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DRUG LIKELINESS AND TOXICITY PREDICTION OF BENZOTHIAZOLE DERIVATIVES WITH THEIR BIOLOGICAL EVALUATION

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ABSTRACT

Drug likeliness and toxicity prediction data determined using Pre-ADMET software plays a vital role in development of newer potent compounds. Further, its outcomes help us to process their synthesis of selected compounds with their biological evaluation. Benzothiazole is one of the important heterocyclic nucleuses which coupled with number of biological activities resulting to develop the newer class of drugs. The assessment of antidiabetic activity can be done by inducing the diabetic conditions in the experimental model using streptozotocin (STZ). This research work was focused on selection of potent benzothiazole derivatives through Pre ADMET toxicity profile and further evaluating their antidiabetic activity in the streptozotocin induced diabetes rat model. Among the entire selected compounds 7d exhibited more potent anti-diabetic activity at 350 mg/kg (p. o.).

Keywords: Pre ADMET, Drug likeliness, Toxicity prediction, Benzothiazole, Streptozotocin, Antidiabetic Activity.

Introduction

About ~20–40% of drug failures in research and drug development may be due to their toxicity concerns (Cheng, Li, Liu, & Tang, 2013). Modern software packages are having main emphasis on carcinogenicity and mutagenicity, at the same time as some packages do also comprise models such as teratogenicity, irritation, sensitization, immunotoxicology, neurotoxicity, QT prolongation, hepatotoxicity and phospholipidosis (Richard & Benigni, 2002). Pre-clinical ADMET information plays an imperative role in designing of new compounds and its outcomes can influence the selection to proceed with synthesis of newer drugs with their biological evaluation (Smith, 2011). The Pharmacokinetic Properties of newly synthesized compounds can determine with the help of computational study (Feinberg *et al*., 2019; Gleeson *et al*., 2011). A Topological polar surface area (TPSA) is one of the descriptor used to predict the passive transportation of molecule through membranes. It helps to determine the kinetics of molecule with crossing the intestine and blood-brain barrier (BBB) (Ertl, Rohde, & Selzer, 2000).

Streptozotocin (STZ) induced diabetic animal is commonly used economical effective method that offers efficient effects in the most strains of rodents (Deeds *et al*., 2011; Graham, 2011). It is a chemical compound that has been most frequently used in clinical trial for induction of diabetes in rats (Akbarzadeh *et al*., 2007; Gheibi, Kashfi, & Ghasemi, 2017). Intra-venous injection of 60mg/kg dose of streptozotocin in adult wistar rats causes swelling of pancreas followed by degeneration of Langerhans islet beta cells and induces experimental diabetes mellitus in the 2-4 days. Three days after degeneration of beta cells, diabetes was induced in all animals. **Nicotinamide-**adenine dinucleotide (NAD) in pancreas islet beta cells and causes histopathological effects in beta cells which probably intermediates induction of diabetes (Engel *et al*., 2019; Mabhida *et al*., 2019; Premilovac *et al*., 2017).

There are number of unwanted effects coupled with currently available drugs and inspire us to develop newer drug moieties for resolving these problems. Among the heterocyclic compounds, the benzothiazoles derivatives have a prominent position. They possess a broad range of biological activities and are found in many potent biologically active molecules and drugs (Ahmadi *et al*., 2017; Rouf & Tanyeli, 2015). Benzothiazole derivatives containing benzimidazole and imidazoline ring have diverse chemical reactivity along with a broad spectrum of biological activity. There was the significant interest to synthesise the benzo-thiazole derivatives with an aim to obtain potent biologically active and safe anti-diabetic agents (Gill, Rawal, & Bariwal, 2015; Kharbanda *et al*., 2016; Yurttaş, Kaplancıklı, Göger, & Demirci, 2016).

Materials and Methods

We were already synthesized and reported the different substituted Benzothiazole compounds (7a-7l) listed in

Table 1: List of Benzothiazole Derivatives with Different Substitutions

S. NO.	Compound Code	R_1	R_2	R_3
1.	7a	CH_3	H	C_6H_{5-}
2.	7b	CH_3	H	$pOHC_6H_{4-}$
3.	7c	CH_3	H	$pOCH_3C_6H_{4-}$
4.	7d	CH_3	H	$m\ NO_2C_6H_{4-}$
5.	7e	NO_2	H	C_6H_{5-}
6.	7f	NO_2	H	$pOHC_6H_{4-}$
7.	7g	NO_2	H	$pOCH_3C_6H_{4-}$
8.	7h	NO_2	H	$m\ NO_2C_6H_{4-}$
9.	7i	H	NO_2	C_6H_{5-}
10.	7j	H	NO_2	$pOHC_6H_{4-}$
11.	7k	H	NO_2	$pOCH_3C_6H_{4-}$
12.	7l	H	NO_2	$m\ NO_2C_6H_{4-}$

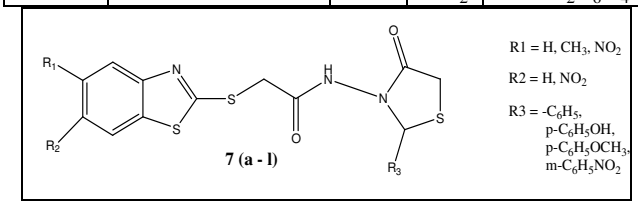

Fig. 1: Basic Nucleus of Substituted Compounds (6a-6l)

Computational Study

The Molinspiration online property calculation toolkit was used to calculate the molecular properties of synthesized compounds like TPSA, number of rotatable bonds (n-ROTB), molecular weight (MW), molecular volume (MV), number of hydrogen donor (n-OHNH), acceptor atoms (n-ON) and violations of Lipinski's rule of five (Lipinski, Lombardo, Dominy, & Feeney, 1997). All these various parameters were calculated and reported in Table 2. A Topological polar surface area (TPSA) is one of the descriptor used to predict the passive transportation of molecule through membranes. It helps to determine the kinetics of molecule with crossing the intestine and blood-brain barrier (BBB) (Ertl *et al*., 2000). The Absorption percentage (%ABS) was calculated using a formula: %ABS = 109-(0.345 x TPSA) (Tripathi, Singh, & Stables, 2011).

The predicted properties of all compounds showed the non violation of Lipinski's rule and further they were selected for the prediction of ADME and toxicity profile. The pharmacokinetics properties and toxicity prediction of all the selected compounds were analyzed were reported in Table 3 and Table 4 and also presented with help of bar graph in the Fig. 2.

Table 2: Physicochemical Parameters for Good Oral Bioavailability of Synthesized Compounds (7a-7l).

S. No	Compound Code	Mol. Wt.	Log P	HBD[a]	HBA[b]	Molar refractivity	TPSA[c]	%ABS	Lipinski's Violation
1.	7a	415.55	2.18	3	2	61.29	49.12	83.05	0
2.	7b	431.55	1.96	2	2	45.24	59.11	79.61	0
3.	7c	445.58	2.32	2	3	60.69	62.29	78.51	0
4.	7d	460.55	3.19	3	3	64.77	65.82	77.29	0
5.	7e	446.52	2.90	2	2	62.59	54.29	81.27	0
6.	7f	462.52	2.91	2	2	49.59	49.87	82.79	0
7.	7g	476.55	3.72	3	3	64.62	58.12	79.95	0
8.	7h	491.52	3.92	3	3	59.82	51.66	82.18	0
9.	7i	446.52	2.77	2	3	55.29	52.28	81.96	0
10.	7j	462,52	2.84	3	3	49.83	46.94	83.81	0
11.	7k	476.55	2.12	3	3	93.22	58.88	79.69	0
12.	7l	491.52	1.87	2	3	52.93	56.29	80.58	0
13.	Glibencl-amide*	494.004	4.17	4	3	70.98	56.65	80.46	0

[a]No of hydrogen bond donor, [b]No of hydrogen bond acceptor, [c]Topological polar surface area *Standard Antidiabetic drug

Table 3: Predicted ADME Profile of Selected Compounds (7a-7l)

Compound Code	BBB	Human intestinal absorption level	Aq. Solubility _mg_L	*Caco-2 cell [d]permeability assay*	CYP2D6 Inhibition	Plasma protein binding
7a	1.28371	95.29381	219.7371	22.782	Non	90.2838
7b	0.99927	85.29382	721.5125	27.6478	Inhibitor	79.2839
7c	1.35482	95.21390	427.9482	31.9282	Inhibitor	89.2838
7d	2.37484	97.48391	1688.662	19.7283	Non	94.2812
7e	1.74732	95.63828	1128.1921	29.8389	Non	93.2939
7f	1.94737	97.03920	438.7338	29.8391	Non	84.9384
7g	2.39481	98.19812	1818.2311	23.89293	Non	96.3849
7h	2.18292	97.72738	1499.1412	26.83891	Non	98.3523
7i	1.293831	94.68229	1122.811	31.83910	Non	88.4667
7j	1.37384	91.67411	487.849	29.11627	Inhibitor	94.8742
7k	1.84742	92.74848	832.190	17.28393	Non	95.2291
7l	1.94851	90. 51921	822.181	19. 17738	Inhibitor	90.8110
Glibenclamide*	2.354679	99.9764	1942.24	49.152	Non	99.15655

[d]Caco2-cell - heterogeneous human epithelial colorectal adenocarcinoma cell lines; Caco2-cells permeability (nm/s): Low(less than 4), Moderate (4-70), High (more than 70); % human intestinal absorption: Well absorbed (70-100 %), Moderately absorbed (20-70%), Poorly

absorbed(0-20%-); % plasma protein binding: Strongly bound (>90),weakly bound (<90%);*Standard Antidiabetic drug.

Table 4: Toxicity Profile of Selected Compounds (7a-7l) using Toxicity Prediction

S. No	Compound Code	AMES Mutagenicity	Carcino_Mouse	Carcino_Rat	hERG_inhibition
1.	7a	Non Mutagen	Negative	Negative	Medium_Risk
2.	7b	Non Mutagen	Positive	Positive	High_Risk
3.	7c	Mutagen	Positive	Positive	High_Risk
4.	7d	Non Mutagen	Negative	Negative	Low_Risk
5.	7e	Mutagen	Negative	Negative	Medium_Risk
6.	7f	Non Mutagen	Negative	Negative	Low Risk
7.	7g	Non Mutagen	Negative	Negative	Low Risk
8.	7h	Non Mutagen	Negative	Negative	Low_Risk
9.	7i	Mutagen	Negative	Negative	Medium_Risk
10.	7j	Non Mutagen	Positive	Negative	Low_Risk
11.	7k	Mutagen	Positive	Negative	Medium_Risk
12.	7l	Non Mutagen	Negative	Positive	Medium risk
13.	Glibenclamide*	Mutagen	Negative	Negative	Low risk

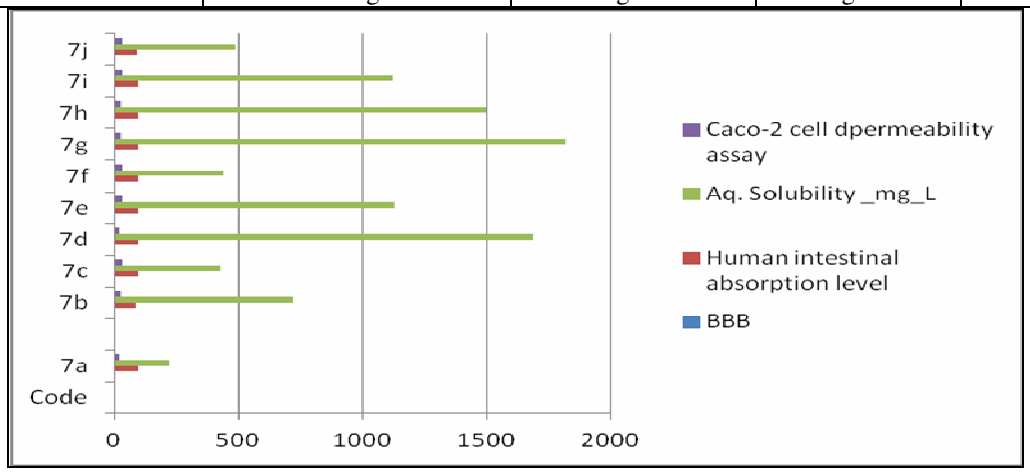

Fig. 2: Predicted ADMET Profile of Selected Compounds (7a-7l)

Biological Evaluation and Assessment of Potent Synthesized Derivative(Nambirajan *et al.*, 2018)

Streptozotocin (STZ) induced diabetes experimental model is the commonly used for biological evaluation of antidiabetic agents. Albino rats of Wister strain of either sex between the age of 2-3 months and weighing 150-200 grams were procured for the present study. They were acclimatized for the seven days by providing standard rat pellet diet with water ad libitum prior to start the study. The animals were administered with the single dose of streptozotocin (35 mg/kg) in normal saline by intra peritoneal injection for the induction of diabetes. The animals showing blood glucose range of 200-400 mg dL^{-1} were used for the experiment and the hyperglycemia was confirmed after 72 hours of Streptozotocin monohydrate administration (i.p.). All the animal experiment protocols were approved by CPCSEA, Institutional Animal Ethics Committee, and Sapience Bio-analytical Laboratory Bhopal, Madhya Pradesh, India reg. no. 1447/PO/a/11 /CPCSEA.

Blood glucose level was monitored by tail dipping method. The blood glucose concentration was checked on dextrostrix reagent pad using microprocessor digital blood glucometer (Sugerchek Glucometer, Wockhardt manufacture, India). A single dose of (7a-7l) was administered in 350 mg/kg body weight p.o. respectively for 14 days. The blood glucose level was monitored at 0^{th} day, 7^{th} day, 14^{th} day, and 21^{st} day respectively. The antidiabetic activities of potent synthesized compounds on diabetic rats were reported in Table 5.

All the data were analyzed statistically using One-way ANOVA followed by Tukey-Kramer test. The values were considered to be significant at $p<0.05$ and $p<0.01$ level.

Table 5: Antidiabetic activity of synthesized Compounds (7a-7l) on diabetic rats .

S. No.	Treatment	Blood Glucose Level (mg/dl)				% Reduction in Blood Glucose
		0^{th} day	7^{th} day	14^{th} day	21^{st} day	
1.	Normal Control	106 ± 0.98	104 ± 1.30	104 ± 0.98	101 ± 0.90	4.08
2.	Diabetic Positive control	338 ± 10.17	357 ± 2.41	344 ± 3.11	336± 6.42	0.65
3.	Glibencl-amide 10 mg/kg	352 ± 2.52	348 ± 3.16	243 ± 4.33	119 ± 6.59	67.30
	Each Test Group receives 350 mg/kg (p.o.) as effective dose.					
4.	7d	366 ± 2.76	346 ± 3.12	238 ± 1.79	125 ±1.01	65.68
5.	7f	348 ± 1.45	275 ± 2.15	232 ± 3.11	168 ± 2.12	52.72

[e]Normal control group: diabetic animals received normal saline solution; [f]Positive diabetic control group: diabetic animals received 1 ml of 0.5% carboxy methyl cellulose.

Results and Discussion

All the compounds were selected for the prediction of their likeliness and toxicity on the basis of non violation of Lipinski's rule. The selected compounds have revealed appropriate values of BBB and human intestinal absorption. They also have shown reasonable Caco2-cells permeability with comparable value of plasma protein binding with standard. Most of the selected compounds are non inhibitor of CYP2D6 and thus reflects fewer chances of interactions with other drugs. 7d, 7e, 7g and 7h have shown maximum aqueous solubility and were in comparable range with standard glibenclamide. Toxicity analysis of 7b, and 7c yielded positive carcinogenicity results in both mouse and rat models. Most of the selected compounds predict medium risk due to hERG inhibition and these results are comparable to that of standard Glibenclamide. In Ames test, 7a, 7b, 7d, 7f, 7g,7j, and 7l have shown non mutagenecity. In amongst all selected compounds 7d, 7f, 7g and 7h can be predicted least toxic molecules.

On the basis of toxicity prediction results, compounds 7d, and 7f were further screened for antidiabetic activity on diabetic rats. This study reveals the result of test groups when significantly compared with positive control (streptozotocin 60 mg/kg) i.v. and standard Glibenclamide 10 mg/kg (p. o.). The antidiabetic activity results exhibited significant antidiabetic response at the end of twenty first day of experimental period.

Conclusions

Drug likeliness and toxicity prediction of Benzothiazole derivatives were determined using Pre ADMET software. The toxicity profile was used to select the potent Benzothiazole derivatives for assessment of anti-diabetic activity in a streptozotocin induced diabetic rat model. The streptozotocin was used to induce the diabetic hyperglycemia condition characterized with elevation of glucose level in plasma. It also considered as significant marker of renal dysfunction. Amongst these selected derivatives compound 7d shown more potent anti-diabetic activity at 350 mg/kg p. o. and would be of better use in drug development to combat the metabolic disorder in future.

References

Smith, A.D. (2011). Discovery and ADMET: Where are we now. Current topics in medicinal chemistry, 11(4): 467-481.

Ahmadi, A.; Khalili, M.; Sohrabi, L.; Delzendeh, N.; Nahri-Niknafs, B. and Ansari, F. (2017). Synthesis and Evaluation of the Hypoglycemic and Hypolipidemic Activity of Sulfonamide-benzothiazole Derivatives of Benzylidene-2, 4-thiazolidnedione. Mini reviews in medicinal chemistry, 17(8): 721-726.

Akbarzadeh, A.; Norouzian, D.; Mehrabi, M.; Jamshidi, S.; Farhangi, A.; Verdi, A.A.; Rad, B.L. (2007). Induction of diabetes by streptozotocin in rats. Indian Journal of Clinical Biochemistry, 22(2): 60-64.

Cheng, F.; Li, W.; Liu, G. and Tang, Y. (2013). In silico ADMET prediction: recent advances, current challenges and future trends. Current topics in medicinal chemistry, 13(11): 1273-1289.

Deeds, M.; Anderson, J.; Armstrong, A.; Gastineau, D.; Hiddinga, H.; Jahangir, A. and Kudva, Y.C. (2011). Single dose streptozotocin-induced diabetes: considerations for study design in islet transplantation models. Laboratory animals, 45(3): 131-140.

Engel, H.; Xiong, L.; Reichenberger, M. A.; Germann, G.; Roth, C. and Hirche, C. (2019). Rodent models of diet-induced type 2 diabetes mellitus: A literature review and selection guide. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13(1): 195-200.

Ertl, P.; Rohde, B. and Selzer, P. (2000). Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. Journal of medicinal chemistry, 43(20): 3714-3717.

Feinberg, E.N.; Sheridan, R.; Joshi, E.; Pande, V.S. and Cheng, A.C. (2019). Step change improvement in ADMET prediction with potentialnet deep featurization. arXiv preprint arXiv:1903.11789.

Gheibi, S.; Kashfi, K. and Ghasemi, A. (2017). A practical guide for induction of type-2 diabetes in rat: Incorporating a high-fat diet and streptozotocin. Biomedicine & Pharmacotherapy, 95: 605-613.

Gill, R.K.; Rawal, R.K. and Bariwal, J. (2015). Recent advances in the chemistry and biology of benzothiazoles. Archiv der Pharmazie, 348(3): 155-178.

Gleeson, M.P.; Hersey, A.; Montanari, D. and Overington, J. (2011). Probing the links between in vitro potency, ADMET and physicochemical parameters. Nature reviews Drug discovery, 10(3): 197-208.

Graham, M.L.; Janecek, J.L.; Kittredge, J.A.; Hering, B.J. and Schuurman, H.-J. (2011). The streptozotocin-induced diabetic nude mouse model: differences between animals from different sources. Comparative medicine, 61(4): 356-360.

Kharbanda, C.; Alam, M.S.; Hamid, H.; Javed, K.; Bano, S.; Ali, Y.; Pasha, M. (2016). Novel benzothiazole based sulfonylureas/sulfonylthioureas: design, synthesis and evaluation of their antidiabetic potential. New Journal of Chemistry, 40(8): 6777-6786.

Kumar, S.; Rathore, D.; Garg, G.; Saxena, R.; Khatri, K. and Sahu, S.K. (2016). Synthesis and evaluation of some 2-((benzothiazol-2-ylthio) methyl)-5-phenyl-1, 3, 4-oxadiazole derivatives as antidiabetic agents. Asian Pacific Journal of Health Sciences, 3(4): 65-74.

Kurar, S.; Rathore, D.; Garg, G.; Khatri, K.; Saxena, R. and Sahu, S.K. (2017). Synthesis and evaluation of some benzothiazole derivatives as antidiabetic agents. Int. J. Pharm. Pharm. Sci., 9: 60-68.

Lipinski, C.A.; Lombardo, F.; Dominy, B.W. and Feeney, P.J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced drug delivery reviews, 23(1-3): 3-25.

Mabhida, S.E.; Johnson, R.; Ndlovu, M.; Louw, J.; Opoku, A. and Mosa, R.A. (2019). Molecular basis of the anti-hyperglycemic activity of RA-3 in hyperlipidemic and streptozotocin-induced type 2 diabetes in rats. Diabetology & Metabolic Syndrome, 11(1): 1-5.

Nambirajan, G.; Karunanidhi, K.; Ganesan, A.; Rajendran, R.; Kandasamy, R.; Elangovan, A. and Thilagar, S. (2018). Evaluation of antidiabetic activity of bud and flower of Avaram Senna (*Cassia auriculata* L.) In high fat diet and streptozotocin induced diabetic rats. Biomedicine & Pharmacotherapy, 108: 1495-1506.

Premilovac, D.; Gasperini, R.J.; Sawyer, S.; West, A.; Keske, M.A.; Taylor, B.V. and Foa, L. (2017). A new method for targeted and sustained induction of type 2 diabetes in rodents. Scientific reports, 7(1): 1-10.

Richard, A. and Benigni, R. (2002). AI and SAR approaches for predicting chemical carcinogenicity: survey and status report.

Rouf, A. and Tanyeli, C. (2015). Bioactive thiazole and benzothiazole derivatives. European journal of medicinal chemistry, 97: 911-927.

Tripathi, L.; Singh, R. and Stables, J.P. (2011). Design & synthesis of N′-[substituted] pyridine-4-carbohydrazides as potential anticonvulsant agents. European journal of medicinal chemistry, 46(2): 509-518.

Yurttaş, L.; Kaplancıklı, Z.A.; Göger, G. and Demirci, F. (2016). Synthesis and anticandidal evaluation of new benzothiazole derivatives with hydrazone moiety. Journal of Enzyme Inhibition and Medicinal Chemistry, 31(5): 714-720.