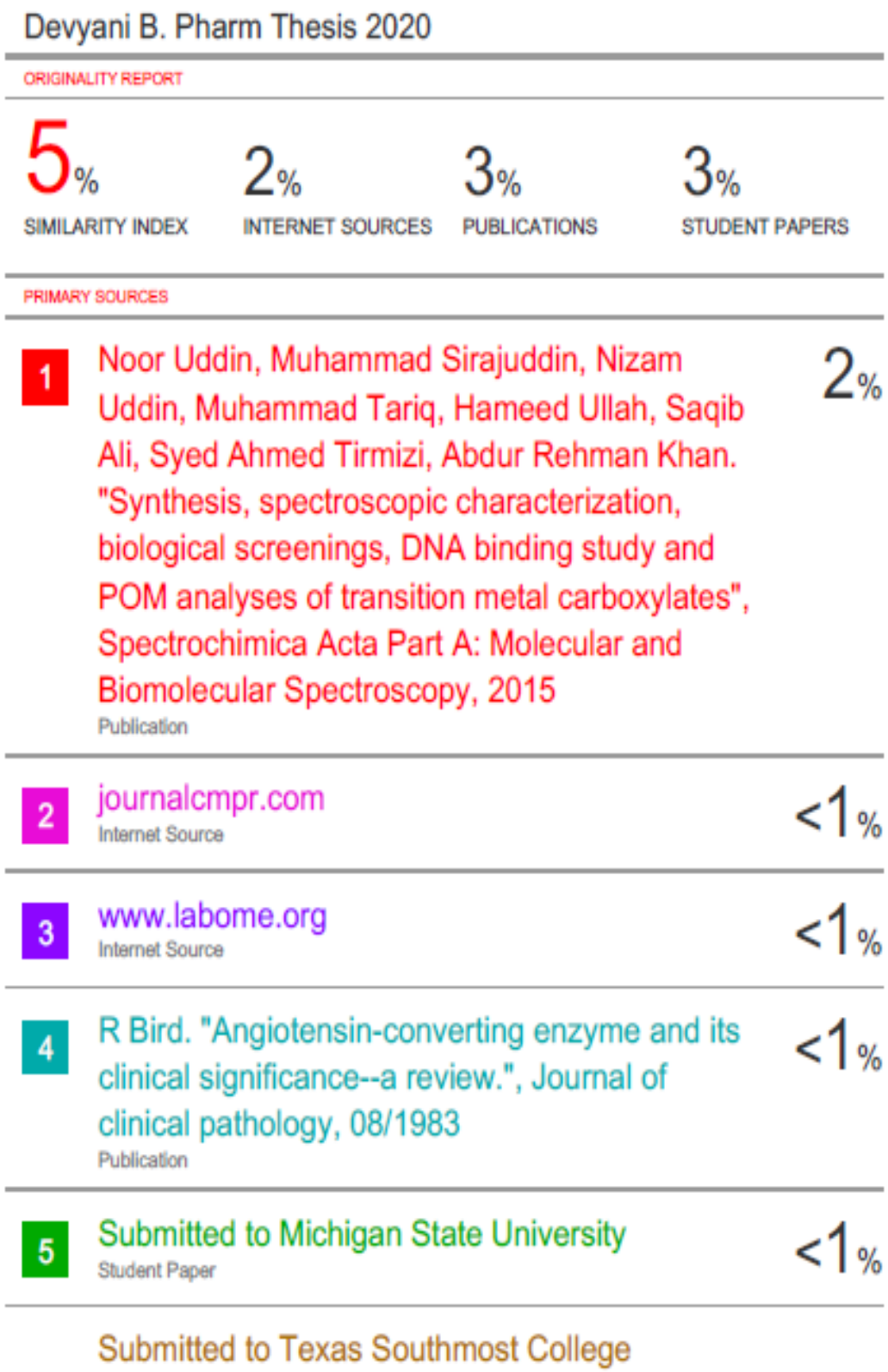
19. Qi SY, Riviere PJ, Trojnar J, Junien JL, Akinsanya KO. Cloning and characterization of Dipeptidyl peptidase 10, a new member of an emerging subgroup of serine proteases. Biochem J 2003; 373:179–89.

20. Amara SG: Neurotransmitter transporters: new insights into structure, function and pharmacology. *Rev Bras Biol.* 1996;56(Su 1 Pt 1):5–19.

21. Blakely RD, DeFelice LJ: All aglow about presynaptic receptor regulation of neurotransmitter transporters. *Mol Pharmacol.* 2007;71(5):1206–8. 10.1124/mol.107.035493

22. Bröer S, Gether U: The solute carrier 6 family of transporters. *Br J Pharmacol.* 2012;167(2):256–78. 10.1111/j.1476-5381.2012.01975.x

23. DeFelice LJ, Goswami T: Transporters as channels. *Annu Rev Physiol*. 2007;69:87–112. 10.1146/annurev.physiol.69.031905.164816



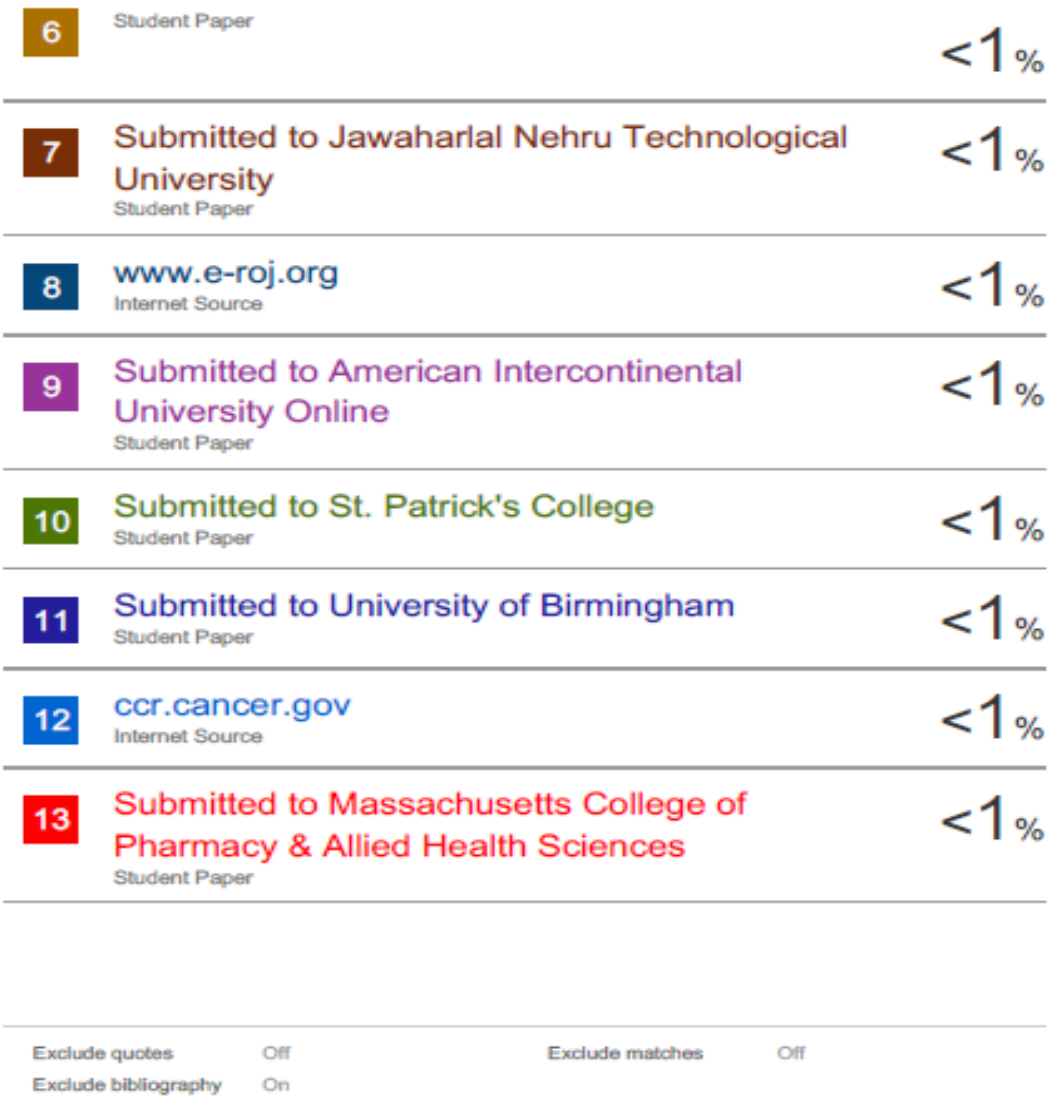
Devyani B. Pharm Thesis 2020

ORIGINALITY REPORT

5%	2%	3%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Noor Uddin, Muhammad Sirajuddin, Nizam Uddin, Muhammad Tariq, Hameed Ullah, Saqib Ali, Syed Ahmed Tirmizi, Abdur Rehman Khan. "Synthesis, spectroscopic characterization, biological screenings, DNA binding study and POM analyses of transition metal carboxylates", Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2015 Publication	2%
2	journalcmpr.com Internet Source	<1%
3	www.labome.org Internet Source	<1%
4	R Bird. "Angiotensin-converting enzyme and its clinical significance--a review.", Journal of clinical pathology, 08/1983 Publication	<1%
5	Submitted to Michigan State University Student Paper	<1%
	Submitted to Texas Southmost College	



6	Student Paper	<1%
7	Submitted to Jawaharlal Nehru Technological University Student Paper	<1%
8	www.e-roj.org Internet Source	<1%
9	Submitted to American Intercontinental University Online Student Paper	<1%
10	Submitted to St. Patrick's College Student Paper	<1%
11	Submitted to University of Birmingham Student Paper	<1%
12	ccr.cancer.gov Internet Source	<1%
13	Submitted to Massachusetts College of Pharmacy & Allied Health Sciences Student Paper	<1%

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	On		