IJBPAS, September, 2024, 13(9): 4285-4299

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

UNDERPINNING ARYLIDENE-2,4 THIAZOLIDINEDIONES AS ANTIDIABETIC AGENTS

KUSHWAHA SP, HASAN SM*, SINGH K, SHAFIURRAHMAN AND BANO J

Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh, 226026, India

***Corresponding Author: Dr. Syed Misbahul Hasan: E Mail: deanphar@iul.ac.in**

Received 18th July 2023; Revised 20th Sept. 2023; Accepted 1st Dec. 2023; Available online 1st Sept. 2024

https://doi.org/10.31032/IJBPAS/2024/13.9.8294

ABSTRACT

People suffering from diabetes are not able to produce enough insulin and/or properly use it in the body, thus they have a high level of blood glucose. It is associated with decreased insulin secretion, increased peripheral (muscle, fat, liver) insulin resistance. It has been observed that treatment of type II diabetes is generally focused on the control of hyperglycemia even though 80% of diabetic patients die from macrovascular complications of the disease. Arylidene-2,4 thiazolidinedione structure is common in a variety of agents, however they differ in side chain modifications which influence their pharmacological actions. Synthesis of arylidene-2,4-thiazolidinedione generally involves reaction between chloroacetic acid and thiourea to form 2,4-thiazolidinedione followed by base mediated substitution at nitrogen and condensation reaction at methylene carbon. Arylidene-2,4 thiazolidinedione as aldose reductase inhibitor prevent or slow the action of aldose reductase leading to prevention or delay of complications of diabetes. Arylidene-2,4 thiazolidinedione has been evaluated as inhibitors of protein tyrosine phosphatases 1B. Investigation of antidiabetic activity of series of 2,4-thiazolidinedione derivatives for their loss of plasma glucose lowering activity has been performed.

Keywords: Diabetes, Arylidene-2,4 thiazolidinedione, Aldose reductase inhibitor, Protein tyrosine phosphatase 1B inhibitor, Antihyperglycemic agents

INTRODUCTION:

Catabolic & anabolic activities are processed in every cell. The catabolic activities produces energy while anabolic activities govern the syntheses of structural and storage components. Mammals are eqiuped with hormonal systems to regulate the physiological response to dietary intake of fatty acids. Genetic and pathogenic faults at any stage of cellular organization can lead to defects called metabolic disorders **[1]**.

METABOLIC SYNDROME:

The 2001 National Cholesterol Education Program guidelines recognize a syndrome consisting of five risk factors: obesity, high triglyceride levels, low levels of high density lipoprotein cholesterol, elevated blood pressure & increased fasting glucose levels. The guidelines arbitrarily define the presence of three or more of these risk factors as indicating that a patient is affected **[2]**.

DIABETES:

An important menace for metabolic syndrome is diabetes and its late complications. People suffering from diabetes are not able to produce enough insulin and/or properly use it in the body, thus they have a high level of blood glucose. It is associated with decreased insulin secretion, increased peripheral (muscle, fat, liver) insulin resistance. Insulin resistance is defined as the reduced biological response of insulin. β cell dysfunction is the reduced ability of β cell to secrete insulin.

Current therapeutic strategies are focused on controlling hepatic glucose production (biguanides), motivating the pancreatic beta cells to secrete more insulin (sulfonylureas), retarding the absorption of starches (α glucosidase inhibitors), sensitizing the body to insulin (thiazolidinediones). Unfortunately adverse effect of these first generation therapies includes hypoglycemia, weight gain and edema **[3]**.

It has been observed that treatment of type II diabetes is generally focused on the control of hyperglycemia even though 80% of diabetic patients die from macrovascular complications due the disease. Thus novel treatment approaches are required to improve the management of individuals at high risk of developing type II diabetes as well as those with established disease, with the aim of preventing the development and progression of diabetic complications **[4]**.

Pharmaceutical chemists have competent methods for optimizing the potency and profile of dynamic moieties. Chemical transformation of known active molecule involves the use of already recognized principles on active molecules for the search

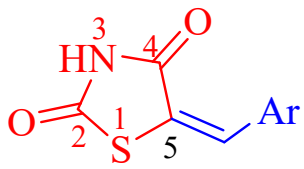
of innovative molecules that can have enhanced potency, a better activity and improved safety profile **[5]**.

ARYLIDENE-2, 4-THIAZOLIDINEDIONES:

Arylidene-2, 4 thiazolidinedione structures is common in a variety of agents; however they differ in side chain modifications which influence their pharmacological actions. The therapeutic attestation for arylidene-2, 4-thiazolidinedione as antidiabetic **[6]**, antioxidant, antilipidemic **[7]**, antiobesity, antiinflammatory agent has been explored, thus is capable of serving as biodynamic agent for treating various components of metabolic syndrome.

CHEMISTRY:

Synthesis of arylidene-2,4-thiazolidinedione **(I)** generally involves reaction between chloroacetic acid and thiourea to form 2,4-thiazolidinedione[11] followed by base mediated substitution at nitrogen and condensation reaction at methylene carbon (scheme 1). As per the requirement the condensation reaction can be performed earlier than the substitution reaction.



(I)

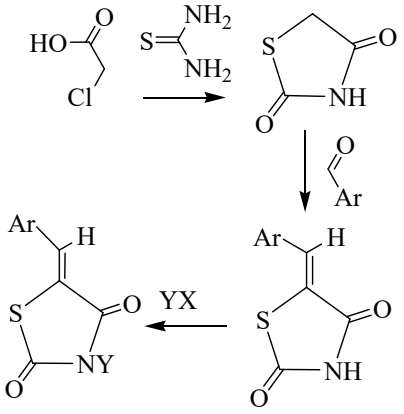
5-Arylidene-2,4-thiazolidinediones are generally synthesized by Knoevenagel reaction between 2,4-thiazolidinedione with suitable aldehyde using base such as piperidine **[8, 9]**, sodium acetate. The treatment of halogen containing compound in the presence of base such as potassium carbonate **[10]**, sodium hydride and sodium hydroxide produces N-substitution.

SPECTRAL FEATURES:

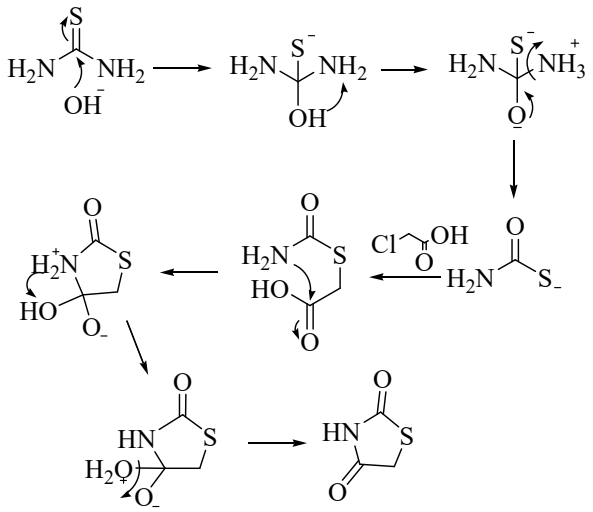
NMR Spectra: (DMSO-d_6) δ 6.95-7-19 (m, Aromatic H), 7.74 (S, 1H, CH). The Z isomer is thermodynamically stable and the methylidene proton appears in the range of 7.72-7.92 ppm as a diagnostic for the structural assignment.

I R Spectra: (KBr, cm $^{-1}$) 1730, 1670, 1600, 1374, 1335, 1138, 820 **[11]**.

Mass spectra: generally indicates the (M-H) peak with 100% intensity.

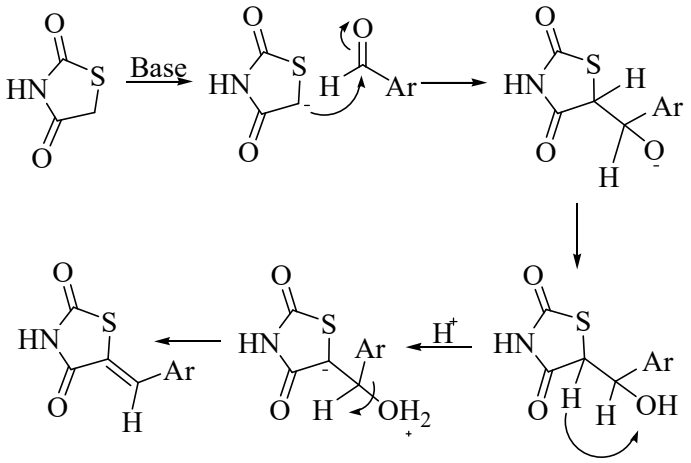


Scheme 1: Synthesis of arylidene-2, 4-thiazolidinedione



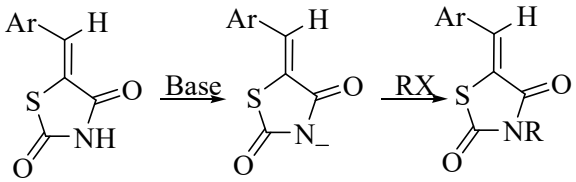
Scheme 2: Plausible mechanism of 2,4-thiazolidinedione formation

When a nucleophile approaches the electrons of the double bond, then the pi bond electrons gets localized on the more electronegative oxygen atom leading the carbon to act as an electrophile. Nucleophile attacks the electrophilic center of the carbonyl group i.e. carbon of thiourea to generate an anion, after protonation, NH_2 gets converted to NH_3^+ (better leaving group) to head off. Sulpher nucleophile undergoes substitution reaction with chloroacetic acid, after that the nuceophilic intramolecular attack by nitrogen at carbonyl carbon generates anion, proton transfer from NH_2^+ to OH group converts it into a better leaving group (H_2O^+), this is followed by loss of water to form the product (Scheme 2).



Scheme 3: Mechanism of Arylidene-2,4-thiazolidinediones formation

The function of base (piperidine, sodium acetate) is to pull out proton to generate a nucleophile (carbanion) which undergoes nucleophilic attack at carbonyl group of aldehyde to generate an anion. Protonation of OH^- converts it into H_3O^+ and is followed by loss of water to produce an unsaturated compound (Scheme 3).



Scheme 4: Mechanism of N-substitution in arylidene-2,4-thiazolidinediones

Electrophilic carbon forms a bond with the nitrogen nucleophile generated after proton abstraction (Scheme 3). The electrophilicity generates from the polarization of the carbon halogen bond. The amount of positive charge on the carbon decreases with decreasing electrophilicity of halogen in the order: fluorine> chlorine> bromine> iodine leading to a decreasing order of reactivity.

The bromo, chloro derivatives can be converted into iodo compounds by the application of Finkelstein Reaction. It involves treatment of a primary alkyl halide or pseudohalide with an alkali metal halide (potassium iodide, potassium fluoride) resulting in the substitution of Br^-, Cl^- (good leaving group/ weak nucleophile) with I^-/F^- (weak leaving group/ good nucleophile) via bimolecular substitution reaction.

The progress of the reaction also depends on the solubility of the metal salt in the solvent. Using acetone as solvent increases the progress of reaction as potassium chloride and potassium bromide are insoluble in

acetone and are there by are eliminated from the reaction mixture.

BIOLOGICAL PROFILE:

ALDOSE REDUCTASE INHIBITORS

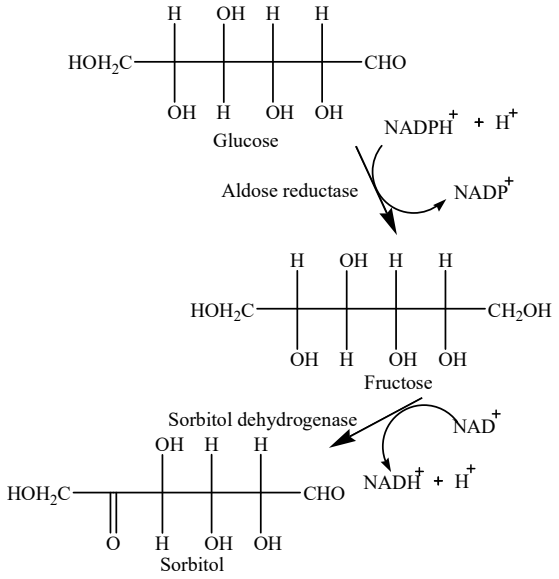
Aldose reductase is a rate limiting enzyme in the polyol pathway carbohydrate metabolism that is associated with the conversion of glucose to sorbitol. The enzyme is located in the eye, kidney, myelin sheath, and also in other tissues **[12]**.

Glucose + NADPH + H^+ → Sorbitol + $NADP^+$

Glucose can be converted into fructose which further undergoes glycolysis followed by phosphorylation by fructokinase (Scheme4). Aldose reductase utililizes NADPH to reduce aldehyde form of glucose into its corresponding sugar alcolhol (Sorbitol). In the preceeding step, sorbitol dehydrogenase utilizes NAD^+ to oxidise sorbitol into fructose.

Aldose reductase activity increases as the glucose concentration rises in diabetes in those tissues that are not insulin sensitive, which include the lenses, peripheral nerves and glomerulus. Sorbitol does not diffuse through cell membranes easily and therefore accumulates, causing osmotic damage which leads to retinopathy and neuropathy **[13]**.

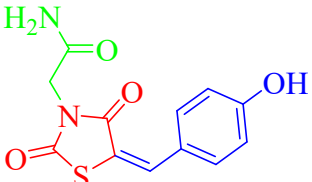
Aldose reductase inhibitor prevent or slow the action of aldose reductase leading to prevention or delay of complications of diabetes. Polyneuropathy is a common complication of diabetes mellitus that causes pain and sensory and motor deficits in the arms and legs leading to foot ulcers and amputation. Aldose reductase inhibitors may potentially slow or reverse progression of neuropathy.



Scheme 5: Polyol pathway

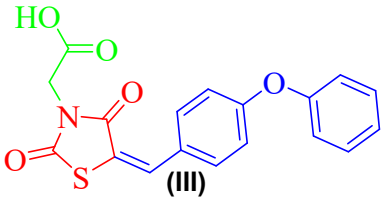
Crystallographic analyses of Aldose reductase 2 have shown that the three-dimensional structures are composed of α/β TIM-barrels. Aldose reductase 2 folds into a α/β -barrel with a core of eight parallel β -strands. Adjacent strands are connected by eight parallel α -helical segments running antiparallel to the β -sheet. The active site is located at the C-terminal end of the b-barrel **[14]**.

Z- (5- Arylidene -2,4-dioxothiazolidin-yl) aetamides **(II)** are known to have enhanced aldose reductase inhibitory – 2 inhibitory activity than N-unsubstituted analogues, although inferior than carboxylic acid analogues **[15]**.



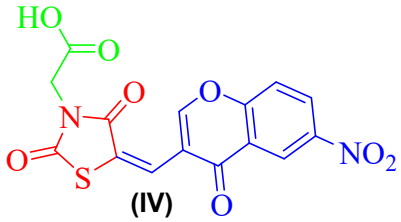
(II)

Knoevenagel condensation between 2,4-thiazolidinedione and aromatic aldehydes offers predominantely the Z isomer **[16]**. The quantitative structure activity relationship analysis series by 3D QSAR analysis, Hansch analysis and Fujita-Ban analysis infers that III position of the phenyl ring and acetic acid substitution at N-position of 2,4-thiazolidinedione **(III)** a key role in Aldose reductase inhibitory activity **[17]**.



(III)

Chromane incorporated 2,4-thiazolidinedione **(IV)** have significant aldose reductase inhibitory -2 inhibitory activity. Carboxylic esters analogue, devoid of acidic proton have slight activity as compared to N-unsubstituted and carboxylic acid analogues **[18]**.

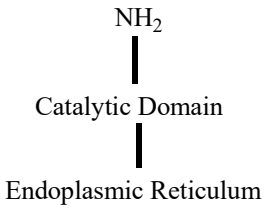


(IV)

PROTEIN TYROSINE PHOSPHATASES 1 B INHIBITORS:

Metabolic insulin signal transduction occurs through activation of insulin receptor, including autophosphorylation of tyrosine residues in the insulin activation loop. This process is negatively regulated by protein tyrosine phosphatase 1B inhibitors and their oral activity has been demonstrated *in vivo* **[19]**.

The protein tyrosine phosphatase 1B is schematically represented as **[20]**:



Protein tyrosine phosphatase 1B (435 amino acid residues) consists of

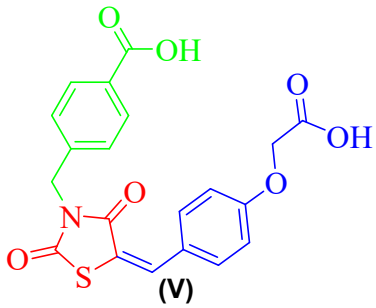
- loop/ active site containg the active site nucleophile Cys 215.
- WPD loop moves close to the phenyl ring of the substrate, which maximizes hydrophobic interactions.
- Secondary aryl phosphate binding site is catalytically inactive as it is more exposed to solvent **[21]**.

Protein tyrosine phosphatase 1B can accommodate acidic as well as hydrophophic residues immediately terminal to phosphothrosine due to different conformations adopted by Arg 47 **[22]**.

It has been reported that numerous protein tyrosine phosphatases inhibitors generally have side effects or a low rate of *in vivo* efficacy, which could be due to limited cell permeability **[20]**.

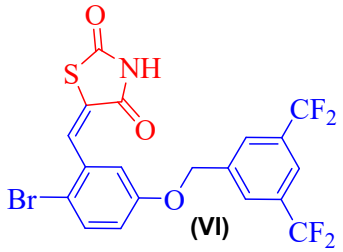
5-arylidene moiety is known to stabilize the complex with the enzyme through hydrophobic interactions with the active site and surrounding subpockets **[23]**.

4-(5-Arylidene-2,4-dioxothiazolidin-3-yl) methylbenzoic acids **(V)** has been evaluated as inhibitors of protein tyrosine phosphatases 1B **[24]**.



(V)

Benzylidene-2,4-thiazolidinedione derivatives with substitutions on the phenyl ring at the ortho or para positions, of the thiazolidinedione **(VI)** as protein tyrosine phosphatases 1 B inhibitors have been investigated for their *in vivo* efficacy as antiobesity and hypoglycemic agent in a mouse model system **[25]**.

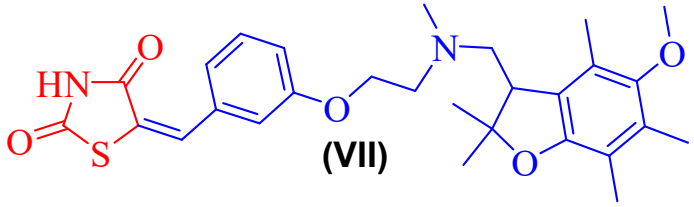


(VI)

ANTIHYPERGLYCEMIC AGENTS:

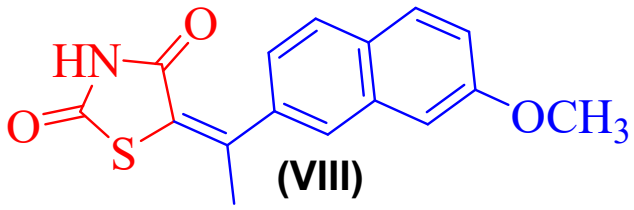
As a general rule branched substituents on the arylidene ring contributes significantly to the biological activity, while the arylidene-thiazolidinedione with electron releasing group in the 4 position produce a significant reduction in the glucose level **[26]**.

Investigation of antidiabetic activity of a series of 2,4-thiazolidinedione derivatives synthesized by introduction of N-alkyl moiety between chroman ring and phenoxyethyl linker **(VII)** has demonstrated that saturation of carbon–carbon double bond lead to the loss of plasma glucose lowering activity **[27]**.



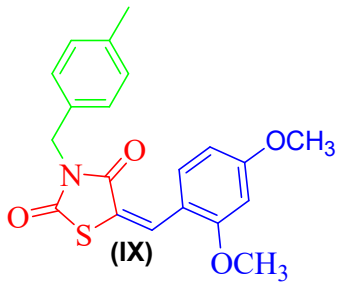
(VII)

Knoevenagel condensation between aryl ketones and 2, 4-thiazolidinedione **(VIII)** lead to a unsaturated mixture of E & Z compounds. The antidiabetic activity of E, Z mixture of the unsaturated compounds was enhanced as compared to the diastereomeric mixture of the saturated compounds **[28]**.



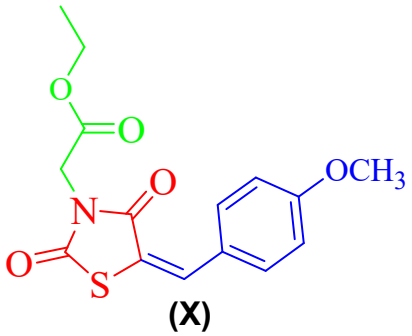
(VIII)

5-arylidene-3-(4-methyl-benzyl)-thiazolidinedione **(IX)** have been obtained as Z isomers and posses promising glucose lowering activity while acridinylidene - thiazolidinedione derivatives have been isolated as isomeric mixture. The ethylene proton is more deshielded in the Z isomer than E isomer, owing to cis position of the exocylic carbonyl group[11].



(IX)

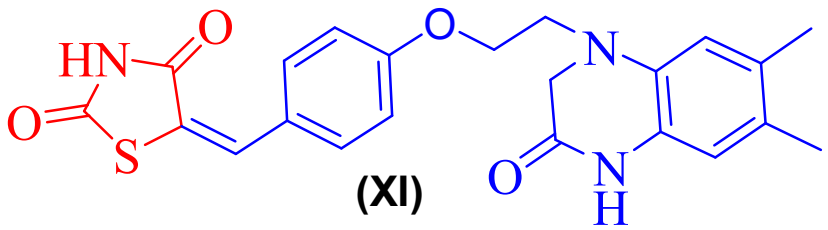
2,4-Dioxo-5-(4-hydroxybenzyl)thiazol idin-3-yl acetic acid ester **(X)** and its o-acylated derivatives show comparable or higher anti hyperglycemic activity than that of rosiglitazone, though they have poor peroxisome proliferator activated receptor γ agonist *in vitro* activity estimated at 10 and 1000 nmol concentration **[29]**.



(X)

Among the series of 6,7-methyl-1,2,3,4-tetrohydroquinoxalin-2-one derivatives **(XI)**, methyl group at C-3 position of 1,2,3,4-tetrohydroquin oxalin-2-one increases the glucose lowering ability. Compounds with ethyl spacer are more active **[30]**.

Thiazolididione may be helpful in Compounds with ethyl



(XI)

CONCLUSION:

Sedentary life style, nutrition rich in animal products are the elements of the so called "westernization" in migrant Asian-Indians which can encourage excessive insulin resistance and therefore shed light on the increased prevalence of type II diabetes in urbanized and migrant Asian-Indians.

Synchronized tyrosine phosphorylat- ion is vital for signaling pathways regulated by insulin and leptin. Type II diabetes and obesity are characterized via resistance to hormones insulin and leptin, perhaps due to attenuated or diminished signaling. Agents competent of inhibiting the negative regulator may be beneficial for the treatment of type II diabetes and obesity. Therapeutic approaches that have lowers glucose level and address diabetic complications are gravely needed.

Arylidene-2,4-hiazolidinediones have a diverse profile as antidiabetic agent. As it is known that still there are no confident agents in the market, they have several side effects therefore we need to investigate new arylidene-2,4-thiazolidinediones to order to obtain agents which improve glycemic control as well as reduce the other late stage complications of diabetes that constitute a major disease burden. The health promotion involves investigations **[31]** and methods **[32]** to achieve optimal health **[33]**. The thiazolidione may be also development as novel pharmaceuticals **[34, 35, 36]**.

ACKNOWLEDGMENTS:

Authors are thankful to Respected Prof. S.W. Akhtar, Chancellor, Integral University, Lucknow; Dr. Syed Nadeem Akhtar, Pro Chancellor, Integral University, Lucknow; Prof. Javed Musarrat, Vice Chancellor, Integral University, Lucknow and Prof. Mohammad Haris Siddiqui, Registrar, Integral University, Lucknow for providing excellent support for carrying out the work (Manuscript communication Number: IU/R&D/2023-MCN0002148). Dr. Shom Prakash Kushwaha humbly acknowledges Integral University Lucknow for the Seed Money Grant for Research (Project Sanction No: IUL/IIRC/SMP/2023/003).

DECLARATION OF CONFLICT OF INTEREST:

None

REFERENCES:

[1] Willson TM, Brown PJ, Sternbach DD and Henke BR: The PPARs; From orphan receptors to drug discovery. *J. Med. Chem.* 2000; *43(4):* 527-550.

[2] Hardman JG, Limbird LE, and Gilman AG: Goodman & Gilman's the pharmacological basis of therapeutics. Mcgraw-Hill Medical Publishing division

Companies, New York, Tenth Edition, 2001, 982.

[3] Rotella DP: Novel "Second generation" Approaches for the control of Type 2 diabetes. *J. Med. Chem.* 2004; 47(17): 411-412.

[4] Lebovitz H: Diabetes: Assesssing the pipeline. Atherosclerosis Supplements 2006; 7:43-49.

[5] Wermuth CG: The practice of medicinal chemistry. Elsevier India Pvt. Ltd., New Delhi, Second Edition, 2004: 69-89.

[6] Oya BG, G¨ulg¨un A, Meral T and Rahmiye E: Studies on the Synthesis of Some Substituted Flavonyl thiazolidinedione Derivatives-I. Turk J Chem 1999; 23:163- 169.

[7] ohray BB, Bhushan V, Rao PB Madhavan GR, Murali N, Rao KN, Reddy KA, Rajesh BM, Reddy PG, Chakrabarti R and Rajagopalan R: Novel indole containing thiazolidinedione derivatives as potent euglycemic and hypoglycemic agents. Bioorganic & Medicinal Chemistry Letter 1997; 7(7):785-788.

[8] Madhavan GR, Chakrabarti R, Kumar SKB, Misra P, Mamidi RNVS, Balraju V, Babu RK, Suresh J, Lohray BB, Lohray VB, Iqbal J, Rajagopalan R: Novel phthalazinone and benzoxazinone containing thiazolidinediones as antidiabetic and hypolipidemic agents. European Journal of Medicinal Chemistry 2001; 36:627-637.

[9] Kim BY, Ahn JB, Lee HW, Kang SK, Lee JH, Shin JS, Ahn SK, Hong C I, Yoon SS: Synthesis and biological activity of novel substituted pyridines and purine containing 2,4-thiazolidinedione. European Journal of Medicinal Chemistry 2004; 39:433-447.

[10] Maccari R, Ottana R, Ciurleo R, Vigorita MG, Rakowitz D, Steindl T, Langer T: Evalution of in vitro aldose redutase inhibitory activity of 5-arylidine-2,4-thiazolidinediones. Bioorganic & Medicinal Chemistry Letter 2007; 17:3886-3893.

[11] Mourao RH, Silva TG, Soares ALM, Vieira ES, Santos JN, Lima MCA, Lima VLM, Galdino SL, Barbe J and Pitta IR: Synthesis and biological activity of novel acridinylidene and benzylidene thiazolidinediones European Journal of Medicinal Chemistry, 2005; 40:1129-1133.

[12] http://www.medterms.com

[13] http://en.wikipedia.org

[14] El-Kabbani O, Wilson DK, Petrash JM and Quiocho FA: Structural Features of the Aldose Reductase and Aldehyde

Reductase Inhibitor-Binding Sites. Molecular Vision 1998; 4:19.

[15] Maccari R, Ottana R, Ciurleo R, Rakowitz D, Matuszczak B, Laggner C, Langer T: Synthesis,induced-fit docking investigation, and in vitro aldose reductase inhibitory activity of non-corboxylic acid containing 2,4-thiazolidinedione derivatives. Bioorganic & Medicinal Chemistry 2008; 16:5840-5852.

[16] Bruno G, Costanino L, Curinga c, Maccari R, Monforte F, Nicolo F, Ottana R, Vigorita MG: Synthesis and aldose reductase inhibitory activity of 5-arylidene-2,4-thiazolidinediones. Bioorganic & Medicinal Chemistry 2002; 10:1077-1084.

[17] Sambasivarao SV, Soni LK, Gupta AK, Hanumantharao P, Kaskhedikar SG, Quantitative structure-activity analysis of 5-arylidene-2,4-thiazolidinediones as aldose reductase inhibitors: Bioorganic & Medicinal Chemistry Letter 2006; 16:512-520.

[18] Dundar OB, Evranos B, Das-evcimen N, Sarikaya M and Ertan R: Synthesis and aldose reductase inhibitory activity of some new chromonyl-2, 4-thiazolidinediones. European Journal of Medicinal Chemistry 2008; 43:2412-2417.

[19] Panday SK, Yu XX, Watts LM, Michael MD, Sloop KW, Rivard AR, LeedomTA, Manchem VP, Samazadeh L, Mckay RA and Monia BP: Reduction of low molecular weight protein-tyrisine phosphatases expression improves hyperglycemia and insulin sensitivity in obese mice.The Journal of biological chemistry 2007; 282(19):14291-14299.

[20] Van H R H, Bombrun A and Swinnen D: Selecting protein tyrosine phosphatases as drug targets. Drug discovery today 2002; 7:1013-1019.

[21] Johnson TO, Ermolieff J and Jirousek MR: Protein tyrosine phosphatases 1B for Diabetes. Drug discovery 2002; 1:696-709.

[22] Sarmiento M, Puius YA, Vetter SW, Keng Y, Wu L, Zhao Y, Lawrence D S, Almo S C and Zhang Z: Structural Basis of Plasticity in Protien Tyrosine Posphate 1B substrate Recognition. Biochemistry 2000; 39:8171-8179.

[23] Murty VS and Kulkarni VM: Molecular Modelling of Protein Tyrosine Phosphatases 1B (PTP 1B) Inhibitors. Bioorganic & Medicinal Chemistry 2002; 10:897-906.

[24] Maccari R, Paoli P, Ottana R, Jacomelli M, Ciurleo R, Manao G, Steindl T, Langer T, Vigorita MG and Camici G: 5-Arylidene-2, 4-thiazolidinediones as inhibitors of protein tyrosine phosphatases. Bioorganic & Medicinal Chemistry 2007; 15:5137-5149.

[25] Bhattarai BR, Kafle B, Hwang JS, Khadka D, Lee SM, Kang JS, Ham SW, Han IO, Park H and Cho H: Thiazolidinedione derivatives AS PTP1B inhibitors with antihyperglycemic and antiobesity effects.: Bioorganic & Medicinal Chemistry Letter 2009; 19:6161-6165.

[26] Leite LFCDC, Mourao RHV, Lima MDCAD, Galdino SL, Hernandes MZ, Neves FDAR, Vidal S, Barbe J and pitta IDR: Synthesis, biological evalution and molecular modeling studies of arylidene-thiazolidinediones with potential hypoglycemic and hypolipidemic activities. European Journal of Medicinal Chemistry 2007; 42:1263-1271.

[27] Reddy KA, Lohray BB, Bhushan V, Reddy AS, Kishore PH, Rao VV, Saibaba V, Bajji AC, Rajesh KV, Reddy KV, Chakrabarti R and Rajagopalan R : Novel euglycemic and hypolipidemic agents: part- 2 antioxident moiety as structural motif. Bioorganic & Medicinal Chemistry Letter 1998; 8:999-1002.

[28] Prabhakar C, Madhusudhan G, Sahadev K, Reddy CM, Sarma MR, Reddy GO, Chakrabarti R, Rao CS, Kumar TD and Rajagopalan R : Synthesis and biological activity of novel thiazolidinediones. Bioorganic & Medicinal Chemistry Letter 1998; 8:2725-2730.

[29] Bhat BA, Ponnala S, Sahu DP, Tiwari P, Tripathi BK and Srivastava AK: Synthesis and antihyperglycemic activity profiles of novel thiazolidinedione derivatives. Bioorganic & Medicinal Chemistry Letter 2004; 12:5857-5864.

[30] Gupta D, Ghosh NN and Chandra R: Synthesis and pharmacological evalution of substituted5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy]ph enyl]methylene]thiazolidine-2,4-dione derivatives as potent euglycemic and hypolipidemic agents. Bioorganic & Medicinal Chemistry Letter 2004; 15:1019-1022.

[31] Ansari J, Kushwaha SP, Ansari VA, Singh K, Hasan SM. Agar well diffusion: A prominent method for in vitro screening of antimicrobials. International Journal of Botany Studies, 2021; 6(5):836-839.

[32] Kushwaha SP, Gupta SK, Kumar S. Phytochemical screening of aqueous extract derived from Stevia rebaudiana leaves, Musa acuminata fruits and Solanum lycopersicum fruits. International Journal of Botany Studies, 2021; 6(2):510-512.

[33] Kushwaha SP, Singh K, Kumar A, Hasan SM. Compassionate role of synergism in herbal formulations. International Journal of Biology, Pharmacy and Allied Sciences. 2022; 11(12):5689-5895.

[34] Kapoor A, Hafeez A, Kushwaha P. Nanocarrier Mediated Intranasal Drug Delivery Systems for the Management of Parkinsonism: A Review. Curr Drug Deliv. 2023 Jun 16. doi:10.2174/1567201820666230523114259.

[35] Izhar, M.P., Hafeez, A., Kushwaha, P. et al. Drug Delivery Through Niosomes: A Comprehensive Review with Therapeutic Applications. J Clust Sci 2023; 34, 2257–2273.

[36] Gupta P, Hafeez A, Kushwaha P. Development and Evaluation of Topical Ethosomal Gel for Fungal Infections. Drug Res (Stuttg). 2023 Jan; 73(1):46-53.