International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(5): September-October 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Original Article……!!!

Received: 20-02-2016; Revised: 14-10-2016; Accepted: 15-10-2016

PREDICTION OF DIPEPTIDYL PEPTIDASE-IV INHIBITORY ACTIVITY OF CYANNOPYRROLIDINE DERIVATIVES BY USING IN SILICO TOOLS

Udugade B.V.*[a], Gawade S. P.[b]

Satara College of Pharmacy, Degaon, Satara[a]

Sahyadri College of Pharmacy, Methawade, Sangola.[b]

Keywords:

Prediction, Dipeptidyl Peptidase-iv Inhibitor, Cyannopyrrolidine Derivatives and In Silico Tools

For Correspondence:

Udugade B.V.

Satara College of Pharmacy, Degaon, Satara

E-mail:

swarajudugade@gmail.com

ABSTRACT

Background: Millions of people worldwide affected by type2 diabetic mellitus, current available therapies showing side effects. New emerging therapy is DDP-IV inhibitors but have less potency and selectivity so there is need to discover new inhibitors with potency and selectivity towards DPP-IV. Cyannopyrrolidine is promising candidate for DPP-IV inhibitory action and needs structural modifications for enhancement of potency and efficacy as well. The main objective of current work is to identify in-silico tools for pharmacological activity prediction and use it to predict pharmacological activity, acute rat toxicity, polypharmacological effects and mutagenicity in terms of Ames test in advance to avoid risk of rejection during clinical evaluation phase and to avoid use of animal use. **Materials and Methods:** Molecular structure of probable DPP-IV inhibitor were sketched by using Chem Draw Ultra 8.0 from Chem office 2004 and converted to SMILES file format using Open babel 2.3.2 software. In-silico tools were identified to predict pharmacological activity, acute rat toxicity, anti target interaction and toxicity in terms of Ames test. Pharmacological activities, polypharmacological effect were predicted by using PASS (Prediction of Activity Spectra for Substances) online tool. In silico prediction of LD50 values for rat's by oral administration were predicted by GUSAR software. ePhysChem software was used to predict toxicity in terms of Ames test, CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 inhibition. **Results:** In- silico prediction performed by using PASS online tool and results were found that all eight molecules show 0.5 or more Pa score (probability "to be active") indicating DPP-IV inhibitory potentials of proposed molecules. Regarding polypharmacological activity compounds with could be used as Vascular (periferal) disease treatment, Neuropeptide Y4 antagonist, Peptidyl-dipeptidase Dcp inhibitor, Cerebrovascular disordes treatment, Irritable Bowel syndrome treatment, Analgesic, Limulus clotting factor C inhibitor, Antiviral (Picornavirus), Transcription factor STAT inhibitor, Transcription factor STAT3 inhibitor, Kinase inhibitor, Muscular dystrophy treatment. Acute Rat Toxicity prediction were done with GUSAR software and Rat Oral LD50 were found to be 452.9, 850.3, 859.8, 1492, 1241, 553.5, 782.5 and 899.5 mg/ kg for 1to 8 compounds respectively. Compounds 2, 5, 6 and 7 were found to be Ames test active indicating mutagenic potentials and 5, 6, 7 and 8 were found to be inhibitor of CYP1A2 enzyme. **Conclusion:** From all results it can be concluded that all cyannopyrrolidine compounds have DPP-IV inhibitory activity and could be further synthesized and evaluated for type 2 anti-diabetic activity by In-Vivo experimentation.

INTRODUCTION

Prevalence of diabetes is rising dramatically, world-wide in 2010 prevalence is 221 million and it is projected to be a 300 million in 2030. The majority (~90%) of patients suffering from type II diabetes mellitus and it is associated with deficient insulin secretion and insulin resistance with islet-cell dysfunction. Currently available therapeutic options for treatment of type II diabetic mellitus are associated with adverse events like weight gain and hypoglycaemia, gastrointestinal toxicities, edema, congestive heart failure, bladder cancer and no one addressing the progressive loss of islet-cell and thus, there is a need to develop novel therapeutic agents.[1]

Recently novel therapies glucose-dependent insulinotropic poly-peptide-1 (GIP) and glucagon like peptide1 (GLP-1) proved to be beneficial for the treatment of type II diabetes mellitus However, GIP and GLP-1 have short duration of action due to enzymatic degradation in vivo by dipeptidyl peptidase IV that's why dipeptidyl peptidase IV inhibitors, which protect GIP and GLP-1 from enzymatic degradation, have been noticed as new oral therapeutic tools for type II diabetes.[2]

Glycine based Dipepetidyl peptidase-IV inhibitors can be of reversible or irreversible type having pyrrolidine containing nitrile functionality and Cyannopyrrolidine is promising candidate for DPP-IV inhibitory action and needs structural modifications for enhancement of potency and efficacy as well.

Animals are used for testing of pharmacological activity and access toxicity of new developing drug candidate. The quantity of animals used in to do research has greater than before with the progress of research and expansion in medical expertise. Each year, numbers of animals are being used for experimentation. The unkindness and death experienced by the animals is a debating issue in scientific community. Moreover the chief concerns of ethics, use of animals in experimentation have some disadvantages like requirement of high funds for man, machine and money to carry experiments with animals.

Development and implementation of test methods that avoid the use of live animals in experiments is an alternatives and best testing method will be use of computers which requires less time man power cost for testing. Computer simulations can be used to predict the different potential pharmacological and toxic effects of prospective drug candidate with no animal dissection. Only promising drug candidate predicted from Computer simulations are used for in vivo experimentation.[3-5]

OBJECTIVES

The main objective of current work is to identify in-silico tools for pharmacological activity prediction and use it to predict pharmacological activity, acute rat toxicity, anti target interaction, polypharmacological effects and toxicity in terms of Ames test in advance to avoid risk of rejection during clinical evaluation phase and to avoid use of animal use

MATERIAL AND METHODS

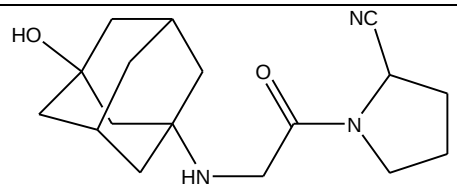
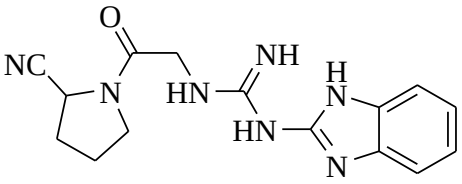
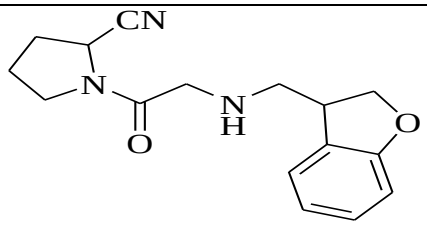
1. Details of software's used for current study

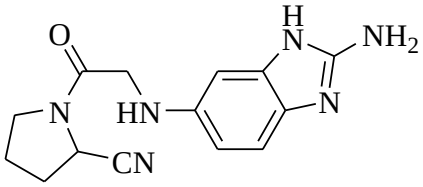
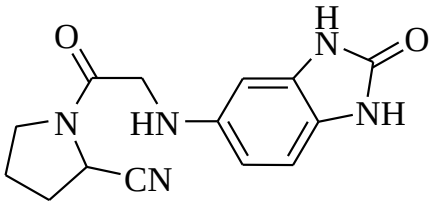
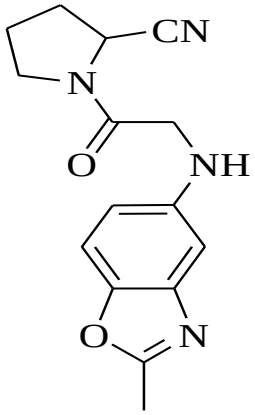
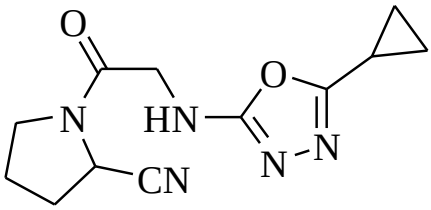
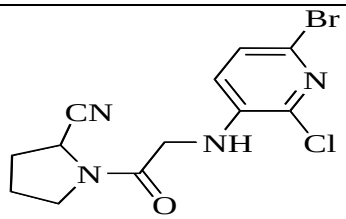
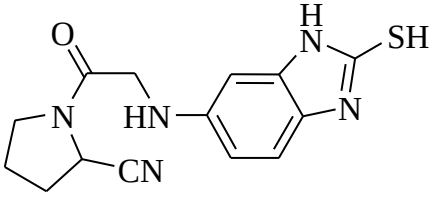
Table No.1.Details of Software's

Sr. No.	Name of software	Use
1	Chem Draw Ultra 8.0	Drawing of molecular structure
2	Open babel 2.3.2	Conversion files in to different file formats
3	iGEMDOCK	Docking studies
4	PASS online (Prediction of Activity Spectra for Substances)	Prediction of pharmacological activity
5	GUSAR	Prediction of Acute rat toxicity
6	ePhysChem from eADMET	Prediction of mutagenicity by Ames test Prediction of CYP 450 inhibition

2. Data Preparation: The compounds used in the present work contains 8 cyannopyrrolidine derivatives previously sketched by Chem Draw Ultra 8.0 and screened on basis of QSAR model and docking studies from set of 350 cyannopyrrolidine derivatives.

Table no. 2 demonstrates structures of all eight screened derivatives with docking score with respect to reference compound vildagliptin.

Molecule ID	Docking Score	Structure
Vildagliptin	-51.167208	
1	-72.731771	
2	-69.554126	

3	-60.534954	
4	-59.372051	
5	-57.834927	
6	-54.814247	
7	-53.333434	
8	-53.212440	

3. Pharmacological activities, polypharmacological effect prediction[6]: Molecular structure of probable DPP-IV inhibitor were sketched by using Chem Draw Ultra 8.0 and converted to SMILES file format using Open babel 2.3.2 software. SMILES of all eight compounds were copy pasted one by one in PASS online software platform as input file and prediction were done. Pa score (probability "to be active") and predicted activities were studied to find out main pharmacological activity and polypharmacological activities. Pa score 0.5 and more considered as main pharmacological activity and Pa score below 0.5 considered as polypharmacological activities.

4. In silico prediction of LD50 values for rat's by oral administration[7]: In silico prediction of LD50 values for rat oral administration were done by GUSAR software. The training sets were created on the basis of data from SYMYX MDL Toxicity Database. For prediction molecular structure of probable DPP-IV inhibitor were sketched by using Chem Draw Ultra 8.0 and converted to MOL file format using Open babel 2.3.2 software. MOL file of all eight compounds were browsed one by one in GUSAR online software platform as input file and prediction were done. Rat oral LD50 in mg/kg were obtained as output.

5. In silico prediction of mutagenicity and CYP450 inhibition potentials[8]: OCHEM incorporated "ePhysChem" suite, a highly predictive algorithm were used to predict mutagenicity in terms of Ames test and CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibition potentials.

RESULTS AND DISCUSSION:

Table No. 3 Results of Pharmacological activities, polypharmacological effect prediction

Comp. ID	Pa score	Predicted activity
1	0,792	**Antidiabetic (type 2)**
	0,786	**Antidiabetic**
	0,652	Analgesic, non-opioid
	0,644	Irritable Bowel syndrome treatment
	0,619	Analgesic
	0,573	**Dipeptidyl peptidase IV inhibitor**
2	0,714	**Antidiabetic**
	0,704	**Antidiabetic (type 2)**
	0,576	**Dipeptidyl peptidase IV inhibitor**
	0,547	**Glucagon-like peptide 1 agonist**
3	0,412	**Dipeptidyl peptidase IV inhibitor**
	0,483	**Antidiabetic (type 2)**
	0,491	**Antidiabetic**

	0,516	Glucagon-like peptide 1 agonist
	0,548	Transcription factor STAT inhibitor
	0,572	Transcription factor STAT3 inhibitor
4	0,663	**Antidiabetic**
	0,585	**Antidiabetic (type 2)**
	0,527	**Glucagon-like peptide 1 agonist**
	0,474	**Dipeptidyl peptidase IV inhibitor**
5	0,536	Vascular (periferal) disease treatment
	0,522	Neuropeptide Y4 antagonist
	0,504	Peptidyl-dipeptidase Dcp inhibitor
	0,464	Cerebrovascular disordes treatment
	0,481	**Antidiabetic**
	0,449	**Glucagon-like peptide 1 agonist**
	0,415	**Antidiabetic (type 2)**
	0,369	**Dipeptidyl peptidase IV inhibitor**
6	0,711	**Antidiabetic**
	0,678	**Antidiabetic (type 2)**
	0,539	**Glucagon-like peptide 1 agonist**
	0,501	**Dipeptidyl peptidase IV inhibitor**
7	0,834	Kinase inhibitor
	0,702	**Antidiabetic**
	0,651	**Antidiabetic (type 2)**
	0,557	Glucagon-like peptide 1 agonist
	0,514	Muscular dystrophy treatment
	0,468	**Dipeptidyl peptidase IV inhibitor**
8	0,479	**Dipeptidyl peptidase IV inhibitor**
	0,023	Dipeptidyl peptidase IX inhibitor
	0,026	Dipeptidyl peptidase VIII inhibitor
	0,160	**Dipeptidyl peptidase inhibitor**

Table No. 4 Results of In silico prediction of LD50 values for rat's by oral administration

Comp ID	Predicted Rat Oral LD50(mg/ kg)
1	452.9
2	850.3
3	859.8
4	1492
5	1241
6	553.5
7	782.5
8	899.5

Table No. 5 Results of In silico prediction of mutagenicity and CYP450 inhibition potentials

Comp ID*	Mutagenicity prediction	CYP1A2 inhibition	CYP2C19 inhibition
1	Ames test inactive	Non inhibitor	Non inhibitor
2	**Ames test active**	Non inhibitor	Non inhibitor
3	Ames test inactive	Non inhibitor	Non inhibitor
4	Ames test inactive	Non inhibitor	Non inhibitor
5	**Ames test active**	**Inhibitor**	Non inhibitor
6	**Ames test active**	**Inhibitor**	Non inhibitor
7	**Ames test active**	**Inhibitor**	Non inhibitor
8	Ames test inactive	**Inhibitor**	**Inhibitor**

CONCLUSION

In- silico prediction performed by using PASS online tool and results were found that all eight molecules show 0.5 or more Pa score (probability "to be active") indicating DPP-IV inhibitory potentials of proposed molecules. Regarding polypharmacological activity compounds with could be used as Vascular (periferal) disease treatment, Neuropeptide Y4 antagonist, Peptidyl-dipeptidase Dcp inhibitor, Cerebrovascular disordes treatment, Irritable Bowel syndrome treatment, Analgesic, Limulus clotting factor C inhibitor, Antiviral (Picornavirus), Transcription factor STAT inhibitor, Transcription factor STAT3 inhibitor, Kinase inhibitor, Muscular dystrophy treatment. Acute Rat Toxicity prediction were done with GUSAR software and Rat Oral LD50 were found to be 452.9, 850.3, 859.8, 1492, 1241, 553.5, 782.5 and 899.5 mg/ kg for 1to 8 compounds respectively. Compounds 2, 5, 6 and 7 were found to be Ames test active indicating mutagenic potentials and 5, 6, 7 and 8 were found to be inhibitor of CYP1A2 enzyme. From all results it can be concluded that all compounds have DPP-IV inhibitory activity and could be further tested by In-Vivo experimentation.

REFERENCES

1. Carolyn F. Deacon, Jens J. Holst. Dipeptidyl peptidase IV inhibitors: A promising new therapeutic approach for the management of type II diabetes. The International Journal of Biochemistry & Cell Biology 38 (2006) 831–844.
2. Fadini GP, Avogaro A. Cardiovascular effects of DPP-4 inhibition: beyond GLP-1. Vascul Pharmacol. 2011; 55:10 –16
3. R E Hester, R M Harrison, Alternatives To Animal Testing: RSC (Issues in Environmental Science and Technology) 1st Edition, 2006, 23, 95-118.
4. https://en.wikipedia.org/wiki/Alternatives_to_animal_testing.
5. Sonali K. Doke , Shashikant C. Dhawale, Alternatives to animal testing: A review, Saudi Pharmaceutical Journal, Volume 23, Issue 3, July 2015, Pages 223–229
6. Lagunin A., Zakharov A., Filimonov D., Poroikov V. QSAR Modelling of Rat Acute Toxicity on the Basis of PASS Prediction. Mol. Informatics, 2011, 30(23), 241–250.
7. http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/
8. http://www.eadmet.com/en/ochem.php