EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 6
54-60
Year: 2022

A REVIEW ON HETEROCYCLIC COMPOUND BENZOTHIAZOLE FOR ANTIDIABETIC ACTIVITY

Gayatri Wagh*[1], Bhad Manoj[2], Nitin Yeole[3], Vaibhav Wagh[4], Ganesh Sonawane[5] and Prerna Dabhade[6]

[1]Department of Pharmaceutical Chemistry, Matoshri Institute of Pharmacy, Yeola, Nashik.
[2,3,5,6]Matoshri Institute of Pharmacy, Yeola, Nashik.
[4]MET Institute of Pharmacy Nashik.

***Corresponding Author: Gayatri Wagh**
Department of Pharmaceutical Chemistry, Matoshri Institute of Pharmacy, Yeola, Nashik.

Article Received on 22/03/2022 **Article Revised on 12/04/2022** **Article Accepted on 02/05/2022**

ABSTRACT
Aromatic heterocyclic compounds are having the wide area of research for the various Pharmacological activities, and having potent pharmaceutical aspects than the exiting derivatives. Heterocyclic compounds bearing nitrogen, sulphur and thiazole moieties are present in various pharmacologically interesting compounds. Benzothiazole, a group of compounds containing a benzene ring fused with a thiazole ring, are used worldwide for a variety of therapeutic applications. Benzothiazole is a bicyclic ring system with multiple applications benzothiazole ring system exhibit significant antitumor, antimicrobial, antidiabetic, anti-inflammatory, anticonvulsant, antiviral, antioxidant, antitubercular, antimalarial, antiasthmatic, anthelmintic, photosensitizing, diuretic, analgesic and other activities. All these pharmacological aspects associated with benzothiazole related drugs has encouraged the medicinal chemists to synthesize a large number of novel therapeutic derivatives of benzthiazole heterocyclic ring system than the existing drugs. During recent years there have been some interesting developments in the biological activities of benzothiazole derivatives. This article is an attempt to present the research work reported in recent scientific literature on antidiabetic activities of benzothiazole compounds.

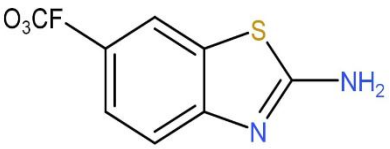
KEYWORDS: Benzothiazole, pharmacological activities, heterocyclic, antidiabetic.

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] Diabetes mellitus is a metabolic disorder resulting from inadequate secretion of insulin characterized by chronic hyperglycemia caused by high calorie diets rich in fat, carbohydrates and proteins. The International Diabetes Foundation (IDF) reports that there were 425 million diagnosed cases of diabetes globally in 2017 which is estimated to increase to 629 million by 2045.[2] Recently, there are more than 46 million diabetics in North America and the Caribbean, 58 million in Europe, 26 million in South and Central America, 39 million in Middle East and North Africa, and 16 million in Africa and 82 million in South-East Asia. There are 352 million people at the risk of developing Type II diabetes. The emerging factors that contribute to the spread of Type II diabetes, comprising a progressively technological society, food habits with high calorie diets rich in fats and carbohydrates, and an increasingly inactive lifestyle.[2] Several drugs such as sulfonylurea and biguanides are presently available to reduce hyperglycemia in diabetes mellitus. These drugs have a number of side effects and thus searching for a new class of compounds is crucial to overcoming these problems. Heterocyclic compounds are the mainstay of antidiabetic therapy for many years. Also, certain hypoglycemic plants may also be useful to develop evidence-based alternative medicine to cure different kinds of diabetes in man and animals.[3] Chemistry of heterocyclic compounds is one of the leading lines of investigations in the organic chemistry. Heterocyclic compounds are widely distributed in nature and are essential for life. They play a vital role in the metabolism of all living cells. There are vast numbers of pharmacologically active heterocyclic compounds, many of which are a regular clinical use. Nitrogen, sulphur and oxygen containing five member hetero-cyclic compounds have occupied enormous significance in the field of drug discovery process.[4] Benzothiazole is a weak heterocyclic base, having varied biological

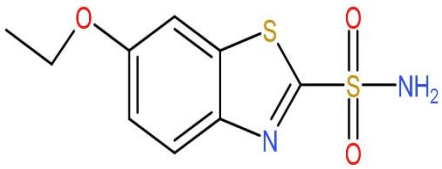
activities and of great scientific interest nowadays. Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds.[4] Benzothiazole ring system is present in various marine and terrestrial natural compounds, which have useful biological activities.[5] The benzthiazole derivatives have demonstrated efficiency in biological fields such as antitumor, antitubercular, antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antifungal, a topical carbonic anhydrase inhibitor and an anti-hypoxic. They are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of diabetes.[6,7] Due to its potent and significant biological activities, it has great pharmaceutical importance.[8,9] Benzothiazole derivatives containing benzimidazole and imidazoline ring have diverse chemical reactivity along with abroad spectrum of biological activity.[10] In view of this literature, it was of significant interest to synthesize the benzo-thiazole derivatives with an aim to obtain potent biologically active and safe anti-diabetic agents.

MARKETED PREPARATION OF BENZOTHIAZOLE

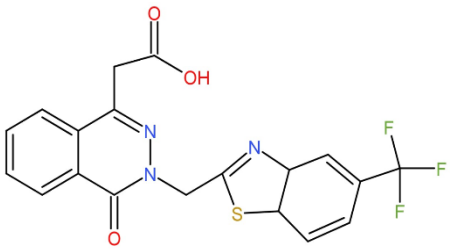
1) Riluzole



2) Zarontin

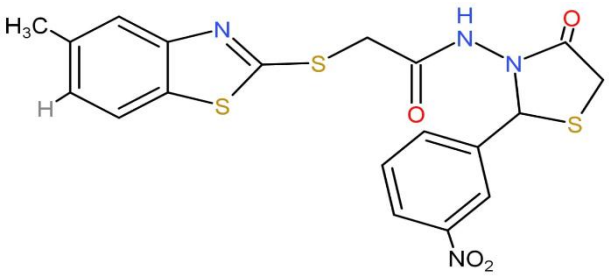


3) Zopolrestat



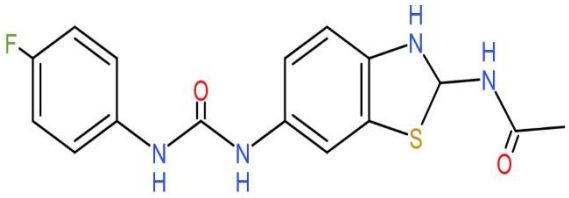
VARIOUS BENZOTHIAZOLE DERIVATIVES AS ANTIDIABETIC AGENTS

Sunil kumarb, D. S. Rathore have synthesized the benzothiazole derivatives. The synthesised derivatives were evaluated for their anti-diabetic activity in an alloxan-induced diabetic rat model. Amongst all these synthesised derivatives compound 7d 2-(5-methylbenzo[d]thiazol-2-ylthio)-N-(2-(3-nitrophenyl)4-oxothiazolidin-3-yl) acetamide demonstrated 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.[3]

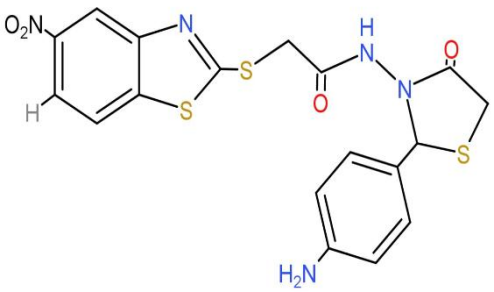


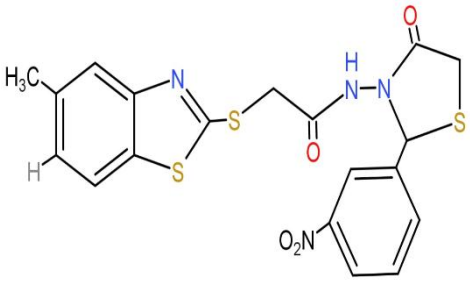
Gnanavel Sadhasivam and Kannan Kulanthai were synthesized A series of new 2,6-disubstitued benzothiazol derivatives and their anti-inflammatory and antidiabetic activities were evaluated in vitro. In anti-diabetic studies the compounds 5a N-(6-{[(4-fluorophenyl)carbamoyl]amino}-1,3-benzothiazol-2-

yl)acetamide may be potent to alpha-amylase inhibition that needs to be further studied.[5]

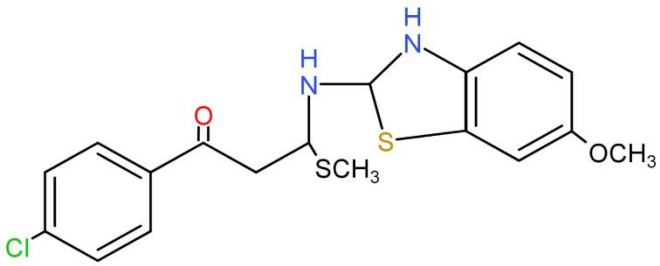


Sunil Kumar, Abhilasha Mittal have performed biological activity for the determination of anti-diabetic activity of all the synthesized benzothiazole derivatives in a Streptozocin induced diabetic rat model. The streptomycin was used to induce the diabetic hyperglycemia condition characterized with elevation of glucose level in plasma. Amongst all these synthesized derivatives compound 6f & 7d given 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.[7]

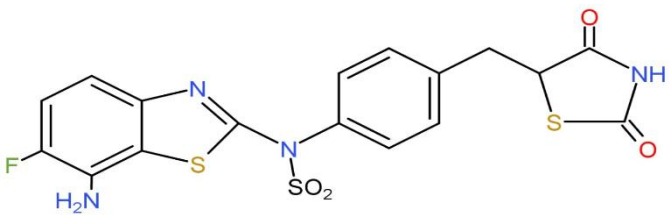




Patil et al. designed a list of novel (E)-3-(Benzo [d]thiazol-2-ylamino) phenylprop-2-en-1-ones with potent α-amylase inhibitory properties. These compounds showed promise as glycosidase inhibitors in male Swiss mice. The anti-diabetic efficacy of these compounds was assessed using standard α-amylase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

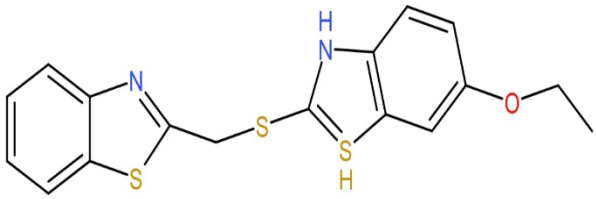


Pattan et al. created a new sequence of 2-amino[5'(4-sulphonylbenzylidine)-2,4- thiazolidinedione]-7-chloro-6-fluoro benzothiazoles, which were tested for anti-diabetic activity in albino rats using the alloxan induced tail tipping process.[13]

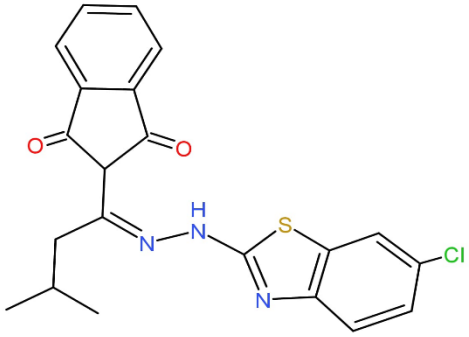


Meltzer-Mats et al. synthesized and tested a variety of substituted benzothiazole derivatives for hypoglycemic (antihyperglycemic) activity. The ethoxy benzothiazole moiety in 2- (benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazole was discovered to be important for increasing glucose transport and AMPK activation in

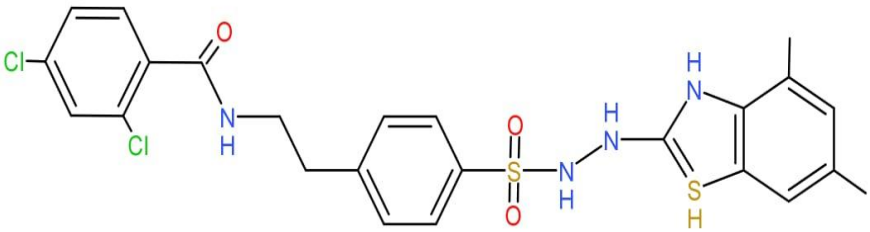
L6 myotubes. At pharmacologically important concentrations, 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazolesignificantly increased the rate of glucose absorption in L6 myotubes. The effect of 2-(benzo[d] thiazol-2-ylmethylthio)-6-ethoxybenzo[d] thiazolein on blood glucose levels in diabetic KKAy mice demonstrated which showed decrease in blood glucose level.[14]



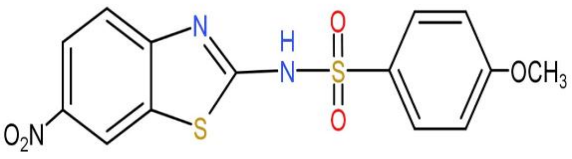
Mor et al. evaluated in vitro α-amylase inhibition activity of the synthesized compounds and in vitro α -glucosidase inhibition activity of the newly synthesized benzothiazolyl hydrazones to screen their antidiabetic activity. The norm was acarbose, and newly synthesized compounds showed promising anti-diabetic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



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 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]

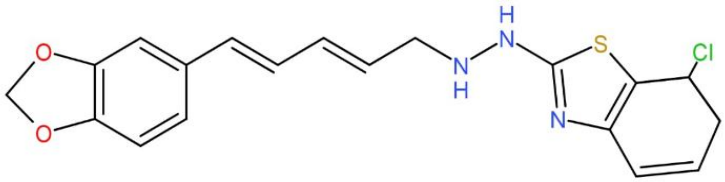


Moreno-Daz et al. synthesized a new sequence of N-(6-substituted-1,3-benzothiazol-2 yl) benzene sulfonamides and tested them for in vivo antidiabetic activity in a non-insulin-dependent diabetes mellitus rat model. Several compounds produced in this model significantly lowered plasma glucose levels.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

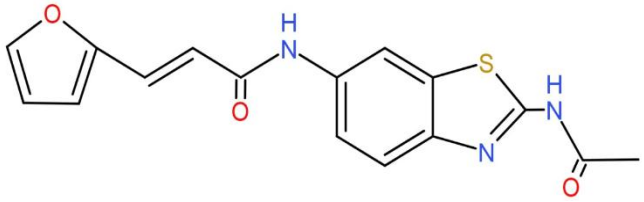


Kharbanda et al. synthesized 28 benzothiazole-based sulfonylureas/sulfonylthioureas and tested their antidiabetic effect in a normoglycemic rat model using an in vivo oral glucose tolerance test (OGTT). Ten active

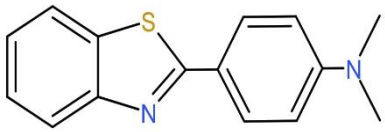
compounds were tested in vitro for PPAR-g transactivation and found to have potent anti-diabetic properties. These ten active compounds were also discovered to transactivate PPAR, so they were tested for their anti-diabetic ability in a diabetic model induced by streptozotocin (STZ). {2-[3-(4-Chloro-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]- 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]



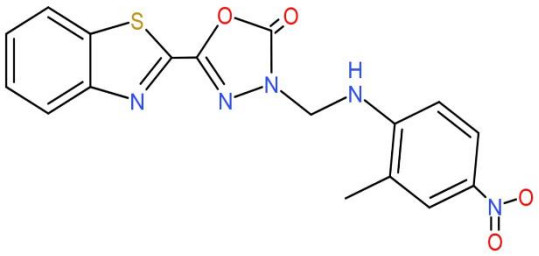
Sadhasivam et al. synthesized a new sequence of benzothiazole derivatives and used the α- amylase assay to assess their anti-diabetic activity. By inhibiting the α-amylase enzyme, (2*E*)-*N*- (2-acetamido-1,3-benzothiazol-6-yl)-3-(2- furyl)acryl amide, *N*-(6-{[(4-fluorophenyl)carbamoyl] amino}-1,3-benzothiazol-2-yl)acetamide and *N*-(6-{[(3-methoxyphenyl) carbamoyl]amino}-1,3-benzothiazol-2-yl) acetamide showed potent antidiabetic activity by inhibition of α-amylase enzyme demonstrated potent antidiabetic activity.[19]



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]



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]



CONCLUSION

The present review article, therefore, highlights the use of benzothiazole derivatives and conclude that they have a marked antidiabetic activity. Hence, this unique molecule must serve as future therapeutic leads to developing various antidiabetic agents. It is anticipated

that this study would give rise to the design of better molecules which can enhance antidiabetic properties and specificity.

REFERENCES

1. Khyati Bhagdev, Sibaji Sarkar, Benzothiazole: As An Antidiabetic Agent Annals of R.S.C.B., ISSN: 1583-6258, 2021; 25(4): 20269-20285. Revised 05 March 2021; Accepted 01 April 2021.
2. Satbir Mor, Suchita Sindhu, Synthesis, Type II diabetes inhibitory activity, antimicrobial evaluation and docking studies of indeno[1,2-c]pyrazol-4(1H)-ones, Synthesis, Type II diabetes inhibitory activity, antimicrobial evaluation and docking studies of indeno[1,2-c]pyrazol-4(1H)-ones, Received: 5 July 2019 / Accepted: 5 October 2019 / Published online: 26 October 2019.
3. Sunil kumar, D. S. Rathore, synthesis and evaluation of some benzothiazole derivatives as antidiabetic AGENTS International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vol 9, Issue 2, 2017.
4. Ivan H. R. Tomi, Jumbad H. Tomma Synthesis, characterization and comparative study the microbial activity of some heterocyclic compounds King Saud University Journal of Saudi Chemical Society, 27 April 2012.
5. Gnanavel Sadhasivam and Kannan Kulanthai, Synthesis, characterization, and evaluation of anti-inflammatory and anti-diabetic activity of new benzothiazole derivatives, Journal of Chemical and Pharmaceutical Research, 2015; 7(8): 425-431.
6. Shubham Abrol, R. B. Bodla and Chatinaya Goswami, A comprehensive review on benzothiazole derivatives for their biological activities, International Journal of Pharmaceutical Sciences and Research IJPSR (2019), Volume 10, Issue 7 Received on 23 October 2018; received in revised form, 07 February 2019; accepted, 08 March 2019; published 01 July 2019.
7. Sunil Kumar, Abhilasha mittal, biological assessments of substituted benzothiazole derivatives in streptozocin induced diabetes rats Plant Archives, 2020; 20(Supplement 2): 3250-3253. e-ISSN:2581-6063 (online), ISSN:0972-5210.
8. Ruhi Ali and Nadeem Siddiqui, Review Article Biological Aspects of Emerging Benzothiazoles: A Short Review, Hindawi Publishing Corporation Journal of Chemistry Volume 2013, Article ID345198, 12 pages, Received 10 May 2013; Accepted 29 June 2013.
9. Mariappan G, Prabhat P, Sutharson L, Synthesis and Antidiabetic Evaluation of Benzothiazole Derivatives, Journal of the Korean Chemical Society, 2012; 56: 2. Printed in the Republic of Korea, (Received February 18, 2012; Accepted March 27, 2012.
10. S. R Pattan, Ch Suresh, Synthesis and antidiabetic activity of 2-amino [5'(4-sulphonylbenzilidine)-2,4-thiazolidinedione]-7-chloro-6-flurobenzothiazole Indian Journal of Chemistry Vol. 44B, November 2005.
11. Prabodh Chander Sharma, Alka Sinhmar, review article, Medicinal significance of benzothiazole scaffold: an insight view, Journal of Enzyme Inhibition and Medicinal Chemistry.
12. Patil VS, Nandre KP, Ghosh S, Rao VJ, Chopade BA, Sridhar B, Bhosale SV and Bhosale SV, "Synthesis, crystal structure and antidiabetic activity of substituted (E)-3-(Benzo [d]thiazol-2-ylamino) phenylprop-2-en-1-one." European journal of medicinal chemistry, Jan 2013; 59: 304-309.
13. Pattan SR, Suresh CH, Pujar VD, Reddy VV, Rasal VP and Koti BC, "Synthesis andantidiabetic activity of 2-amino [5'(4-sulphonylbenzylidine)-2, 4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole." Indian Journal of Chemistry, 2005; 44B: 2404-2408.
14. Meltzer-Mats E, Babai-Shani G, Pasternak L, Uritsky N, Getter T, Viskind O, Eckel J, Cerasi E, Senderowitz H, Sasson S and Gruzman A, "Synthesis and mechanism of hypoglycemic activity of benzothiazole derivatives." Journal of medicinal chemistry, July 2013; 56(13): 5335-5350.
15. Mor S, Sindhu S, Khatri M, Singh N, Vasudeva N and Panihar N, "Synthesis, type II Diabetes inhibitory activity, and antimicrobial tests of benzothiazole derivatives bridged with indenedione by methylenehydrazone." Russian Journal of General Chemistry, Sept. 2019; 89(9): 1867-1873.
16. Ahmadi A, Khalili M, Ghaderi P, Rastegar G and Nahri-Niknafs B, "Synthesis and bloodglucose and lipid-lowering effects of benzothiazole-substituted benzenesulfonylurea derivatives." Monatshefte für Chemie-Chemical Monthly, Jan 2015; 146(12): 2059-2065.
17. Moreno-Díaz H, Villalobos-Molina R, Ortiz-Andrade R, Díaz-Coutiño D, Medina-Franco JL, Webster SP, Binnie M, Estrada-Soto S, Ibarra-Barajas M, Leon-Rivera I and NavarreteVázquez G, "Antidiabetic activity of N-(6-substituted-1, 3-benzothiazol-2-yl) benzenesulfonamides." Bioorganic & Medicinal Chemistry Letters, May 2008; 18(9): 2871-2877.
18. Kharbanda C, Alam MS, Hamid H, Javed K, Bano S, Ali Y, Dhulap A, Alam P and Pasha MA, "Novel benzothiazole based sulfonylureas/sulfonylthioureas: design, synthesis and evaluation of their antidiabetic potential." New Journal of Chemistry, 2016; 40(8): 6777-6786.
19. Sadhasivam G, Kulanthai K, "Synthesis, characterization, and evaluation of antiinflammatory and anti-diabetic activity of new benzothiazole derivatives." J. Chem. Pharm. Res, 2015; 8: 425-431.
20. Puranik NV, Puntambekar HM, Srivastava P, "Antidiabetic potential and enzyme kineticsof benzothiazole derivatives and their non-bonded interactions with α-glucosidase and αamylase." Medicinal Chemistry Research, Apr 2016; 25(4): 805-816.

21. Bhutani R, Pathak DP, Kapoor G, Husain A, Kant R and Iqbal MA, "Synthesis, molecularmodelling studies and ADME prediction of benzothiazole clubbed oxadiazole-Mannich bases, and evaluation of their anti-diabetic activity through in vivo model." Bioorganicchemistry, Apr 2018; 77: 6-15.