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Biological activity of substituted Benzothiazoles

Vidya Sagar[1]*, Dr. Ashish Sarkar[2]

[1] Research Scholar, school of Pharmacy, YBN University, Ranchi, Jharkhand, India

Email: vidyasagarindupati@gmail.com

[2] Professor, School of Pharmacy, YBN University, Ranchi, Jharkhand, India

Abstract - The aim of this work was to assess the biological activity of benzothiazoles, substituted with diverse groups, with respect to their role as antidiabetic compounds. Twenty four new benzothiazole compounds were newly developed, These compounds were tested for their efficacy in alloxan and streptozotocin-induced diabetic rats. Initially, the given compounds underwent computational models via ADMET and Toxicity Prediction models for testing oral bioavailability and toxicity. As recommended by ADME prediction profiles, chosen compounds were subjected to in vivo experiments at 350 mg/kg body weight. Several derivatives exhibited substantial blood glucose lowering activity as compared to the diabetic control group of animals and among those derivatives, compounds 6f and 7d were found to possess more potent antidiabetic activity similar to that of glibenclamide. Similarly, subsequent research on diabetic rats provoked by streptozotocin also revealed the efficacy of compounds 6e, 6f, 6i, 7d and 7f to control diabetes. The findings here presented reveal that the title substituted benzothiazoles, especially compound 6f and 7d have the potential to be considered as future antidiabetic drugs. To search the real potential therapeutic application of these compounds in the management of diabetes, there is need for further research on the efficacy and safety of these compounds.

Keywords: Benzothiazoles, Antidiabetic agents, Alloxan, Streptozotocin, Blood glucose

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INTRODUCTION

It is possible to trace the origins of Indian medicine back to Charak and Sushrut. Their treatments were drawn from a broad range of plants and animals from throughout the world.1–5 India experiences a tremendous deal of pride in the fact that it has the most biodiversity in the world. In order to satisfy the growing demand for pharmaceuticals and the scarcity of medicines that are produced from natural sources, there is an urgent need to progress synthesis chemistry via the production of the creation of new chemicals that are physiologically active in the laboratory. [1] Through the process of synthesis, it is possible to introduce unique biological and pharmacological characteristics into products, while at the same time making them safer and more effective. [2]

"Put together" was the original meaning of the word "synthesis" when it was first adopted from Greek. The term "synthesis" refers to the process of generating more complex organic compounds by arranging simpler organic molecules in accordance with your preferences. The only reason why chemistry is distinguished from other areas is because of synthesis. [3] The process of synthesis is largely responsible for the development of chemistry and other scientific disciplines.9:30 to 10:00 o'clock the use of complex organics in the improvement of sickness conditions, the maintenance of quality of life, the protection against hazardous crops as agrochemicals, and the production of sophisticated materials and products connected to biotechnology often results in the synthesis of these substances employing the most basic processes. [4]

The number of hetero atoms that make up a heterocyclic molecule may vary anywhere from one to five members, as in the case of quinolines, or they can be as small as single-member molecules or as large as linked rings. [5] There are a wide range of compounds that include heterocyclic nuclei, and the number of these compounds continues to grow, and they are always reaching new heights. [6]

There is a large abundance of heterocyclic compounds in nature, and they are essential to all kinds of life. In addition to being key components of biological systems, haemoglobin, bile pigments, biotin, folic acid, serotonin, histamine, and other hormones, as well as the pyrimidine and purine bases of DNA, and a variety of amino acids (including proline, histidine, and tryptophan) are required for the metabolism of cells. Phytoconstituents include carbohydrates, chlorophyll, and vitamins, notably those belonging to the B12 and E classes. [7] Vitamin C, in instance, is

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a molecule that contains one oxygen atom and may exist in either a five-member (furan) or six-member (pyran) ring shape. Phytoconstituents are also known as phytochemicals. Between the ages of As a result of their extensive range of actions, heterocyclic structures are excellent candidates for the development of synthetic pharmaceuticals that can cure a broad variety of different health problems. This has significant implications for the design of synthetic drugs.[8]

As vulcanization accelerators, heterocyclic compounds are used in the rubber business. Additionally, many of these compounds are utilized in the photography industry, as well as in the dye reagent, copolymer, and solvent industries. [9] The widespread use of heterocyclic compounds in the field of chemistry may be attributed to a number of factors, including their reactivity, stability, physical, chemical, and biological properties.It has been hypothesized by some individuals that functionalized non-heterocyclic structures, such as Indomethacin and Suilindac, display distinct chemical reactivity. [10]

Each and every compound that has a cyclic ring that is composed of more than one kind of atom is referred to as a heterocyclic compound. Among the several types of cyclic compounds, homocyclic compounds are those in which every single ring is made up of carbon atoms. Compounds such as benzene, naphthalene, cyclohexanol, and a great number of others are examples of such substances. [11] Compounds are said to be heterocyclic if the rings of the compound include components other than carbon. Some examples of these elements are sulphur, nitrogen, and oxygen. Ring systems of these compounds are often either common (consisting of five or six members) or tiny (consisting of three or four members). [12] The heterocyclic compounds may be derived from a variety of natural and synthetic sources, and they can also be found in the natural world. One of the factors that has contributed to their sudden rise to fame is the fact that they are associated with a large variety of physiological processes that occur in the natural environment. As a result of their vast use in the fields of medicine, pharmacology, agriculture, and other economic sectors, they soon came to prominence as a scientific subject that is fast increasing. [13]

There are a great number of natural chemicals that include heterocyclic compounds. These compounds are also necessary for the functioning of biological systems. They consist of components such as nucleic acids, vitamins, enzymes, coenzymes, ATP, sarotin, heme, chlorophylls, and terpenoids, flavonoids, and alkaloids. [14]

Examples of complexes that play significant roles in metabolic processes include heme, chlorophyll, and others. These complexes are created when metals combine with certain heterocyclic molecules. Compounds generated from the heterocyclic moiety are used extensively in medicinal chemistry and contemporary drug development due to the extensive spectrum of biological activities that they possess. [15] These activities include antiviral, anticancer, antibacterial, anti-tuberculous, anti-malarial, and anti-oxidant properties, amongst many more. In terms of significance, heterocyclic compounds have overtaken organic chemicals. This is because heterocyclic compounds provide a lower risk to human cell lines. [16]

METHODOLOGY

Insufficiency of the body to manufacture the appropriate quantity of insulin or faults in the pancreas to discharge the insulin are the two primary causes of diabetes, which is a chronic or long-term illness that will mostly result from one of these two states or circumstances. Insulin acts as a stabiliser, which helps to manage the amount of sugar in the blood [17. With diabetes mellitus (DM), the body is unable to control the amount of glucose that is present in the circulation. Diabetes mellitus is a group of disorders that are interconnected. Insulin is the sole hormone that is created by the pancreas, and it is responsible for regulating the amount of sugar (glucose) that is present in the blood. According to the World Health Organisation (WHO, 2019), there are more than 220 million individuals throughout the world who are affected by diabetes, and it is estimated that this figure will more than double by the year 2030. [18]

We are able to categorise DM:

- Type-1 diabetes or Insulin Dependent Diabetes Mellitus (IDDM).
- Type-2 diabetes or Non- Insulin Dependent Diabetes Mellitus (NIDDM).

There is a possibility that the illness may result in a number of consequences, such as high blood sugar, high cholesterol, and high triglycerides. These complications may be brought about by insulin resistance or insufficient insulin release. [19]

The prevalence of diabetes is estimated to be about 10% of the total population, with Type 2 diabetes accounting for 90% of all occurrences. In the treatment of diabetes mellitus and the reduction of blood glucose levels, sulfonylureas and biguanides are two of the numerous drugs that are used that are available. [20] There is a pressing need for the identification of innovative molecules to address these challenges, which is highlighted by the vast variety of bad effects that are linked with the conventional diabetes medications that are now available. As a therapy for diabetes, heterocyclic compounds were used for a considerable amount of time. [21]

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- **Models For The Biological Assessment Of Anti-Diabetic**

For the purpose of biologically evaluating antidiabetic medicines, two primary kinds of chemically generated diabetes experimental models are used.

- **The model that is induced by streptozotocin (STZ).**

The glucosamine-nitrosourea combination streptozotocin (STZ) has been the subject of therapeutic trials since 1967. Most often, adult wistar rats are injected with 35 mg/kg of STZ intraperitoneally to induce diabetes. As a result of pancreatic swelling, it causes Langerhans islet beta cells to degenerate, which in turn triggers diabetes mellitus symptoms within two to four days. Islet beta cells in the pancreas contain nicotinamide adenine dinucleotide (NAD), a substance that has histopathological effects and likely causes the onset of diabetes. [22]

A. Alloxan induced model

Alloxan is a uric acid derivative, which is in the same category as its chemical synonyms. Pyimidinetetrone, 2, 4, 5, 6-tetraoxohexa hydropyrimidine, mesozalylurea, and mesoxalylcarbamide are some of the other names that have been given to this substance. After reaching a pH of neutral, it becomes highly unstable in water, but when it reaches a pH of 3, it becomes practically stable. Dialuric acid and reactive oxygen species are the primary compounds that are discovered after the oxidation of alloxan through a cyclic redox process. Moreover, the production of hydrogen peroxide and superoxide radicals is a consequence of the autoxidation of dialuric acid. A typical method for inducing diabetes in adult Wistar rats involves administering an intraperitoneal injection of 120 mg/kg of Alloxan monohydrate. When all of the radicals are exposed to iron, which eventually results in the production of hydroxyl radicals, the beta cells are broken down.

- **Assessing The Biological Effects Of Certain Compounds**

Animal model

The Wister strain of albino rats is the animal model that is used for the purpose of conducting research on biological activities. In order to conduct this study, rats of the species specified, independent of their gender, weighing between 150 and 200 grammes, and being between two and three months old were employed.

The rats were all housed in a controlled environment that adhered to the normal norms of animal husbandry. This environment consisted of a 12-hour light-dark cycle, a temperature of 25±5 degrees Celsius, and humidity levels ranging from 40-60 percent. A regular rat pellet diet and water were provided to the rats for a period of seven days in order to facilitate their acclimatisation prior to the begin of the experiment. Under the supervision of the CPCSEA, also known as the Institutional Animal Ethics Committee, all of the techniques that were used in the animal research were officially approved.

Acute toxicity assessment

Female albino rats weighing between 20 and 25 grammes were used to evaluate the acute toxicity of all of the benzothiazole derivatives that were synthesised. These rats were housed in an environment that was suitable for their needs. Immediately before to the beginning of the experiment, five animals that had been used to the environment were given the opportunity to abstain from drinking water for a period of twelve hours. The test chemicals were administered to the animals in a single dose of 2,000 milligrammes per kilogramme, and the death rate of the animals was tracked over a period of fourteen days. In this continuing experiment, the behavioural, economic, and neurological profiles were tracked, with the exception of a little drop in activity that lasted for up to two weeks. This occurred when the dose was raised to 1000 mg/kg. We determined the dose to be at the point where there were no more adverse effects or fatalities, even after a period of fourteen days. This threshold is referred to as the LD50. It was thus determined that the antidiabetic effect was evaluated at the same dose of 350 mg/kg, which was also established as the LD50 for the compounds that were being tested.

- **Activity evaluations against diabetes in rats caused by alloxan**

Experimental diabetes induction with alloxan monohydrate

To induce diabetes, rats were intraperitoneally injected with a single dosage of 120 mg/kg of alloxan monohydrate or 35 mg/kg of streptozotocin in normal saline. To ensure the rats did not experience hypoglycemia, they were additionally given a 5% (w/v) dextrose solution via feeding bottles for the next 24 hours after injection (intrasperitoneal). We chose animals for the experiment based on their blood glucose levels, which were found to be between 200 and 400 mg dL-1, after 72 hours after injection, when we verified that they were hyperglycemic. Over the course of 14 days, the animals were also observed for signs of persistent hyperglycemia, defined as fasting blood glucose levels between 200 and 400 mg/dl.

The Experimental Design

Each of the fifteen groups of six creatures was given the following name:

The first group is the control group, which consisted of non-diabetic animals given a regular saline solution.

Group 2: One millilitre of 0.5% carboxymethyl cellulose was administered to diabetic animals in the positive control group.

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The third group was the control group, which had 10 mg/kg of glibenclamide (p.o.)153 for the diabetic animals.

The fourth through fifteenth groups: For a period of 14 days, diabetic mice were given a single dosage of 350 mg/kg body weight of chemicals (7a-7l) in that order.

Glycemic monitoring

Glucose levels were measured using the standard tail dipping technique. A microprocessor digital blood glucometer (Accu-Check Glucometer, Roche Pvt. Ltd. India) was used to measure the concentration of glucose in the blood, which was measured on a dextrostix reagent pad. “At zero, seven, fourteen, and twenty-one days in, the participants' blood glucose levels were measured.

- **Statistical analysis**

The mean ± S.E.M. was used to represent the values. Tukey-Kramer test and one-way ANOVA were used to analyse the data. At the $p<0.05$ and $p<0.01$ levels, the results were deemed significant.

RESULTS AND DISCUSSION

All compounds' computed attributes were given in Table, and those that did not violate Lipinski's criterion were chosen for ADME profile prediction. Tables and Figures the findings of the pharmacokinetic and toxicity profile analyses performed using the Pre ADMET programme.

Table 1: Oral bioavailability of synthetic substances as measured by physicochemical characteristics (6a-6l)

Compd. Code	Mol. Wt.	Log P	HBDa	HBAb	Molar refractivity	TPSAc	%ABS	Lipinski's Violation
6a	339.43	1.85	3	2	51.67	44.15	84.77	0
6b	354.45	1.92	3	2	55.22	52.37	81.93	0
6c	384.43	1.95	3	3	62.637	52.18	82.00	0
6d	369.46	1.89	3	3	54.51	55.13	80.98	0
6e	370.41	2.90	3	2	42.56	46.82	83.85	0
6f	385.42	2.91	3	2	43.58	41.87	85.55	0
6g	415.40	2.82	3	3	62.61	55.19	80.96	0
6h	400.43	1.98	3	3	50.22	52.11	82.02	0
6i	370.41	1.89	2	2	41.53	59.81	79.37	0
6j	385.42	1.96	3	2	42.52	49.81	82.82	0
6k	415.40	2.03	3	2	61.62	52.11	82.02	0
6l	400.43	1.97	2	3	52.52	55.16	80.97	0
Glibenc-lamide*	494.004	4.17	4	3	70.98	56.65	80.46	0

Table 2: Oral bioavailability of synthetic substances as measured by physicochemical characteristics (7a-&l)

Compd. Code	Mol. Wt.	Log P	HBDa	HBAb	Molar refractivity	TPSAc	%ABS	Lipinski's Violation
7a	415.55	2.18	3	2	61.29	49.12	83.05	0
7b	431.55	1.96	2	2	45.24	59.11	79.61	0
7c	445.58	2.32	2	3	60.69	62.29	78.51	0
7d	460.55	3.19	3	3	64.77	65.82	77.29	0
7e	446.52	2.90	2	2	62.59	54.29	81.27	0
7f	462.52	2.91	2	2	49.59	49.87	82.79	0
7g	476.55	3.72	3	3	64.62	58.12	79.95	0
7h	491.52	3.92	3	3	59.82	51.66	82.18	0
7i	446.52	2.77	2	3	55.29	52.28	81.96	0
7j	462,52	2.84	3	3	49.83	46.94	83.81	0
7k	476.55	2.12	3	3	93.22	58.88	79.69	0
7l	491.52	1.87	2	3	52.93	56.29	80.58	0
Glibenc-lamide*	494.004	4.17	4	3	70.98	56.65	80.46	0

Table 3: Expected adverse drug event profile for chosen substances (6a-6l)

Compd. Code	BBB	Human intestinal absorption level	Aq. Solubility mg/L	*Caco-2celld permeability assay*	CYP2D6 Inhibition	Plasma protein binding
6a	0.983351	94.6573	49.6478	29.4431	Non	89. 1321
6b	0.717584	84.0943	61.54634	23.4738	Inhibitor	75.4132
6c	1.268976	96.5470	117.5427	29.0236	Non	75. 7499
6d	0.955345	91.7589	88.6647	17.7493	Non	89.6749
6e	1.163352	95.11324	1228.657	28.4324	Non	95.6489
6f	1.26333	95.11324	1738.9478	28.4324	Non	84.6415
6g	0.976437	92.15453	1217.2312	22.7365	Non	84.379
6h	0.946478	94.78398	429.1467	22.5678	Inhibitor	82.3569
6i	0.983436	93.64783	349.839	13.2542	Non	78.4670
6j	1.929884	97.67488	787.467	19.518	Inhibitor	89.87423
6k	1.183935	94.3672	625.62	14.3782	Non	97.29672
6l	1.281926	94. 5453	423.10	29. 1781	Non	87.86721
Glibencl amide*	2.354679	99.9764	1942.24	49.152	Non	99.15655

Table 4: Expected adverse drug event profile for chosen substances (7a-&l)

Compd. Code	BBB	Human intestinal absorption level	Aq. Solubility mg/L	*Caco-2celld 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
Glibencl amide*	2.354679	99.9764	1942.24	49.152	Non	99.15655

Low (less than 4), Moderate (between 4 and 70), and High (more than 70) caco2-cell permeability in nanometers per second %absorption in the human intestines: In terms of plasma protein binding, there

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are three levels of absorption: well (70–100%), moderate (20–70%), and poorly (0–20%). Types of binding: strongly bound (>90%), weakly bound (<90%); *Drug used for treating diabetes

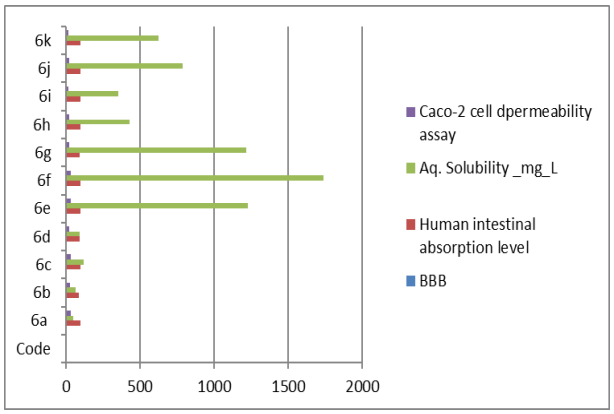

Figure 1: Analysis of substances' predicted ADMET profiles (6a-6l)

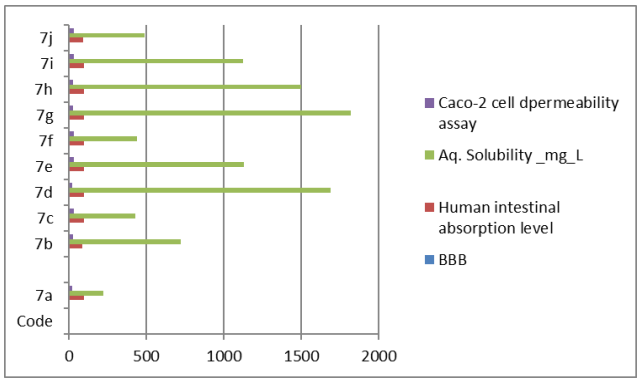

Figure 2: Analysis of substances' predicted ADMET profiles (7a-7l)

Tables included the findings of the biological activity for the artificial substances. Using PreADMET data, the best and safest predicted molecules were found as 6e, 6f, 6i, 7d, and 7f. Then, their antidiabetic efficacy was further investigated in a diabetic rat model generated by alloxan and streptozotocin.

Table 5: The effects of synthetic chemicals on the blood sugar levels of rats made diabetic by alloxan

S. No.	Treatment	Blood Glucose Level (mg/dl)				% Reduction in Blood Glucose
		0th day	7th day	14th day	21st day	
1.	Normal Control	105.09±1.2	102±0.3	102±0.9	100±1.2	-
2.	Diabetic Positive control	274±1.3	273±1.6	271±1.4	270±1.9	-
3.	Glibenclamide 10 mg/kg (p.o.)	278±2.1	219±2.4	168±1.8	95±1.7	65.82 %
	Each Test Group receives 350 mg/kg as effective dose.					
4.	7a	274±1.4	243±2.8	206±1.3	158±2.3	42.33 %
5.	7b	271±2.7	235±3.1	191±0.8	144±3.3	46.86%
6.	7c	270±1.9	246±2.7	199±1.9	161±1.5	40.37 %
7.	7d	279±3.6	222±3.4	167±2.2	102±1.8	63.44 %
8.	7e	281±2.8	238±2.9	192±1.3	149±4.1	46.97 %
9.	7f	272±1.7	254±3.2	205±1.6	159±2.9	41.54%
10.	7g	283±1.3	230±2.5	174±1.4	110±3.1	61.13 %
11.	7h	281±4.2	235±2.7	179±1.5	114±2.6	59.43 %
12.	7i	276±3.4	250±2.2	210±0.5	165±3.2	40.21 %
13.	7j	273±1.6	240±2.6	192±2.2	136±2.4	50.18 %
14.	7k	269±2.8	244±2.3	199±1.9	146±2.1	45.72 %
15.	7l	274±1.5	242±2.5	186±1.1	123±1.8	55.10 %

Table 6: Research on the effects of synthetic chemicals on streptozotocin-induced diabetes in rats (6e, 6f, 6i)

S. No.	Treatment	Blood Glucose Level (mg/dl)				% Reduction in Blood Glucose
		0th day	7th day	14th day	21st 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.	Glibenclamide 10 mg/kg (p.o.)	352±2.52	348±3.16	243±4.33	119±6.59	67.30 %
	Each Test Group receives 350 mg/kg as effective dose					
4.	6e	371 ± 1.08	353 ± 2.77	258 ± 1.35	142 ±5.24	61.58
5.	6f	362 ± 1.33	348 ± 1.66	245 ± 2.34	126 ± 6.10	65.15
6.	6i	331 ± 2.23	313 ± 4.99	244 ± 7.80	163 ±6.60	50.73

Table 7: Synthesised compounds' antidiabetic effects in rats with diabetes caused by streptozotocin (7d, 7f)

S. No.	Treatment	Blood Glucose Level (mg/dl)				% Reduction in Blood Glucose
		0th day	7th day	14th day	21st 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.	Glibenclamide 10 mg/kg (p.o.)	352±2.52	348±3.16	243±4.33	119±6.59	67.30 %
	Each Test Group receives 350 mg/kg 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

The biological activity of all the synthesised compounds was examined in an animal model of alloxan-induced diabetes. After taking the initial weight and normal blood glucose levels of the rats (which were determined to be between 200 and 400 mg/dL), alloxan monohydrate was given to them. After 72 hours, their blood glucose levels were tested again to confirm that they had hyperglycemia. In Table you can see all 24 of the synthesised compounds' physicochemical characteristics (6a-6l and 7a-7l). Many of the produced compounds showed their antidiabetic effect on the 21st day of the testing period, according to the performed research. Compounds (6e, 6f, 6i, 7d, 7f) from both series were shown to significantly lower blood glucose levels at a dosage of 350 mg/kg body weight when tested in Streptozotocin-induced diabetic rats. When tested in diabetic rats induced with Alloxan, it was shown that compounds (7d, 7g, 7h, and 7l) from

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both series significantly reduced blood glucose levels at a dosage of 350 mg/kg body weight." Additionally, it was noted that two compounds, 6f and 7d, had the strongest impact on reducing glucose levels, while another pair of molecules, 6d and 7i, had the weakest effects. Results from the test groups were statistically different from those of the positive control group (alloxan 120 mg/kg) and the standard group (glibenclamide 10 mg/kg), according to this research.

Compounds 6e, 6f, 6i, 7d, and 7f were the only ones to undergo further testing for antidiabetic efficacy in streptozotocin-induced diabetic rats, based on the results of the toxicity prediction. Compounds 6f and 7d were shown to have strong antidiabetic effects.

CONCLUSION

Out of the twenty-four derivatives that were synthesised, two compounds, 6f and 7d, had the highest anti-diabetic activity when administered intraperitoneally at a dose of 350 mg/kg. Such compounds have to be taken into consideration for potential future applications in the development of drugs to treat metabolic diseases. Six additional derivatives, including 6e, 6g, 6h, 7g, 7h, and 7l, were also shown to dramatically lower blood glucose levels when supplied to diabetic rats at a set dose of 350 mg/kg body weight. This was in comparison to drugs that were not provided.

In rats that were induced with streptozotocin and Alloxan, compounds 6e, 6f, 6i, 7d, and 7f revealed their ability to reduce the risk of developing diabetes. Furthermore, based on the findings of the PreADMET study, it was expected that these compounds would be safe. Both compounds 6f and 7d were shown to have a powerful anti-diabetic effect, which was also confirmed. We were able to find a limited number of potent benzothiazole derivatives (6f and 7d) by using the sequencing approach and analysing the drug's ability to treat diabetes.

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Corresponding Author

Vidya Sagar*

Research Scholar, school of Pharmacy, YBN University, Ranchi, Jharkhand, India

Email: vidyasagarindupati@gmail.com