RESEARCH ARTICLE

Synthesis, Characterization and Biological Evaluation of Glycogen Synthase Kinase-3β Inhibitors as Antidiabetic Agents

Ankit Mangal[1*], Neelesh Malviya[2]

[1]*Mandsaur University, Mandsaur, Madhya Pradesh, India.*
[2]*Smriti College of Pharmaceutical Education, Indore, Madhya Pradesh, India.*

Received: 20th December, 2022; Revised: 28th March, 2023; Accepted: 29th May, 2023; Available Online: 25th June, 2023

ABSTRACT

Diabetes is a substantially growing unhealthiest in the globe that causes severe morbidity and mortality. Currently a day's there's an imperative for the invention, development and improvement of novel antidiabetic drug molecules. A chain of compound (5-imidazol-2-yl-4-phenylpyrimidin-2-yl) [2-(2- pyridyl amino) ethyl] amine were developed and synthesized by using suitable chemical synthetic techniques. These recently synthesized derivatives were characterized with the help of modern analytical techniques. This compound was evaluated for glycogen synthase kinase-3 enzyme inhibitor activities for managing of polygenic disease. GSK-3 inhibitors may advance and emerge as a novel strategy for the management of diabetes.

Keywords: Diabetes, Glycogen synthase kinase, Synthesis, Characterization, Hypoglycemic activity.

International Journal of Pharmaceutical Quality Assurance (2023); DOI: 10.25258/ijpqa.14.2.15

How to cite this article: Mangal A, Malviya N. Synthesis, Characterization and Biological Evaluation of Glycogen Synthase Kinase-3β Inhibitors as Antidiabetic Agents. International Journal of Pharmaceutical Quality Assurance. 2023;14(2):330-333.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Diabetes mellitus (DM) is a long-standing metabolic disorder signalized by excessively high glucose levels in blood called hyperglycemia.[1] DM is one of the primary disorders related to the endocrine gland, affecting about 5% of the entire globe's populace. DM is one of the oldest sicknesses and has been referred for approx three thousand years a long gone.[2,3] Polygenic sickness can be a cluster of metabolic disorders with a trendy manifestation- hyperglycemia. Continual hyperglycemia harms various body parts and organs like kidneys, eyes, nervous system, cardiac and blood vessels. It is due to a deficiency of innate and/or not acquired inside the manufacturing of exocrine gland inner emission, or a deficiency of inner secretion.[4] Its outcomes are either from the scanty secretion of the hormone insulin, a scanty reaction of goal cells to insulin, or a mixture of those factors. This disorder calls for clinical analysis, remedy and adjustments in lifestyle. The management of diabetes is an international difficulty now and worthwhile treatment isn't yet observed. Many synthetic treatments are designed for patients, but the truth is that no one should be cured of diabetes.[5] DM is classified based on its etiology and pharmacological representation. Consequently, DM are classified in four major category- type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types of diabetes. Some diabetic cases in individual patients cannot be appropriate in any category.[6] Glycogen synthase kinase-3 (GSK-3) was identified more than two decennia ago to control glycogen metabolism. Glycogen synthase kinase-3 is an enzyme having ability to phosphorylate and inhibit glycogen synthase. The phosphorylation and inactivation of the rate-limiting enzyme glycogen synthase reduces glycogen production in resting cells.[7,8] Three GSK-three eye types had been identified in mammals, GSK3α, GSK-three β, and GSK threeβ2 (distinct from GSK-three β). α and β isoforms are show remarkable deviations in the protein abundance.[9]

MATERIAL AND METHODS

The starting materials such as required chemicals, raw materials, solvent and reagents used within the synthesis of the designed ad mixture, have been of synthetic class. Compounds' Melting points were determined using a capillary melting pointed apparatus and Thiele's apparatus. The development of response turned into monitored by means of TLC performed on a silica gel G-covered plate. The purification of compounds obtained in the intermediate step was carried out through the recrystallization method and column chromatography technique.[10-12]

General Synthesis of the Compound

For the synthesis of the compound equimolar amounts of tert-butyl 2-aminoethylcarbamate and tert-butyl 2-guanidinoethylcarbamate were added in presence of 1H-pyrazole-1-carboxamidine hydrochloride. In the clean and

**Author for Correspondence: ankitmangal75@gmail.com*

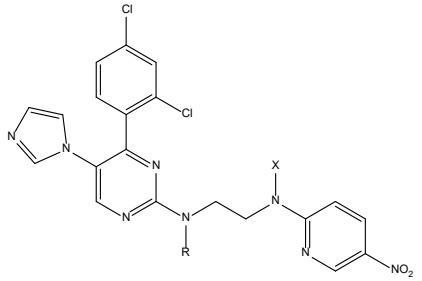

Figure 1: Chemical structure of (5-Imidazol-2-yl-4-Phenylpyrimidin-2-yl) [2-(2-Pyridylamino) Ethyl] Amine derivative

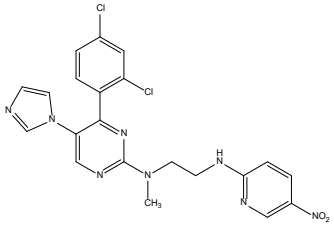

Figure 2: Structure of compound A-01 Considered for Synthesis

dry round bottom flask (100 mL) this mixture was taken and heated with stirring at reflux condition for 24 hours at 80°C. The end of the reaction progress was examined by using TLC techniques. The resulting product obtained was poured into crushed ice, filtered and extracted with petroleum ether and ethyl acetate (2:8). The compounds were recrystallized from ethanol to give a pure product.[13]

Structure of Proposed Synthesise Compound[14]

Structure of proposed Synthesise compound chemical structure of (5-Imidazol-2-yl-4-Phenylpyrimidin-2-yl) [2-(2-Pyridylamino) Ethyl] Amine derivative as shown in Figure 1.

Compound Code and Structure of Selected Compounds Considered for Synthesis

Compound Code and structure of selected compounds considered for synthesis as shown in Table 1 and Figures 2 to 6.

General Synthetic Scheme

The designed compounds had been synthesized by the usage of the subsequent scheme, which is divided into different steps as shown in Figure 7.

Reagents and Conditions[15]

Reagents and Conditions of proposed Synthesise compound as shown in Table 2.

Biological Evaluation of Compounds

To start with, enzyme solution becomes organized through in 10 mL ethyl alcohol dissolving 0.5 mg of enzyme to and in another clean and dry beaker a 0.1 molar of phosphate buffer was prepared for maintain pH and mixture of 5 mM p-nitrophenyl-α-D-glucopyranoside prepared by way of adding 15 mg substrate solution to 100 mL ethyl alcohol. The manipulated test sample changed into formed by taking a concentration of 200 mL enzyme,1200 mL buffer solution and substrate. For 5 mL, ethyl alcohol was turned into brought to

Table 1: Compound Code and structure of selected compounds

Compound No.	*R*	*X*
Compound A-01	CH_3	H
Compound A-02	OH	C_2H_5
Compound A-03	CH_3	CH_3
Compound A-04	OH	H
Compound A-05	OH	OCH_3

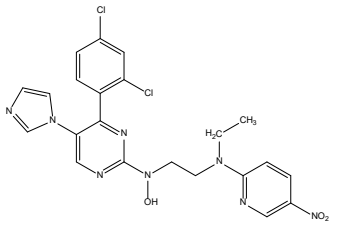

Figure 3: Structure of compound A-02 considered for synthesis

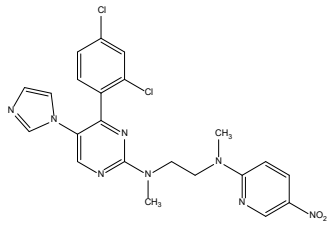

Figure 4: Structure of compound A-03 considered for synthesis

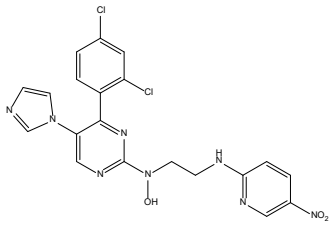

Figure 5: Structure of compound A-04 considered for synthesis

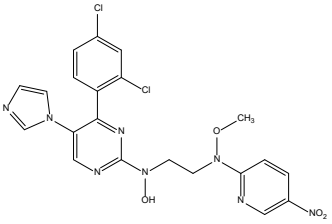

Figure 6: Structure of compound A-05 considered for synthesis

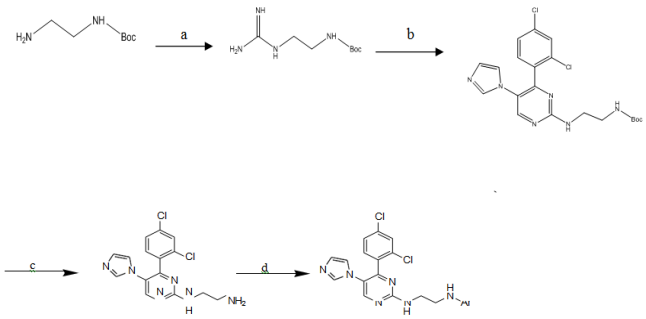

Figure 7: General synthetic scheme of designed compound

Table 2: Reagents and conditions during synthesis

Step	*Reagent*	*Temperature (°C)*	*Time (hours)*
(1)	1H-pyrazole-1-carboxamidine hydrochloride, methyl cyanide	80	24
(2)	1-(2,4-dichlorophenyl)-3-(dimethylamino)-2-imidazolylprop-2-en-1-one, Cesium Carbonate, n-methyl-2-pyrrolidone (NMP)	100	48
(3)	aqueous Hydrochloric Acid (3 Molar), Methyl cyanide	25	16
(4)	chloro-arene, hunig's base (N, N-Diisopropylethylamine) Dimethylformamide (DMF)	80	12

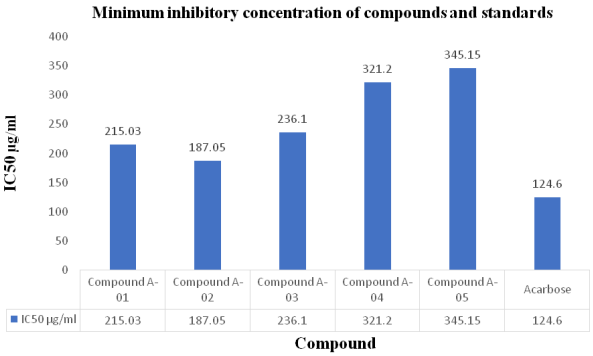

Figure 8: Minimum inhibitory concentration (MIC) of synthesized compounds and standards

this tube, then incubated for half an hour. Reading taken the use of UV spectrophotometer at wavelength 400 nm. Various concentrations of selected compound of test samples have been made in six exceptional concentrations (50, 100, 150, 200, 250 and 300 mL, respectively) by adding to the enzyme-substrate mixture in the clean and dry test tube. This was kept for half hour under incubation conditions at 400 nm their absorbance reading was taken. Acarbose is used as a standard, and finally, in the samples, enzyme inhibitory rates were calculated.[16]

$$\% \text{ inhibition} = 100 \times [1 - (X - MIN) / (MAX - MIN)]$$

RESULT AND DISCUSSION

This study synthesized a series of 05 (A01 to A05) new compounds. Then determine purity of the newly synthesized compounds with the help of TLC the by applying specific concentration of mobile bases in TLC. Spectral analysis also is done to determine all newly synthesized compounds during identification and study (Table 3).

The entire novel synthesized compounds and their spectral analytical data have been in full conformation and chemical structures. The data and records of analytical data of novel synthesized compounds are shown in Tables 4-8.

Synthesized compounds were also screened for antidiabetic activity. Antidiabetic activities of the synthesized compounds are shown in Table 9.[17-19]

Table 4: Spectral data and analytical records of compound A01

IR ($cm^{-1,}$ KBr)	1627 (Ar), 3286, 3109 (N-H, Str), 1627, 1542 (N-H, Bend), 1697, 1627 (C=N), 1697, 1542 (C=C), 1627 & 1442 (Ar).
^{1}H-NMR (δ ppm)	7.26; 7.28; 7.71; 7.75 (q, 4H, Ar - H), 4.49 (s, 1H, N - H), 6.92; 6.94 (d, 1H, but - CH), 7.15; 7.21; 7.30 (m, 5H, Ar - H)
^{13}C-NMR (δ ppm)	115.4; 122.4; 123.4; 115.4; 137.86; 139.1 (m, 6C, Ar - C), 142.35 (s, 1C,N- C), 113.2; 134.1 (d, 2C, but- CH), 127.06; 128.17; 128.17; 128.16; 127.06; 135.3 (m, 6C, Ar -C)
Mass (m/z)	484

Table 5: Spectral data and analytical records of compound A02

IR ($cm^{-1,}$ KBr)	1596 & 1350 (Ar), 3471, 2985 (N-H, Str), 1666, 1573 (N-H, Bend), 1704, 1666 (C=N), 1704, 1596 (C=C), 1573 & 1350 (NO_2).
^{1}H-NMR (δ ppm)	7.66; 7.26; 7.26; 7.66 (q, 4H, Ar - H), 4.39 (s, 1H, N - H), 7.13; 7.28 (d, 1H, but - CH), 7.56; 7.57; 8.14; 8.14 (q, 4H, Ar - H).
^{13}C NMR (δ ppm)	114.92; 140.27; 141.92; 114.92; 123.4; 123.9 (m, 6C, Ar - C), 141.9 (s, 1C,N- C), 114.9; 132.51 (d, 2C, but- CH), 127.3; 121.8; 147.19; 120.8; 127.03; 141.9 (m, 6C, Ar - C).
Mass (m/z)	516.45

Table 6: Spectral data and analytical records of compound A03

IR ($cm^{-1,}$ KBr)	1596 & 1350 (Ar), 3471, 2985 (N-H, Str), 1666, 1573 (N-H, Bend), 1704, 1666 (C=N), 1704, 1596 (C=C), 1573 & 1350 (NO_2).
^{1}H NMR (δ ppm)	7.70; 7.26; 7.26; 7.70 (q, 4H, Ar - H), 5.0 (s, 1H, N - H), 7.24; 7.10 (d, 1H, but - CH), 7.69; 7.47; 8.07; 8.23 (q, 4H, Ar - H).
Mass (m/z)	498

Table 3: Melting point, Rf value, %yield of synthesize compound

Compound code	*Thin layer chromatography*		*%yield (%)*	*Solubility*	*Melting point (°C)*
	Solvent system	*Rf value*			
A-01	Hexane and ethyl acetate (3:7)	0.62	78.52	Ethyl acetate, DMSO	155–158
A-02	Hexane and ethyl acetate (3:7)	0.69	58.58	Ethyl acetate, DMSO	135–137
A-03	Hexane and ethyl acetate (3:7)	0.63	32.62	Ethyl acetate, DMSO	117–120
A-04	Hexane and ethyl acetate (3:7)	0.52	65.53	Ethyl acetate, DMSO	112–115
A-05	Hexane and ethyl acetate (3:7)	0.52	76.32	Ethyl acetate, DMSO	181–184

Table 7: Spectral data and analytical records of compound A04

IR ($cm^{-1,}$ KBr)	1596 & 1350 (Ar), 3471, 2985 (N-H, Str), 1666, 1573 (N-H, Bend), 1704, 1666 (C=N), 1704, 1596 (C=C), 1573&1350 (NO_2).
^{1}H NMR (δ ppm)	7.96; 8.19; 8.63 (t, 4H, Ar - H), 5.49 (s, 1H, N - H), 6.99; 6.99 (d, 1H, but - CH), 7.90; 7.21; 7.14: 7.21 (m, 5H, Ar - H)
Mass (m/z)	486

Table 8: Spectral data and analytical records of compound A05

IR ($cm^{-1,}$ KBr)	1589 & 1357 (Ar), 3456, 3116 (N-H,Str), 1666, 1558 (N-H, Bend), 1712, 1656 (C=N), 1586 & 1359 (Ar), 1558 & 1357 (CH_3).
^{1}H NMR (δ ppm)	7.70; 7.26; 7.26; 7.70 (q, 3H, Ar - H), 5.08 (s, 1H, N - H), 6.88; 6.93; 6.72 (t, 4H, Ar - H), 3.73; 3.73 (d, 1H, OCH_3)
Mass (m/z)	516

Table 9: Minimum inhibitory concentration(MIC) of synthesized compounds and standards

S. No.	*Compound*	*IC_{50} (μg/mL)*
1	Compound A-01	215.03 ± 3.42
2	Compound A-02	187.05 ± 0.20
3	Compound A-03	236.1 ± 0.3
4	Compound A-04	321.2 ± 2.20
5	Compound A-05	345.15 ± 1.09
11	Acarbose	124.6 ± 0.16

CONCLUSION

We have synthesized a series of five new compounds. All the synthesized compounds were characterized with suitable analytical methods. As per the synthetic point of view, the entire synthesized final compounds have a good percentage yield in a range of 32 to 78%. The novel synthesized compounds have been evaluated for their *in-vitro* glycogen synthase kinase-3 inhibitory activities. Further, newer substituted (5-Imidazol-2-yl-4-Phenylpyrimidin-2-yl)[2-(2-Pyridylamino) ethyl]amine analoges in progress to evaluate more potent antidiabetic agents with minimal side effects. The reported five compounds are possibly the best drug candidates for the next level of research and can be better candidates for future investigations to produce new drugs.

REFERENCES

1. Demir S, Nawroth PP, Herzig S, Ekim Üstünel B. Emerging Targets in Type 2 Diabetes and Diabetic Complications. Adv Sci (Weinh). 2021;8(18):e2100275. doi:10.1002/advs.202100275
2. Robertson, R.P., Harmon, J.S.,Diabetes, glucose toxicity, and oxidative stress: A case of double jeopardy for the pancreatic islet [beta] cell. Free Radical Biol. Med. 2006; 41:177-184
3. Ahmed AM. History of diabetes mellitus. Saudi Med J 2002; Apr 23(4):373- 378.
4. Malviya N, Jain S, Malviya S. Antidiabetic potential of medicinal plants, Acta Pol Pharm 2010;67(2):113-118.
5. Mangal, A., & Malviya, N. Antidiabetic Potential of Glycogen Synthase Kinase (GSK-3) Inhibitors. International Journal of Recent Scientific Research.2021;12(07):42240–42243.https://dx.doi.org/10.24327/ijrsr.2021.1207.6054.\
6. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med. 2020;10(4):174-188. Published 2020 Oct 13. doi:10.4103/ajm.ajm_53_20
7. Keerti J, Sapna M, Arun Kumar G and Anil K: Design, Synthesis and Biological Evaluation of Glycogen Synthase Kinase -3 B Inhibitors as Antidiabetic Agents. Int J Pharm Sci Res 2014; 5(11): 5025-41.
8. Prachand S. and Gupta A.K. Design, Synthesis and Biological Evaluation of Glycogen Synthase Kinase-3βInhibitors as Antidiabetic Agent. Int. J. Pharm. Life Sci. 2015; 6(10):4775-4779.
9. Xu M, Wang SL, Zhu L, Wu PY, Dai WB, Rakesh KP. Structure-activity relationship (SAR) studies of synthetic glycogen synthase kinase-3β inhibitors: A critical review. Eur J Med Chem. 2019;164:448-470. doi:10.1016/j.ejmech.2018.12.073
10. Pandey, Jyoti, Gilhotra, Ritu and Gupta, Arun K. Design, Synthesis and Evaluation of Substituted 5-(2-methoxybenzylidene)-rhodanine Ester Analogs as Aldose Reductase Inhibitors. Biological Forum – An International Journal 2019;11(1): 217-221
11. Agrawal, Y.P., Agrawal, M.Y., Gupta, A.K. Emerging molecular targets for the treatment and management of diabetes mellitus - A review. Int J Pharm Sci. 2013;5(1): 2000-2015.
12. Agrawal, Y.P., Agrawal, M.Y., Gupta, A.K. Design,synthesis and evaluation of rhodanine derivatives as aldose reductase inhibitors. Chem. Biol Drug Des. 2015; 85(2): 172-180
13. Novac O, Lisa G, Barbu E, Alhaique F, Popa MI. Synthesis and characterization of N-(2-aminoethyl)-2-acetamidyl gellan gum with potential biomedical applications. Carbohydr Polym. 2013;98(1):174-177. doi:10.1016/j.carbpol.2013.04.085
14. He Q, Han C, Li G, et al. In silico design novel (5-imidazol-2-yl-4-phenylpyrimidin-2-yl)[2-(2-pyridylamino)ethyl]amine derivatives as inhibitors for glycogen synthase kinase 3 based on 3D-QSAR, molecular docking and molecular dynamics simulation. Comput Biol Chem. 2020;88:107328. doi:10.1016/j.compbiolchem.2020.107328
15. Wagman AS, Boyce RS, Brown SP, et al. Synthesis, Binding Mode, and Antihyperglycemic Activity of Potent and Selective (5-Imidazol-2-yl-4-phenylpyrimidin-2-yl)[2-(2-pyridyl amino)ethyl]amine Inhibitors of Glycogen Synthase Kinase 3. J Med Chem. 2017;60(20):8482-8514. doi:10.1021/acs.jmedchem.7b00922
16. Joshi D, Yadav S, Sharma R, Pandya M, Bhadauria RS. Molecular Modelling Studies on Thiazole-Based α-Glucosidase Inhibitors Using Docking and CoMFA, CoMSIA and HQSAR. Curr Drug Discov Technol.2021;18(6):e130921187100. doi:10.2174/1570163817666201022111213
17. Valmik A, Nitin G, Sambhaji C, Sonal M, Julie B, Smriti K, Chandrika B. R, Neeta D, Kishori S. S, Anagha D, Rajiv S, Sambhaji P, Abhijit C. Europ. J. Med. Chem. 2015; 92:246-256
18. Khan N, Gautam G, Gupta AK.Synthesis and Biological Evaluation of Some New Rhodanine Analogues as Aldose Reductase Inhibitors (ARIs), Journal of Drug Delivery and Therapeutics2019;9(1-s):161-167.
19. Michael M. S, Albert R, Jim E, Dominick Q, William S, Ping Z, Morris K, Jim T, Erik W, Kristi F, Andrea O, Steve J, Peter R, David R, Menelas P. Design and synthesis of amino hydantoins as potent and selective human b-secretase (BACE1) inhibitors with enhanced brain permeability. Bioorg. Med. Chem. Lett. 2010; 20: 6597–6605.