DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF HETEROCYCLE BASED α-GLUCOSIDASE INHIBITORS

Abstract of Thesis

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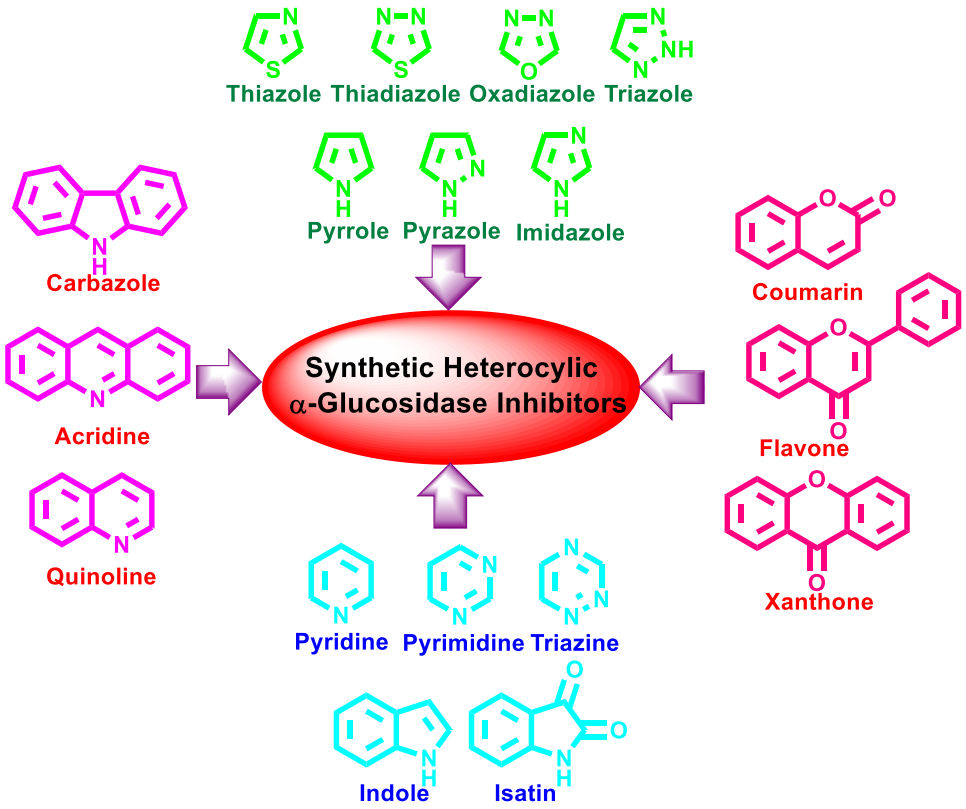
Abstract

The thesis entitled "**DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF HETEROCYCLE BASED α-GLUCOSIDASE INHIBITORS**" consists of four chapters.

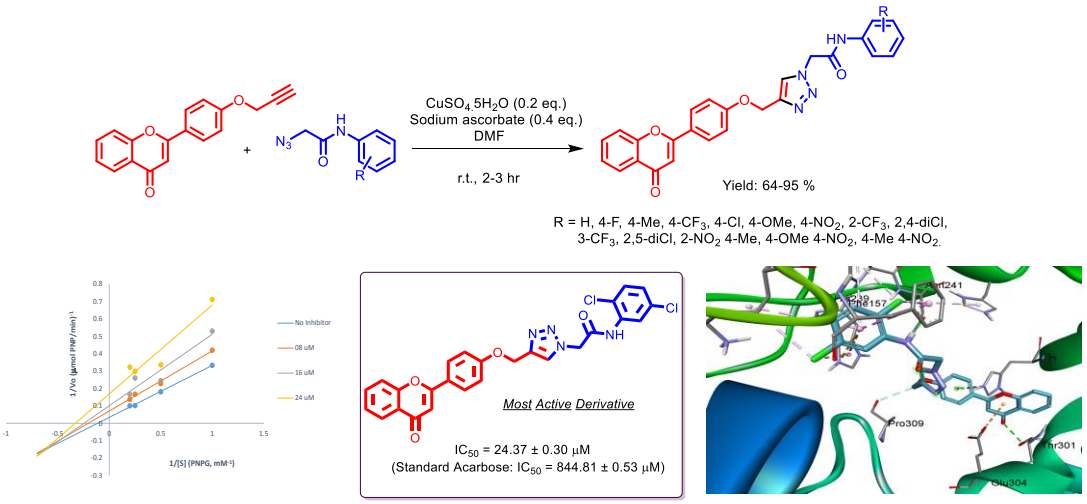
Chapter 1: An Overview of Synthetic Heterocyclic α-Glucosidase Inhibitors

The chapter starts with a brief discussion on diabetes and its current therapeutic targets followed by α-glucosidase inhibitors. The literature survey of diverse heterocyclic compounds discovered as α-glucosidase inhibitors has been summarized. The compounds based on pyrrole, pyrazole, imidazole, thiazole, triazole, thiadiazole, oxadiazole, pyridine, pyrimidine, triazine, quinoline, isatin, indole, carbazole, acridine, coumarin, xanthone and flavone have been explained with their structure-activity relationship, kinetic studies and molecular docking studies. The chapter well describes why there is a need for the development of new α-glucosidase inhibitors and highlights the importance of heterocyclic scaffolds in the search for promising lead molecules in this field.



Chapter 2: Design, Synthesis, Characterization and Biological Evaluation of Flavone-1,2,3-Triazole Amide Derivatives: Enzyme Inhibition, Kinetic Analysis and Molecular Docking Studies

This chapter describes the importance of flavone and triazole scaffolds in the introduction section followed by the emphasis on the design, synthesis, characterization and biological evaluation of flavone-1,2,3-triazole amide derivatives. The flavone-1,2,3-triazole amide derivatives were synthesized from alkyne precursor 4'-*O*-propargyl flavone and azide precursors phenylacetamide azides by utilizing "Click" chemistry protocol in good to excellent yields. All the synthetic steps were chromatographic separation free. The synthesized flavone-1,2,3-triazole amide derivatives were tested for *in vitro* α-glucosidase inhibition activity (*Saccharomyces cerevisiae* origin). The flavone-1,2,3-triazole amide derivative bearing 2,5-dichloro substituents at the side chain phenyl ring was the most active compound with the IC_{50} value of 24.37 ± 0.55 μM as compared to acarbose (IC_{50} = 844.81 ± 0.53 μM). The most active derivative showed a mixed mode of inhibition in the kinetic study. Mixed inhibitors can bind to either the enzyme-substrate complex or the free enzyme.



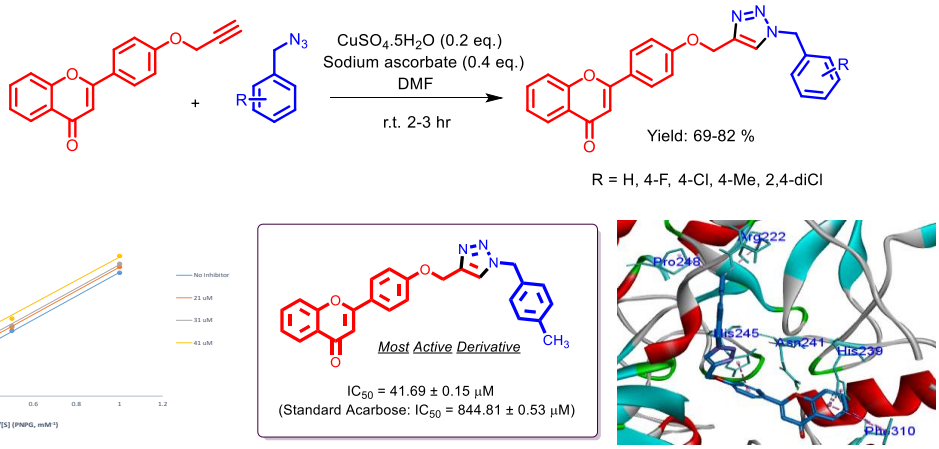
FLAVONE-1,2,3-TRIAZOLE AMIDE DERIVATIVES

The molecular modelling of α-glucosidase using the query sequence P53341 and 3AJ7 template was accomplished. The best homology α-glucosidase model was selected and validated by Ramachandran plot. Then, blind molecular docking studies of all the derivatives were performed to find the possible binding positions and interactions. The most active derivative was visualized to bind at the entrance of the active site of

modelled α-glucosidase with the binding affinity of -8.75 Kcal/mol (binding affinity of acarbose = -3.87 Kcal/mol). It formed four hydrogen bonds with His279, Thr301 and Asn241 amino acid residues as main interactions. Furthermore, the most active derivative showed *in silico* toxicity profile similar to acarbose. Thus, the current study suggested that the flavone-1,2,3-triazole amide derivatives could serve as the new future leads in the development and discovery of effective and safe type-2 diabetes drugs.

Chapter 3: Design, Synthesis, Characterization and Biological Evaluation of Flavone-1,2,3-Triazole Benzyl Derivatives: Enzyme Inhibition, Kinetic Analysis and Molecular Docking Studies

This chapter summarises the synthesis, characterization and biological evaluation of flavone-1,2,3-triazole benzyl derivatives. The "Click" chemistry protocol was used to procure the flavone-1,2,3-triazole benzyl derivatives from alkyne precursor 4'-*O*-propargyl flavone and azide precursors benzyl azides in good yields. The synthesized flavone-1,2,3-triazole benzyl derivatives were evaluated against yeast α-glucosidase. The flavone-1,2,3-triazole benzyl derivative bearing 4-methyl group at the side chain phenyl ring was the most active compound with the IC_{50} value of 41.69 ± 0.15 µM as compared to acarbose (IC_{50} = 844.81 ± 0.53 µM). The derivative showed an uncompetitive mode of inhibition in the kinetic study. The uncompetitive inhibitors only bind to the enzyme-substrate complex. The blind molecular docking studies of all the derivatives were performed to find the possible binding positions and interactions.

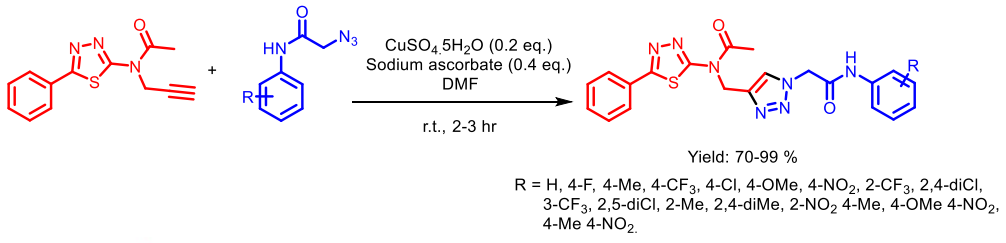


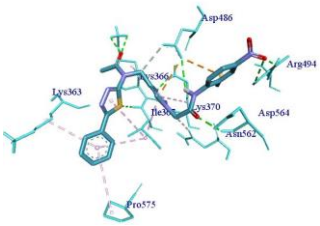
FLAVONE-1,2,3-TRIAZOLE BENZYL DERIVATIVES

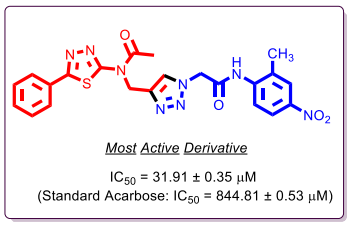
The most active derivative was demonstrated to bind at the allosteric site of modelled α-glucosidase with the binding affinity of -7.89 Kcal/mol. It made one hydrogen bond with Asn241 amino acid residue as the main interaction along with several electrostatic and hydrophobic interactions. The most active derivative showed *in silico* toxicity profile similar to acarbose. The present study strengthened the scope of flavone-1,2,3-triazole benzyl derivatives as anti-diabetic agents.

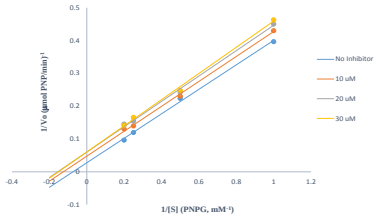
Chapter 4: Design, Synthesis, Characterization and Biological Evaluation of 1,3,4-Thiadiazole-1,2,3-Triazole Derivatives: Enzyme Inhibition, Kinetic Analysis and Molecular Docking Studies

This chapter describes the design, synthesis, characterization and biological evaluation of novel 1,3,4-thiadiazole-1,2,3-triazole derivatives. The 1,3,4-thiadiazole-1,2,3-triazole derivatives were synthesized from novel alkyne precursor based on 1,3,4-thiadiazole and azide precursors phenylacetamide azides by utilizing "Click" chemistry protocol in good to excellent yields. The synthesized 1,3,4-thiadiazole-1,2,3-triazole derivatives were studied for *in vitro* α-glucosidase inhibition activity (*Saccharomyces cerevisiae* origin). The 1,3,4-thiadiazole-1,2,3-triazole derivative bearing 2-methyl and 4-nitro substituents at the side chain phenyl ring was the most potent inhibitor with the IC_{50} value of 31.91 ± 0.35 µM as compared to acarbose (IC_{50} = 844.81 ± 0.53 µM).









In the kinetic study, the most active derivative showed a mixed mode of inhibition. Blind molecular docking studies of all the derivatives were performed to find the possible binding positions and interactions. The most active derivative was visualized to bind at the entrance of the active site of modelled α-glucosidase with the binding

affinity of -8.10 Kcal/mol. It formed four hydrogen bonds with Lys366 and Arg494 residues as main interactions. Thus, the present study signifies the anti-diabetic nature of the thiadiazole-triazole derivatives that may find a lead place in the development of α-glucosidase inhibitors.