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Prediction of Pharmacokinetic Parameters, Toxicological Study and Druglikeliness properties of oral hypoglycemic agents of Sulfonylfureas class-I using *In-Silico* Methods

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Abstract

Diabetes is one of the disorder of the body in and it is spreading in higher rate in Indian due to rapid urbanization, sedentary lifestyles, unhealthy diets. Sulfonylureas a class of oral drugs of hypoglycemic agent is widely used in the treatment of this disease .In this research work and Attempt has been made to analyze the properties of first class of oral hypoglycemic agents by using insilico studies using open source online software. In in Silico Studies bioavailability, Drug likeliness property determination, Toxicological study of all the first generation oral hypoglycemic agents were done. It was observed that all the Oral hypoglycemic agents revealed good GIT absorption, Drug likeliness properties but results of insilico toxicological study reveal that only Glimepride was safe as long as the matter of liver toxicity is concerned as compared to Tolbutamide, Tolinase, Glipizide and Chlorpropamide. which Concluded that Glimepride is the best Drug of First class of Sulfonylureas class of oral hypoglycemic agents .

Keywords: In-silico, Toxicity, Sulfonylureas, bioavailability, Glimepride.

Introduction

Diabetes is a challenge in India with the esmtimation of 8.7% diabetic population in the age group of 20 and 70 years. The rising is due to combination of factors like rapid urbanization, tobacco use, sedentary lifestyles, unhealthy diets, and increasing life expectancy[1].

The major way to treat it using Oral anti-diabetic agents which is an important therapeutic strategy for the management of diabetes. There are many new agents available approved for use as monotherapy when diet and exercise are inadequate.

There are many types and classes of drug which are used as oral hypoglycemic agent in the treatment of Diabetes like Sulfonylureas, It is oldest, widely recommended, prescribed and use as safe and effective Hypoglycemic Agent[2,3] Oral sulfonylurea therapy is safe and

effective in the short term in most patients with diabetes and successfully replace treatment with insulin injections.

It has been mentioned that Sulfonylureas is good for CV and renal safety. Sulfonylureas are effective, well-tolerated and inexpensive treatments for T2DM, and widely recommended as add-on therapy in evidence-based international consensus reports[3,4]. Sulfonylureas are effective first-line treatment of choice in the majority of patients with MODY[5].

ADME study has been majorly used in current research and its Applications includes bioavailability studies, permeability, metabolism and active transport even drug-drug interactions (DDIs) or additional ADME properties can be estimated[6,7]. Thus, It opens new framework for the multi-parametric and wide data analysis in drug discovery in which ADME behaviors of molecules are condensed in one map. ADME profiles, also warning on potential ADME problems and select proper *in vitro* experiments. These properties helped in systematic curation and analysis of ligand and target complex data and clusters[8]. Different review articles have been published exhibited ADME, pharmacogenomics-related databases, potential drug-drug interaction information[9] pharmacovigilance databases and identified human drug safety data resources of, specific to country. These informations gave a radical reason of doing this research work.

Material and Methods

Following studies were conducted using online open accessible software The software used for the in-silico study was mainly coded in Python 2.7 The process of screening of drug molecule adopted on the basis of favorable properties of oral hypoglycemic agents related to in-silico physiochemical properties, ADME study and toxicological studies. The process of screening of surfactant adopted on the basis of Favorable properties of Surfactant molecules on the basis of in-silico physiochemical properties, ADME study and toxicological studies.

Result and Discussion

Bioavailability Radar: The bioavailability score radar plot enables a first glance at the drug-likeness of a molecule. The pink area represents the optimal range for each properties lipophilicity: XLOGP3 between -0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 Å2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. In this example, the compound is predicted not orally bioavailable, because too flexible and too polar. within the pink region of the score radar which revealed that all the oral hypoglycemic agent are within the acceptable range of the bioavailability radar .

Drug Likeliness Property: All the oral hypoglycemic agents exhibited better drug likeliness properties , all were within the range of Molecular weight ,all of them are highly absorbed by the Gastrointestinal track. Glimepride Tolbutamide, Tolinase, Glipizide and Chlorpropamide they all are not permeable to Blood Brain Barrier and All of them bioavailability score 0.55.

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In silico toxicological Study: Glimepride in in silico toxicological study it was observed that rest all the four drug molecules Tolbutamide, Tolinase, Glipizide and Chlorpropamide have shown signs of liver toxicity only Glimepride does not exhibit sign any sign of liver toxicity. Three drug molecules showed maximum dose which could be taken in a day is Chlorpropamide 1500mg/ day, Glipizide 485 mg/day and tolazamide 1722 mg/day. None of the oral hypoglycemic agent revealed Metabolism related inhibitory activity, Similarly no membrane transport based inhibition. All these oral hypoglycemic agent did not show any property of BBB transport. If we conclude the in silico toxicological data that Glimepride is the safest sulfonylurea among all the five oral hypoglycemic agent[10].

Egg Plot: All the oral hypoglycemic agents come under white region is for high probability of passive absorption by the gastrointestinal tract, Glimepride Tolbutamide, Tolinase, Glipizide and Chlorpropamide, In addition to it color in red predicted as non-substrate of P-gp (PGP-). All the oral hypoglycemic agents Glimepride Tolbutamide, Tolinase, Glipizide and Chlorpropamide showed red color which exhibited that all these drug molecules are not substrate of P-gp.

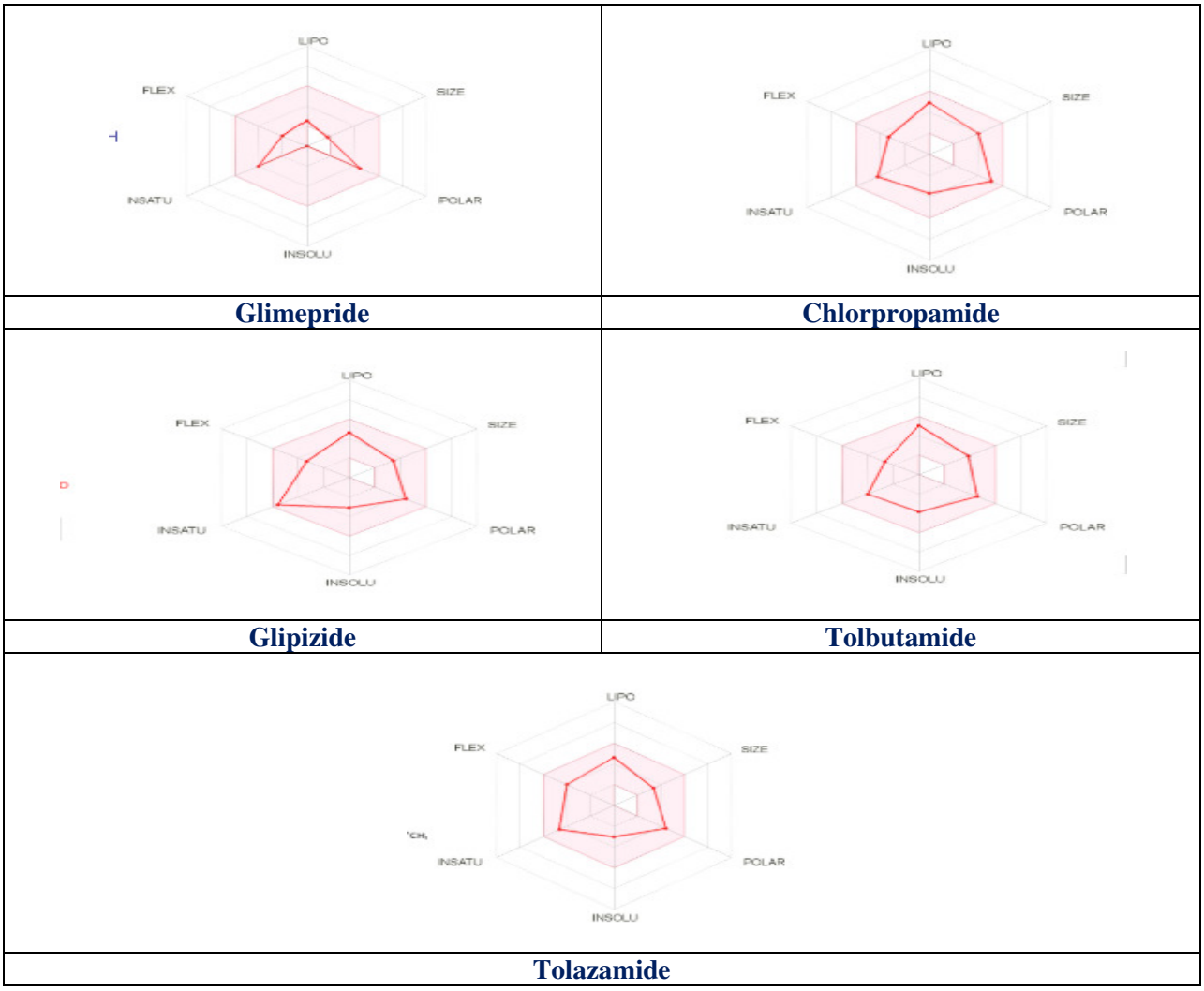

Figure 1.Bioavailabilty Radar plots of oral hypoglycemic agent of first class of Sulfonylureas

(Table 1, 2 and 3 end of the paper)

Conclusion

From this insilico study it could be concluded that best gastrointestinal absorption was exhibited by Glimepiride which was good as compare to other oral hypoglycemic agent of first class of Sulfonylurea Tolbutamide, Tolinase, Glipizide and Chlorpropamide. The insilico toxicity study of Tolbutamide, Tolinase, Glipizide and Chlorpropamide exhibited liver toxicity. Glimepiride exhibited the best result of all the in-silico study.

Acknowledgement

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Conflict of Interest

There is no conflict of interest.

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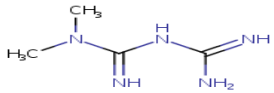
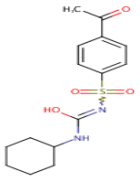
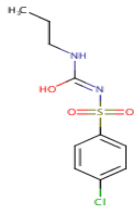
Table 1.Drug likeliness properties of all the oral hypoglycemic agents

Molecule	Structure	Property						
		Molecule weight	Hydrogen Bond Acceptor	Hydrogen Bond Donner	GI absorption	TPSA	BBB Permeant	Bioavailability Score
1	 Glimepride	129.16g/mol	2	4	High	88.99 Å²	NO	0.55
2	 Chlorpropamide	324.40g/mol	5	2	High	104.21 Å²	NO	0.55
3	 Glipizide	276.74g/mol	4	2	High	87.14 Å²	NO	0.55

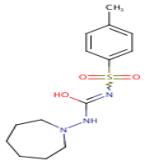
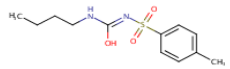
4	 Tolbutamide	311.40g/mol	5	2	High	90.38 Å²	NO	0.55
5	 Tolazamide	270.35g/mol	4	2	High	87.14 Å²	NO	0.55

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Table 2.In silico toxicity of all the oral hypoglycemic agents

Amaryl (Glimepride)

Liver Toxicity		Metabolism						Membrane Transporters			Others			
		Cyp Inhibitors for												
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	No	⊘	⊘	⊘

Chlorpropamide

Liver Toxicity		Metabolism						Membrane Transporters			Others			
		Cyp Inhibitors for												
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
Yes	⊘	⊘	No	No	No	No	No	⊘	⊘	⊘	No	No	No	1500

Glucotrol (Glipizide)

Liver Toxicity		Metabolism						Membrane Transporters			Others			
		Cyp Inhibitors for												
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
Yes	⊘	⊘	No	No	No	No	No	⊘	No	⊘	No	No	No	485

Tolbutamide

Liver Toxicity		Metabolism						Membrane Transporters			Others			
		Cyp Inhibitors for												
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
Yes	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	No	⊘	⊘	No	No	⊘

Tolinase (tolazamide)

Liver Toxicity		Metabolism						Membrane Transporters			Others			
		Cyp Inhibitors for												
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
Yes	⊘	⊘	No	No	No	No	No	No	No	⊘	⊘	No	No	1722

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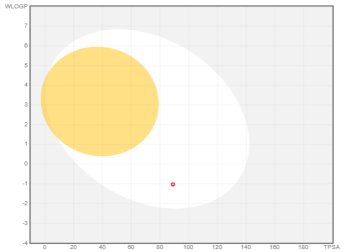
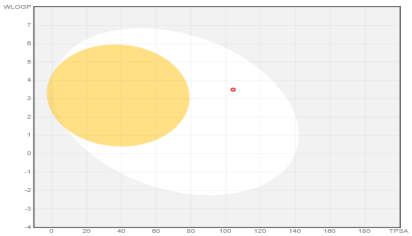
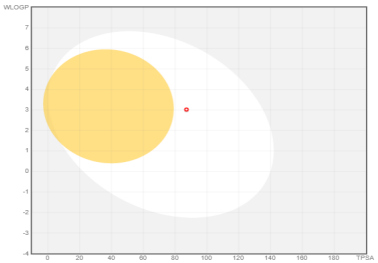
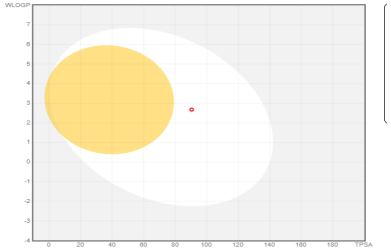
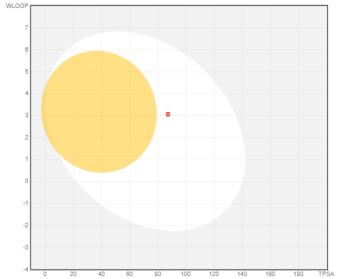
Table 3.Boiled Egg model of all the oral hypoglycemic agents

	
Glimepride	Chlorpropamide
	
Glucotrol (Glipizide)	Tolbutamide
	
Tolinase (tolazamide)	

