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Bio-Informatics Analysis Of Isoflavone Derivatives Against Aldose Reductase: A Key Enzyme In Diabetes Associated Cataract

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ABSTRACT:
Aldose reductase inhibitors (ARI) provide a viable mode to fight against diabetic complications. Nevertheless to the date, most of the ARIs have met with the limited success, and some of the synthetic ARIs were associated with deleterious side effects or else poor penetration of target tissues such as nerve and retina. Therefore, a novel series of N-((5-phenyl-1H-imidazol-2-yl)alkyl)-2H-chromene-3-carboxamides were rationally designed based on natural isoflavonoids. The compounds were screened in vitro for Aldose reductase (ALR2) inhibitory activity. Our in silico analysis and biochemical assays confirmed that 19 has the best inhibitory activity in this novel series of synthesized compounds. Design of N-(imidazole)-2H-chromene-3-carboxamides as aldose reductase inhibitors. Our Insilico analysis shows that 19 compound holds the promise to treat diabetic secondary complications.
19 in the active site groove of ALR2

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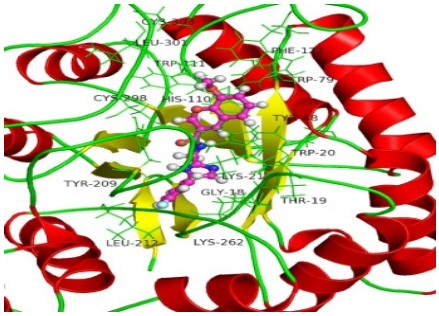

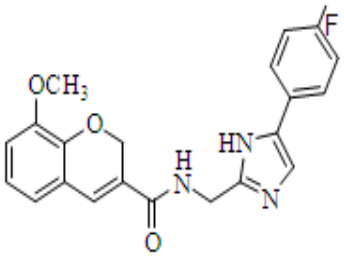

19 compound Aldose reductase (ALR2) inhibitor

N-((5-(4-fluorophenyl)-1H-imidazol-2-yl)methyl)-8-methoxy-2H-chromene-3-carboxamide

Keywords: Chromene-3-carboxylicacid; Imidazole; Diabetic complications; Aldose reductase inhibitor; Molecular Docking.

INTRODUCTION:

Diabetes mellitus

Diabetes mellitus is a complex metabolic disorder primarily characterized by chronic, persistent and sustained hyperglycemia (high blood glucose levels) resulting from defects insulin secretion, insulin action, or both, often simply referred to as diabetes mellitus (Mellitus, 2005), in which a person has high blood sugar in postprandial condition, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria, polydipsia and polyphagia.

There are three types of diabetes.

- Type-1 (insulin dependent or juvenile diabetes mellitus)
- Type-2 (non-insulin dependent or adult onset diabetes mellitus)
- Gestational diabetes mellitus

Type-1 (insulin dependent or juvenile diabetes mellitus)

In type-1 diabetes mellitus (T1D), insulin is completely absent because the pancreas lacks or has defective β cells. This condition results in genetically susceptible individuals from an autoimmune response that selectively destroys them β cells. Their life spans are nevertheless reduced by up to one third as a result of degenerative complications such as kidney malfunction, nerve impairment, and cardiovascular diseases as well as blindness. The

WHO and American Diabetes Association (World Health Organization, 1999) have proposed that T1D can be divided into type 1A (autoimmune diseases) and type 1B (idiopathic diabetes with β -cell obstruction) [1].

Type 2 or Non-insulin Dependent Diabetes Mellitus

It is characterized by decreased insulin secretion in response to glucose levels and insulin resistance which leads to the improper absorption of glucose into the cell for energy and there is an excess production of glucose from the liver. It accounts for over 90% of the diagnosed cases of diabetes and affects 18% of the population over 65 years of age, usually occurs in obese individuals with genetic predisposition foe the condition. Insulin resistance describes an impaired biological response to insulin. Insulin resistance characterized by defects in insulin signaling pathway, at many levels. These defects result into multiple metabolic abnormalities. The major sites of insulin resistance are liver, muscle, adipose tissue and kidney.

Gestational diabetes mellitus

Gestational diabetes mainly develops during pregnancy. It occurs due to the hormonal changes in pregnancy which can change body's ability to use insulin leads to carbohydrate intolerance resulting in hyperglycemia of variable severity. It occurs in about 2%-5% of all pregnancies and may improve or disappear after delivery [2].

Complications of Diabetes

Without proper management diabetic patients are prone to long- term complications such as cataract, retinopathy, atherosclerosis, neuropathy and nephropathy and impaired wound healing. As a consequence, their life expectancy is only two-third of the general population. Hyperglycemia or high blood sugar is a condition in which an excessive amount of glucose circulates in blood plasma. This is generally a glucose level higher than 13.5 mmol/ L (243 mg/dl) but symptoms may not start to become noticeable until even higher values such as 15-20 mg/l (270-360 mg/dl). However, chronic levels exceeding 7 mmol/L (125 mg/dl) can produce organ damage.

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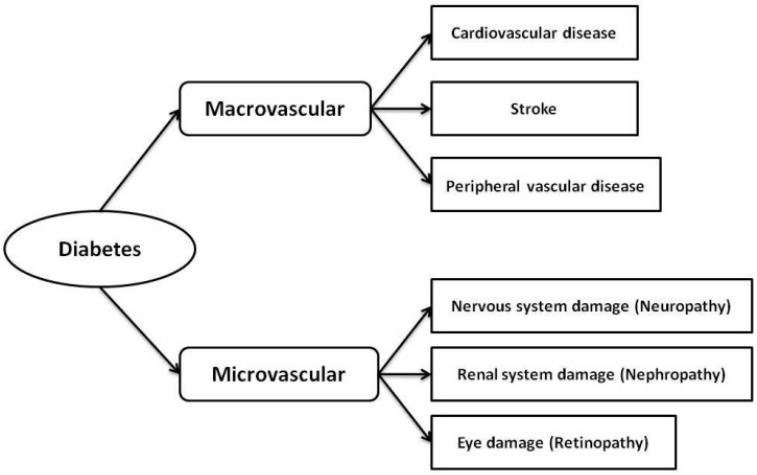

Figure 1: Classification of diabetic complications

Intervention trails aimed to achieving lower blood glucose levels has reflected a lower glucose index (HbA1c), shows that the rate of developing complications is related glycemic control. However, glycemic control alone might not be able to prevent diabetic complications. Several molecular mechanisms have been implicated in the development of these diverse pathologies. Each may have different mechanisms of development, although some factors are common to all. One common denominator in the development of all complications of diabetes is elevated blood glucose levels (hyperglycemia) [3].

Acute metabolic complications

Hyperglycemia can be a serious problem if not treated in time. Untreated hyperglycemia can lead to a condition called ketoacidosis. Ketoacidosis develops when the body does not have enough insulin. Without insulin, the body will not be able to utilize the glucose for fuel, so the body starts to break down fats for energy. When the body breaks down fats, it produces waste product called ketones. The body cannot tolerate large quantity of ketones and will try to remove it though the urine. Unfortunately, the body has to remove all the ketones and thus they build up in the blood stream and also in brain, which can lead to ketoacidosis. Ketoacidosis is a life-threatening condition which needs immediate treatment. However, diabetic ketoacidosis is seen primarily in individuals with T1D than T2D. The symptoms include shortness of breath, breath that smells fruity, nausea and vomiting and very dry mouth.

Lens growth in diabetes

Huggert observed that lenses of diabetics were thicker than those of non-diabetics (1953). Brown and Hungerford (1982) confirmed that diabetic lenses are about 10 years older by thicker than their non diabetic counterparts. This increased growth may be due to increased fiber cell number or size, or to an expanded extracellular fluid volume. It is of interest that IGF (insulin-like growth factor) is a powerful stimulus of lens fiber growth in vitro [4].

Refractive changes in diabetes

Refractive changes may be a presenting symptom of hyperglycemia, or be associated with treatment. Visual symptoms in 34% of diabetics at onset of diabetes, most commonly of refractive origin, with a further 47%asymptomatic. The mechanism for diabetic refractive change is generally regarded to be osmotic, uptake of water reducing and removal of water increasing the refractive index. The osmotic events are attributed to stimulation of the polyol pathway and the generation of an osmotic load by sorbitol in the epithelium and superficial cortex. The refractive changes initiated by treatment and related to falling glucose levels are also not fully explained. Glucose diffuses readily into the lens. Therefore, when aqueous glucose levels fall there should be rapid equilibrium between the glucose inside and outside the lens, and only a transient osmotic effect from this cause alone.

Cataract

Cataract is a vision-impairing disease characterized by thickening of the lens. The amount of incoming light is reduced due to cloudiness of the lens that affects vision which is often being similar looking through a waterfall or waxed paper. Cataract is an age related disorder which is the most ancient disease to man. The daily functions like reading, driving may be difficult due to impairment of vision. There are no perfect medical interventions established so far to mitigate the problem of cataract. The prophylactic measures are still a great choice in the treatment or to prevent the onset and progression of cataract.

Prevalence and Incidence

Several previous reports give details about the prevalence and incidence of cataract worldwide. “Prevalence” is the total number of people having cataract in a population at a given time. While, “Incidence” means the number of new cases that occur over a given period of time. A very high incidence of cataract has been noted by Minassian and Mehra. They have correlated the incidence of cataract with age. There was a steep rise in cataract incidence after the age of fifty that leads to 4 million blindness per year [5].

Incidence of blindness by cataract in India Age group (in years)	Incidents (per 10,000 population p.a)

35-39	190
40-44	253
45-49	595
50-54	1336
55-59	2388
60-64	3734
65	5860

Table 1: Incidence of blindness by cataract in India age groups (in years)

Mechanism associated with cataract

Numerous complex metabolic and physiological mechanisms are responsible behind the loosing of lens transparency during cataract formation which acts in combination to change the refractive index of the lens. The adverse chemical reactions like oxidation, glycation, Schiff base formation, proteolysis, transamidation, carbamylation, phosphorylation and elevated calcium level results in the post translational modification of lens protein during cataract development.

Polyol Pathway

Under normal conditions, cellular utilization of glucose is initiated by hexokinase catalyzed phosphorylation of glucose to glucose-6-phosphate. Phosphorylated glucose enters the glycolytic pathway / the hexose monophosphate shunt pathway or is utilised for biosynthesis of amino sugars and nucleosides. In addition, a mirror of non-phosphorylated glucose is metabolized in most cells via an accessory pathway known as the polyol pathway. The rate limiting step of this pathway is the reduction glucose to sorbitol catalyzed by aldose reductase (AR or ALR2) (EC 1.1.1.21). Sorbitol is subsequently oxidized to fructose by sorbitol dehydrogenase, thus constituting the polyol pathway. Under normoglycemia, most of the glucose is channelled preferentially into the glycolytic pathway due to the high affinity of hexokinase for glucose (low Km- 0.1mM) and glucose is hardly utilized by polyol pathway because low affinity of AR for glucose (high Km- 0.1mM). Increased conversion of glucose to sorbitol stimulates the sorbitol dehydrogenase activity, thus the net effect of

accelerated polyol pathway activity would be a shift of reductive equivalent from NADPH to NADH. The ratio of NADH/NAD was found to increase in diabetic lens [6].

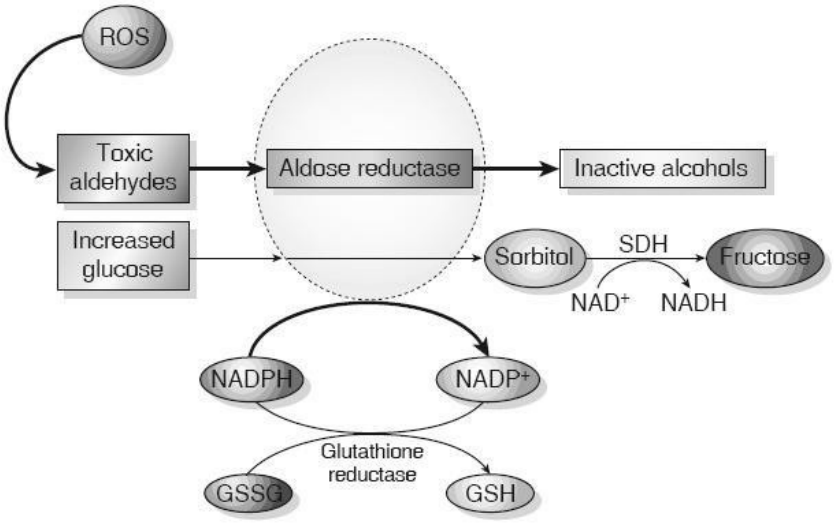

Figure 2: The polyol pathway.

Aldose reductase normally has the function of reducing toxic aldehydes in the cell to inactive alcohols, but when the glucose concentration in the cell becomes too high, aldose reductase also reduces excess glucose to sorbitol, which is later oxidized to fructose. In the process of reducing high intracellular glucose to sorbitol, the aldose reductase consumes the cofactor NADPH. The figure shows that NADPH is an essential cofactor for regenerating a critical intracellular antioxidant, reduced glutathione. By reducing the amount of reduced glutathione, the polyol pathway increases susceptibility to intracellular oxidative stress.

Aldose reductase (AR or ALR2)

Aldose reductase belongs to aldo-keto reductase (AKR) family and it has received considerable attention due to its proposed involvement in the development of diabetic complications. AR is present in lens, retina, testis, placenta, ovary, kidney, erythrocytes, and brain (Yabe-Nishimura, 1998). The enzyme is located in the cytoplasm of the most of the cells. In retina it is located in the pericytes and endothelial cells, in kidney it is detected in Henley's loop, collecting tubules, outer inner medulla and peripheral nerve Schwann cells are the main site of AR.

Oxidative stress

Diabetes mellitus was found to be inextricably connected with increased oxidative stress both in diabetic humans and hyperglycemic animals. Among the number of mechanisms proposed as a pathogenic link between hyperglycemia and diabetic complications, oxidative stress is an equally tenable hypothesis as the Maillard advanced glycation hypothesis or the AR-mediated osmotic hypothesis. It is now widely accepted that oxidative free-radical damage is an initiating or very early event in the overall sequence that leads to cataract. Oxidative stress may cause direct modification of the inner lens proteins, such as cross-linking, aggregation, and precipitation. Toxic aldehydes generated by peroxidation of lens epithelium and by oxidative damage of the vulnerable retina may contribute to the final damage.

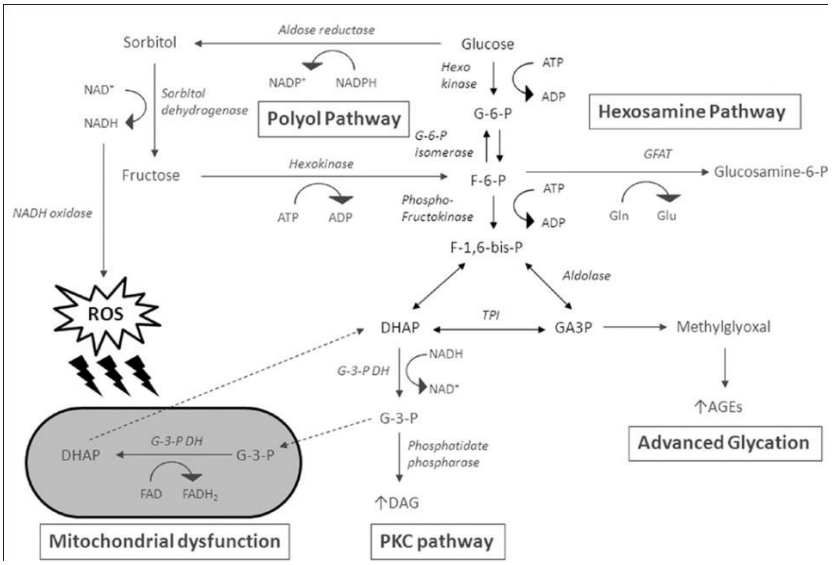

Figure 3: Glucose flux through the polyol pathway.

Glucose flux through the polyol pathway has been associated with the pathogenesis of diabetic complications via several potential mechanisms. Intracellular accumulation of sorbitol is implicated in osmotic stress [7].

Relationship between polyol pathway and oxidative stress

Polyol pathway is the major source of diabetes-induced oxidative stress in lens. There are three potential mechanisms for the polyol pathway to contribute to oxidative stress, (1) AR activity depletes its co-factor NADPH, which is also required for glutathione reductase to regenerate GSH. Under hyperglycemic condition, as much as 30% of the glucose is channelled into the polyol pathway(Cheng and González, 1986), causing a substantial depletion of NADPH and consequently a significant decrease in the GSH level. Thus, during hyperglycemia, AR activity diminishes the cellular antioxidant capacity, (2)

Oxidation of sorbitol to fructose by SDH causes oxidative stress because its co-factor NAD_ is converted to NADH in the process, and NADH is the substrate for NADH oxidase to generate ROS (Moore, 2007), (3) The polyol pathway converts glucose to fructose. Because fructose and its metabolites fructose-3-phosphate and 3- deoxyglucosone are more potent nonenzymatic glycation agents than glucose, the flux of glucose through the polyol pathway would increase advance glycation end products (AGE) formation. AGEs, as well as binding of AGE to their receptors, are known to cause oxidative stress.

Nonenzymatic glycation

In 1912, the French chemist Louis Camille Maillard reported the formation of yellow, brown substance after heating of the amino acids with sugars. He investigated the browning reaction between glucose and glycine on heating. He proposed that the brown pigmented product or melanoids involved an initial interaction between amines andsaccharides forming Schiff's base adducts. This is now called the "Maillard reaction". Non- enzymatic glycation is a common postranslational modification of proteins, which takes place through Maillard reaction, and lead to browning, fluorescence, and cross-linking of protein and finally to the formation of advanced glycation end products (AGEs).

Biochemistry of AGEs formation

The Maillard reaction occurs in three main steps. The acyclic form of the monosaccharide reacts reversibly with the lysyl side chain amino group to form an initial Schiff's base adducts. This exists mainly in the cyclic glycosylamine form. The acyclic form of the Schiff's base rearranges reversibly to form an Nε-(1-deoxy –d-fructose-yl) amino acid residue, this reaction is called as Amadori rearrangement and the product is a fructosamine or 'Amadori product'. This is the early glycation process and Schiff's base and fructosamine have been called collectively early glycation adducts.

Wolf pathway: Glucose may undergo metal-catalyzed autoxidation to produce reactive carbonyl precursors of AGEs.

Namiki pathway: Schiff bases formed on reaction of glucose with protein undergo reverse aldol reaction and antioxidative cleavage to produce AGEs precursors.

Hodge pathway: AGE precursors are formed by rearrangement and autoxidation of Amadori product. Highly reactive α -oxoaldehydes are involved in AGE formation. α -oxoaldehydes are formed by the degradation of glucose, Schiff's base adducts, fructosamines and glycolytic intermediates and by lipid peroxidation. Important α –oxoaldehydes involved in AGE formation are glyoxal (GO), methylglyoxal (MGO), and 3-deoxyglucosone (3-DG). The formation of AGEs is increased when the concentrations of α-oxoaldehydes and fructosamines

are increased. This may arise as a consequence of increased rates of formation or decreased rates of metabolism of α –oxoaldehydes and fructosamine.

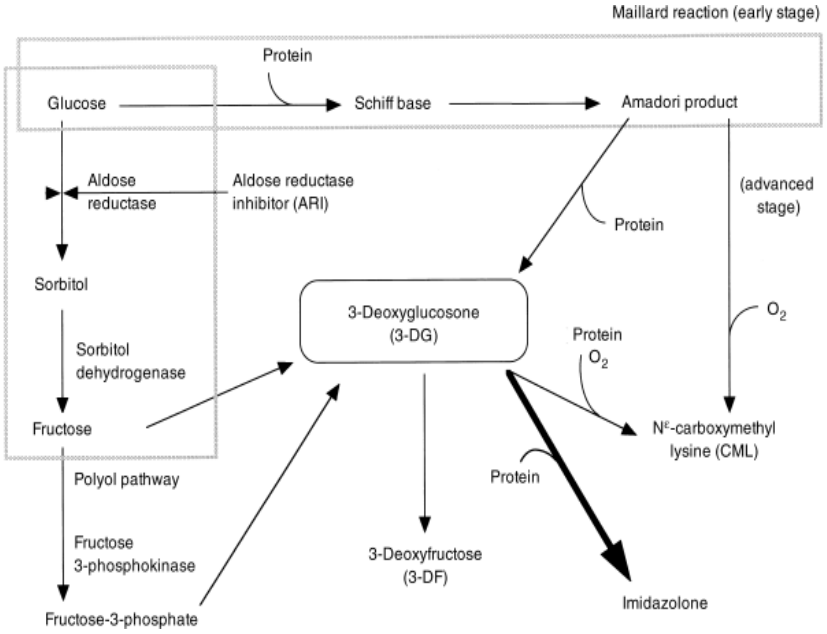

Figure 4: The 3-DG schematic diagram

Biological aspects of AGEs

The glycation or Maillard (Chemical) hypothesis explains that complications in diabetes are a direct consequence of accelerated, cumulative modification of protein and other biomolecules by glucose or its metabolic intermediates during hyperglycemia in diabetes. AGEs are formed upon modification of primarily arginine and lysine residues in proteins, though other residues like cysteine and histidine are also involved [8].

Aldose Reductase Inhibitors (ARI)

These drugs are aimed to block the metabolic pathways of glucose responsible for diabetic vascular dysfunctions. Their role in the prevention of diabetic cataract in animals is now well established. There are number of AR inhibitors known to possess anticataract potential and delaying the galactose induced cataract in different animal models. Some of these include alrestatin, sorbinil, sulindac, naproxen, aspirin, tolrestat, statil and bioflavonoids. Studies have also shown significant delay in the onset and progression of galactose cataract in rats by flavonoids quercetin and myricetin.

Aldose Reductase Enzyme

Structure and properties of enzyme

Aldose reductase (EC: 1.1.1.21; alcohol: NADPH oxidoreductase, ALR2) belongs to the aldo-ketoreductase (AKR) superfamily and most of the AKR superfamily proteins are involved in detoxification processes as they catalyze the reduction of a wide variety of substrates such as aliphatic and aromatic aldehydes, monosaccharides, steroids, polycyclic aromatic hydrocarbons and isoflavonoids (Kumar and Reddy, 2007). Aldose reductase is a cytoplasmic enzyme and it consists of a group of enzymes with the (beta/alpha) 8 barrel class. Aldose reductase is a globular protein composed of a single polypeptide chain of 315 residues, with molecular weight of 36,000 dalton and it does not contain any metal group.

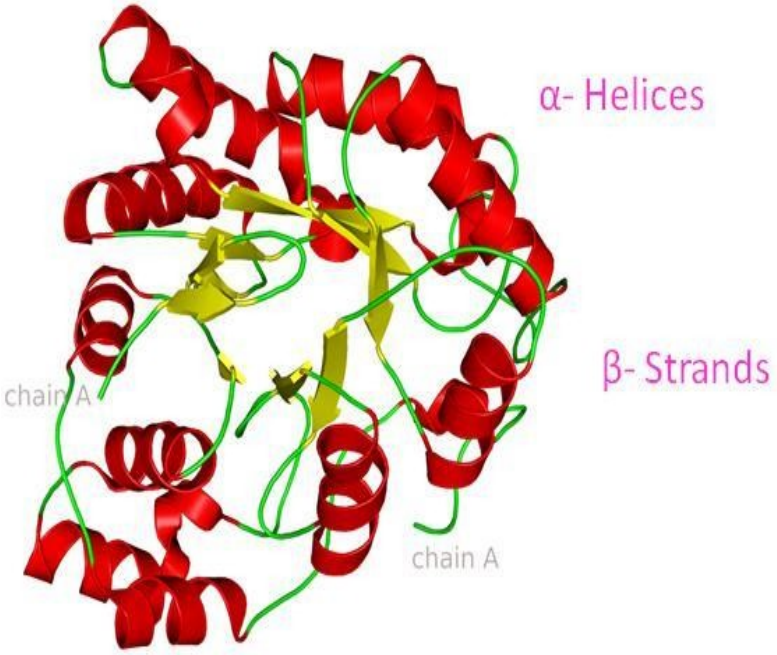

Figure 5: Secondary structure of Aldsoe reductase.

The active site of aldose reductase is placed at COOH terminal of the β barrel. The active site of the aldose reductase has highly hydrophobic residues and some amino acids presented in cavity are nonpolar. In the enzyme –NADPH binary complex, the C-4 of the nicotinamide of NADPH, the reactive end of the molecule is in close proximity to 3 polar residues Cys-298, Tyr-48, and His-110, and one of these residues may be the acid- base catalyst for the oxidation/reduction

reactions. Also NADPH is bound to the enzyme by 19 hydrogen bonds in an extended conformation across the barrel which has the nicotinamide ring in the center of cavity.

Implication of Aldose Reductase in Diabetic Cataract

The beginning of interest in the role of Polyol Pathway in Diabetic Cataract was marked in as early as 1959 with the discovery of polyol pathway in diabetic lens. Lenses of experimentally diabetic animals have been shown to contain excessive amounts of sorbitol and fructose. Various studies conducted by Chylack and Kinoshita, 1969, led to conclude that aldose reductase initiates the cataractous process in both diabetic and galactosemic rats. Studies performed by Kinoshita et al in 1969 on Tetamethylglutaric acid (TMG) an early Aldose Reductase inhibitor, showed that in lens culture, TMG completely blocked the accumulation of galactitol in Galactose- exposed lens. This supported the idea that it was polyol that caused the osmotic change. Studies carried on human diabetic lenses have presented ample evidence that aldose reductase may play a substantial role in the development of lens opacity in diabetic individuals.

Biological activities of purified bael compounds

A large number of compounds have been isolated from various parts of the bael tree and a few of them have been studied for their biological activity (Table 1). The structures of some of these bioactive compounds are presented in Fig.1. The bioactive compounds isolated from the various parts of this tree and their biological activities are:

Leaf: Several compounds such as skimmianine, aegelin, lupeol, cineole, citral, citronellal, cuminaldehyde, eugenol and marmesinin have been purified from bael leaves. Skimmianine (**1**) (C14H13NO4), an alkaloid, is also found in the immature bark of the tree. It has shown anticancer activity in A2780 human ovarian cancer cell line. It also inhibits spontaneous motor activity, exploratory behavior, cataleptogenic activity and conditioned avoidance response in animals [9].

Traditional uses and Pre clinical studies on bael

Crude extracts from multiple parts of the bael plant are used to treat various disorders in different Indian traditional systems. Roots are used to cure cardiac malfunction, abdominal pain, fever, urinary troubles, hypochondriasis and melancholia. Leaves are used as an astringent, laxative, digestive and febrifuge when fresh. They are also useful in opthalmia,

hearing loss and inflammation. The unripe fruit is also helpful in curing dysentery. The ripe fruit is used as an astringent, appetizer, laxative, tonic, restorative, and febrifuge and also used in biliousness. Different parts of this plant are used to cure various diseases in folklore medicine. A number of ethno-medicinal uses of bael tree have already been documented.

RESULTS & DISCUSSION

Rational design of new molecules:

Considering the structures of well established aldose reductase inhibitors like Sorbinil, Fidarestat and Quercitin we designed a few molecules which is anticipated to have aldose reductase inhibition properties with low side effect profile due to its natural isoflavonoid base. The designing base can be seen in the figure.

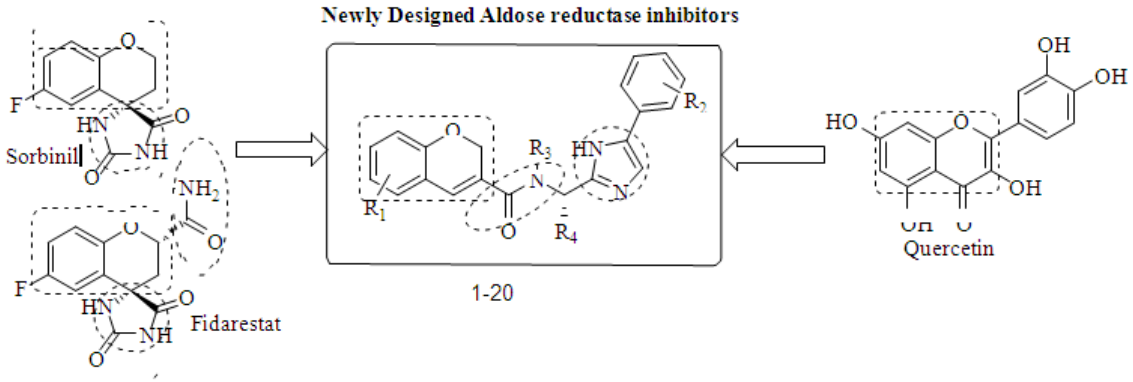

Figure 6: Designed ALR2 inhibitors as hybrids of sorbinil, fidarestat and quercetin.

Human ALR2 crystal complexes have suggested that the inhibitors bind to the enzyme active site and are held in place through hydrogen bonding and van der Waals interactions formed within the hydrophobic pockets 16. These ligand-dependent conformations indicate a remarkable induced fit or flexibility of the active site in the human ALR2 from the earlier studies, nevertheless, at least three distinct binding pockets in the active site can be proposed according to a number of earlier studies on crystal structures of ALR2 by X-ray crystallography and mutagenesis 17. The first site is usually occupied by the anion head of ligand and thus named “anion binding pocket”. It consists of Tyr48, His110, Trp20, and Trp111 side chains and the

positively charged nicotinamide moiety of the cofactor NADP+ 18. The second is a hydrophobic pocket, known as specificity pocket, and lined by the residues Leu300, Cys298, Cys303, Trp111, Cys303, and Phe122. The specificity pocket displays a high degree of flexibility and the third is another hydrophobic pocket formed by the residues Trp20, Trp111, Phe122, and Trp219 19. By using above information we designed N-(imidazole)-2H-chromene-3-carboxamides with the help of Marvin sketch vs 5.6; calculated docking scores by Molegrow Virtual docker.

The docking of compound 19 in the binding site of human ALR2 receptor illustrated that the chromene, phenyl-imidazole ring and carboxamide play a vital role in inhibiting diabetic. The docking results showed hydrogen bonding interactions between chromene ring oxygen with

Trp111 (2.7 Å), carboxamide NH with Tyr48 (2.8 Å) [10].

The 19 ligand was well placed in the vicinity of the active site of human AR residues (Trp20, Tyr48, Trp79, Lue300, Cys298, Trp111, Phe122, His110 and Trp110) (Figure 3a, b & c). This class readily shown activity in the AR inhibition because of the structural feature of carboxylate anion head group which may fit well in the so-called anion binding pocket of human ALR2. Results from our molecular docking studies are consistent with the pattern of binding of proven ARI's core part in the active site human AR. Structural superposition of fidarestat, sorbinl and 19 aligned well with crystal structures.

Calculation of drug-likeness properties

Bioichemical assays of proven ARIs, such as sorbinil, tolrestat, zopolrestat, fidarestat, were shown to prevent cellular inflammation 20-22. These findings suggested that AR inhibition could be a useful strategy not only in the management diabetes and other related chronic complications but also in the treatment of other serious human diseases that are associated with increased tissue inflammation, such as rheumatoid arthritis, sepsis and atherosclerosis. Thus, the development of effective ARIs with improved therapeutic potential is demanded and insilico analysis of novel compounds helps us in great deal .Drug-likeness of a compound can be considered as a delicate balance among the molecular properties of a compound that influences its pharmacokinetics and ADME (absorption, distribution, metabolism and excretion) in human body 23. Tight binding of molecules to receptors is achieved through polar interactions and most importantly through the optimization of specific hydrophobic interactions. These parameters allow in ascertaining oral absorption, or membrane permeability that occurs when evaluated molecules obey Lipinski's rule-of-five 24. Other parameters that included are number of rotatable bonds, molecular volume, topological polar surface area (TPSA) and liphophilicity. The above mentioned parameters were calculated for and the results.

We calculated the compliance of compounds to the Lipinski's rule of five 25 which is a widely used filter for drug-like properties and states that most biological active molecules have good membrane permeability with a molecular weight (MW) of 500 or less, a logP value less than 5, five or fewer hydrogen bond donor sites and ten or fewer hydrogen acceptor sites (N or O atoms). As shown in Table 4, all of these benzopyran derivatives have optimum logP (<5), efficient in hydrogen bonding donors, which may also be a necessary requirement to exhibit the activity and have no violations from Lipinski's rule-of-five. Within the series of these compounds, most active compound 19 has lipophilicity with miLogP=2.54 and with a higher topological polar surface area (TPSA) value (76.25). Drug-likeness of the compounds were estimated from predicted ADME values and Molinspiration software and found to score well. In particular, optimum lipophilicity (<5) and the presence of hydrogen bonding donor make the molecules likely to have a good drug-likeness and absorption [11].

Table 2: Molecular docking scores of designed compounds

S.No	Mol-Dock Score	RMSD	S.No	Mol-Dock Score	RMSD
1	-173.79	31.97	11	-184.72	33.12
2	-180.96	30.90	12	-186.96	32.45
3	-180.67	31.00	13	-184.12	33.35
4	-182.55	30.98	14	-187.70	34.42
5	-187.55	31.54	15	-186.11	34.92
6	-184.54	35.22	16	-184.97	34.41
7	-187.54	33.42	17	-183.25	29.36

8	-186.01	31.59	18	-184.07	30.87
9	-194.25	31.76	19	-190.51	31.17
10	-193.22	30.51	20	-193.37	33.05
Sorbinil	-111.47	31.28	Quercetin	-142.49	35.30
Fidarestat	-124.56	30.64			

Table 3: Prediction of bioactivity properties of designed compounds calculated by using Molinspiration program

S.NO	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor	miLogP	TPSA
1	0.10	-0.07	0.07	0.48	-0.05	0.12	2.56	67.02
2	0.09	-0.07	0.05	-0.48	-0.09	0.08	3.24	67.02
3	-0.00	-0.14	0.02	0.57	-0.16	0.04	3.37	67.02
4	0.10	-0.08	0.10	-0.44	0.07	0.10	2.73	67.02
5	0.06	-0.11	0.04	-0.47	-0.08	0.07	2.62	76.25

6	0.04	-0.12	0.03	-0.54	-0.12	0.06	2.38	76.25
7	0.03	-0.12	0.01	-0.55	-0.16	0.02	3.05	76.25
8	-0.05	-0.18	-0.02	-0.63	-0.22	-0.01	3.18	76.25
9	0.04	-0.13	0.05	-0.51	-0.14	0.04	2.54	76.25
10	0.03	-0.12	0.01	-0.50	-0.11	0.05	2.43	85.48
11	0.03	-0.05	-0.06	-0.54	0.03	0.07	3.40	58.23
12	0.02	-0.06	-0.07	-0.54	-0.01	0.04	4.07	58.23
13	0.08	0.01	0.07	-0.55	0.08	0.15	2.32	71.12

Table 4: Physico-chemical properties of designed compounds

S. No	Nato	MW	nON	nOHNH	nviolation	nrotb	volume
1	25	331.08	5	2	0	4	298.2
2	26	365.82	5	2	0	4	311.77
3	26	410.27	5	2	0	4	316.12
4	26	349.37	5z	2	0	4	303.17
5	27	361.40	6	2	0	5	323.79
6	27	361.40	6	2	0	5	323.79
7	28	395.85	6	2	0	5	337.32

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8	28	440.30	6	2	0	5	341.67
9	28	379.39	6	2	0	5	328.72
10	29	391.43	7	2	0	6	349.33
11	28	371.44	5	1	0	3	338.21
12	29	405.88	5	1	0	3	351.75
13	28	372.43	6	1	0	3	334.05
14	30	401.47	6	1	0	4	363.76
15	31	453.91	6	1	0	4	377.29
16	30	402.45	7	1	0	4	359.60
17	28	373.46	5	2	0	5	348.21
18	29	452.35	5	2	0	5	366.10
19	30	403.48	6	2	0	6	373.76
20	31	482.38	6	2	0	6	391.65

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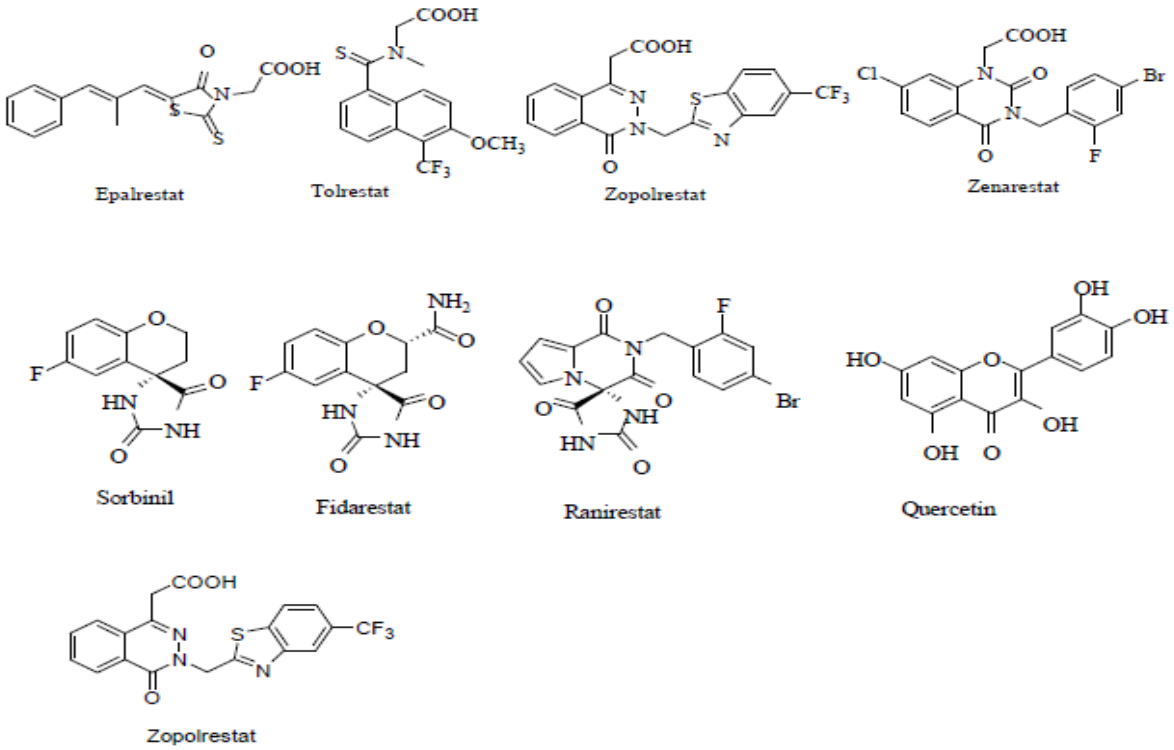

Figure 7: A well known Aldose reductase known inhibitors [12]

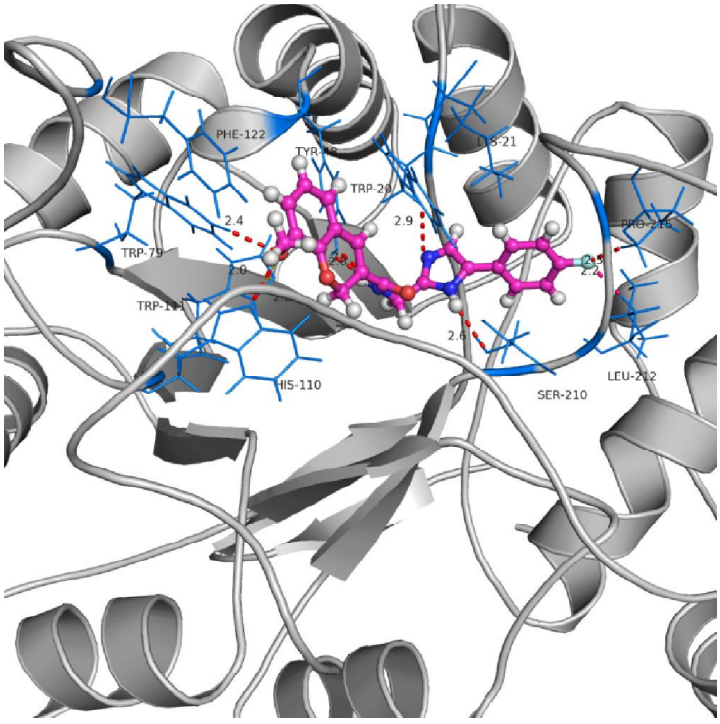

Figure 8: (a) The 19 and human AR structure are represented in cartoon, ball & stick model, respectively. Hydrogen bonds are shown as red dashed lines, with distance unit in Å.

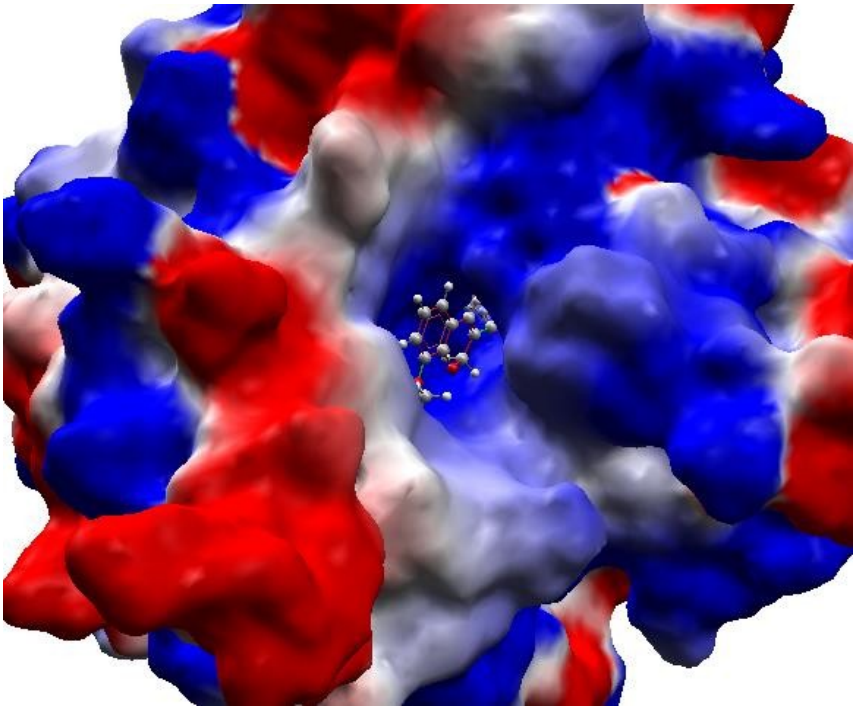

Figure 8: (b) Electrostatic surface representation of Human AR and 19 in the active site groove.

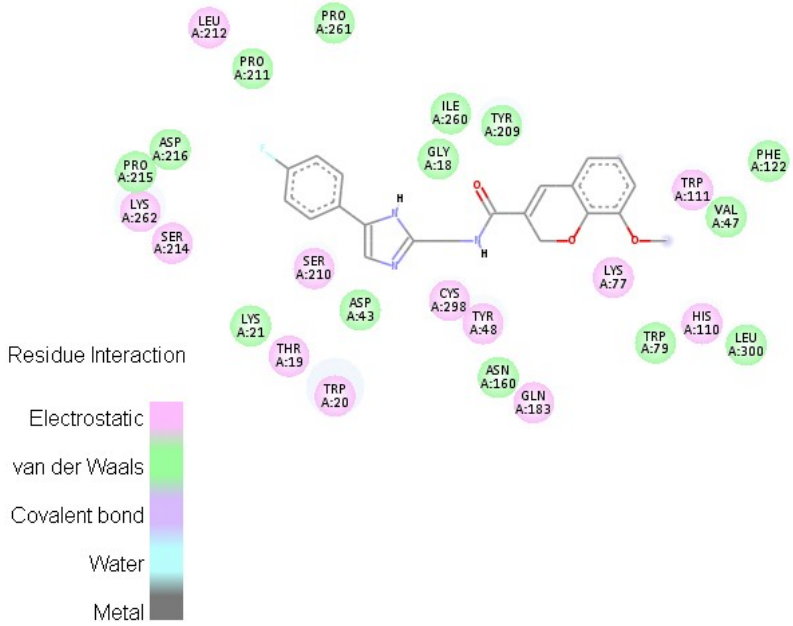

Figure 8: (c) 2D representation of stacked amino acids in the binding pocket of human AR and 19 compound in the vicinity of active site [13].

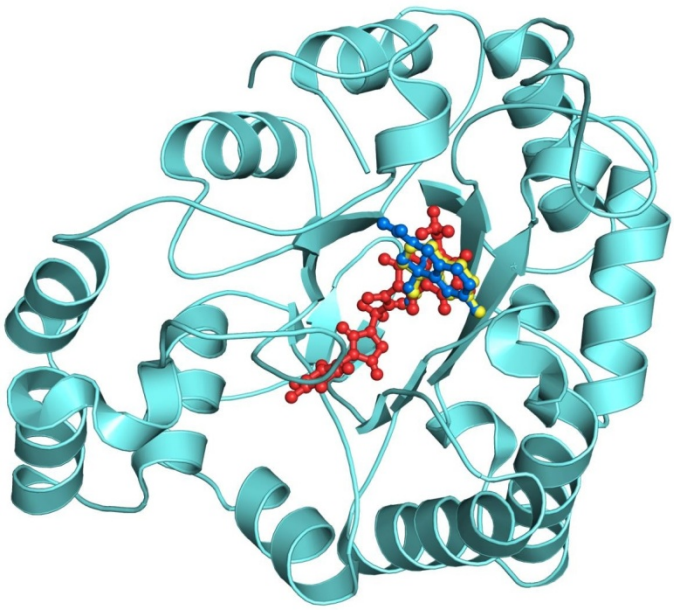

Figure 9: Structural alignement of known ARI in comparison to 18i. Inhibitors represented in ball& stick model in active site, 19, fidarestat and sorbinil are depicted using red, blue and yellow, respectively [14].

CONCLUSION

In this study, we have described the rational designed the compounds, followed by in-silico analysis and protein-ligand interactions of novel series of N-(imidazole)-2H-chromene-3-carboxamide analogues. Molecular docking studies gave an idea about the binding pattern of these inhibitors, which in turn helped us to understand the interactions of chromene, imidazole and phenyl rings with human Aldose Reductase. Among the several promising compounds described here, 4-fluorophenyl group of imidazole derivative 19 emerged with best ALR2 biochemical inhibitory activity. The results insilco studies indicate that 19 inhibit human ALR2 with excellent drug-likeness properties. Thus, data also suggest that 19 might aid in guiding the development of highly specific aldose reductase inhibitor without any side effects.

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