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A Study on Determination of *In-vitro* Antidiabetic Potential of Synthetic Oxadiazole Derivatives

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Abstract

Synthetic oxadiazole-containing compounds have a wide range of pharmacological effects, including analgesic, antibacterial, antitubercular, antioedema, anti-inflammatory, and anticonvulsant properties. One of the major public health issues of the twenty-first century is the prevalence of type 2 diabetes, which is rising in both developed and developing nations. Pharmaceuticals used to treat diabetes often contain a number of compounds with heterocyclic rings. The oxadiazole derivatives belong to the heterocyclic family and have numerous promising pharmaceutical uses. Very few studies have been done on the anti-diabetic properties of synthetic oxadiazole derivatives. The current study was conducted with the main aim of determination of *in-vitro* antidiabetic activities of synthetic oxadiazole derivatives. Three commercially available synthetic oxadiazole derivatives (SODZs) *viz.* $SODZ_1$, $SODZ_2$, andSOD_3 were determined for *in-vitro* antidiabetic activity by alpha-glucosidase inhibitory activity method. Results revealed that $SODZ_1$ showed significant inhibition for alpha-glucosidase enzyme. $SODZ_1$ exhibited high percentage inhibition (37.97%) and the IC_{50} value of SODZ1 was found to be 48.12µg which was comparable with that of the IC_{50} value of standard acarbose (31.23µg). In conclusion, $SOZD_1$ was proved to probable drug molecule for the treatment of diabetes.

Keywords: Synthetic oxadiazole derivative (SOZD).Diabetes, Alpha-glucosidase, Inhibition,

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Introduction

Diabetes mellitus, a chronic, progressive condition associated with multiple metabolic disorders is caused either by the body's inability to produce adequate amounts of insulin or lack of response to the produced insulin or both. Genetically defective pancreatic cells act as one of the causes for the inefficiency of insulin. Age, obesity and lack of physical activity also contribute to the cause. This leads to a significant increase in the blood glucose level for a prolonged period of time. Insufficient metabolism of carbohydrates, lipids and proteins as well as hypertension and hyperlipidemia are some of the major symptoms associated with diabetes. The disease not only causes prolonged damage, dysfunction and failing of different body organs, but also ketoacidosis or non-keto hyperosmolar state in severe conditions, leading to stupor, coma and death if not treated effectively.[1-4]

Type 2 diabetes is one of the global public health concerns in the 21st century,[5]in both developed and the developing countries are experiencing increasing rates of diabetes.[6] Hyperglycemia impairs endogenous antioxidant defenses due to the induction of oxidative stress, which induces the destruction of pancreatic beta cells by the uncontrolled production of free radicals such as ROS, leading to multiple micro and macrovascular disorders.[7-10] Onestrategy to manage type 2 diabetes is to delay glucose uptake by inhibiting α-glucosidase enzymes, which can reduce postprandial hyperglycemia.[11-15]

Insulin, an endocrine peptide hormone, produced in the beta cells of pancreas, is responsible for the glucose uptake and its utilization by the body tissue rendering hypoglycemic effects and the autoimmune destruction of these cells leads to insulin deficiency causing type I diabetes or insulin abnormalities which results in resistance to insulin action, leading to type II diabetes.[16,17]Type I accounts for about 10% while Type II, also called adult-onset diabetes, makes up to 90% of the global diabetic cases.[18-20]By 2030, 50% of the adult population of economically advanced countries are predicted to be diagnosed

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with type II diabetes, mainly due to the contributions of increasing urbanization, aging populations, obesity and sedentary lifestyles.[21,22]

Several compounds containing heterocyclic rings are important components of antidiabetic pharmaceutical products. Nitrogen, sulfur, and oxygen containing heterocyclic compounds have attracted the attention of medicinal chemical due to their wide range of biological applications. Among the heterocyclic family, 1,3,4-oxadiazole derivatives have shown many promising applications in pharmaceuticals.[23,24]Literature reports revealed that Oxadiazole-derivatives possess biological activities such as antibacterial,[25] antifungal,[26] anti-inflammatory,[27] antihypertensive,[28] antiviral,[29] antidiabetic,[30]anticonvulsant,[31] and anticancer activities.[32] With this background, present study was conducted with the main purpose of determination of in-vitro antidiabetic activities of synthetic oxadiazole derivatives.

Materials and Methods

All the chemicals and reagents were of Analytical grade and procured from Ranbaxy. Three different varieties of synthetic oxadiazole derivatives(SODZ) *viz.* $SODZ_1$, $SODZ_2$, and $SODZ_3$used in this study were purchased commercially.

***In-vitro* Antidiabetic Activity Determination**

The in-vitro antidiabetic activity of three different varieties of SODZs*viz.* $SODZ_1$, $SODZ_2$, and $SODZ_3$was determined by alpha-glucosidase inhibitory activityby modified method of Shai et al. Briefly, 400 µl of α-glucosidase (0.067 U/mL) was preincubated with different concentrations (i.e., 25, 50, and 100 µg) of the SODZsfor 30 min. Then 200 µl of 3.0 mM (pNPG) used as substrate dissolved in 0.1M sodium phosphate buffer (pH 6.9) was then added to start the reaction. The reaction mixture was incubated at 37°C for 30 min and stopped by adding 2 mL of 0.1 M Sodium carbonate (Na_2CO_3) solution. The α-glucosidase activity was determined by measuring the yellow-colored para-nitro phenol released from pNPG at 400 nm. The results were expressed as a percentage of inhibition. The same procedure was done with Acarbose (1mg/ml stock) which was used as standard. The

inhibition percentage was calculated by using below formula;[33] IC_{50} value was calculated by using regression analysis.[34]

$$\% \text{ Inhibition} = (A_{standard} - A_{sample}) / A_{standard} \times 100.$$

Results and Discussion

The results and alpha-glucosidase inhibition percentage of Standard (Acarbose), $SODZ_1$, $SODZ_2$, and $SODZ_3$ was represented in Table 1. The IC_{50} values of Standard (Acarbose)and $SODZ_1$, $SODZ_2$, and $SODZ_3$was plotted in Figure 1. Results depicted that $SODZ_1$ showed significant inhibition for alpha-glucosidase enzyme (Figure 1). The $SODZ_1$ exhibited high percentage inhibition of alpha-glucosidase (37.97%) and the IC_{50} value of $SODZ_1$ was found to be 48.12µg (Table 1) which was comparable with that of the IC_{50} value of standard (31.23µg).

Table 1: Effect of SODZs on alpha-glucosidase inhibition activity

Sample	Conc. (µg)	Inhibition (%)	IC_{50}
Standard	25	62.13	31.23
	50	85.46	
	100	86.64	
$SODZ_1$	25	9.42	48.12
	50	15.55	
	100	37.97	
$SODZ_2$	25	7.90	61.03
	50	10.85	
	100	21.95	
$SODZ_3$	25	7.54	69.45
	50	15.86	
	100	24.23	

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Values were expressed as Mean; n=3

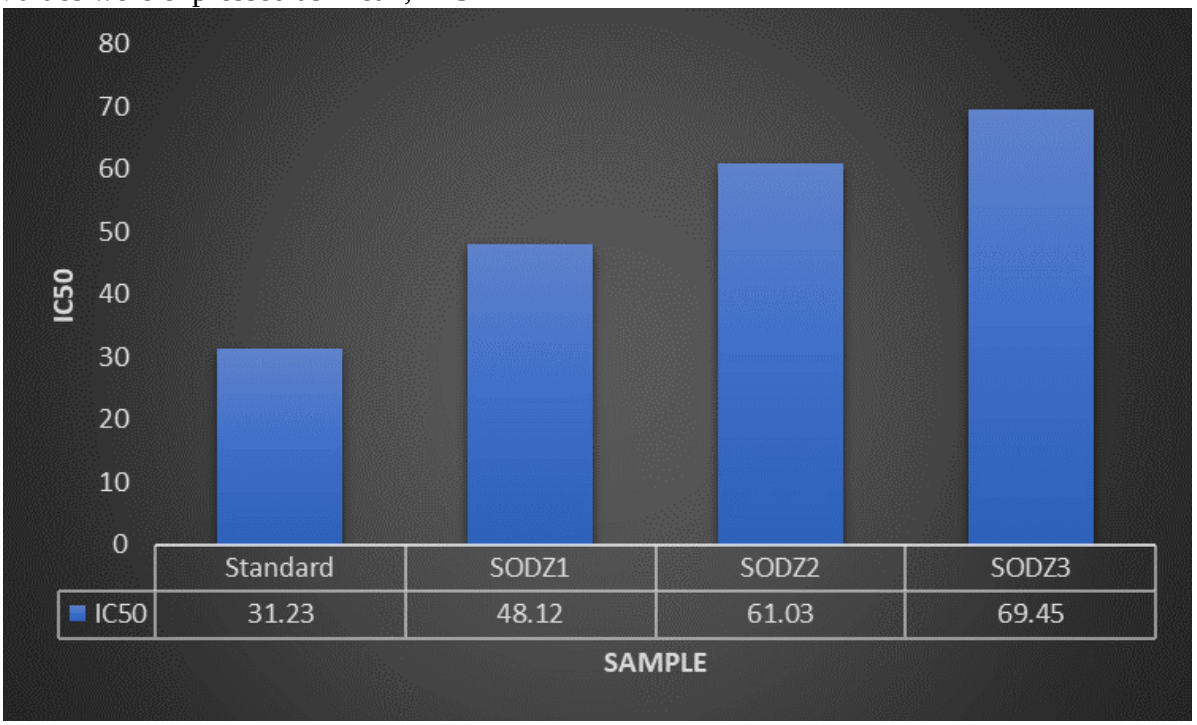

Figure 1: IC_{50} values of SODZs and standard (Acarbose)

Digestive enzymes such as alpha-glucosidase and alpha-amylase convert starch into glucose and maltose in the intestine.[35] Therefore, the inhibitors of such enzymes are used to manage Type-II diabetes.[36] In the present study, the results of alpha-glucosidase inhibition assay of SODZs depicted that maximum inhibition percent (37.97%) with $SODZ_1$ at the concentration 100µg with IC_{50} value of 48.12µg. These findings indicated that SODZs may be used to decrease glucose availability from the intestine from digestible carbohydrates, hence may be used as an oral anti-hyperglycemic agent. Furthermore, in the present study the percentage inhibition of alpha-glucosidase activity of SODZs was in the rage of 7-38% and IC_{50} values of SODZs was in the range of 48-60µg. Gani et al., reported the IC_{50} value of the compounds *viz.*oxadiazole-2-thiols for inhibition of α-glucosidase in the range of 46.01-81.65 µg/ml and has good glucose lowering potential in comparison to the standard Acarbose.[37]

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Conclusion

The results of our study clearly demonstrated that $SODZ_1$ exhibited high percentage inhibition with IC_{50} value 48.12µg which was comparable with that of the IC_{50} value of standard Acarbose. Hence, findings of our study delineated $SOZD_1$ was proved to probable drug molecule for the treatment of diabetes. However, further studies could be recommended to carried to elucidate the exact mechanism of action of $SOZD_1$ as potential antidiabetic drugs.

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References

1. Mahler RJ, Adler ML. Clinical review 102: Type 2 diabetes mellitus: update on diagnosis, pathophysiology, and treatment. J Clin Endocrinol Metab. 1999;84(4):1165-71.
2. Nishath M, Azeem A, Veena S, Kumar KR. An overview on newer antidiabetic agents. Pharm Res. 2019;9(09).
3. Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R et al. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol. 2017; 8:6.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33; Suppl 1(Supplement_1): S62-9: S62-9.
5. Ginter E, Simko V. Type 2 diabetes mellitus, Pandemic in 21st Century Diabetes. Adv Exp Med Biol. 2012; 771:42-50.
6. Misra A, Gopalan H, Jayawardena R, P Hill A, Soares A, Reza-Albarran AA, Ramaiya KL. Diabetes in developing countries. J Diabetes. 2019:11(7):522539.
7. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress-A concise review. Saudi Pharm J. 2016;24(5):547-53.
8. Tiwari BK, Pandey KB, Abidi AB, Rizvi SI. Markers of oxidative stress during diabetes mellitus. J Biomark. 2013; 2013:378790.
9. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ Med J. 2012;12(1):5-18.
10. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J. 2013;34(31):2436-43.

11. Leroux-Stewart J. Rabasa-Lhoret R, Chiasson J-L. In:. In: α-Glucosidase inhibitors DeFronzo RA, Ferrannini E, Zimmet P, Alberti KGMM, editors. International textbook of diabetes mellitus; 2006. p. 322-31.
12. Hati S, Madurkar SM, Bathula C, Thulluri C, Agarwal R, Siddiqui FA et al. Design, Synthesis and biological evaluation of small molecules as potent glucosidase inhibitors. Eur J Med Chem. 2015; 100:188-96.
13. Kumar S, Narwal S, Kumar V, Prakash O. αglucosidase inhibitors from plants: A natural approach to treat diabetes. Pharmacogn Rev. 2011;5(9):19-29.
14. Yin Z, Zhang W, Feng F, Zhang Y, Kang W. α-glucosidase inhibitors isolated from medicinal plants. Food Sci Hum Wellness. 2014;3(3-4):136-74.
15. Khosravi A, Vaezi G, Hojati V, Abdi K. Study on the interaction of triaryl-dihydro-1,2,4-oxadiazoles with α-glucosidase. Daru. 2020;28(1):109-17.
16. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ et al. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015;1(1):15019.
17. Kahn CR. The molecular mechanism of insulin action. Annu Rev Med. 1985;36(1):429-51.
18. Kaul K, Tarr JM, Ahmad SI, Kohner EM, Chibber R. Introduction to diabetes mellitus. Diabetes. 2013:1-.
19. Forouhi NG, Wareham NJ. Epidemiology of diabetes. Medicine. 2010;38(11):602-6.
20. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010;39(3):481-97.
21. Ginter E, Simko V. Type 2 diabetes mellitus, pandemic in 21st century. Diabetes. 2013:42-50.
22. Antony J, Debroy S, Manisha C, Thomas P, Jeyarani V, Choephel T. In-vitro cell line models and assay methods to study the anti-diabetic activity. Res J Pharm Technol. 2019;12(5):2200-6.

23. Mohammed Iqbal AKM, Khan AY, Kalashetti MB, Belavagi NS, Gong YD, Khazi IAM. Synthesis, hypoglycemic and hypolipidemic activities of novel thiazolidinedione derivatives containing thiazole/triazole/oxadiazole ring. Eur J Med Chem. 2012; 53:308-15.
24. McCoull W, Addie MS, Birch AM, Birtles S, Buckett LK, Butlin RJ et al. Identification, optimization and in vivo evaluation of oxadiazole DGAT-1 inhibitors for the treatment of obesity and diabetes. Bioorg Med Chem Lett. 2012;22(12):3873-8.
25. Suresh L, Sagar Vijay Kumar P, Poornachandra Y, Ganesh Kumar C, Chandramouli GVP. Design, synthesis and evaluation of novel pyrazolo-pyrimido[4,5d] pyrimidine derivatives as potent antibacterial and biofilm inhibitors. Bioorg Med Chem Lett. 2017;27(6):1451-7.
26. Zhang J, Peng JF, Bai YB, Wang P, Wang T, Gao JM et al. Synthesis of pyrazolo[1,5a]pyrimidine derivatives and their antifungal activities against phytopathogenic fungi in vitro. Mol Divers. 2016;20(4):887-96.
27. Mohamed MS, Kamel R, Fatahala SS. Synthesis and biological evaluation of some thio containing pyrrolo[2,3-d]pyrimidine derivatives for their anti-inflammatory and anti-microbial activities. Eur J Med Chem. 2010;45(7):2994-3004.
28. Alam O, Khan SA, Siddiqui N, Ahsan W, Verma SP, Gilani SJ. Antihypertensive activity of newer 1,4-dihydro-5-pyrimidine carboxamides: synthesis and pharmacological evaluation. Eur J Med Chem. 2010;45(11):5113-9.
29. Hafez HN, Hussein HA, El-Gazzar AR. Synthesis of substituted thieno[2,3-d]pyrimidine-2,4dithiones and their S-glycoside analogues as potential antiviral and antibacterial agents. Eur J Med Chem. 2010;45(9):4026-34.
30. Hese SV, Meshram RJ, Kamble RD, Mogle PP, Patil KK, Kamble SS et al. Antidiabetic and allied biochemical roles of new chromeno-pyrano pyrimidine

compounds: synthesis, in vitro and in silico analysis. Med Chem Res. 2017;26(4):805-18.

31. Wang SB, Deng XQ, Zheng Y, Yuan YP, Quan ZS, Guan LP. Synthesis and evaluation of anticonvulsant and antidepressant activities of 5alkoxytetrazolo[1,5-c]thieno[2,3-e]pyrimidine derivatives. Eur J Med Chem. 2012; 56:139-44.
32. Ismail KB, Thalari G, Bommarapu V, Mulakayala C, Chitta SK, Mulakayala N. Synthesis of novel spiro pyrazolo [4,3-d] pyrimidinones and spiro[benzo[4,5]thieno[2,3-d]pyrimidine-2,3′indoline]-2′,4(3H)-diones and their evaluation for anticancer activity. Bioorg Med Chem Lett. 2017; 27:1446-50.
33. Xiao Z, Storms R, Tsang A. A quantitative starch? Iodine method for measuring alpha amylase and glucoamylase activities. Anal Biochem. 2006;351(1):146-8.
34. Uddin N, Hasan MR, Hossain MM, Sarker A, Hasan AH, Islam AF et al. In vitro α–amylase inhibitory activity and in vivo hypoglycemic effect of methanol extract of *Citrus macroptera* Montr. fruit. Asian Pac J Trop Biomed. 2014;4(6):473-9.
35. Bhat M, Zinjarde SS, Bhargava SY, Kumar AR, Joshi BN. Antidiabetic Indian plants: a good source of potent amylase inhibitors. Evid Based Complement Alternat Med. 2011; 2011:810207.
36. Winterbourn CC, Metodiewa D. The reaction of superoxide with reduced glutathione. Arch Biochem Biophys. 1994;314(2):284-90.
37. Gani RS, Kudva AK, Timanagouda K, Mujawar SB, Joshi SD, Raghu SV. Synthesis of novel 5-(2, 5-bis (2, 2, 2-trifluoroethoxy) phenyl)-1, 3, 4-oxadiazole-2-thiol derivatives as potential glucosidase inhibitors. Bioorg Chem. 2021; 3:4-.