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# Computational Molecular Modelling of Benzothiophene Derivatives as Anti-Diabetic Agents

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**ABSTRACT**

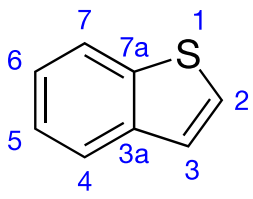
The project aims to design benzothiophene derivatives as potent modulators of PPARγ, thereby enhancing their agonistic activity for the treatment of diabetes. Through computational modeling, the study converts two-dimensional structures of these derivatives into three-dimensional conformations using Novopro Bioscience Online tools. Molecular docking simulations using Autodock evaluate the binding affinity of the proposed ligands to PPARγ, with visualization of the docked complexes facilitated by PyMol. Ipragliflozin serves as the standard molecule for comparison, and promising ligands exhibiting significant docking scores with PPARγ are identified as potential antidiabetic agents.

**Keywords:** Benzothiophene, Anti -diabetic, Autodock, Ipragliflozin, *In-silico*

## INTRODUCTION

Drug discovery endeavors to pinpoint compounds harboring therapeutic potential for addressing various diseases. This intricate process encompasses candidate identification, synthesis, characterization, validation, optimization, screening, and assays to confirm therapeutic efficacy. Upon demonstrating significance, the compound proceeds to drug development. Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood sugar levels over an extended period. It arises from either insufficient insulin production by the pancreas or ineffective response of the body's cells to insulin. Diabetes is broadly categorized into three types: Type 1 Diabetes manifests as an autoimmune disorder characterized by the immune system's assault on the insulin-producing beta cells within the pancreas, leading to their destruction. Typically diagnosed in children and young adults, lifelong insulin therapy is essential for management. Type 2 Diabetes: the most prevalent form, usually occurring in adults over 45 years but increasingly detected in younger age groups. It involves insulin resistance, where the body's cells fail to respond adequately to insulin, often linked with obesity and a sedentary lifestyle. Management includes lifestyle modifications, oral medications, and sometimes insulin therapy. Gestational Diabetes: occurring during pregnancy, it typically resolves after childbirth but heightens the risk of developing type 2 diabetes later in life for both the mother and child. Diabetes management focuses on maintaining blood sugar levels within a target range to avert complications.[2,3]

PPARγ exerts its gene regulatory potential via transactivation and transrepression Transactivation involves a mechanism by which PPARγ binds as a heterodimer complex with RXR to PPAR response elements(PPREs).PPARG2 produces the PPARγ2 isoform, with an additional 28 amino acids, primarily found in adipose tissue and urothelial cells, as well as regulatory T cells and other T cell populations. Recently, two more isoforms, PPARγ1Δ5 and PPARγ2Δ5, have been identifiedPPARγ2Δ5, expressed in adipose tissue, lacks the ligand binding domain due to exon 5 skipping and is correlated with higher BMI in overweight or obese and type 2 diabetic patients.[4,5]



Benzothieno[3,2-b]benzothiophene (BTBT), featuring two benzene rings as its outermost rings, is recognized as a diacene-fused ladder-type π-conjugated thienothiophene compound. Benzothiophene is aromatic organic compound with a molecular formula C8H6S and an odour similar to naphthalene. Benzothiophene can be synthesised by the reaction of an alkyne-substituted 2-bromobenzene with either by sodium sulfide or potassium sulfide to form benzothiophene with an alkyl substitution at position.[6,7,8]

In this study, we have designed and docked a series of new Benzothiophene derivatives in search of potent antidiabetic agents through *insilico* studies using AutoDock4.

Ipragliflozin is an SGLT2 inhibitor in clinical development for the treatment of type 2 diabetes mellitus (T2DM). . It is used for the treatment of type 2 diabetes mellitus (T2DM) to help lower blood sugar levels. By inhibiting SGLT2 in the kidneys, ipragliflozin reduces the reabsorption of glucose from the urine, thereby promoting the excretion of excess glucose from the body. This mechanism of action helps to lower blood glucose levels and improve glycemic control in patients with type 2 diabetes.[9]

## MATERIALS AND METHODS

### *In-silico* screening

*In-silico* screening of all the proposed structures of novel benzothiophene derivatives were carried out using various computational chemistry softwares such as ACD Lab/ChemSketch 12.0, Molinspiration , PASS and AutoDock4.[10]

### ACD/Chemsketch

ACD/ChemSketch Freeware provides a comprehensive platform for creating chemical structures, accommodating organics, organometallics, polymers, and Markush structures. It also includes features such as calculation of molecular properties (eg., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures(fewer than 50 atoms and 3 rings ), and prediction of log P.

ACD/ChemSketch has the following major capabilities in that it provides for:

Structure Mode for drawing chemical structures and calculating their properties,Draw Mode for text and graphics processing.

Molecular Properties calculations for automatic estimation of formula weight, percentage composition, molar volume, parachor, surface tension, density, dielectric constant, polarizability. It also includes features such as calculation of molecular properties (eg., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures(fewer than 50 atoms and 3 rings ), and prediction of log P. [11,12,13]

### Molinspiration

Molinspiration" is an independent research organization focused on development and application of modern cheminformatic techniques, especially in connection with the internet.It offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure search or similarity and pharmacophore similarity search.(Figure:3)

All the designed compounds were then subjected to Lipinski rule analysis using Molinspiration software to identify the biologically active compounds. Lipinski rule is also known as Pfizer rule of five / Lipinski's rule of 5. The rule was formulated by the scientist Christopher A Lipinski.

The Lipinski rule of five states that an orally active drug should obey the following criteria in that it will have:

1.Not more than 5 hydrogen bond donors

2.Not more than 10 hydrogen bond acceptors

3. An octanol-water partition coefficient of log P not greater than 5

5.Not more than 5 rotatable bonds.It offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure search or similarity and pharmacophore similarity search.(Figure:3)

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1.Not more than 5 hydrogen bond donors

2.Not more than 10 hydrogen bond acceptors

3. An octanol-water partition coefficient of log P not greater than 5

5.Not more than 5 rotatable bonds.[14]

**PASS**

PASS is a computer program for estimating sample size or determining the power of a statistical test or confidence interval.NCSS LLC is the company that produces PASS. PASS includes over 920 documented sample size and power procedures. PASS is the leading sample size software for clinical trials, pharmaceutical, medical and many other research areas. Using structural formula of a drug like substance as an input, one obtains its estimated biological activity profile as an output.[15]

**PDB (Protein Data Bank)**

The protein databank is a database for 3 dimensional structure data. It is mainly used for obtaining the data of large biological molecules like proteins and nucleic acid. The data in PDB is available after X-ray crystallography, NMR spectroscopy, cryoelectron microscopy and submitted by biologists and biochemists from all over the world.The database is freely accessible on the internet via the websites of its member organisation(PDBe, PDBj, RCSB and BMRB0. The PDB is controlled by Worldwide Protein Data Bank(wwPDB.NCSS LLC is the company that produces PASS. PASS includes over 920 documented sample size and power procedures. PASS is the leading sample size software for clinical trials, pharmaceutical, medical and many other research areas. Using structural formula of a drug like substance as an input, one obtains its estimated biological activity profile as an output.[15]

**NovoPro Biosciences Inc**.

NovoPro Biosciences provide online tools conversion of SMILES to 3D structure.The 3D structure can be downloaded in any one of the desired format like .pdb, .mol, .sdf. The various derivatives cab be converted to SMILES and their 3D structures can be computed.

**AutoDock**

Autodock is a software specifically designed for docking ligands to a set of grids representing the target protein. AutoGrid, a component of Autodock, is utilized for the pre-calculation of these grids, facilitating efficient and accurate ligand-protein docking simulations.AutoDock is a molecular modelling simulation software. It is effective for protein-ligand docking. AutoDock 4 is avilalable under the GNU General Public License .This application is one of the most cited docking software appplications. It consist of two main programmes. Autodock is for docking of the ligand to set of grids describing the target protein.Auto Grid can be used for pre calculating these grids. Prior to docking of the molecule within Autodock, it requires preparation of the protein and ligands.[17]

**PyMol**

PyMol is an open source and also a proprietary molecular visualization system. With PyMol, high quality 3D images of small molecules and biological macromolecules are obtained. The software is an open source but proprietary molecular visualization system. The images of docked complex has been visualized by PyMol. [18]

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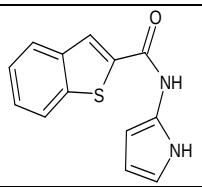
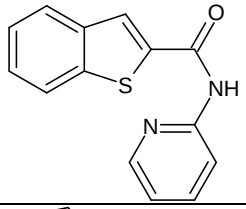
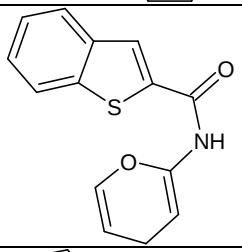
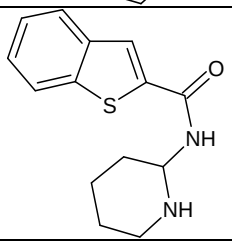
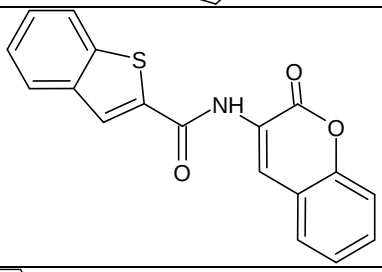
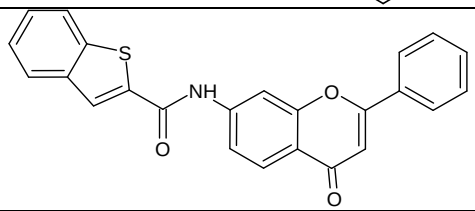
## RESULTS AND DISCUSSIONS

Fifty analogues of Benzothiophene were designed using ACD Lab ChemSketch 12.0. Initially the designed fifty analogues were subjected to Lipinski rule analysis using Molinspiration software. From the Lipinski rule analysis, eleven compounds were selected for further studies, since these compounds did not show any violations from the Lipinski rule of five.

**Table No: 1 Structure and name of hetrocyclic rings**

| S.NO | STRUCTURE | IUPAC | SMILE |
|---|---|---|---|
| 1. |  | *N*-(1*H*-pyrrol-2-yl)-1-benzothiophene-2-carboxamide | O=C(Nc1ccc[NH]1)c1cc2ccccc2s1 |
| 2. |  | *N*-(pyridin-2-yl)-1-benzothiophene-2-carboxamide | O=C(Nc1ccccn1)c1cc2ccccc2s1 |
| 3. |  | *N*-(4*H*-pyran-2-yl)-1-benzothiophene-2-carboxamide | O=C(NC1=CCC=CO1)c1cc2ccccc2s1 |
| 4. |  | *N*-(piperidin-2-yl)-1-benzothiophene-2-carboxamide | O=C(NC1CCCCN1)c1cc2ccccc2s1 |
| 5. |  | *N*-(2-oxo-2*H*-1-benzopyran-3-yl)-1-benzothiophene-2-carboxamide | O=C1Oc2ccccc2C=C1NC(=O)c1sc2ccccc2c1 |
| 6. |  | *N*-(4-oxo-2-phenyl-4*H*-1-benzopyran-7-yl)-1-benzothiophene-2-carboxamide | O=C(Nc1cc2OC(=CC(=O)c2cc1)c1ccccc1)c1sc2ccccc2c1 |

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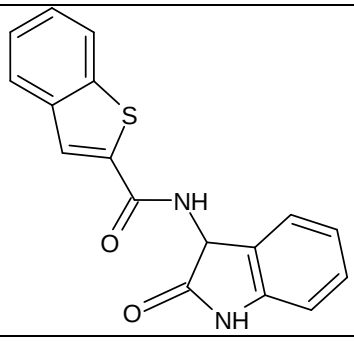
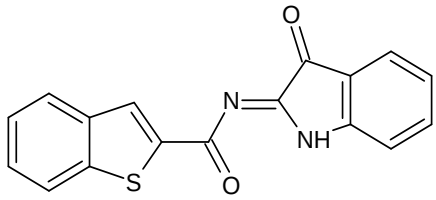
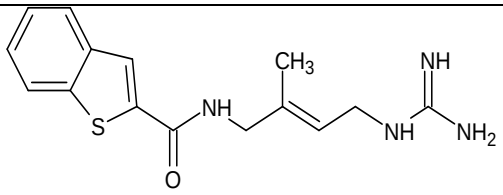
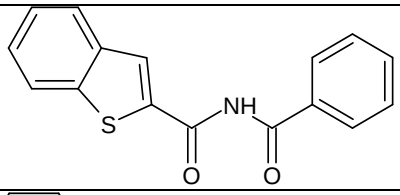
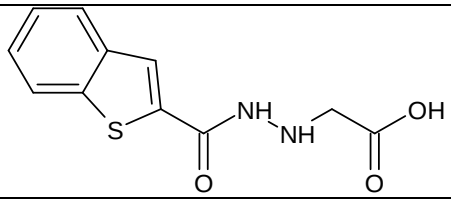
| | | | |
|---|---|---|---|
| 7. |  | *N*-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1-benzothiophene-2-carboxamide | O=C1Nc2ccccc2C1NC(=O)c1cc2ccccc2s1 |
| 8. |  | *N*-[(2*Z*)-3-oxo-1,3-dihydro-2*H*-indol-2-ylidene]-1-benzothiophene-2-carboxamide | O=C(\N=C1/Nc2ccccc2C1=O)c1cc2ccccc2s1 |
| 9. |  | *N*-[(2*E*)-4-(carbamimidoylamino)-2-methylbut-2-en-1-yl]-1-benzothiophene-2-carboxamide | O=C(NC/C(C)=C/CNC(=N)N)c1cc2ccccc2s1 |
| 10. |  | *N*-benzoyl-1-benzothiophene-2-carboxamide | O=C(NC(=O)c1ccccc1)c1sc2ccccc2c1 |
| 11. |  | [2-(1-benzothiophene-2-carbonyl)hydrazin-1-yl]acetic acid | O=C(NNCC(O)=O)c1cc2ccccc2s1 |

Based on the docking score, eleven designed derivatives were selected as antidiabetic agents . The docking score of selected derivatives are shown in the table.

**Table no: 2 Docking score of selected eleven compounds**

| SL NO | COMPOUNDS | BINDING AFFINITY |
|---|---|---|
| 1 | 1 | -7.9 |
| 2 | 2 | -8.4 |
| 3 | 3 | -6.5 |
| 4 | 4 | -7.7 |
| 5 | 5 | -9.2 |
| 6 | 6 | -11.4 |
| 7 | 7 | -9.4 |
| 8 | 8 | -8.6 |
| 9 | 9 | -8.1 |
| 10 | 10 | -7.8 |
| 11 | 11 | -7.5 |
| | IPRAGLIFLOZIN | -9.9 |

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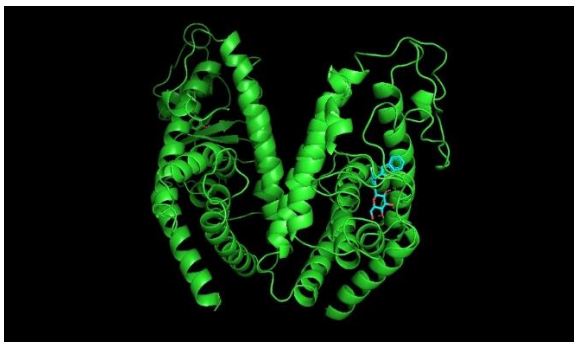
Fig 1: Ipragliflozin with 4JAZ

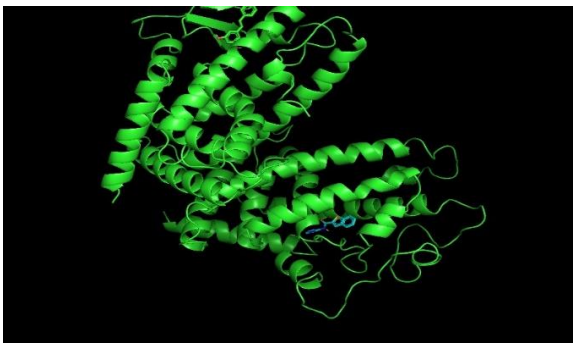
Fig 2: Compound 1 with 4JAZ

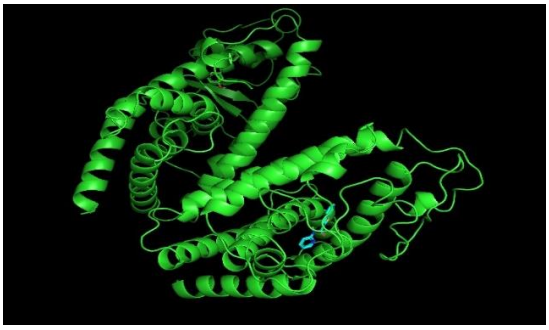
Fig 3:Compound 2 with 4JAZ

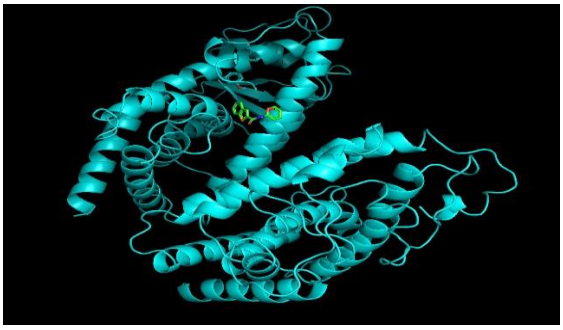
Fig 4: Compound 3 with 4JAZ

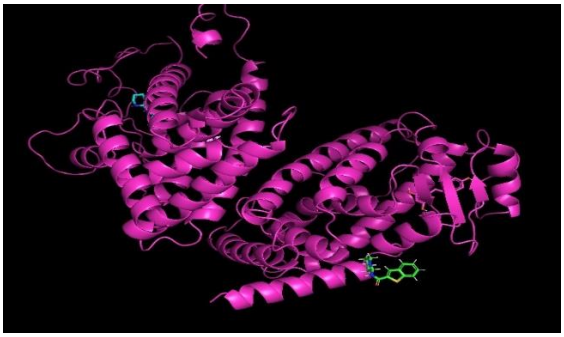
Fig 5:Compound 4 with 4JAZ

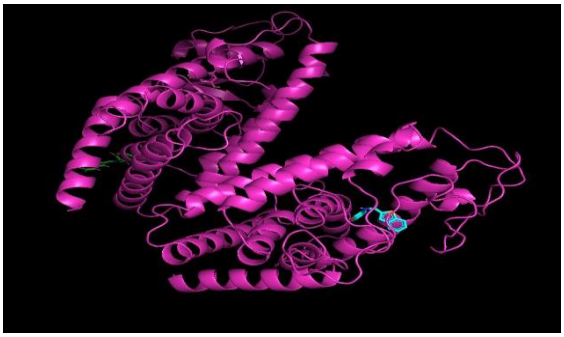
Fig no 6:Compound 5 with 4JAZ

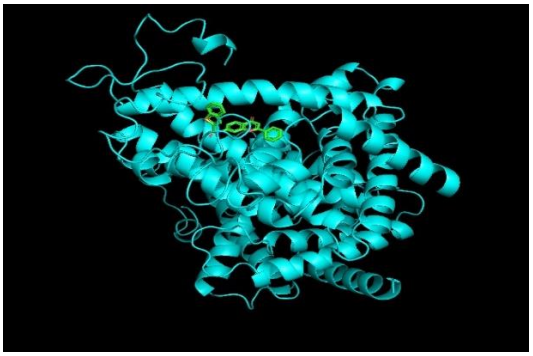
Fig no 7:Compound 6 with 4JAZ

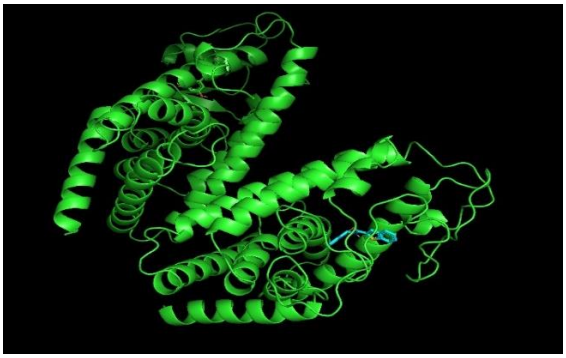
Fig no 8:Compound 7 with 4JAZ

**International Journal of Pharmacy and Pharmaceutical Research (IJPPR)**
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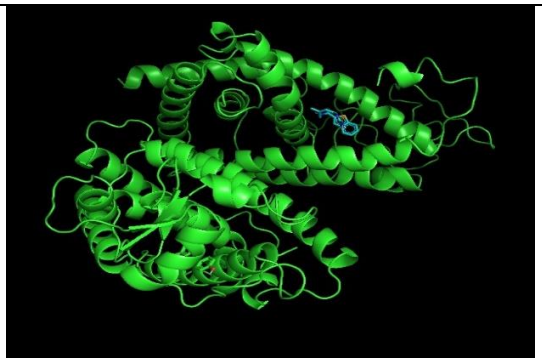

Fig no 9: Compound 8 with 4JAZ

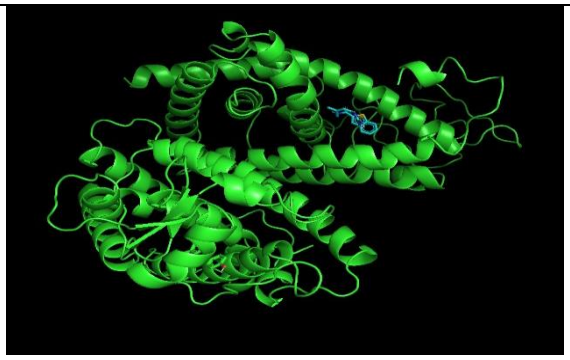

Fig no 10: Compound 9 with 4JAZ

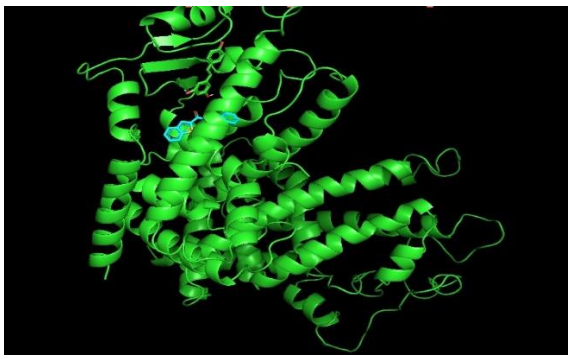

Fig no 11:Compound 10 with 4JAZ

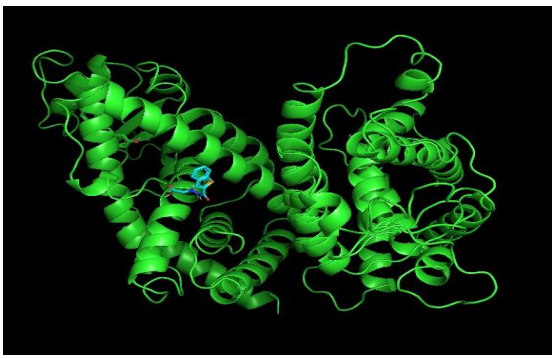

Fig no 12:Compound 11 with 4JAZ

DOCKING: The images of standard drug and selected eleven derivatives were shown in figure.

## CONCLUSION

The investigation that has been carried out in the present project, the results obtained for the same and the corresponding observations made were in accordance with the objectives laid down during commencement of the work.

Based on the literature survey, it was revealed that benzothiophene derivatives can exert anti diabetic activity. So fifty novel hybrid molecules benzothiophene nucleus were designed using the ACD Lab ChemSketch 12.0 software. All the designed leads were then subjected to Lipinski rule analysis using Molinspiration software to identify the theoretically active compounds. In the present study, eleven theoretically active lead compounds were identified. The identified compounds were subjected to docking studies against the selected target proteins, PPARγ(4JAZ) for antidiabetic activity. From the docking results, compounds 1-11 which had the highest docking scores ranging from – 11.4 to -6.5. The newly designed benzothiophene derivatives are expected to possess potent antidiabetic activity than the available drugs.

## ACKNOWLEDGEMENT

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