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Development of a novel android mobile phone application for Diabetes Type II syndrome by using Molecular modelling through Virtual Screening and Molecular docking tool - a Molecular level medical data mining approach

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Abstract

Android and iPhones are the two most popular mobile devices today. Each of these mobile Operating System is constantly trying to surpass the other, both in terms of the software developer and the user. While each one is just as powerful as another one, they are not without their own exceptional disadvantages. In this article, we analyze the pros and cons of both Android and iPhone from the point of view of medical applications of developers and medical researchers. Intravenous glucose tolerance level are called as Diabetes mellitus syndrome which is a group of metabolic disorder disease resulting in increased blood sugar level, either because of the pancreas will not able to secrete enough insulin as fluid or because human cells will not respond or revert to the insulin produced in human body. The Diabetes mellitus type 2 (NIDDM) is a human metabolic disorder and which is characterized by the high glucose contend in the blood on context of the body insulin resistance as well as deficiency in the human body.Over the past few decades, the human receptors of nuclear family, in particular the activated receptors of peroxisome proliferator (PPARs), has emerged as one of the most important drug targets the metabolic syndrome.Consequently, compounds that activate the PPARs have served as a potential therapeutics for the treatment of T2DM and anomalities associated with this disorder. The present investigation has been designed with a focus to identify novel ligands using TZDs that could facilitate the drug action for T2DM. These identified ligands can be interrogated by using the developed app through android phone.

Keywords: *Molecular docking; Medical data mining; Diabetes; Android app; Virtual screening.*

INTRODUCTION

The people of global majority are not aware,exactly what diabetes is. Most of them heard about diabetes on the news or through the people who has suffered through this worst disease however, this doesn't mean that everyone knows about this disease and how to manage it.Type 2 diabetes makes up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease (Bong - Soo Cha *et al.*, 2005). Abnormalities in the homeostasis of glucose and lipids will lead to diabetes mellitus, dyslipidaemia, inflammatory abnormalities and vascular dysfunctions, which are collectively known as 'Metabolic syndrome'. Insulin resistance and Obesity are the two important underlying causes of metabolic syndrome.

Chronic hyperglycaemia, a key feature of diabetes mellitus, can adversely affect various organs like heart, kidney, nerves, blood vessels, eye, immune system etc. leading to vascular complications, cardiopathy, nephropathy, neuropathy and retinopathy. Hyperglycaemia and dyslipidaemia coupled with inflammation and oxidative stress are major risk factors for the development of atherosclerotic cardio vascular disease (ASCVD) (Roy Eldor*et al.*2013). Diabetes and its associated conditions pose severe challenge to the global health. According to a recent estimate, more than 288 million people were affected by diabetes in 2015 and the number is expected to increase by 54% in just 20 years.These scenarios are quantum jump on burden of the global economy by means of expenses on diabetes research, diagnosis and management. Although to address these issues a number of drugs are currently available to control metabolic disorders of the diabetes II but still the issue remains insolvable and unconquered. Depending on the needs of the individual, android health apps can be very beneficial, especially from the standpoint of possible support. However, the person choosing the android App needs to consider what they want or needs to track as well as how safe in health wise they are. First Step in this process of developing android apps choice should be to narrow down the apps based on individuals to track blood glucose and learn about their patterns through molecular modeling and docking.With the developed android app, one can connect with friends and family to know how they are doing and for a great motivational system.The developed app will allow the people to see blood pressure and vital signs along with its own diary including trends for what spikes the diabetes and energy level of human body.

The Android OS

The android is an open source mobile operating system intended to run on a range of mobile devices, ranging across different mobile device brands and different models. Android is an actual cellular phone Operating System and not merely a mobile phone devise. Android application is more dynamic in the sense that, the manufacturers may license the Operating System for any devices of their interest and also make some modifications in the OS as their preferred requisite. There will be no centralized manufacturer with Android mobile app as in the case of Apple I phone. The developer has number of online Android mobile software sources to select from, or and apart from the main Android manufacturing and distribution Market. While Android applications help the producer and software developer provides the user to the greater amount of models and application features, the problem is, that the Operating System software is highly fragmented, so that it, becomes much more complex in nature. Also, testing medical applications gets that much of simpler with a lot less Operating System versions to be dealt with. The iPhone and Android mobile phones are basically excellent devices, each of those having its own feedback and drawbacks. Anyway, both software developers and medical scientists must analyze fully the prospectus and configuration of each mobile platform before developing or approving medical application software for the devices.

Peroxisome proliferator - activated receptors (PPARS)

In this present investigation the chosen peroxisome and proliferator activated receptors of(PPARs) are form a gang of nucleotide receptors protein and drug molecules that are mainly functioning as a transcript model factors and they are regulating mechanism in the gene expression of genetically arranged manipulation.The PPARs ligands play main and important key roles in the regulatory mechanism of cellular

modification and differentiation. In to the development, the metabolic state (carbohydrate, lipid, protein) and tumorigenesis of the higher number of organisms (Berger J, Feige JN *et al.*, 2002). The nucleotide receptor peroxisome proliferator activated receptor vizgamma (PPARγ) has emerged from a relatively slow and smart beginning as a regulatory factor adipocyte improvement and development to become a potential and important therapeutic drug target for deal with the diverse group of medical disorders, including the type II diabetes class of the dyslipidaemia and inflammation and malignancy.

Peroxisome proliferator-activated receptor (PPAR) belongs to the nuclear hormone receptor (NHR) superfamily. Three subtypes, PPARα, PPARγ and PPARδ, for this receptor have been identified and found to be important targets for the treatment of type 2 diabetes, dyslipidemia, atherosclerosis, etc. It is now accepted that there are three related but quite distinct PPAR proteins, PPAR -α , PPAR-δ (also called PPAR β , Nuc-1, or FAAR), and PPARγ. Interestingly, two forms of the protein, γ1 and γ2, exist as products of alternative promoter usage. The two forms differ in that PPARγ 2 has an NH2 terminal extension of 30 amino acids (Tejprakash Singh *et al.,* 2013). In addition, PPARγ 2 is found selectively in fat tissue, whereas γ1 is expressed at low levels in many tissues. All three PPAR subtypes bind to DNA as obligate heterodimers with the nuclear receptors for 9-cis retinoic acid (RXRα, RXRβ or RXRγ), having the RXRα receptor as the preferential partner for the PPARγ receptor (TM Larsen *et al.,* 2003). The selected DNA-binding site (called peroxisome proliferator-activated receptor response element, PPRE) in each class of the PPAR/RXR heterodimers are directly repeat of the compensating sequences of AGGTCA, which separated by a single nucleotide spacer molecule.

A key report that led to identification of TZDs as ligands for PPAR-γ came from Harris and Kletzien in 1994. Importantly, the TZDs were also shown to be highly selective for PPAR-γ, as they had very minimal activity toward PPAR-α or PPAR-δ. The identified PPARγ agonists andt hiazo-lidinediones are the potential insulin drug sensitizers, which enhances the insulin secretion and improves the glucose tolerance level through metabolism. The ligands of Thia zolidinedione - mediated to improving he insulin sensitivity in T2DM is actedthrough the multiple metabolism of PPARγ induced activation and enhanced insulin channeling and signaling which increased sugar transport as glucose and enhanced glycogen synthesis in human body to improve the mitochondrial activities and fat mobilization out of muscular/liver function i.e., reversal function of lipo-toxicity (Naoto Kubota *et al,*. 2006). The latest survey and research studies suggested that the metabolic effects and changes of thiazolidinediones are coordinated by mitochondrial channeling namely MTOT1 and MTOT2 as they are represented the pyruvate transporter in human metabolism. The evidence that PPARγ is the major receptor mediating the anti-diabetic activity of the TZDs is now very strong, based on the following multiple lines of pharmacological evidence (Alarcón de la Lastra C. *et al.,* 2004).

- Every TZD drug molecule binds and activates PPARγ in the same level of concentration range that has anti-diabetic activity.
- In many of the TZDs surveyed, the rank order of potentiality of their anti diabetic activity of molecule is closely matches the rank order of drugs affinities toPPARγ (Prasanna A. Datar*et al.* 2012).

- Potential and selective ligand of the PPARγ outside of the TZD segment has been developed on the basis of their own activation of PPARγ. These have anti-diabetic identity actions in pre-clinical prototype models of insulindrug resistance and diabetes.
- Stimulated Ligands of RXR, the hetero dimeric partner of PPARγ, has developed insulin sensitivity in vivo (Hebe N. Gouda *et al*.,2009).
- None of the receptor for the TZD drugs class has been identified so far.

Radiolabeled TZD ligands have enabled development of a displacement assay that allowed a search for natural ligands of PPARγ (H.H. Parekh *et al.*, 2004). The disorienting activators of all ligands of the PPAR family are numbers of fatty acids which are marked as the PPARs are mainly involved in lipid based metabolic activities. PPAR regulates certain kinds of gene expressions in a series such as the fatty amino acidsas cluster of demarcation (CD36), lipoprotein lipase of human metabolism, sterol-responsive a element-binding protein-1c of human body and perilipin as protien, that promote lipid consumption and synthesis finally leads to storage in cells (MisakiIwashita *et al.*,2012). More recently, several polyunsaturated fatty acids, such as linoleic acid, have also been found to bind directly to PPARγ.

Molecular docking

The molecular modeling and docking is a method of tool which predicts normally the preferred arrangements of selected molecules to another one molecule when combined to each other to form new stable and strong complex ligands (Nolte *et al*., 2006). The better understanding of the preferred arrangements in turn may be used to find the strength of associated ligands or binding affinity between two molecules by using the scoring functions. The molecular Docking tool is very useful for predicting the affinity of small drug molecules to the protein based ligands in order to estimate the affinity level and the complete activities of the small molecules in the metabolic channels.Hence molecular docking plays an important role in the molecular design of drug elements (Holger Gohlke *et al.,* 2000).

Molecular docking tool is one which considered as a problem of *"lock-and-key"*, where one is interested to investigate the correct orientation of the *"key"*whichhelp to open the *"lock"* Here, the protein can be considered as the "lock" and the ligand can considered as a "key". The Molecular docking tool may be defined as an orientation and optimizationtechnique used in genetics, which would reveals the "best-fit" method of a ligand that binds to a particular protein of interest. However, since both the ligand and the protein are flexible, a *"hand-in-glove"* analogy is more appropriate than *"lock-and-key"* (Kitchen DB *et al*., 2004). There are two different methods and approaches are popular in the field of the molecular docking technique. The first approach has been used to match the technique which describes the level of protein and the ligandspresent as balancing surfaces (Wei BQ, Meng EC *et al*., 2004). The another approachto simulates the actual docking process of gene in which the ligand-proteins pair wise interaction and energies are estimated (Morris.G M. *et al*., 1998).The MolecularDocking will be performed where the energy evaluation is combined through the grids of affinity potential employed various search algorithms to find the correct binding position for a ligands on a chosen protein. While molecular docking, the polar hydrogen's will be attached to the ligands. Docking was performed normally by using the tool Autodock 4 (Feig M *et al.*, 2004), which combines all the energy evaluations through the grids of affinity potential employing various search algorithms to

find the exact binding position of a protein ligand on a chosen protein (Morris et al., 1998). While docking, polar hydrogen's were added to ligands using the hydrogen's module in Autodock tool and thereafter, Kollman united atom partial charges were assigned (Darko Butina *et al*., 2002). Docking of PPAR to ligands was carried out using LGA with standard docking protocol on the basis a population size of 150 randomly placed individuals; a maximum number of 2.5 *107 energy evaluations, a mutation rate of 0.02, a crossover rate of 0.80 and an elitism value of 1. Some independent molecular docking runs were carried out for each ligand and results were clustered as data mining according to the 1.0 Å rmsd criteria. The grid maps representing the proteins were calculated by using auto grid and grid size was set to 60*60*60 points with grid spacing of 0.375 Å. The coordinate of the docked protein along with the ligand was visualized using UCSF chimera (Pettersen EF *et al.,* 2004) within 6.5 Å region.

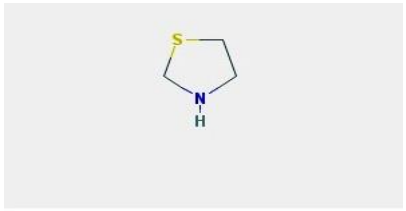
MATERIALS AND METHODS

Extraction of PDB structure of PPAR gamma

PDB stands for protein data bank (www.pdb.org), the sole international repository of all published 3D macro molecular structure data such as proteins and nucleic acids. PDB ID of PPAR gamma protein is 2PRG which is regarded as the target site for the anti-diabetic activity.

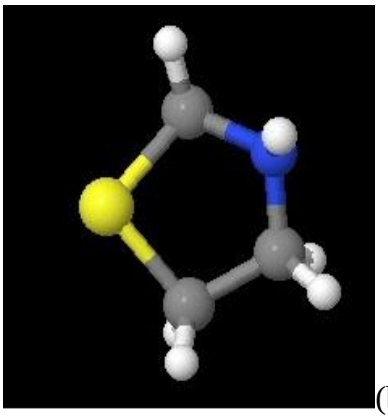
Substrate selection

More than five hundred structures of thiazolidine were chosen based on screening from the Chem Bank. The selected ligands are having very good stability and structural diversity by means of the bound ligands present in the thiazolidine crystal structure. The structures of selected ligands are used to docking function from the chem-bank protein and molecule compound databases and the Ligands were recognized and accepted as per the pharmacokinetic parameter and solubility during metabolism. The active site i.e. HIS 323 in the protein interacts with ligands of the substrate and gives rise to the catalytic activity to test ligands that helps in determining the binding pattern of the ligands to the active site of Thiazolidine (PPARγ) (PDB.ID: 2PRG).



Compound ID	10444
Molecular Weight	89.15938 [g/mol]
Molecular Formula	C_3H_7NS
XLogP3-AA	0.3
H-Bond Donor	1
H-Bond Acceptor	1

(a)



(b)

Fig 1.(a) *- Chemical structure of Thiazolidine(b) - 3D Structure of Thiazolidine*

Thiazolidine is a class of heterocyclic organic compounds with a 5-membered saturated ring with a thio ether group and an amino group in the 1 and 3 positions respectively. It's a sulfur analogue of oxazolidine. Thiazolidines may be

synthesized by the condensation reaction between a thiol and an aldehyde or a ketone. The reaction is reversible. Therefore, many thiazolidines are liable towards the hydrolysis in the aqueous solution.

For Molecular docking

The following steps were carried out for molecular docking:

- Select 2PRG protein from the read molecules option in the File menu.
- The protein was modified by the addition of polar only hydrogen atoms, Kollman charges, AD4 type atoms were assigned to the protein molecule

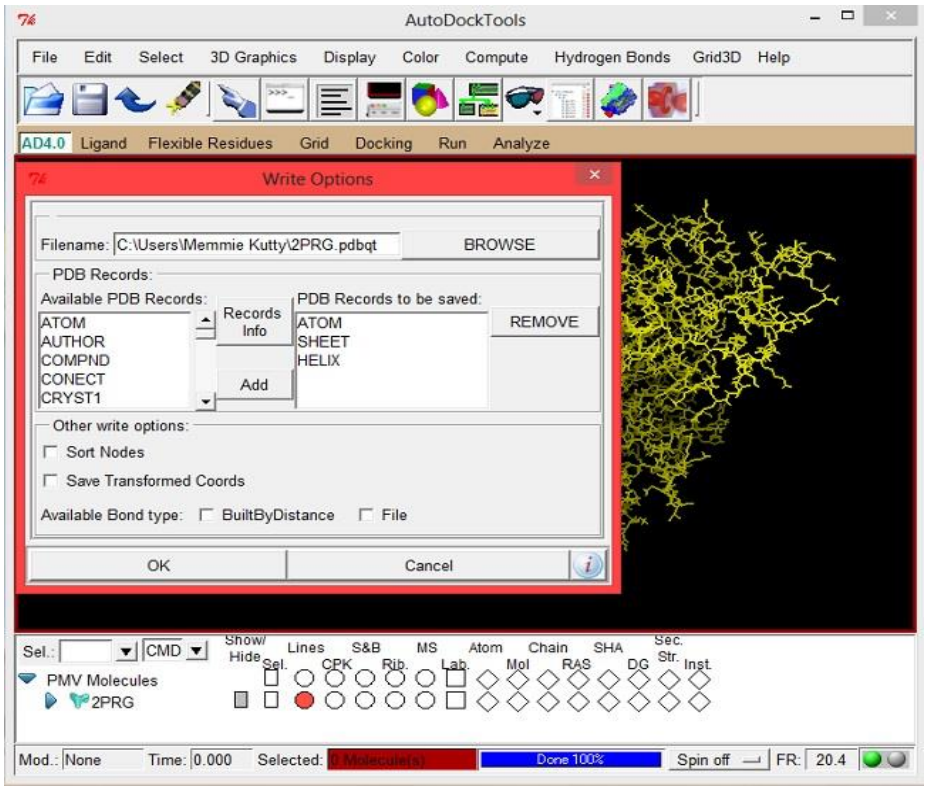


Fig2.*Autodock window for molecular docking*

- The modified molecule was saved in PDBQT format.
- The entire 500 ligand molecules were prepared one by one for docking.
- Initially the torsion root was detected and chosen for the ligand molecule.
- This modified ligand molecule was also saved in PDBQT format.
- Then the macromolecule and ligand were re-loaded on to the working window for obtaining grid parameter file from the grid tool bar menu.
- Before setting up the grid box parameter the active site residue was chosen as HIS 323.
- The grid box was generated by selecting a particular atom and parameters were setup to the dimensions of 60, 60, and 60 corresponding to x, y, z coordinates.
- The grid output was saved as 2PRG.gpf.
- Now macromolecule and the respective ligand were chosen from docking menu.
- Using Lamarckian genetic algorithm (LGA), the output was obtained and saved as 2PRG.dpf.

  The GLG file and DLG file (run docking algorithm) was obtained using cygwin. Cygwin software was opened

and the following commands were given:

- ./autogrid4.exe –p 2PRG.gpf –l 2PRG.glg &
  On the successful completion of autodock, the following command was given:
- ./autodock4.exe –p 2PRG.dpf –l 2PRG.dlg &
  On the completion of the program both dlg and glg files are generated.
- The dlg file was opened in WordPad and the minimum binding energy and the respective run was recorded for the corresponding molecule. Similarly a table for all the 500 molecules was prepared.
- Now, top 21 molecules out of 500 were selected which showed the least/minimum binding energies. Further work was done on these 21 molecules only.
  Opened Cygwin and reached out for the first molecule of those top 21 molecules. Then extracted dockings from DLG and typed the following command:
- grep '^DOCKED' 2PRG.dlg | cut –c9- > 2PRG_run.pdbqtThen, typed
- cut –c-66 2PRG_run.pdbqt > 2PRG_run.pdb.
  Opened the generated 2PRG_run.pdbqt file and copied all the atoms of that particular run and pasted it into the original protein (2PRG.pdb) before end. Removed all the END BRANCH, BRANCH, TORSDOF, etc. if any and then saved it as DOCKED PROTEIN. PDB. The hydrogen bonds of the docked protein were analyzed using visualization tool-UCSF Chimera.

Lipinski's rule analysis

The best 21 ligand molecules obtained on the basis of minimum binding energy were subjected to the Lipinski's rule analysis in Mol inspiration web server. Lipinski's rulesays that, in general, an orally active drug has no more than one violation of the following criteria:

- Not more than 5 hydrogen bond donors (nitrogen or oxygenatoms with one or more hydrogenatoms).
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygenatoms).
- A molecular weight under 500 daltons.
- An octanol-water partition coefficient log *P* of less than 5.

Drug likliness

The Drug likeliness is a qualitative concept used in drug design for how "drug like" a substance is with respect to factors like bio availability and bioactivity. It is estimated from the molecular structure before the substance is even synthesized and tested using PASS online server.

Previous research in the area

The proteins mutation activities and their analysis on attachment to this five hundred pair and base-pair segments of DNAs are identified as main sources of nuclear factor which termed ARF6.These DNAs are normally bound to two different active sites (ARE6 and ARE7) in this introduced enhancer. This phenomenal DNA attachment activity was observed and earmarked only in the extracts of molecules which are termed as fat cells. Duplicating and cloning of this functional factor exposed to be a associated part of the peroxisome proliferator of functional activated molecular receptor of (PPAR) subfamily of nucleotide hormonal receptors and there are three related but quite distinct PPAR proteins, PPARα, PPARγ (also called Nuc-1, or FAAR), and PPARδ. PPARγ is expressed in an adipose-selective fashion in both rodents and human. Interestingly, two forms of the protein, γ1 and γ2, exist as products of alternative promoter usage. The two forms differ in that PPARγ2 has an NH2-terminal extension of 30 amino acids.It was earmarked as that of both the conventional and Lamarckian genetic

expression and algorithms can be handled ligands of more numbers of degrees of freedom corresponding to the replicated and annealing method used in the oldest versions of AUTODOCK tool and that the Lamarckian genetic expression algorithm is one of the most competent, effective, more reliable and most successful of these three.TZD imposed against co-crystal ligand (2S)-2-(4-benzylphenoxy)-3-phenylpropanoic acid. The hydrogen bond network of His323, His449, and Tyr473 interacted with the polar head of TZD. All lignan derivatives from nutmeg seeds was favorably docked against PPARγ (3HOD). Interestingly, macelignan gave the smallest of binding free energies (-11.07 kcal/mol), while neolignan had the highest free energy (FEB) (-8.00) kcal/mol.

RESULT AND DISCUSSION

Correlation was established between the docked score of the tested molecule with their pharma cokinetic parameters. The binding energies were in the range of -2.26 kcal/mol to -8.80kcal/mol with minimum binding energy of -8.80 kcal /mol. 21 molecules maintained essential H bond interaction with the binding pocket near His 323. Docked conformations were rated by a scoring functions that include terms for Van der Waal's, hydrogen bond & electrostatic interactions plus internal energy of ligands. The solubility of the docked compound was related with the binding energy with the help of the log P value. The ligands also showed hydrophobic bonds with active site residue HIS 323 with PPARγ.

Thiazolidinediones (TZDs) are one important class of synthetic agonists of PPARγ. TZDs are anti-diabetic agents currently used in the treatment of T2DM that target adipose tissue and improve insulin sensitivity. Thus, our novel selective PPARγ agonists can act as potent drugs for the treatment of hyper glycaemia and insulin resistance. On selective screening 21 TZDs- PPARγ agonists are characterized by making a hydrogen bond network with the binding pocket comprising of His 323 residue.

More numbers of molecular drugs have been regularized from the class of TZDs to treatthe diabetes disorders like Rosiglitazone syndrome, Pioglitazone syndrome, Ciglitazone syndrome and many more disorder and eventhough the drugs available in the market shows additive effect with other anti – hyper glycemic agents which are also prone to show and increase the toxicity mechanism during metabolic activity in cell. For example, Rosiglitazone shows hepato toxicity. Hence there is a need to find more potent and orally safe thiazolidine 2,4-diones with less toxicity which made possible for our research work.

CONCLUSION

Based on the molecular docking we found that 10 compounds as of structure similarity of thiazolidine-4-one showed better binding affinities with the active site pocket (comprising of HIS 323) of the PPARγ which also act as the substrate binding site. All the 500 molecules were docked using the Auto Dock4 and were visualized in UCSF Chimera as shown above have the same orientation which further validate our Docking Result. The extension of the basic work relates to conventional in silicos-approaches for estimating and find out the attached mode in gene sequential order. As an extend there is necessity to formulate in-vitro and in-vivo function of the generated data to synthesize examining to design new molecular drugs with better specifications and metabolic activity in human cells.

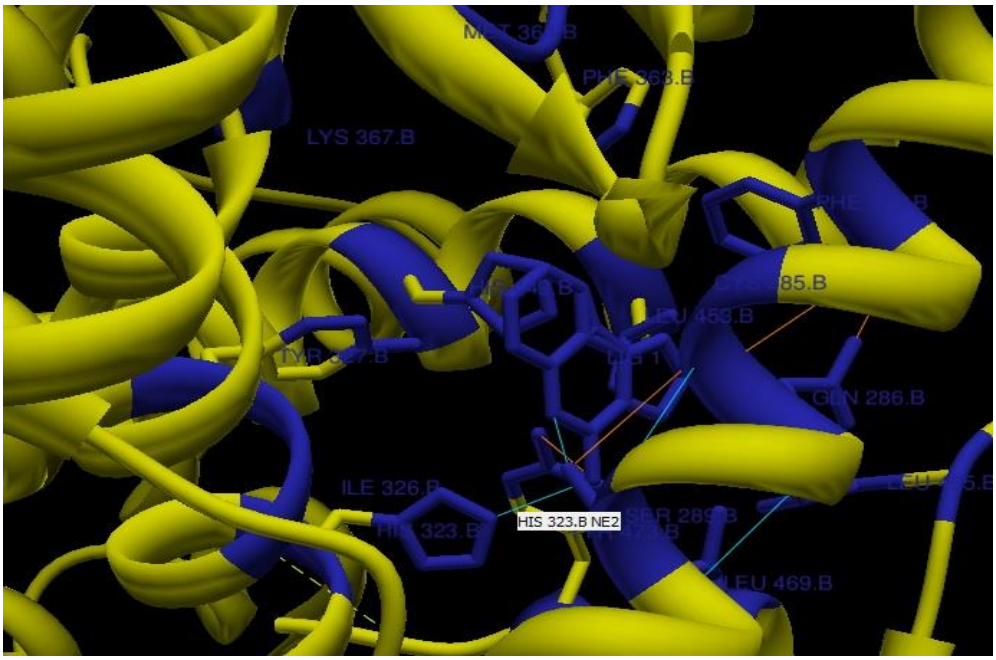


Fig 3.*Visualization of docked protein (2- (3- ethoxyphenyl) - 3- (2- methoxyethyl) 1,3- thiazolidin- 4- one with 2PRG)*

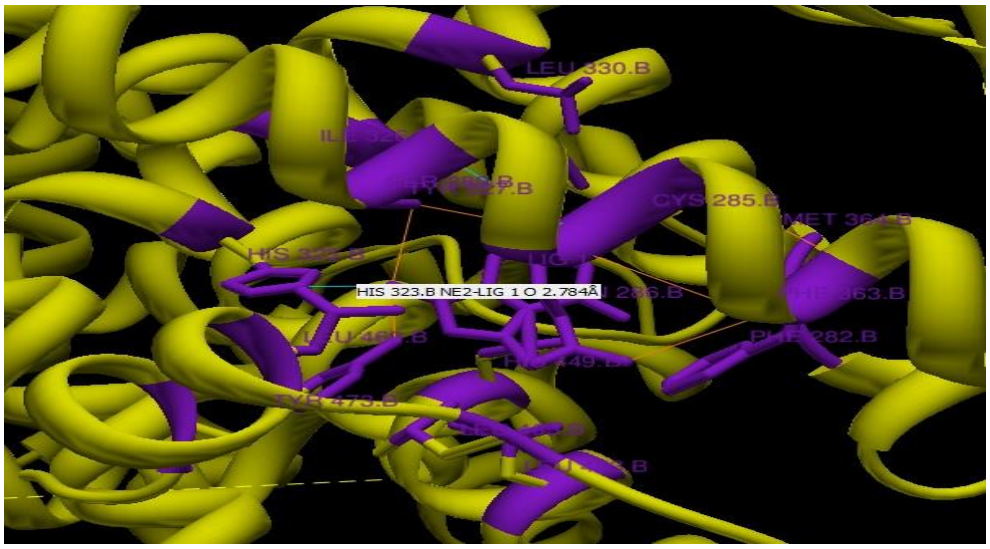
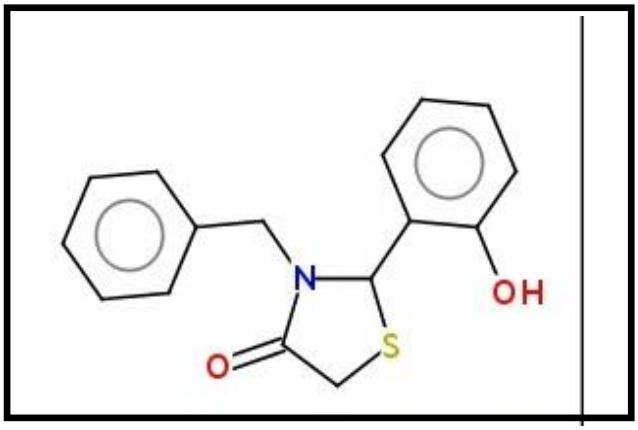


Fig4. *Visualization of docked protein(5-{[cyclohexyl(2-hydroxyethyl) amino]methyl}- 2- thioxo- 1,3- thiazolidin- 4- one with 2PRG)*

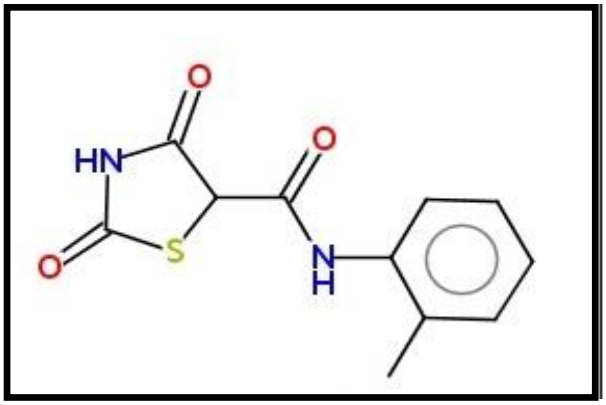
Lipinski's prediction and Drug likeliness – Molecular data Mining



Molinspiration property

miLogP	2.958
TPSA	40.537
natoms	20.0
MW	285.368
nON	3
nOHNH	1
nviolations	0
nrotb	3
volume	252.955

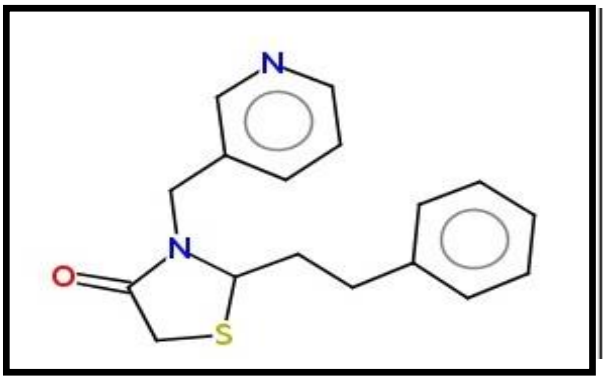
Fig 5. *3- benzyl- 2- (2- hydroxyphenyl) - 1,3- thiazolidin- 4- one*



Molinspiration property

miLogP	0.862
TPSA	75.267
natoms	17.0
MW	250.279
nON	5
nOHNH	2
nviolations	0
nrotb	2
volume	206.474

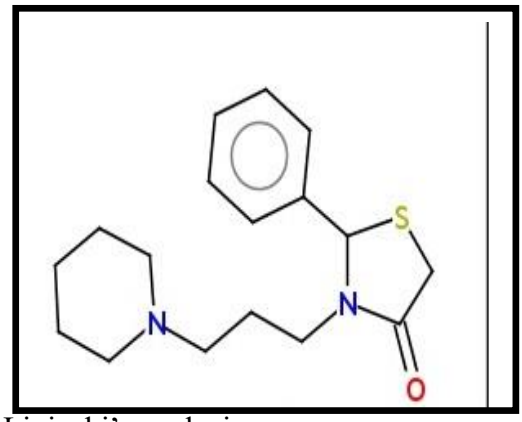
Fig 6. *2- (3- ethoxyphenyl) - 3- (2- methoxyethyl) - 1,3- thiazolidin- 4- one*



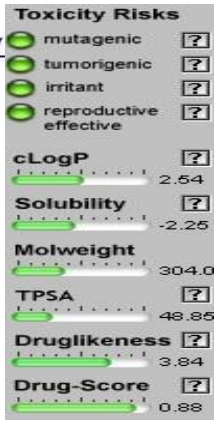
Molinspiration property

miLogP	2.509
TPSA	33.201
natoms	21.0
MW	298.411
nON	3
nOHNH	0
nviolations	0
nrotb	5
volume	274.385

Fig 7. *2- (2- phenylethyl) - 3- (pyridin- 3- ylmethyl) - 1,3- thiazolidin- 4- one*

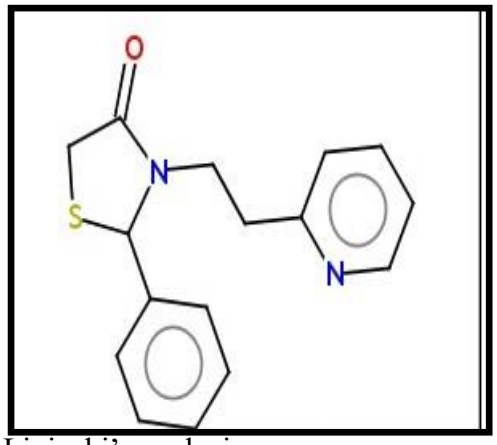


Molinspiration property	
miLogP	2.828
TPSA	23.547
natoms	21.0
MW	304.459
nON	3
nOHNH	0
nviolations	0
nrotb	5
volume	293.084

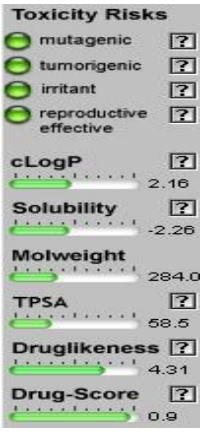


(a) Lipinski's analysis (b) Drug score

Fig8. *2- phenyl- 3- (3- piperidin- 1- ylpropyl) - 1,3- thiazolidin- 4- one*

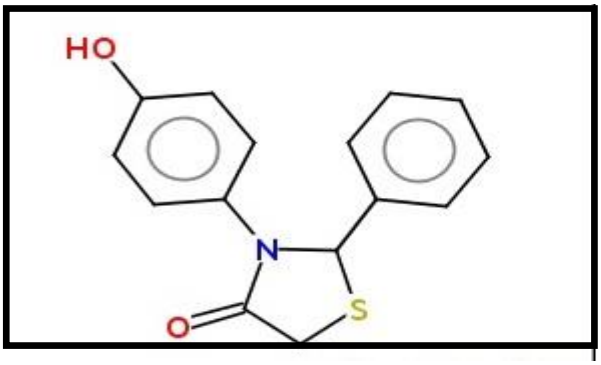


Molinspiration property	
miLogP	2.253
TPSA	33.201
natoms	20.0
MW	284.384
nON	3
nOHNH	0
nviolations	0
nrotb	4
volume	257.583



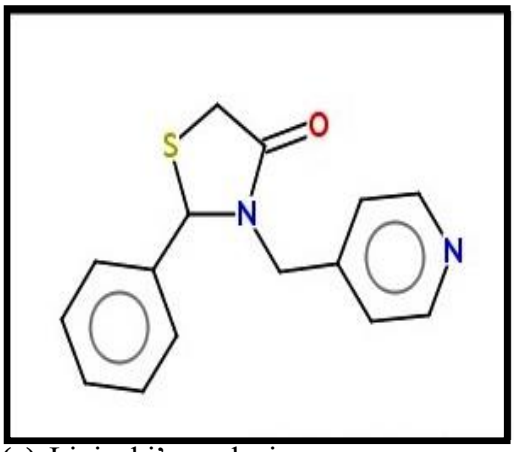
(a) Lipinski's analysis (b) Drug score

Fig 9. *2- phenyl- 3- (2- pyridin- 2- ylethyl) - 1,3- thiazolidin- 4- one*



Molinspiration property	
miLogP	2.837
TPSA	40.537
natoms	19.0
MW	271.341
nON	3
nOHNH	1
nviolations	0
nrotb	2
volume	236.154

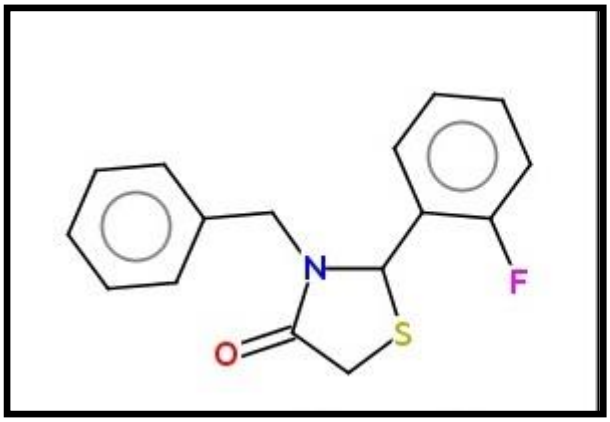
Fig 10. *3- (4- hydroxyphenyl) - 2- phenyl- 1,3- thiazolidin- 4- one*



Molinspiration property	
miLogP	1.729
TPSA	33.201
natoms	19.0
MW	270.357
nON	3
nOHNH	0
nviolations	0
nrotb	3
volume	240.781

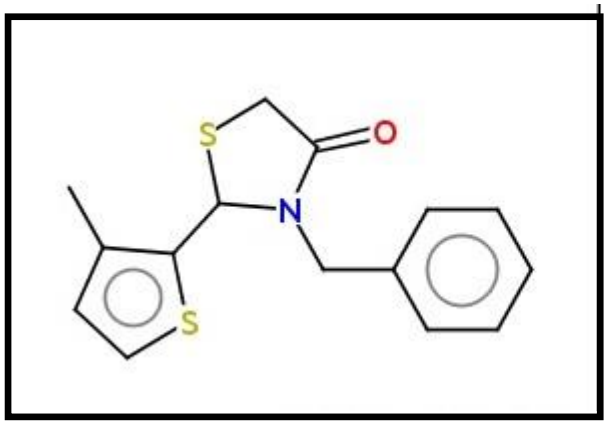
(a) Lipinski's analysis (b) Drug score

Fig11. *2- phenyl- 3- (pyridin- 4- ylmethyl) - 1,3- thiazolidin- 4- one*



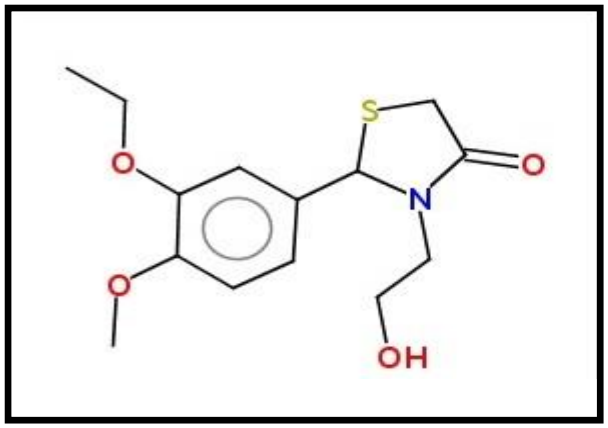
Molinspiration property	
miLogP	3.134
TPSA	20.309
natoms	20.0
MW	287.359
nON	2
nOHNH	0
nviolations	0
nrotb	3
volume	249.869

Fig12. *(2S) - 3- benzyl- 2- (2- fluorophenyl) - 1,3- thiazolidin- 4- one*



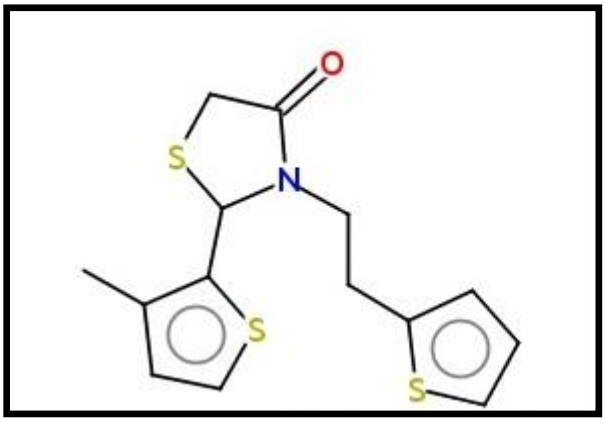
Molinspiration property	
miLogP	3.294
TPSA	20.309
natoms	19.0
MW	289.425
nON	2
nOHNH	0
nviolations	0
nrotb	3
volume	252.21

Fig13. *3- benzyl- 2- (3- methyl- 2- thienyl) - 1,3- thiazolidin- 4- one*



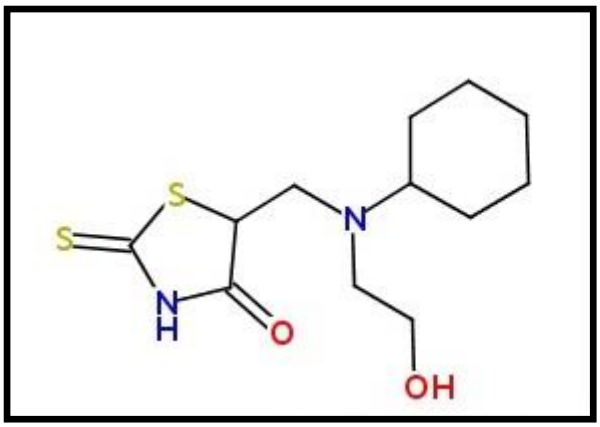
Molinspiration property	
miLogP	1.01
TPSA	59.005
natoms	20.0
MW	297.376
nON	5
nOHNH	1
nviolations	0
nrotb	6
volume	266.242

Fig14.*2- (3- ethoxy- 4- methoxyphenyl) - 3- (2- hydroxyethyl) - 1,3- thiazolidin- 4- one*



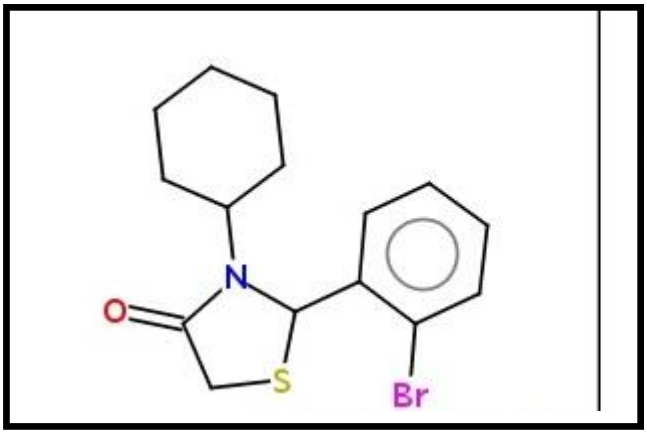
Molinspiration property	
miLogP	3.598
TPSA	20.309
natoms	19.0
MW	309.481
nON	2
nOHNH	0
nviolations	0
nrotb	4
volume	259.724

Fig15. *2- (3- methyl- 2- thienyl) - 3- [2- (2- thienyl) ethyl]- 1,3- thiazolidin- 4- one*



Molinspiration property	
miLogP	1.502
TPSA	52.564
natoms	18.0
MW	288.438
nON	4
nOHNH	2
nviolations	0
nrotb	5
volume	257.199

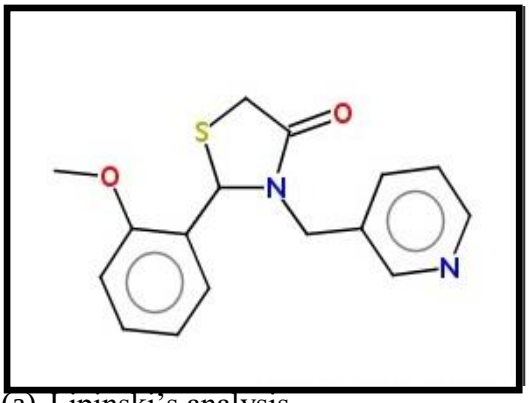
Fig16. *5-{[cyclohexyl(2-hydroxyethyl)amino]methyl}-2-thioxo-1,3-thiazolidin-4 one*



Molinspiration property

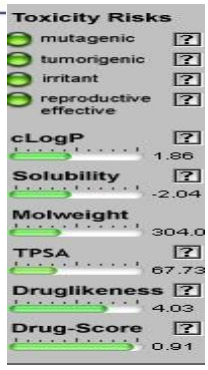
miLogP	4.286
TPSA	20.309
natoms	19.0
MW	340.286
nON	2
nOHNH	0
nviolations	0
nrotb	2
volume	264.607

Fig17. 2- (2- bromophenyl) - 3- cyclohexyl- 1,3- thiazolidin- 4- one



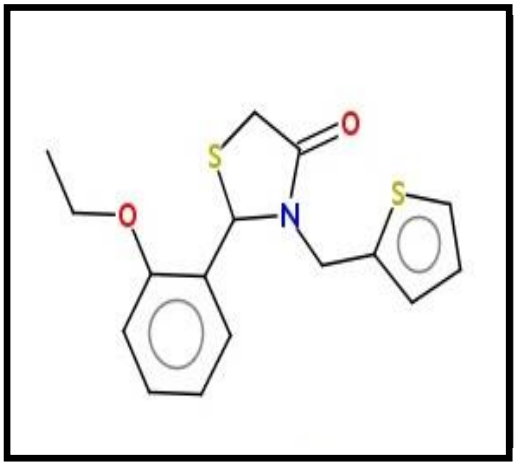
Molinspiration property

miLogP	1.79
TPSA	42.435
natoms	21.0
MW	300.383
nON	4
nOHNH	0
nviolations	0
nrotb	4
volume	266.327



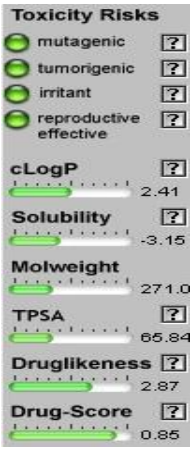
(a) Lipinski's analysis (b) Drug score

Fig18. *2- (2- methoxyphenyl) - 3- (pyridin- 3- ylmethyl) - 1,3- thiazolidin- 4- one*



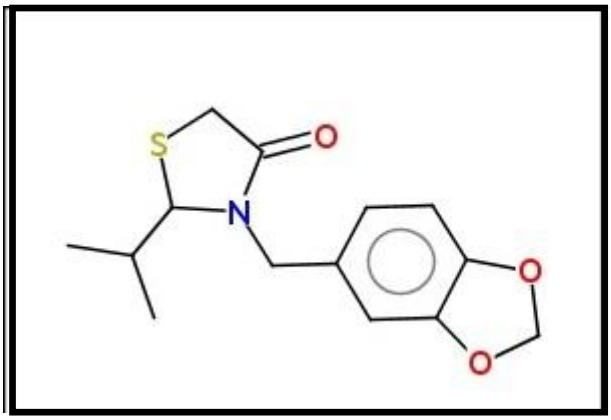
Molinspiration property

miLogP	3.302
TPSA	29.543
natoms	21.0
MW	319.451
nON	3
nOHNH	0
nviolations	0
nrotb	5
volume	277.997



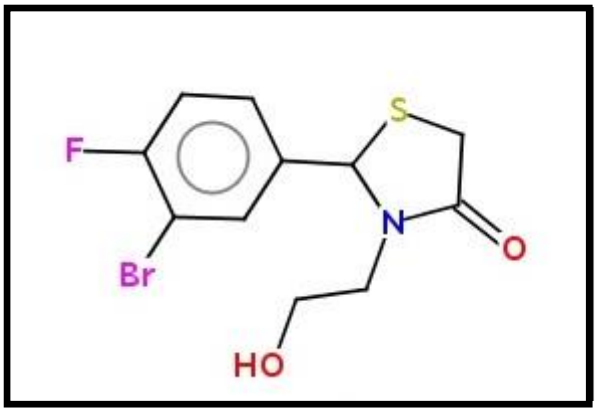
(a) Lipinski's analysis (b) Drug score

Fig19. *2- (2- ethoxyphenyl) - 3- (2- thienylmethyl) - 1,3- thiazolidin- 4- one*



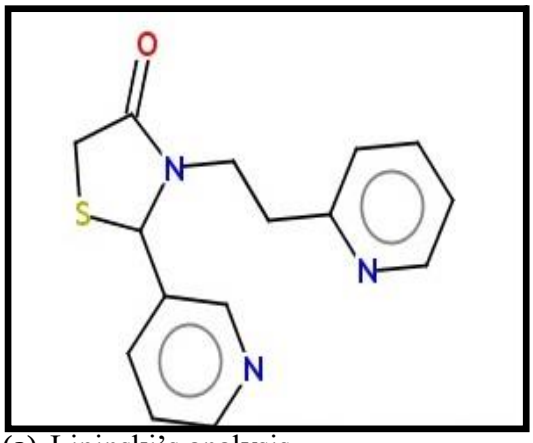
Molinspiration property	
miLogP	2.436
TPSA	38.777
natoms	19.0
MW	279.361
nON	4
nOHNH	0
nviolations	0
nrotb	3
volume	247.408

Fig20. *3- (1,3- benzodioxol- 5- ylmethyl) - 2- isopropyl- 1,3- thiazolidin- 4- one*



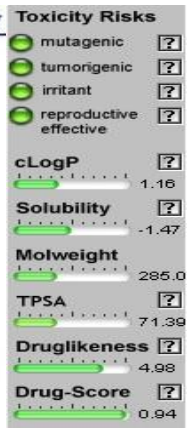
Molinspiration property	
miLogP	1.888
TPSA	40.537
natoms	17.0
MW	320.183
nON	3
nOHNH	1
nviolations	0
nrotb	3
volume	221.165

Fig21. *2- (3- bromo- 4- fluorophenyl) - 3- (2- hydroxyethyl) - 1,3- thiazolidin- 4- one*



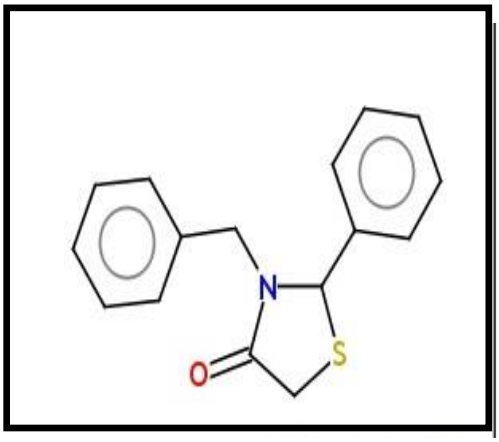
(a) Lipinski's analysis

Molinspiration property	
miLogP	1.017
TPSA	46.093
natoms	20.0
MW	285.372
nON	4
nOHNH	0
nviolations	0
nrotb	4
volume	253.427

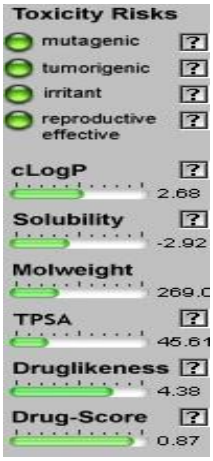


(b) Drug score

Fig22. *2- pyridin- 3- yl- 3- (2- pyridin- 2- ylethyl) - 1,3- thiazolidin- 4- one*

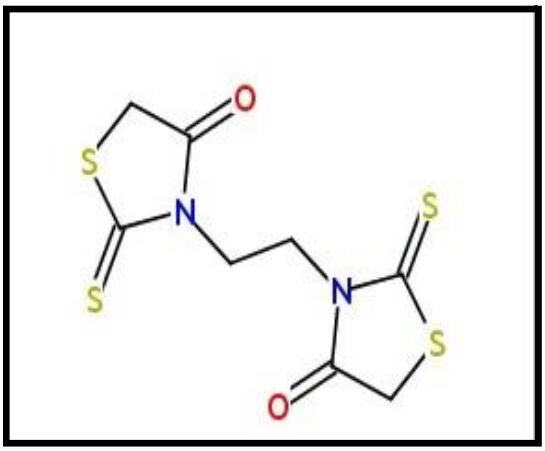


Molinspiration property	
miLogP	3.018
TPSA	20.309
natoms	19.0
MW	269.369
nON	2
nOHNH	0
nviolations	0
nrotb	3
volume	244.938



(a) Lipinski's analysis (b) Drug score

Fig23. *(2S) - 3- benzyl- 2- phenyl- 1,3- thiazolidin- 4- one*



Molinspiration property	
miLogP	0.6
TPSA	40.618
natoms	16.0
MW	292.432
nON	4
nOHNH	0
nviolations	0
nrotb	3
volume	213.673

Fig24.*3,3'- ethane- 1,2- diylbis(2- thioxo- 1,3- thiazolidin- 4- one)*

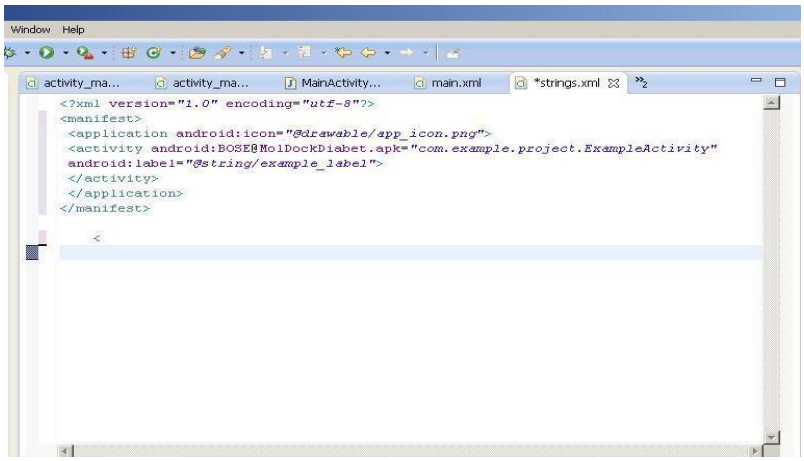
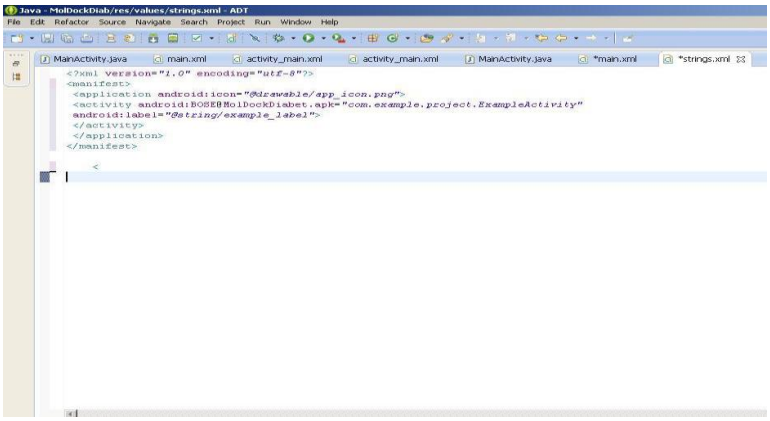
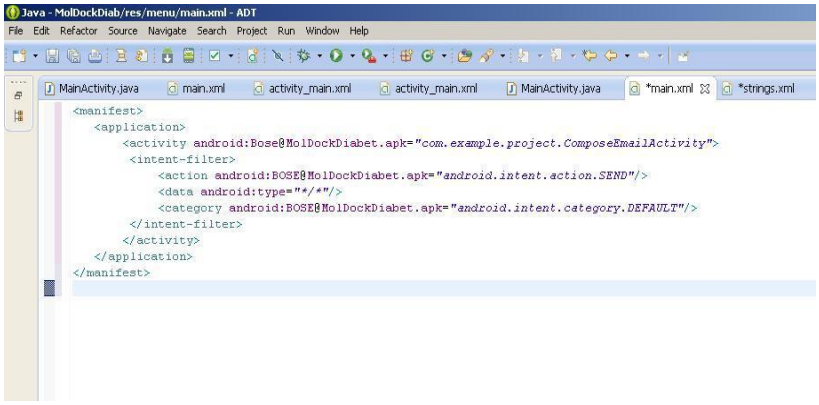


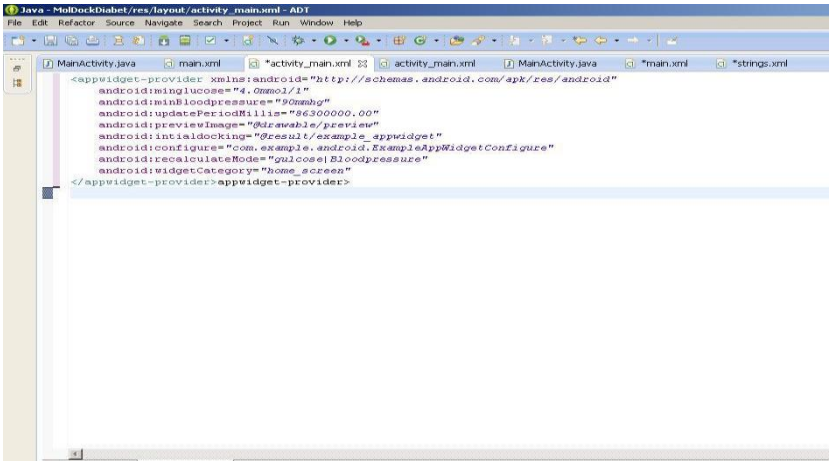
Fig 25.*Adroid application programe (a) Programme Window: 1 - model*



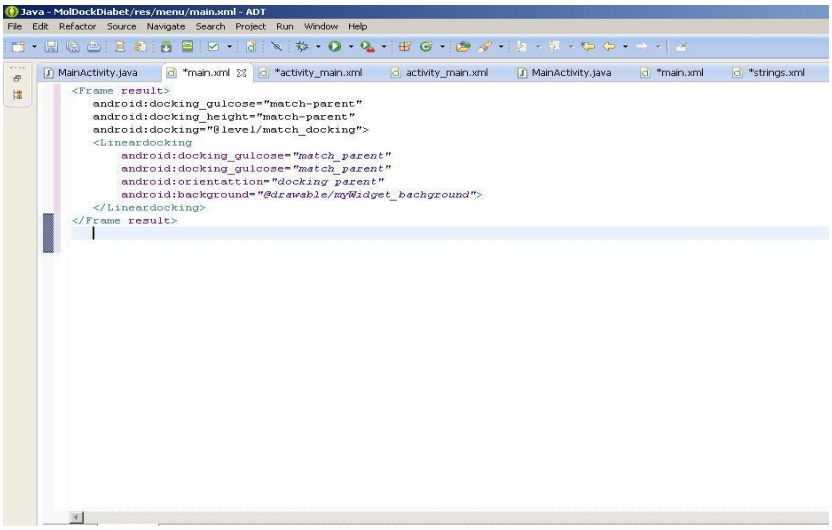
(b) Programme Window: 2 – model



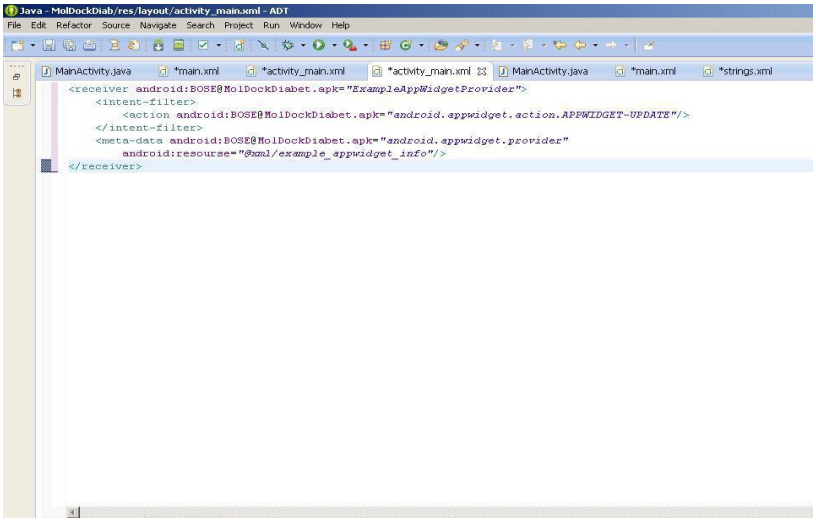
(c) Programme Window: 3 – model



(d) Programme Window: 4 - model



(e) Programme Window: 5 – model



(f) Programme Window: 6 - model

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