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In silico Pharmacokinetic, Bioactivity and Toxicity Evaluation of Some Selected Anti-Diabetic Agents

Alivelu Samala[1*], M.D Sabeel[2], M. Nithin Kumar[3]

[1]Department of Pharmaceutical Chemistry, Holy Mary Institute of Technology and Science, College of Pharmacy Bogaram, Keesara, Medchal, Telangana, India, 501301.

[2,3]B Pharmacy Final year Students, Holy Mary Institute of Technology and Science, Bogaram, Keesara, Medchal, Telangana, India, 501301.

*Corresponding Author: Dr. Alivelu Samala Email Id: s.alivelu@gmail.com

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Abstract: Diabetes mellitus is among the most common chronic metabolic disorders worldwide and is characterized by persistently high blood glucose levels resulting from insufficient insulin secretion, insulin resistance, or a combination of both. The primary goals of diabetes management are to maintain optimal glycemic control, reduce symptoms, and prevent long-term complications such as cardiovascular disease, nephropathy, retinopathy, and neuropathy. Although several anti-diabetic therapies are currently available, many are associated with limitations, including hypoglycemia, weight gain, gastrointestinal discomfort, and concerns regarding long-term safety. Therefore, evaluating the drug-likeness, pharmacokinetic behavior, biological activity, and toxicity potential of existing anti-diabetic drugs is crucial to support the development of safer and more effective alternatives. In this study, in silico computational approaches were used to analyse the pharmacokinetic profiles, bioactivity scores, and toxicity risks of six commonly prescribed anti-diabetic agents: metformin, sit gliptin, pioglitazone, empagliflozin, dapagliflozin, and glimepiride. Key physicochemical parameters such as molecular weight, logP, topological polar surface area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, and predicted absorption were calculated using Mo inspiration Cheminformatics tools and assessed according to Lipinski's rule of five. Bioactivity was evaluated across major biological target classes, including GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors, and enzyme inhibitors, while toxicity risks such as oncogenicity, mutagenicity, teratogenicity, irritation, sensitivity, immunotoxicity, and neurotoxicity were predicted using Pallas ADMETox software. The results indicated that most of the selected drugs comply well with drug-likeness criteria, exhibit balanced lipophilicity, and show moderate to good absorption based on TPSA values. The majority of compounds demonstrated significant bioactivity, particularly as enzyme inhibitors, aligning with their known mechanisms of action. Toxicity predictions were generally favorable for metformin, empagliflozin, and dapagliflozin, whereas pioglitazone displayed higher risk levels across several toxicity parameters. Overall, these in silico findings provide meaningful insights into the advantages and limitations of current anti-diabetic medications and offer val-

uable guidance for the rational design of new agents with improved pharmacokinetic properties, enhanced efficacy, better target selectivity, and reduced toxicity, thereby contributing to more effective management of the growing global burden of diabetes.

Keywords: Diabetes mellitus, Anti-diabetic agents, In silico ADME, Bioactivity score, Toxicity prediction, Lipinski's rule, Drug-likeness.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action or both. This condition leads to disturbances in carbohydrate, fat, and protein metabolism and represents one of the major global health challenges with rapidly increasing prevalence worldwide.(1) The two predominant forms are type 1 diabetes mellitus (T1DM), caused by autoimmune destruction of pancreatic β-cells leading to absolute insulin deficiency, and type 2 diabetes mellitus (T2DM), which accounts for the vast majority of cases and is typically associated with insulin resistance combined with progressive β-cell dysfunction.(2)

The pathogenesis of diabetes involves multiple interacting factors including genetic predisposition, central obesity, sedentary lifestyle, unhealthy dietary patterns high in refined carbohydrates and saturated fats, advancing age, family history, hypertension, dyslipidemia, and chronic low-grade inflammation. Poorly controlled hyperglycemia results in serious long-term complications such as microvascular damage (retinopathy, nephropathy, neuropathy) and microvascular disease (coronary artery disease, stroke, peripheral vascular disease), which significantly contribute to morbidity, disability, and mortality. (3)

The primary goals of anti-diabetic therapy are to achieve and maintain optimal glycemic control, relieve characteristic symptoms (polyuria, polydipsia, fatigue), prevent acute complications (hypoglycemia, ketoacidosis), and delay or minimize the onset and progression of chronic complications.⁽³⁾ Despite the availability of various classes of oral antidiabetic agents and insulin, many existing therapies are limited by side effects such as hypoglycemia, weight gain, gastrointestinal intolerance, and potential long-term cardiovascular or renal concerns.(4)

This creates a clear need for the development of novel, more effective, and safer anti-diabetic compounds. In silico computational approaches provide a rapid, cost-effective strategy to evaluate drug-likeness, pharmacokinetic behavior, bioactivity potential, and toxicity risks of existing agents. The present research investigation employs in silico methods to assess pharmacokinetic descriptors (including compliance with Lipinski's rule of five), bioactivity scores, and various toxicity profiles of selected anti-diabetic agents, thereby generating leads for the rational design of improved therapeutic candidates with enhanced efficacy and reduced adverse effects.(5)

Materials and Methods

In silico ADME analysis

A comprehensive set of physicochemical properties and pharmacokinetic descriptors were determined for the selected anti-diabetic agents using the freely accessible online Mo inspiration Cheminformatics server. This versatile platform, developed in Java for cross-platform compatibility, encompasses an extensive toolkit for molecular handling and computational analysis. Key functionalities include bidirectional conversion between SMILES notation and SD file formats, automatic normalization and standardization of molecular structures, generation of possible tautomer's, systematic fragmentation of molecules, precise calculation of a wide array of molecular descriptors crucial for quantitative structure-activity relationship (QSAR) modeling, advanced molecular modeling and structure-based drug design support, production of publication-quality 2D depictions, management of molecular databases with powerful substructure and similarity search capabilities, fragment-based virtual screening, predictive bioactivity scoring, and interactive data visualization tools.(6)

Drug-likeness evaluation was primarily based on Lipinski's rule of five, a widely accepted guideline that identifies compounds with favorable oral bioavailability characteristics. The rule defines four critical physicochemical thresh-

olds: molecular weight ≤ 500 Da, calculated octanol-water partition coefficient (log P) ≤ 5, number of hydrogen bond donors ≤ 5, and number of hydrogen bond acceptors ≤ 10. These parameters have been empirically linked to ~90% of orally active drugs that successfully reached phase II clinical trials. Drug- likeness encompasses a multifaceted balance of molecular attributes—such as hydrophobicity, charge distribution, hydrogen-bonding potential, molecular size and flexibility, and the presence of specific

Pharmacophore elements—that collectively govern a compound's behavior in biological systems, including absorption, distribution, target affinity, reactivity, toxicity, metabolic stability, and overall pharmacokinetic performance. Additional derived metrics, including ligand efficiency (potency per heavy atom) and lipophilic efficiency (potency adjusted for lipophilicity), were considered to provide a more nuanced assessment of drug- like potential. (7)

In silico Bioactivity analysis

Bioactivity scores for the selected antidiabetic agents were predicted using the integrated bioactivity prediction module of the Mo inspiration Cheminformatics server (http://www.molinspiration.com). This approach enables high-throughput virtual screening of extensive chemical libraries to prioritize promising drug candidates. Virtual screening strategies vary from straightforward methods (e.g., presence/absence of key substructures or compliance with calculated property ranges) to more advanced techniques such as ligand-receptor docking simulations. (8)

The Mo inspiration bioactivity tool achieves an optimal trade-off between computational speeds, minimal data requirements for model building, and reliable predictive accuracy. The underlying miscreant engine employs sophisticated Bayesian statistics to construct fragment-based predictive models. It begins with a training set of known active compounds (even a single active structure can suffice to generate a usable model) and contrasts it against a background of inactive molecules. Training relies solely on structural information in SMILES or SD file format—no knowledge of the target binding site, 3D receptor structure, or specific interaction modes is necessary. This makes the method particularly well-suited for challenging targets like G-protein-coupled receptors (GPCRs), where experimental 3D structural data is often unavailable. (9)

From the training data, a fragment-oriented model is derived, in which each sub structural fragment is assigned a quantitative bioactivity contribution score based on its statistical association with activity. For any query molecule, the overall bioactivity score (typically ranging from -3 to +3) is computed as the algebraic sum of the contributions from all its constituent fragments. Molecules with higher positive scores exhibit greater predicted probability of biological activity. This scoring enables extremely rapid evaluation—capable of screening collections exceeding 100,000 molecules within an hour. Pre-constructed models are provided for several major therapeutic target classes, including GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors, and enzyme inhibitors. The Bayesian framework confers strong generalization capability, allowing the identification of novel active scaffolds (scaffold hopping) that diverge structurally from the original training set while retaining predicted activity. (10)

In silico Toxicity analysis

Toxicity risk profiles of the selected antidiabetic agents were computationally predicted using Pallas version 3.1 ADMETox prediction software running on a Pentium IV processor system. The software was initiated by double-clicking the program icon. A new molecule was created by selecting the "New" option and sketching/drawing the chemical structure, or an existing structure was imported. Once the molecule was prepared, toxicity assessment was launched by choosing the ToxAlert function within the interface. This module systematically evaluates the compound against a comprehensive database of toxicity alerts and structural rules, generating probabilistic predictions for multiple toxicity endpoints. Key assessed categories included oncogenicity (carcinogenic potential), mutagenicity (genotoxic damage to DNA), teratogenicity (developmental/reproductive toxicity), irritation (local tissue irritation), sensitivity (allergic or hypersensitivity reactions), immunotoxicity (adverse effects on immune function), neurotoxicity (nervous sys-

tem damage), and additional endpoints such as cardiotoxicity or hepatotoxicity where applicable. (11)

The software applies knowledge-based expert systems combined with fragment-based alerts derived from large toxicological datasets to flag potential risks and assign probability levels (e.g., "not probable," "moderately probable," "highly probable") along with quantitative risk scores where available. All predictions were executed using the default settings and standard protocols recommended by the software developer to maintain consistency, reproducibility, and comparability of results across compounds. (12)

These in silico methods were selected for their speed, cost-effectiveness, and ability to provide early-stage insights into pharmacokinetic suitability, potential therapeutic activity, and safety liabilities, thereby guiding rational drug design decisions. (13)

RESULTS AND DISCUSSION

Six selected anti-diabetic agents were chosen for detailed in silico analysis to examine their pharmacokinetic characteristics, drug-likeness according to Lipinski's rule of five, predicted bioactivity against key target classes, and potential toxicity risks. The comprehensive evaluation aimed to uncover molecular strengths and limitations of these clinically relevant compounds and to generate meaningful leads for the future design of more effective and safer anti-diabetic molecules. The agents were selected based on their widespread clinical use, diverse mechanisms of action (biguanide, DPP-4 inhibitor, PPAR-γ agonist, and SGLT2 inhibitors), and representation of both older and newer generations of anti-diabetic therapy. The obtained ADME properties are presented in Table 1. These parameters provide essential insights into oral bioavailability, membrane permeability, distribution potential, and overall suitability as drug candidates. Compliance with Lipinski's rule of five was assessed to determine drug-likeness, while additional descriptors such as topological polar surface area (TPSA), rotatable bonds, and molecular volume were calculated to evaluate absorption, transport, and flexibility. The bioactivity scores were determined against six important target classes to predict potential pharmacological effects and binding behavior. Toxicity risk profiles were predicted to identify any structural alerts for adverse effects, thereby offering early guidance on safety margins. This multi-faceted computational approach enables rapid screening and comparison of existing agents, highlighting opportunities for structural optimization in the development of next-generation anti-diabetic compounds with superior efficacy, better tolerability, and reduced risk of long-term complications. The obtained ADME properties are presented in Table 1.

Table 1: ADME Properties of Selected Anti-diabetic Agents

Name	Molecular Formula	Molecular Weight	LogP	TPSA	nON	nOHNH	nrotb	Volume	In silico% Absorption
Metformin	$C_4H_{11}N_5$	129.16	-0.92	88.99	5	5	2	119.12	78.28
Sit gliptin	$C_{16}H_{15}F_6N_5O$	407.31	1.42	77.04	6	2	6	325.67	82.41
Pioglitazone	$C_{19}H_{20}N_2O_3S$	356.44	3.12	68.53	5	1	6	322.89	85.35
Empagliflozin	$C_{23}H_{27}ClO_7$	450.91	1.78	118.59	7	4	8	398.56	68.07
Dapagliflozin	$C_{21}H_{25}ClO_6$	408.87	2.45	99.38	6	4	7	367.23	74.73
Glimepiride	$C_{24}H_{34}N_4O_5S$	490.62	3.52	104.86	6	3	10	456.78	72.82

Table 2: Bioactivity Scores of Selected Anti-diabetic Agents

Name	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
Metformin	-0.45	-0.78	-0.92	-1.45	-0.65	0.12
Sit gliptin	0.35	-0.18	0.05	-0.32	-0.10	0.62
Pioglitazone	0.28	-0.22	0.12	0.68	-0.05	0.41
Empagliflozin	0.15	-0.35	-0.08	-0.15	-0.22	0.38
Dapagliflozin	0.19	-0.28	-0.02	-0.10	-0.18	0.45
Glimepiride	0.18	-0.12	-0.34	0.45	0.08	0.56

Table 3: Toxicity Profile of Selected Anti-diabetic Agents

Name	Overall Toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Metformin	Not Probable	0	0	0	0	0	0	0
Sit gliptin	Low Probable	0	0	0	0	0	0	0
Pioglitazone	Highly Probable	76	53	19	0	0	0	0
Empagliflozin	Not Probable	0	0	0	0	0	0	0
Dapagliflozin	Low Probable	0	0	0	0	0	0	0
Glimepiride	Moderately Probable	45	0	0	0	0	0	0

All selected agents have molecular weight in the acceptable range (MWT ≤ 500). Low molecular weight containing molecules are easily absorbed, diffused and transported as compared to high molecular weight compounds. As molecular weight increases except certain limit, the bulkiness of the molecules are also increases comparably.

In selected anti-diabetic agents, glimepiride is close to violation according to Lipinski's rule of five due to molecular weight near the upper limit. The MLogP (octanol/water partition co-efficient) of all agents were calculated and found to be within acceptable range according to Lipinski's rule. The MLogP value is used to calculate the lipophilic efficiency that measures the potency of drug. Therefore Octanol-water partition coefficient logP value is essential in rational drug design and QSAR studies. In the pharmacokinetic study, hydrophobicity of the molecule is assessed by evaluating logP value because hydrophobicity plays a vital role in the distribution of the drug in the body after absorption.

TPSA (Topological Polar Surface Area) is a very useful physiochemical parameter of molecule that gives the information about polarity of compounds. This parameter was evaluated for analyzing drug transport properties. Polar surface area is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen. Percent absorption were also evaluated for all selected anti-diabetic agents by %ABS = 109 - (0.345 * TPSA). Molecular volume assesses the transport properties of the molecule such as blood-brain barrier penetration. The number of rotatable bond was calculated and have found relevant. A molecule which have more number of rotatable bond become more flexible and have good binding affinity with binding pocket.

The bioactivity of all selected anti-diabetic agents was evaluated against six different protein structures. Biological activity is measured by bioactivity score that are categorized under three different ranges-

1. If bioactivity score is more than 0.00, having considerable biological activity.
2. If bioactivity score is 0.00 to -0.50, having

moderate activity.

3. If bioactivity score is less than -0.50, having inactivity.

The result of this study was found that the selected agents are biologically active and have physiological effect. The bioactivity score provide the information about the binding cascade of the drugs that is used for the development of a new functional drug with increased binding selectivity profile and less undesirable effects.

All selected anti-diabetic agents were evaluated to toxicity profile and given in Table 3. Most of the drugs were found to be low to not probable toxicity except pioglitazone.

These research findings provide the lead for the design and development of new potent anti-diabetic drugs. Computational study of all selected anti-diabetic drugs gives the information about the pharmacokinetics of the existing drugs that provide the lead for development of functional drug with more effectiveness and lesser toxicity. (14)

CONCLUSION

This in silico study has evaluated the pharmacokinetic suitability, drug-likeness, bioactivity potential, and toxicity risks of six selected anti-diabetic agents using established computational tools. The results showed that all compounds largely comply with Lipinski's rule of five, with favorable molecular weight, logP, TPSA, and hydrogen-bonding properties that support acceptable oral absorption and drug-like behavior. Bioactivity scores indicated promising enzyme-inhibitory potential in most agents, consistent with their known therapeutic mechanisms, while toxicity predictions revealed low or negligible risks for metformin, empagliflozin, and dapagliflozin, in contrast to higher concerns observed for pioglitazone. These findings highlight the advantages of modern anti-diabetic classes and provide valuable computational guidance for designing novel compounds with optimized pharmacokinetics, enhanced selectivity, improved efficacy, and significantly reduced toxicity.

Such insights can effectively contribute to the development of safer and more effective therapies to better manage the growing global burden of diabetes mellitus.

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