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Benzothiazole: As An Antidiabetic Agent

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ABSTRACT

Diabetes is a slow poison. It is the disease that affects major organs of the human body like the heart, kidney, blood vessels, liver, etc. There are many hypoglycemic drugs available in the market. Benzothiazole derivatives are also good hypoglycemic agents. Researchers continuously work on benzothiazole molecule to get more effective derivatives that can be used as antidiabetic drugs. We hope this review article will provide all the information about benzothiazole molecule as antidiabetic agents like structure-activity relationship of benzothiazole derivatives as antidiabetic agents, synthesis schemes for the derivation of novel antidiabetic benzothiazole derivatives, and in vitro and in vivo methods for evaluation of hypoglycemic activity of novel synthesized compounds.

Keywords
Antidiabetic, Benzothiazole, Methods of Evaluation, SAR, Schemes of Synthesis

INTRODUCTION

Defect in insulin secretion, insulin action, or both can result in a group of metabolic diseases characterized by hyperglycemia which is called diabetes mellitus. Blood sugar level which is elevated beyond the range (greater than 130mg/dl) is defined as diabetes mellitus and this chronic hyperglycemia is associated with long-term damage, dysfunction and failure of various organs including eyes, kidneys, nerves, heart, and blood vessels. Diabetes mellitus can be classified into two types: insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus according to the pathogenesis [1].

Pathogenesis involves autoimmune destruction of β-cells of the pancreas which can produce insulin deficiency to abnormalities that result in resistance to insulin action. Disturbance in the metabolism of carbohydrates, fat, and protein is characterized by a deficiency of insulin action which is generated by inadequate insulin secretion and/or decreased tissue responses to insulin in the complex pathways of hormone activity. Thus, the primary cause of hyperglycemia is the deficiency of insulin secretion or defects in insulin action which frequently coexist in the same patient [2].

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [3]. Several pathogenic processes are involved in the development of diabetes. This ranges from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues [4]. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist with the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of hyperglycemia [5].

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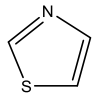
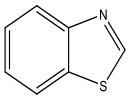
Literature review reveals that Benzothiazole is such a versatile moiety that can be used as a parent molecule to synthesize new derivatives that can be used as antidiabetic agents. Benzothiazole has many advantageous physical and chemical characteristics that could be helpful in designing new antidiabetic drugs. It has relatively stable aromaticity, heterocyclic structure, slight viscosity, the lower melting point of 2◦C, and higher boiling point of 227-228◦C. The density of benzothiazole is 1.24 g/mL, and its molecular weight is 135.19 $gmol^{-1}$ [6].
Because of such wonderful characteristics, benzothiazole is a compound of interest of researchers and is widely used in the pharma industry. Structurally it contains a benzene ring clubbed with a thiazole ring and all nine atoms coplanar. It has many active sites for substitution, and different substitution at different sites, give various biological and pharmacological activities [7].

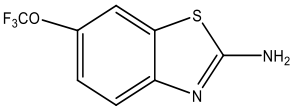


Thiazole



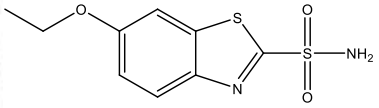
Benzothiazole

Some commercially available drugs contain benzothiazole nucleus which proves its excellent activities. Riluzole [8] which is a neuroprotective and antidepressant drug is a structurally benzothiazole derivative. It is marketed as Rilutek[9]) film-coated tablet manufactured by Sanfoi.



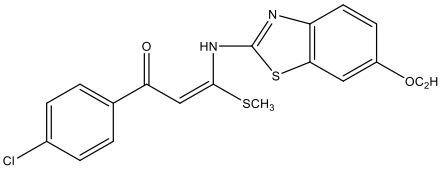
Riluzole

Another drug is ethoxzolamide [10] which is also a benzothiazole derivative is a diuretic. It is marketed as Zarontin [11] capsules manufactured by Pfizer.



Ethoxzolamide

Various benzothiazole derivatives as antidiabetic agent
Patil et al. designed a list of novel (E)-3-(Benzo [d]thiazol-2-ylamino) phenylprop-2-en-1-ones with potent α-amylase inhibitory properties. These compounds showed promise as glycosidase inhibitors in male Swiss mice. The anti-diabetic efficacy of these compounds was assessed using standard α-amylase inhibition and glucosidase inhibition assays [12].



(*E*)-1-(4-chlorophenyl)-3-((6-(ethynyloxy)benzo[*d*]thiazol-2-yl)amino)-3-(methylthio)prop-2-en-1-one

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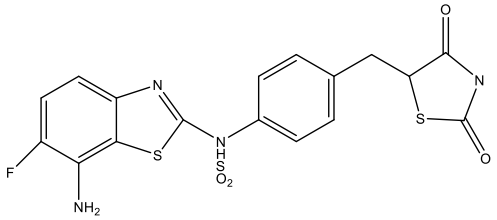
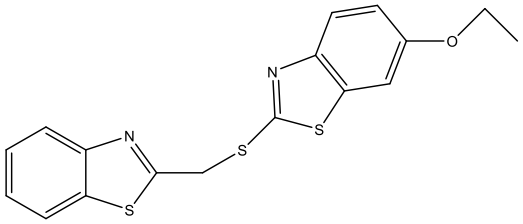
Pattan et al. created a new sequence of 2-amino[5'(4-sulphonylbenzylidine)-2,4-thiazolidinedione]-7-chloro-6-fluoro benzothiazoles, which were tested for anti-diabetic activity in albino rats using the alloxan induced tail tipping process [13].



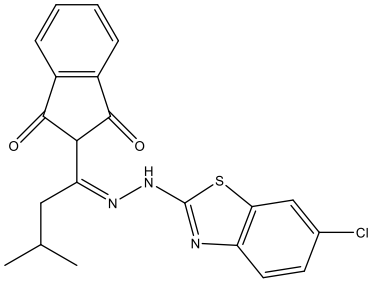
5-(4-((7-amino-6-fluorobenzo[*d*]thiazol-2-yl)amino)benzyl)-3λ^2-thiazolidine-2,4-dione compound with sulfur dioxide (1:1)

Meltzer-Mats et al. synthesized and tested a variety of substituted benzothiazole derivatives for hypoglycemic (antihyperglycemic) activity. The ethoxy benzothiazole moiety in 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazole was discovered to be important for increasing glucose transport and AMPK activation in L6 myotubes. At pharmacologically important concentrations, 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazole significantly increased the rate of glucose absorption in L6 myotubes. The effect of 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazolein on blood glucose levels in diabetic KKAy mice demonstrated which showed decrease in blood glucose level [14].



2-((benzo[*d*]thiazol-2-ylmethyl)thio)-6-ethoxybenzo[*d*]thiazole

Mor et al. evaluated in vitro α-amylase inhibition activity of the synthesized compounds and in vitro α -glucosidase inhibition activity of the newly synthesized benzothiazolyl hydrazones to screen their antidiabetic activity. The norm was acarbose, and newly synthesized compounds showed promising anti-diabetic activity [15].



(*Z*)-2-(1-(2-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazineylidene)-3-methylbutyl)-1*H*-indene-1,3(2*H*)-dione

Ahmadi et al. synthesized substituted aminomethyl benzothiazoles and measured blood glucose levels in rats after administration of substituted aminomethyl benzothiazoles to see if they had

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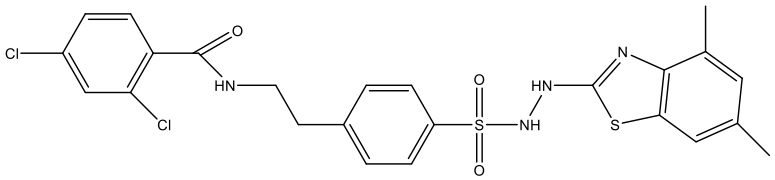
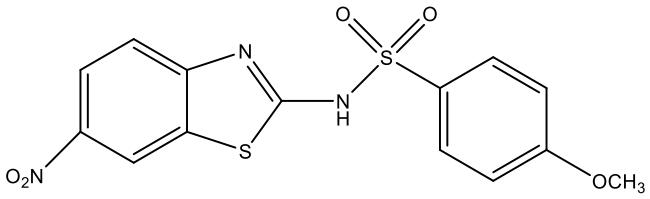
anti-diabetic activity. The anti-diabetic activity of 2,4-Dichloro-N-[2-[4-[(4,6- dimethyl -2 benzothiazolylamino) sulfamoyl] phenyl]ethyl]benzamide and 2,4-Dichloro-N-[2-[4-[(4-methyl-2-benzothiazolyl amino)-sulfamoyl] phenyl]ethyl]benzamide was found to be greater than others [16].



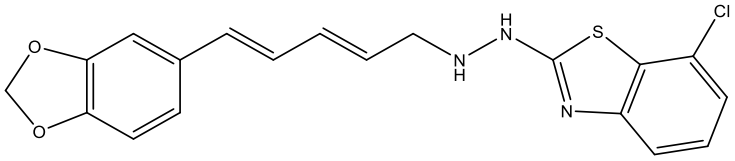
2,4-dichloro-*N*-(4-((2-(4,6-dimethylbenzo[*d*]thiazol-2-yl)hydrazineyl)sulfonyl)phenethyl)benzamide

Moreno-Daz et al. synthesized a new sequence of N-(6-substituted-1,3-benzothiazol-2 yl) benzene sulfonamides and tested them for in vivo antidiabetic activity in a non-insulin-dependent diabetes mellitus rat model. Several compounds produced in this model significantly lowered plasma glucose levels. As a possible mode of action, the compounds were investigated in vitro as 11b hydroxysteroid dehydrogenase type 1 (11b-HSD1) inhibitors [17].



4-methoxy-*N*-(6-nitrobenzo[*d*]thiazol-2-yl)benzenesulfonamide

Kharbanda et al. synthesized 28 benzothiazole-based sulfonylureas/sulfonylthioureas and tested their antidiabetic effect in a normoglycemic rat model using an in vivo oral glucose tolerance test (OGTT). Ten active compounds were tested in vitro for PPAR-g transactivation and found to have potent anti-diabetic properties. These ten active compounds were also discovered to transactivate PPAR, so they were tested for their anti-diabetic ability in a diabetic model induced by streptozotocin (STZ). {2-[3-(4-Chloro-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-benzothiazole-6-sulfonylN0-benzylthiourea is the most powerful compound. The OGTT was used to test the effect of {2-[3-(4-Chloro-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-benzothiazole-6-sulfonylN0-benzylthiourea a on PPAR-g gene expression activity [18].



2-(2-((2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dien-1-yl)hydrazineyl)-7-chlorobenzo[*d*]thiazole

Sadhasivam et al. synthesized a new sequence of benzothiazole derivatives and used the α-amylase assay to assess their anti-diabetic activity. By inhibiting the α-amylase enzyme, (2*E*)-*N*-(2-acetamido-1,3-benzothiazol-6-yl)-3-(2- furyl)acryl amide, *N*-(6-{[(4-fluorophenyl)carbamoyl] amino}-1,3-benzothiazol-2-yl)acetamide and *N*-(6-{[(3- methoxyphenyl)carbamoyl]amino}-1,3-

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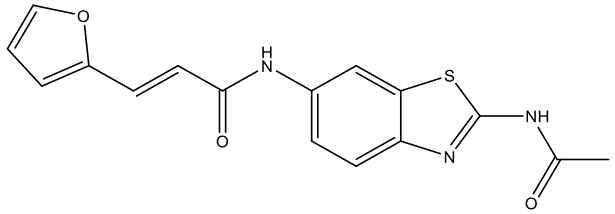
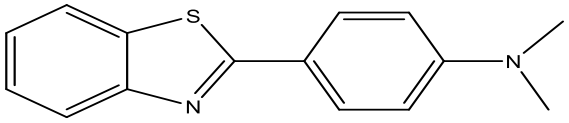
benzothiazol-2-yl) acetamide showed potent antidiabetic activity by inhibition of α-amylase enzyme demonstrated potent antidiabetic activity [19].



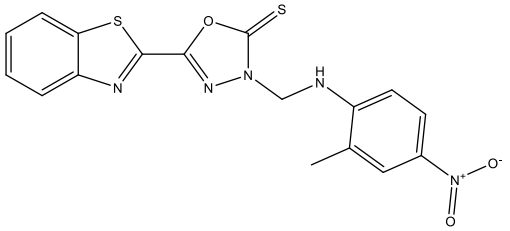
(*E*)-*N*-(2-acetamidobenzo[*d*]thiazol-6-yl)-3-(furan-2-yl)acrylamide

Puranik et al. synthesized benzothiazole derivatives and tested their anti-diabetic efficacy using -glucosidase, α -amylase, non-enzymatic glycosylation of haemoglobin, and advanced glycation end product inhibition assays. The most active compound was discovered to be 2-(4'-(N,N-Dimethyl amino) phenyl)-1,3-benzothiazole. Non-bonded interactions were formed by the enzymes α -glucosidase and α -amylase with 2-(4'-(N,N-Dimethylamino) phenyl)-1,3-benzothiazole [20].



4-(benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylaniline

Bhutani et al. synthesized new benzothiazole clubbed oxadiazole-Mannich bases and tested them in vivo for anti-diabetic activity using the Oral Glucose Tolerance Test (OGTT) in normal rats supplemented with Streptozotocin (STZ). The research revealed that 5-(Benzothiazol-2-yl)-3-[(2 fluorophenylamino) methyl] -1,3,4-oxadiazol-2(3H)-thione In the STZ model, demonstrated the greatest decrease in blood glucose levels, which was equivalent to the regular medication glibenclamide. Other compounds demonstrated hypoglycemic activity ranging from mild to excellent [21].



5-(benzo[*d*]thiazol-2-yl)-3-(((2-methyl-4-nitrophenyl)amino)methyl)-1,3,4-oxadiazole-2(3*H*)-thione

From the study of these various benzothiazole derivatives synthesized by various authors, we can conclude the structure activity relationship of benzothiazole as an antidiabetic agent.

Structure activity relationship of Benzothiazole as antidiabetic agent

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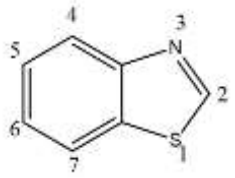
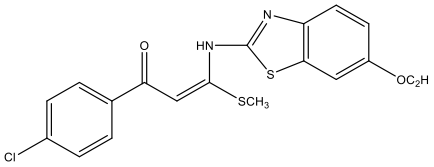
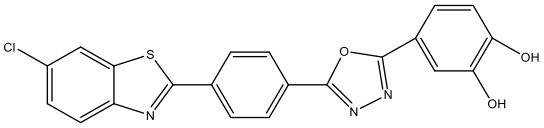


- Thiazole moiety is responsible for antidiabetic activity benzothiazole.



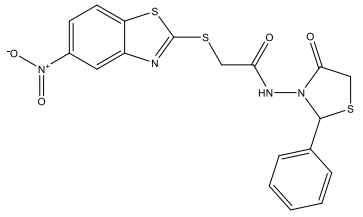
(*E*)-1-(4-chlorophenyl)-3-((6-(ethynyloxy)benzo[*d*]thiazol-2-yl)amino)-3-(methylthio)prop-2-en-1-one

- Dihydroxy analogs of benzothiazole are potent antidiabetic agents.

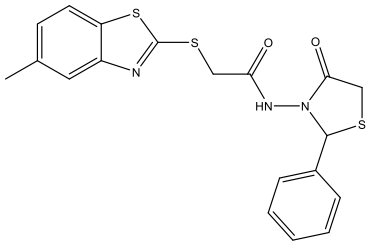


4-(5-(4-(6-chlorobenzo[*d*]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,2-diol

- Substitution of NO2 and methoxy group on 6th position of benzothiazole gives antidiabetic activity.

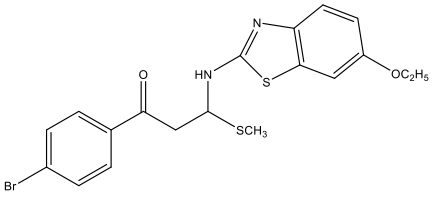


2-(5-nitrobenzo[d]thiazol-2-ylthio)-N-(4-oxo-2-phenylthiazolidin-3-yl)acetamide



2-(5-methylbenzo[d]thiazol-2-ylthio)-n-(4-oxo-2-phenylthiazolidin-3-yl)acetamide

- Methyl substitution on benzothiazole ring imparted less significant antidiabetic activity than ethoxy followed by methoxy substitution.



1-(4-bromophenyl)-3-((6-ethoxybenzo[*d*]thiazol-2-yl)amino)-3-(methylthio)propan-1-one

- Among halide substitution, fluoro substitution on benzothiazole will give the least antidiabetic activity.

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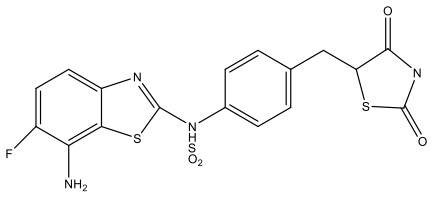
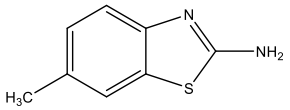
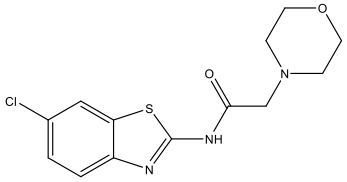


5-(4-((7-amino-6-fluorobenzo[*d*]thiazol-2-yl)amino)benzyl)-3λ^2-thiazolidine-2,4-dione compound with sulfur dioxide (1:1)

- The derivatives containing C(O)-N-N bond were found to be more active as an antidiabetic agent than derivatives with amide link.
- Three pharmacophoric features (hydrophobic, aromatic, and hydrogen-bonded interactions) are important for the antidiabetic activity of benzothiazole.
- Amino methyl benzothiazole gives higher hypoglycemic activity.

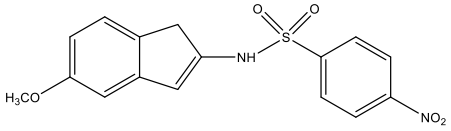


- Substitution of morpholino group on benzothiazole gives maximum antidiabetic activity while substitution of chloroanilino group gives minimum antidiabetic activity.

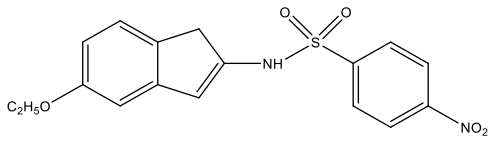


N-(6-chlorobenzo[d]thiazol-2-yl)-2-morpholinoacetamide

- Substitution of methoxy or ethoxy group at 6th position, it gives good antidiabetic activity.

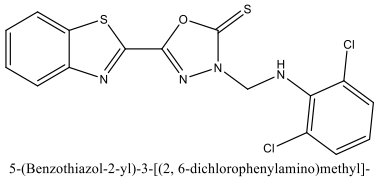


N-(5-methoxy-1*H*-inden-2-yl)-4-nitrobenzenesulfonamide



N-(5-ethoxy-1*H*-inden-2-yl)-4-nitrobenzenesulfonamide

- Presence of electron-withdrawing group(s) increased the anti-diabetic action as compared to electron-donating group(s) and It was observed that the presence of two electron-withdrawing groups (chloro) further increased the anti-diabetic action as shown by the compounds M-7 and M-19.



5-(Benzothiazol-2-yl)-3-[(2, 6-dichlorophenylamino)methyl]-1,3,4-oxadiazol-2(3H)-thione

Schemes for synthesis of benzothiazole derivatives as antidiabetic agent

Sunil kumar et al. synthesized 1-benzothiazol-2-yl -3-chloro-4-substituted-azetidin-2-ones by reacting 2-(benzo[d]thiazol-2-ylthio)-N'-methyl-eneacetohydrazide with mercapto acetic acid in DMF containing a pinch of Zncl2 and refluxing for 8 hrs [22]. (Scheme 1).
Mariappan G. et al. synthesized N-(6-chlorobenzothiazol-2-yl)-2- (substituted amino) acetamide derivatives by reacting 2-chloro-N-(6-chlorobenzothiazol-2-yl) acetamide with absolute alcohol and different secondary and primary amine, refluxing in water bath for 4 to 6 hours [23]. (Scheme 2)

Compound 1(Piperine) was extracted and added to alcoholic potassium hydroxide and refluxed for 24 hr. The reaction mixture was added to ice and neutralized with dilute HCl and filtered to obtain solid mass. Solid mass was recrystallized with ethanol and known as piperic acid which is compound 2. This compound 2 is reacted with series of compounds named (3a-3j) to obtain series of (5a-5j) and with (4a-4j) to get series of (6a-6j) in presence of a pinch of HoBt (1-hydroxybenzotriazole) and 1-ethyl-3-(3-dimethylamino propyl)carbodiimide (EDC) at room temperature [24]. (Scheme 3).
Compound 1 was prepared from 6-ethoxybenzo[d]thiaole-2-thiol by reaction with aluminum chloride in presence of ethyl chloride at room temperature. Compounds 2-4 were prepared from compound 1 by reaction with NaH, alkyl halide in presence of tetrahydro fluorine t 0° C to room temperature for 24 hrs. Compounds 5-9 were synthesized from 6-ethoxybenzo[d]thiaole-2-thiol by reaction with NaH, alkyl halide in presence of tetrahydro fluorine t 0° C to room temperature for 24 hrs. compound 10 was synthesized from series 5-9 by reaction with n-propylamine, HOBt, EDC, CHCl3 at room temperature, overnight.
6-ehoxybenzo[d]thiazole-2 sulfonamide was prepared from 6-ethoxybenzo[d]thiaole-2-thiol by reaction with 28% NH4OH, 5.25% NaOCl, 6% NaOH, 0 °C, 15 min. and 6% KMnO4, Me2CO, rt, 1.5 hrs [25]. (Scheme 4)

METHODS:

Literature review reveals many methods to evaluate antidiabetic activity of the natural as well as synthetic compounds. Two types of methods are available for evaluation:
In vitro methods and in vivo methods.
In vitro methods include glucose uptake in yeast cells and evaluation of hemoglobin glycosylation

1. Glucose uptake in yeast cells:[26]

In this method, the commercial's baker's list is dissolved in distilled water and is centrifuged until clear supernatant fluid is obtained. Then 10%v/v of suspension is prepared in distilled water. Various concentrations of test compound are prepared in glucose solution (e.g. 5,10,15,20,25 mM) and incubated together for 10 min at 37° C. Now, 100µl of yeast suspension is added to each concentration solution and incubated at 37° C for 60 minutes. After 60 min, the tubes are centrifuged, and the amount of glucose was estimated in the supernatant liquid. The percentage of glucose uptake by yeast cells is calculated using the following formula:

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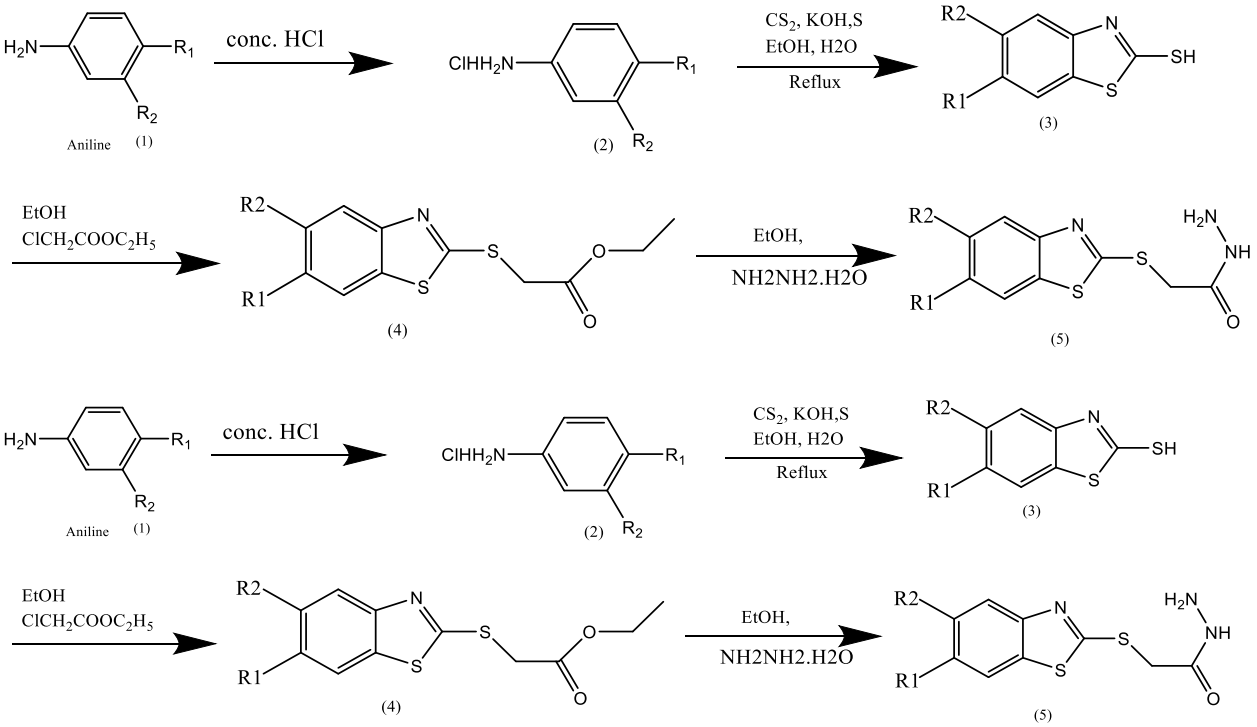

Sr.no	Compound	R_1	R_2	R_3
1	7a	$-CH_3$	-H	C6H5-
2	7b	$-CH_3$	-H	$pOHC_6H_5$-
3	7c	$-CH_3$	-H	$pOCH_3C_6H_4$-
4	7d	$-CH_3$	-H	mNO_2C6H_4-
5	7e	$-NO_2$	-H	C_6H_5-
6	7f	$-NO_2$	-H	$pOHC_6H_4$-
7	7g	$-NO_2$	-H	$pOCH_3C_6H_4$-
8	7h	$-NO_2$	-H	C_6H_5-
9	7i	-H	$-NO_2$	pOC_6H_4-
10	7j	-H	$-NO_2$	$pOCH_3C_6H_4$-
11	7k	-H	$-NO_2$	$pOCH_3C_6H_4$-
12	7l	-H	$-NO_2$	$mNO_2C_6H_4$-

Scheme 1: Synthesis of 1-benzothiazol-2-yl -3-chloro-4-substituted-azetidin-2-ones

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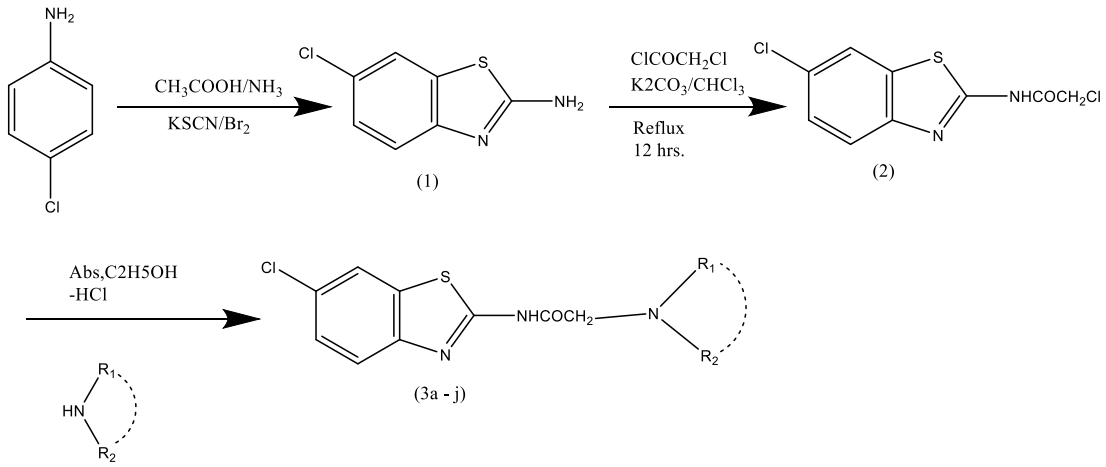

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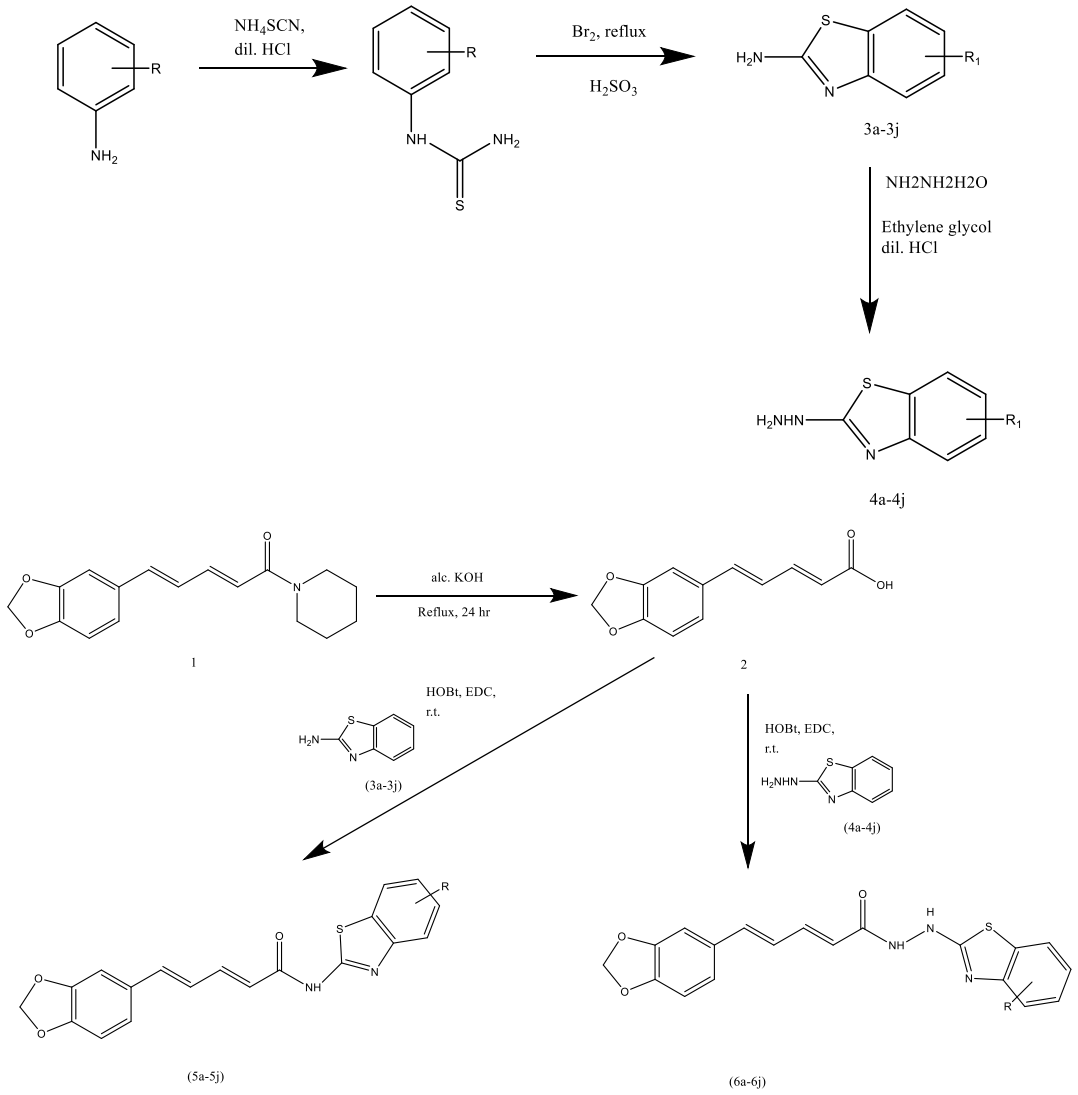
Compound no	-NR1R2
3a	Dimethylamino
3b	Diethylamino
3c	Diethanolamino
3d	Morpholino
3e	Piperidino
3f	4-fluoroanilino
3g	3-chloroanilino
3h	4-pyridino
3i	2-pyridino
3j	4-sulfanilido

Scheme 2: Synthesis of N-(6-chlorobenzothiazol-2-yl)-2- (substituted amino) acetamide derivatives



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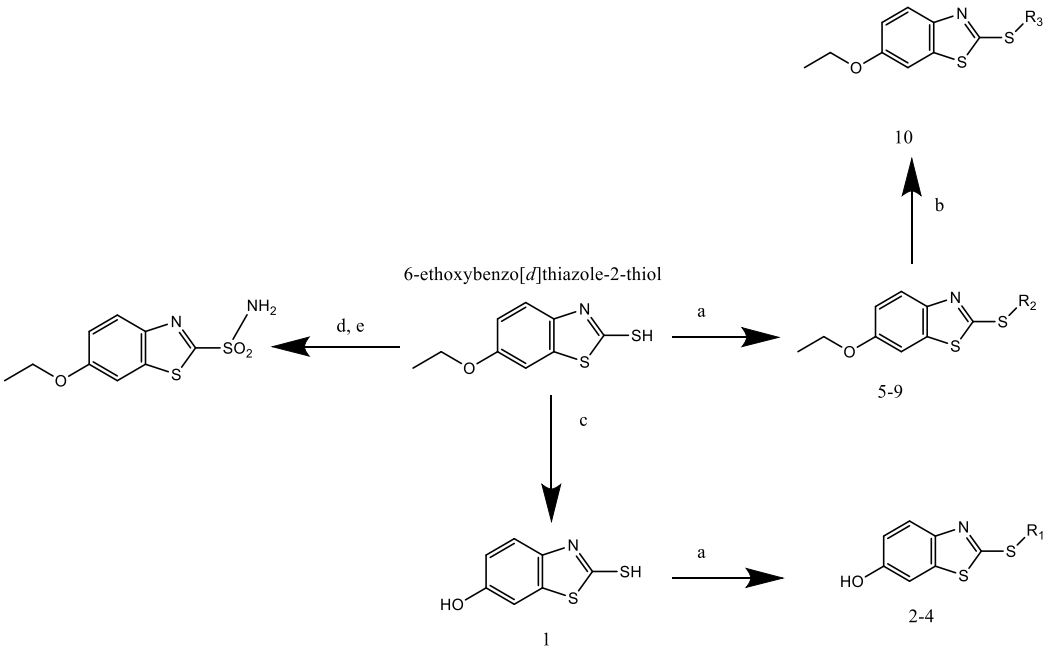
Compound	R_1	Compound	R_1
3a, 4a	4-Cl	3f,4f	4-OCH_3
3b,4b	5-Cl	3g,4g	6- OCH_3
3c,4c	6-Cl	3h,4h	6-OCH_2CH_3
3d,4d	6-Br	3i,4i	4-CH_3
3e, 4e	6-F	3j,4j	6-NO_2

Scheme 3: Synthesis of benzothiazole derivatives



Compound no.	R_1
2	-$CH_2CH(OCH_3)_2$
3	-$CH_2CH(CH_2CH_3)_2$
4	-$CH2CH_2CH_2CH_3$
Compound no.	**R_2**
5	-CH_2CO_2H
6	-$CH_2CH_2CO_2H$
7	-$CH_2CH_2CH_3$
8	-$CH_2CH(CH_2CH_3)_2$
9	-$CH_2CH_2CH_2CH_3$
Compound no.	**R_3**
10	-CH_2-CONH-$CH_2CH_2CH_3$

Scheme 4: Synthesis of 6-ehoxybenzo[d]thiazole-2 sulfonamide

Increase in glucose uptake (%) =

$$\frac{Abs_{sample} - Abs_{control}}{Abs_{sample}} \quad X\ 100$$

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Here, $Abs_{control}$ is the absorbance of the control reaction (i.e. containing all the reagents without sample) and Abs_{sample} is the absorbance of the test sample.

2. Hemoglobin glycosylation:[27]

a. Hemoglobin preparation:

Here, blood from the healthy human body is collected and transferred into test tubes containing EDTA as an anticoagulant. Then we prepare hemolysate based on the principle of hypotonic lysis. The collected red blood cells are washed thrice with 0.1M Nacl solution, and one part of RBC suspension is lysed with two parts of 0.01 M phosphate buffer, pH 7.4 and 0.5 volume of carbon tetrachloride. The hemolysate is then freed from the debris by centrifuging the solution at 2300 rpm for 15 min at room temperature. The upper layer of suspension is separated and dispensed into a test tube for storage and refrigerated until use.

b. Estimation of hemoglobin glycosylation:

Here, 1 ml of hemoglobin fraction is transferred into three test tubes, each with 1 ml solution of various concentrations of glucose in 0.01M phosphate buffer (pH 7.4). The contents are incubated at room temperature for 72 hours. A blank solution, without glucose solution, is used as standard. Test solutions are now estimated for their antidiabetic activity at the different incubation period, in comparison to standard.

c. Effect of the test compound on hemoglobin glycosylation:

Here, we take 1 ml of hemoglobin solution with 5 µl of gentamycin and 25µl of the sample. The reaction takes place by the addition of 1 ml of 2% glucose in 0.01M phosphate buffer (pH 7.4) and the solution is incubated in the dark at room temperature. The concentrations of glycated hemoglobin at the incubation period of 0, 24, 72 hrs are estimated at 443 nm.

d. Effect of sample compound at physiological glucose concentration:

Here, we take 1 ml of hemoglobin solution with 1 ml of glucose solution of different concentrations like 2 mg, 10 mg, 20 mg in 20 ml, each containing 0.01M phosphate buffer, pH 7.4 and 5µl of gentamycin in 0.01M phosphate buffer pH 7.4, are mixed and incubated in the darkroom temperature in the presence of 30 µg/ml of gallic acid and sample solution. Hemoglobin concentrations are estimated over an incubation period of 72 hrs spectrophotometrically at 443 nm, as an index for measuring the degree of hemoglobin glycosylation.

In vitro animal models are also used to evaluate the antidiabetic activity of the synthetic compound.

In vitro animal models:[28]-[29]

Adipose tissue of rat epididymal fat pad has been widely used for this study. The epididymal rat adipose tissue is incubated in glucose-containing media and glucose uptake is measured by glucose concentration of the media. Glucose uptake by incubated rat epididymal adipose tissue is regulated by the rate of glucose transport across the cell membrane.

Another procedure of evaluation is by using radiolabeled carbon C^{14} in glucose structure.[30]

In vivo models:[31]-[33]

The animals are used for so many years for the evaluation of the pharmacological activity of newly synthesized compounds. Here, non-diabetic animals and diabetic animals are used as normal control and diabetic control respectively to measure hypoglycemic condition. Among

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various animals, rodents are widely used in the evaluation of the hypoglycemic activity of novel compounds for various reasons like the time of diabetes induction in these animals is short and the cost of maintenance is very low. Genetically, rodents are in favor of inducing diabetes also.
Diabetes can be induced in animals by the following ways:

1. Chemically induced diabetic model:[34]

Streptomycin and alloxan like drugs are widely used to induce diabetes in animals. Both drugs can be administered by using the intravenous, intraperitoneal or subcutaneous route of administration. Streptomycin and alloxan are cytotoxic agents and destroy pancreatic β cells. Streptomycin and alloxan are glucose analogs so they are transported to pancreatic beta cells by GULT2 glucose transporters. Streptomycin induces destruction of β cells by alkylation and alloxan induces destruction of β cells by reactive oxygen species (ROS) [35] Here, beta cells are lysing and therefore insulin is not produced in enough quantities and that's why diabetes mellitus takes place.

2. Surgically induced diabetic model:[36]

In this method, the pancreas is removed from the body of the test animal so that it can't produce insulin. This method has an advantage over chemical induction in that the test animal has not to bear toxic side effects drugs that are used to induce diabetes.

3. Genetically induced diabetic model:[37]

Here, gene transcription for insulin production is modified.

4. Virus-induced diabetic model:[38]-[40]

Type 1 diabetes is linked with virus infection and autoimmune conditions on the specific beta-cell. Swiss mice are the susceptible species for the virus and therefore we can use swiss mice for the virus-induced diabetic model.
Whichever way is used to induce diabetes, to evaluate antidiabetic activity of the novel synthesized compound, we take two groups of animals that are diabetic and non-diabetic. Then we administer solutions of different concentrations to both groups one after another and predict the results in both groups. We take a standard antidiabetic drug like metformin or glibenclamide [41] as standard.

CONCLUSION

Diabetes mellitus is a lifestyle disease nowaday so it is necessary to develop various drugs for it with more efficacy and potency. From this review, we can conclude that benzothiazole is a potent hypoglycemic agent, and therefore it is of great interest to develop antidiabetic drugs. Various synthetic pathways show that the 2^{nd} position of benzothiazole molecule is very important for substitution. The amino group at this position has great importance to develop hypoglycemic derivatives. The 6^{th} position is also of great significance. SAR is very helpful for the synthesis of novel hypoglycemic derivatives of benzothiazole. This article gives an idea about various evolutionary methods for the evaluation of the antidiabetic activity of novel benzothiazole compounds. These methods include in vitro and in vivo methods.

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