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Heterocyclyl linked phenyl containing Thiazolidinediones and its Cyclic analogs as potential novel Antidiabetic agents

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Thiazolidinediones derivatives represent a vital class of organic compounds with broad biological activities for treatment of diseases such as diabetes, cancer etc. We describe here different class of synthetic heterocyclic α-glucosidase inhibitors resulting from incorporation of different fragments on desired heterocycle, from literature, which were evaluated for vast range of antidiabetic, anti-inflammatory functions by successful binding interactions of molecule with enzyme which induced significant structural alterations. Kinetic studies of most active compounds in terms of selective mode of inhibition and dissociation constant were examined in order to develop an effective therapeutic strategy and management for controlling post-prandial hyperglycemia in diabetic patients. Our studies identify different novel series of potent α-glucosidase inhibitors for further investigation and new opportunities to develop antidiabetic drugs.

Keywords: α-glucosidase inhibitors, Diabetes Mellitus, Thiazolidinediones, IC_{50}

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic issue portrayed by insulin obstruction and hyperglycemia. Diabetes is a metabolic issue burdening around 5% of the populace in the industrialized countries and is currently quickly extending in the other world, particularly in those vigorously populated agricultural nations like China and India. Non-Insulin Dependent Diabetes Mellitus (NIDDM) additionally recognizable as Type 2 Diabetes Mellitus (T2DM) represents over 90% of the cases. It is portrayed by insulin opposition in the liver and fringe tissues and by pancreatic β-cell brokenness. The basic foundations for T2DM are perplexing. Other than hereditary and other neurotic factors, the beginning of T2DM has been plainly connected to way of life changes like eating routine, exercise, and age and is progressively joined by other metabolic issues including heftiness, dyslipidemia, and atherosclerosis. The mix of these gamble factors named metabolic condition, essentially expands bleakness and mortality. It is likewise a significant general medical problem and a worldwide clinical concern. While way of life changes would altogether enhance the gamble or seriousness of this sickness state, consistence with existing treatments stays a long-standing issue inferable from by and large unfortunate bearableness of most T2DM designated drugs.

Diabetes mellitus (DM) is an illness portrayed by obsessively raised glucose levels because of insulin discharge disappointment or insulin opposition, and is known to be a gamble factor for different extreme entanglements, like diabetic neuropathy, retinopathy and nephropathy. The quantity of patients with diabetes is relied upon to be 592 million by 2035 [11]. α-Glucosidase is a layer bound chemical that situated on the brush line film of small digestive system for the processing of carbs, catalyzes the cleavage of absorbable

monosaccharides and oligosaccharides [24]. The inhibitors of glucosidase chemical are profoundly valuable for clinical treatments, like diabetes, disease, hyperlipoproteinemia, corpulence and HIV. α-Glucosidase inhibitors, for example, acarbose, miglitol, and voglibose are clinically utilized in the viable treatment of type-2 diabetes mellitus. These inhibitors really decline the postprandial glucose levels in type-2 diabetic patients. Nonetheless, they cause different incidental effects, like loose bowels, stomach and tooting inconvenience. Consequently, planning of new α-glucosidase inhibitors with least aftereffects is as yet a sensible case. There is a need to foster new helpful systems for diabetes the board. Out of different remedial methodologies one is to lessen glucose assimilation, to control postprandial hyperglycemia, to remember weight on β cells and to deal with the two sorts of diabetes by α-amylase and α-glycosidase inhibitors. In the assimilation and ingestion cycle of sugars pancreatic α-amylase hydrolysis the starch [9]. Besides, α-amylase as the most plentiful protein in the human salivation, it fills a few particular roles in the oral depression. Right off the bat, it breaks the carbs in oral hole and besides it ties to viridans streptococci in the oral depression. Microscopic organisms bound α-amylase hydrolyses the starch atoms. α-Glycosidase chemical assumes key part in gastrointestinal carbs processing, glycogen corruption, development and glycoprotein collapsing [8]. Inhibitors of these compounds diminish starch hydrolysis to basic sugars by easing back the activity of these chemicals. Thiazolidine-2,4-diones and their analogs are significant moieties because of their expansive scope of natural exercises, including antidiabetic, anticancer [15], hostile to microbial, cancer prevention agent [17] and antibacterial [20]. As of late, from writing have been accounted for that an original series of thiazolidinedione subordinates go about as another class of α-glucosidase inhibitors III and IV (Fig. 1) [2]. As needs be, phthalimide, quinazoline, chromone and thiazolidine-2,4-dione could be utilized as pharmacophore to plan new dynamic mixtures for α-glucosidase hindrance.

Heterocyclyl linked phenyl containing 2,4-thiazolidenediones (TZD) and its cyclic analogs [viz. rhodanine (RHD), hydantoin (HYD), thiohydantoin (THYD)] as the hydrogen bonding part have been well established as potent PPAR activators in the literature. The quinazoline, chromone and phthalamide nucleus as heterocylces constitute an important class of therapeutic agents in medicinal chemistry including anti-diabetic activity. A para/meta-substituted phenyl ring was directly linked at position-3 of quinazoline and position-2 of phthalamide nucleus, synthetically and pharmacologically valuable moieties namely, 2,4-thiazolidinedione (TZD), rhodanine (RHD), hydantoin (HYD), thiohydantoin (THYD) were taken as the hydrogen bonding groups for the proposed NCE's. Keeping in view the importance of above cited facts coupled with the proposed hypothesis, we, in the present protocol can planned to synthesize, novel heterocyclyl linked para/meta-substituted phenyl containing thiazolidinediones and their analogs as potential ligands with α-Glucosidase Inhibitory activity for Type 2 Diabetes and metabolic syndrome followed by their docking and biological studies. Docking of the newly designed molecules on the basis of Theoretical Structure Activity Relationships in the active sites of the protein concerned will be carried out using the C-score module available in our in-silico Drug Design Lab.

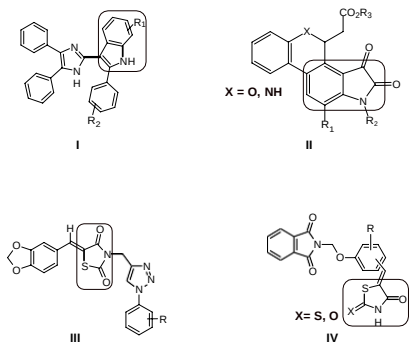

Figure 1. Representative examples for new class of α-glucosidase inhibitors.

2. Review of Literature

Manoj Dhameja and Preeti Gupta dissected specific novel heterocyclic atoms and their subordinates, which are powerful in restraint of α-Glucosidase compound. They analyzed their further job in administration of postprandial hyperglycemic condition in T2DM. They further summed up that such restraints are proper for Asian nations where carb rich food is by and large devoured. SAR and docking study give stage to additional productive improvements in this area. Guang-cheng Wang et al orchestrated thiazolidine-2,4-dione or rhodanine subsidiaries and assessed their hindrance action as far as IC50 values. They additionally contrasted such boundary and standard medication acarbose. They likewise performed sub-atomic docking to comprehend the limiting cooperations among particle and catalyst. They chose such class of heterocyclic mixtures because of their expansive scope of natural exercises like antidiabetic, antioxidative, mitigating and so forth They summed up that compound containing chloro and rhodanine bunches at 2 -and 4-places of the phenyl ring individually were successful in restraint of α-Glucosidase action.

A portion of the blended mixtures with half and half framework were tried for their in vitro α-Glucosidase inhibitory movement. Sara Shahidpour et al blended new subsidiaries of pyrimidine melded heterocyclic mixtures and inspected their inhibitory exercises in weakening of postprandial hyperglycemia in mouse and yeast. Cancer prevention agent exercises of such class of heterocyclic mixtures were evaluated. They additionally observed that PFH ring show moderate restraint properties against α-Glucosidase which is alluring based on their lower vulnerability for conceivable improvement of the gastrointestinal incidental effects. FarhadPanahi et al orchestrated a bunch of pyrimidine-melded subsidiaries by joining of various parts on the pyrimidine-combined heterocyclic mixtures. They talked about the enzymatic system of hindrance. Moreover, round dichroism and fluorescence spectroscopy were led to inspect the association among ligands and protein for successful docking.

Reza Yousefi et al incorporated different poly-hydroxy functionalized pyrimidine-intertwined heterocyclic (PHPFH) particles, having either aliphatic or sweet-smelling side chains and inspected their inhibitory action spectroscopically against yeast and mouse gastrointestinal α-Gls.They uncovered solid inhibitory action with non-cutthroat and serious restraint modes.They observed that limiting initiated huge primary modification which was went with the decrease of hydrophobic surfaces. HamdyKashtoh, Shafqat Hussain, Ajmal Khan, Syed Muhammad Saad, Jalaluddin A. J. Khan, Khalid Mohammed Khan, Shahnaz Perveen, M. Iqbal Choudhary incorporated different oxadiazoles and thiadiazoles subordinates and assessed their inhibitory exercises. They further concentrated on their energy and method of restraint and ascertain their separation constants. They found and recognized numerous strong thiadiazoles as aggressive inhibitors.

Discovered Synthetic heterocyclic α-glucosidase inhibitors from literature, their analysis and inhibitory role in Tables 1-5.

Table:1 Indole derivatives and hybrids

Synthetic heterocyclic α-glucosidase inhibitors	Researchers	Devised derivatives and their substituents	Features
Indole derivatives and hybrids	Taha and coworkers	Derivative 12 Derivative 12a	It showed good inhibition activity. Range IC50=2.3 to 22l.4µM It is 400 times more potent than standard compound.
	Naureen and coworkers	Derivative 13 Derivative 13a Derivative 13b	Range 5.4 to 76µM Range IC50= 5.4µM Range IC50= 7.1µM
	Taha and coworkers	tris-indole hybrid 14 with oxadiazoles ring Derivative 14a	Range 2 to 292µM.Acc. to SAR studies, unsubstituted hybrids were 45 folds more active than standard. Activity was reduced on shifting methyl group from R4 to R5. Most active inhibitor. Range IC50= 2.0µM
	Barakat and group	Derivative 15 (enantiomerically pure propanone) Derivative 15a	Range 4.3 to 43µM Most active inhibitor.
	Wang et al	3,3-di(indolyl)indolin-2-ones 16 Derivative 16a	Range 5.9 to 145µM. introduction of alkyl or substituted benzyl group at N1 position of indole scaffold increased the activity. Range IC50= 5.9µM
	Taha and coworkers	Bis-indolylmethane sulfonylhydrazide derivative 17 Derivative 17a	Range 0.10 to 5.1µM. Number of derivatives were found non toxic in the cytotoxicity tests.

Table 2: Imidazole and benzimidazole derivatives and hybrids

Synthetic heterocyclic α-glucosidase inhibitors	Researchers	Devised derivatives and their substituents	Features
Imidazole and benzimidazole derivatives and hybrids	Yar et al.	2,4,5 trisubstituted imidazoles	Showed less or no inbibition against α-glucosidases.
	Naureen and coworkers	imidazles 28 Hybrid 28a	Range 8.3 to 98μM. Amongst 10, eight hybrids were found more active. Hybrid 28a having fluoro and NHCOCH3 substitution displayed highest potential with range 8.3μM.
	Ali and coworkers	Derivative 29	Shows highest potency.
	Arshad et al.	Derivative 30	Shows highest activity. IC50=8.3μM.
	Ozil and coworkers	Derivative 31	Most active derivative. IC50=0.49μM.
	Taha and coworkers	Derivative 33 Derivative 33a having 2chloro phenyl substitution as R group	Range 5.3 to 725μM. Most active with 162 times more activity than the standard.
	Khan and coworkers	2- aryl-5-bromo benzimidazole derivatives 34 Derivative 34a	Range of inhibition almost similar to the reference compound. Shows highest inhibitory activity with 8.3μM IC50
	Ozil and coworkers	Benzimidazoles having morpholine 36 or piperazine 37 moiety at C-6 Derivative 36a and 37a	Range 2.2 to 21μM. Range 3.4 to 20μM.respectively. morpholine or piperazine moiety acted as activity synergizer. The compounds were studied for antioxidant activity.
	Taha and co workers	Benzimidazoles 38 Derivative 38a with p-nitro group	Range 35 to 297μM.electron withdrawing group at para position display better activity. Showed maximum inhibition.

Table 3: Thiazolidinone hybrids

Synthetic heterocyclic α-glucosidase inhibitors	Researchers	Devised derivatives and their substituents	Features
Thiazolidinone hybrids	Wang et al.	Phthalimide 86 Derivative 86a	Range to 5.4to 50μM. replacement of oxygen with sulphur in thiazolidinone showed increased activity. Range 5.4μM.showed highest potency.
	Saeed	Derivative 87 Derivative 88a and 88b Derivative 89a and 89b	The compounds displayed moderate α-glucosidase inhibitory activity and α-amylase inhibitory activity. Range 5.3 and 3.6μM respectively. Range 0.91 and 0.51μM respectively.
	Mall and coworkers	Thiazolidinone 88 or rhodanine 89	Good α-glucosidase inhibitor.
	Senthilkumar et al.	Derivative 90a	Shows good antidiabetic properties. Most active. Range 0.55μM (α-glucosidase)

Table 4: Benzofuran and benzoxazole derivatives.

Synthetic heterocyclic α-glucosidase inhibitors	Researchers	Devised derivatives and their substituents	Features
Benzofuran and	Hsieh et al.	2-arylbenzo furans 93 Derivative 93a,93b,93c	Range 1.9,2 and 3.0μM.respectively.

benzoxazole derivatives.	Spasov et al	Benzofurans 94 Derivative 94e Derivative 94a, 94c and 94d Derivative 94b	Range to 2.3to 25μM. Most active. Range 6.5 μM. respectively. Shows very weak inhibition. Found inactive.
	Sun et al.	Benzofuranones Derivative 95a	Range9.8 to >100μM. Shows highest activity. Range 9.8μM.
	Wang et al.	N-arylbenzo oxazole-2-amine derivatives 96 Derivative 96a	Range 32 to 120μM. Was found to be non-competitive type of inhibitor.

Table 5: Chromone, Flavone and Xanthone derivatives and hybrids

Synthetic heterocyclic α-glucosidase inhibitors	Researchers	Devised derivatives and their substituents	Feature.
Chromone or Flavone derivatives and hybrid	Wang et al.	Chromone hydrazones 105 Derivative 105a	Range 20to 96μM.remarkable decrease in activity was observed when right phenyl moiety was replaced with thiophene moiety. Range 20μM.non-competitive inhibitor.
	Zhen et al.	Derivative 106 Derivative 106a, 106b and 106c Derivative 106a	Solubility and activity is far better. Range 4.1μM, 23μM and 65μM. Most active non-competitive inhibitor.
Xanthone derivatives	Wang and coworkers	3-hydroxyl moiety of 1,3-dihydroxyanthone 108 Derivative 108a,108b and 108c	They observed enhanced α-glucosidase inhibitory activity after esterification as compared to parent xanthone 107 Range 10μM, 13μM and 11μM.respectively.
	Wang's group	Oxazolxanthone derivative 109	Range 6.3 to 38μM.more potent with 30 fold more inhibitory activity.

3. Conclusions

Conclusions derived on the basis of theoretical SAR studies helped us to generate the pharmacophoric (Figure 2) features required for the NCEs to act as potent (α-Glucosidase Inhibitor) in the management of T2DM with a novel mechanism of action:

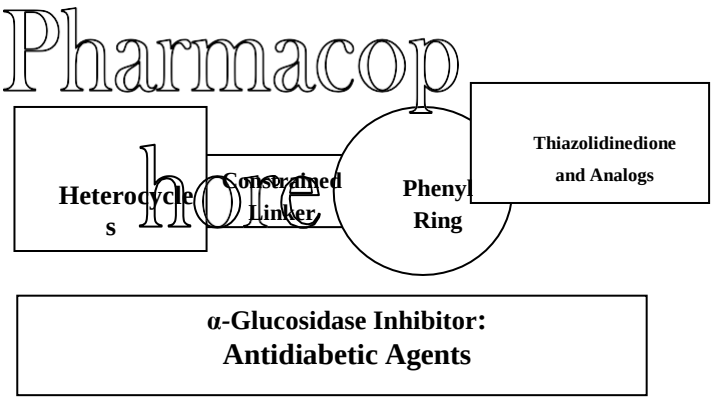

Figure 2: Pharmacophore Representation

Theoretically designed molecules fulfilling the pharmacophoric requirements can be synthesized followed by their activity prediction through docking studies. Further support to these molecules to behave as α-Glucosidase Inhibitor will be provided by carrying out their biological activity studies.

4. Research Design and Methodology

These theoretically designed compounds will be prepared from easily available starting materials using routine chemistry in a crafted manner to link various pharmacophoric units leading to the synthesis of the final molecules as per methodologies following the scheme shown below fig. 3:

Heterocycles Selected:
Variously substituted Phthalimide, Quinazoline and Chromones etc. Some alternative routes for synthesis may be opted and modifications can be carried out in synthetic sequence. The number of atoms constituting the linker can varies from 0-2.

Structural Characterization, Docking and Biological Studies:
All classes of compounds can be synthesized, as per designed synthetic strategies or through some other routes if the need arises, and will be subjected to spectral studies for characterization of their structure. Spectroscopic techniques that can be applied for structural illucidation are Double Beam UV-Visible Spectrophotometer, IR Spectrometer, 1H and 13C NMR Spectrometer. The final docking studies and validation of these compounds to act as α-Glucosidase inhibitors in the management of T2D may be carried.

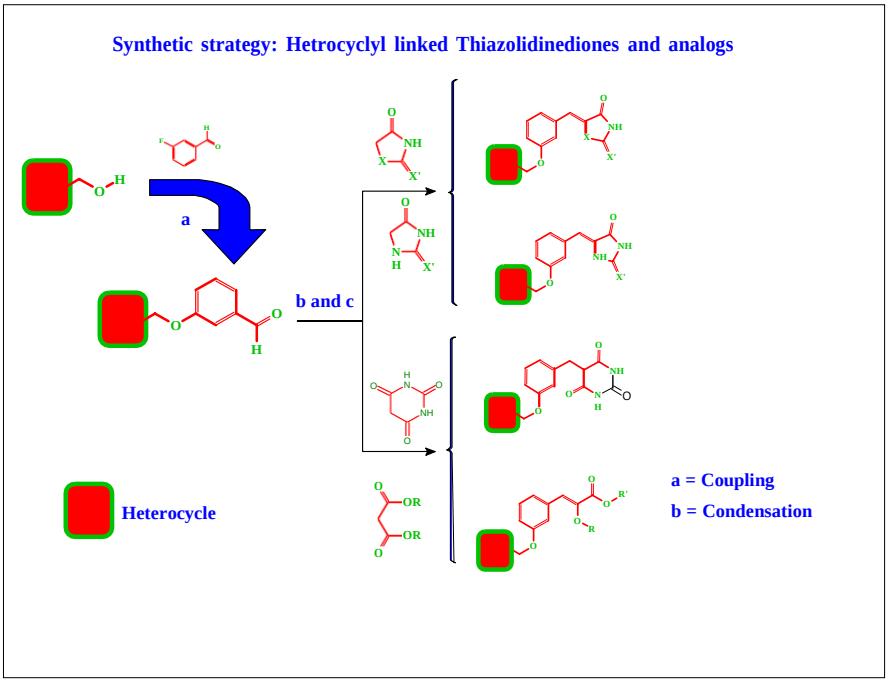

Figure 3: Synthetic strategy of Hetrocyclyl linked Thiazolidinediones and analogs

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