DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3,4-THIADIAZOLE BASED HETEROCYCLES

Abstract of Thesis

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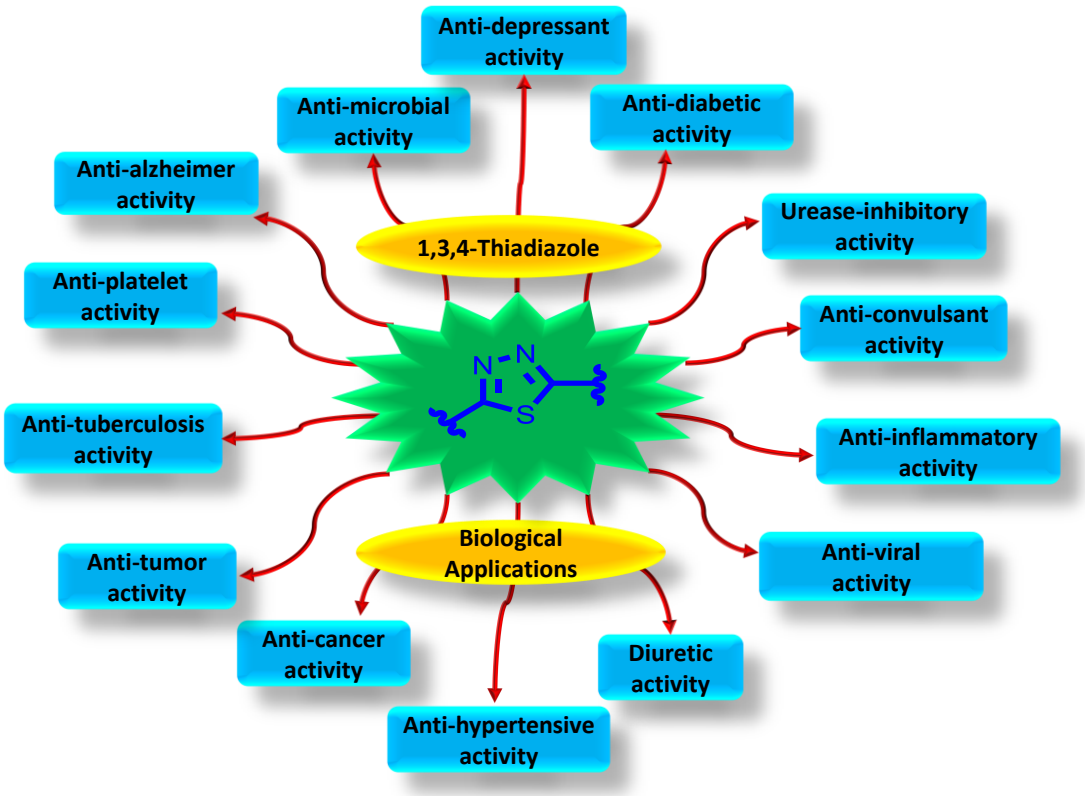
Abstract

The thesis entitled "**DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3,4-THIADIAZOLE BASED HETEROCYCLES**" consists of four chapters.

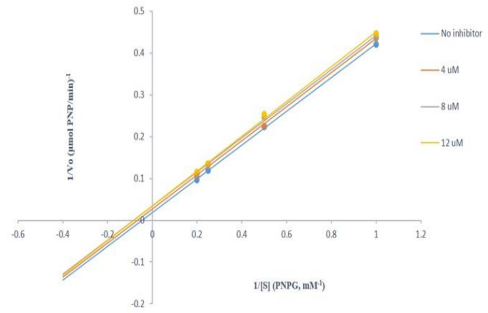
Chapter 1: Biological Applications of 1,3,4-Thiadiazole Derivatives: An Overview

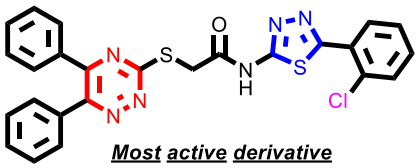
Nitrogen and sulphur containing heterocyclic scaffolds form the basis of more than 80 % of the FDA approved drugs. The 1,3,4-thiadiazole is a common and significant nitrogen and sulphur containing pharmacophoric moiety that interacts with biological targets through various secondary interactions. The chapter starts with a brief discussion on the importance and synthetic routes of 1,3,4-thiadiazole scaffold. The 1,3,4-thiadiazole scaffold is a heterocyclic structure recognized for its diverse pharmacological applications. These include anti-cancer, anti-inflammatory, anti-microbial, anti-viral, anti-tubercular, anti-hypertensive, anti-depressant, anti-parasitic, anti-obesity, anti-platelet, anti-influenza, anti-alzheimer, diuretic, anti-HIV, anti-convulsant, anti-diabetic, herbicidal properties etc. The detailed literature survey of above stated biological activities of 1,3,4-thiadiazole based compounds has been summarized in the chapter.



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

This chapter presents the design, synthesis, characterization and biological activity assessment of 1,2,4-triazine-1,3,4-thiadiazole hybrids based on molecular hybridization approach between triazine and thiadiazole scaffolds. The 1,2,4-triazine-1,3,4-thiadiazole hybrids were fabricated by the nucleophilic substitution reaction between 5,6-diphenyl-1,2,4-triazine-3-thiol and corresponding 1,3,4-thiadiazole acetamide derivatives in moderate to excellent yields. The synthetic methods employed are chromatographic separation free. The fabricated 1,2,4-triazine-1,3,4-thiadiazole hybrids were assessed for *in vitro* α-glucosidase inhibition performance (*Saccharomyces cerevisiae* origin). The 1,2,4-triazine-1,3,4-thiadiazole hybrid possessing *ortho*-chloro substitution at the 1,3,4-thiadiazole phenyl ring was the most active compound with the IC_{50} value of 14.36 ± 0.70 μM as compared to acarbose (IC_{50} = 844.81 ± 0.53 μM). This derivative showed a mixed mode of inhibition as confirmed

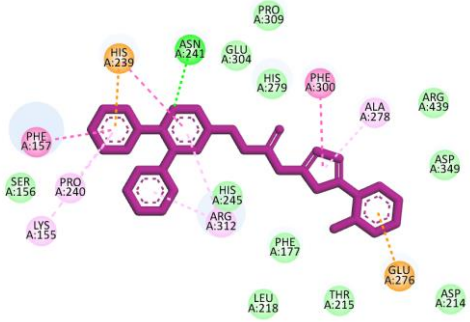


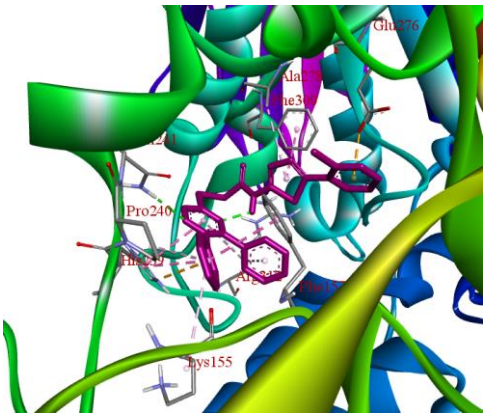


Most active derivative

IC_{50} = 14.36 ± 0.70 μM

(Standard Acarbose IC_{50} = 844.81 ± 0.53 μM)

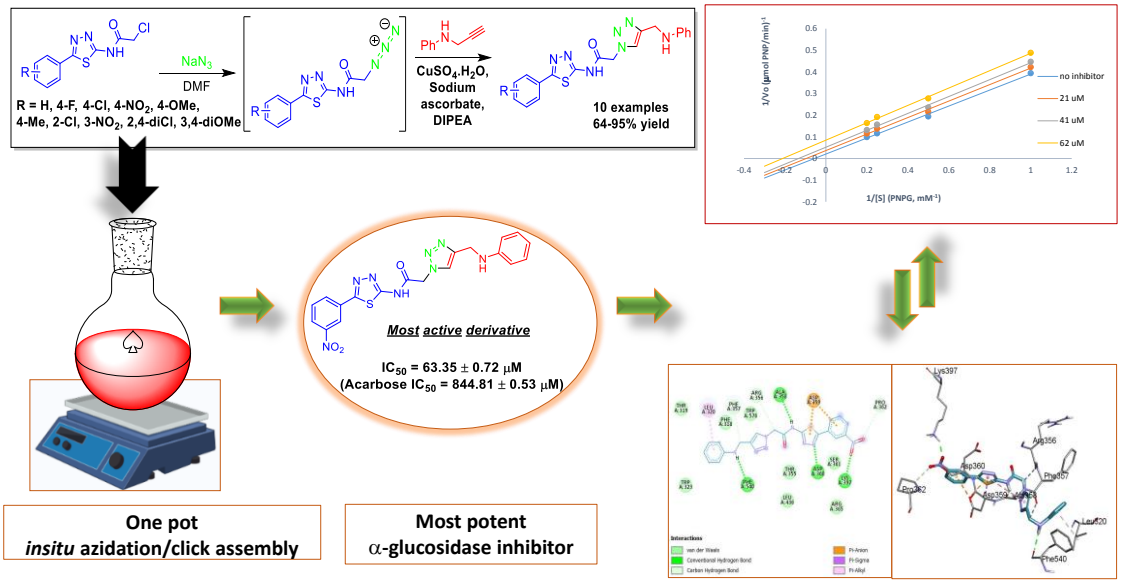




from kinetic study. Mixed inhibitors can either bind to the enzyme-substrate complex or the free enzyme. The molecular modelling of α-glucosidase using the query sequence P53341 and 3AJ7 template was performed. The best homology α-glucosidase model was designated and validated by Ramachandran plot. Then, blind molecular docking studies of all the derivatives were accomplished to assess the plausible binding sites and interactions. The most active derivative was seen to bind at the active site of modelled α-glucosidase with the binding affinity of -10.16 Kcal/mol (binding affinity of acarbose = -4.60 Kcal/mol). One hydrogen bond with Asn241 amino acid residue as key interaction was made by it. Thus, the current study suggested that 1,2,4-triazine-1,3,4-thiadiazole hybrids could serve as new future leads in the development of heterocycle based α-glucosidase inhibitors.

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

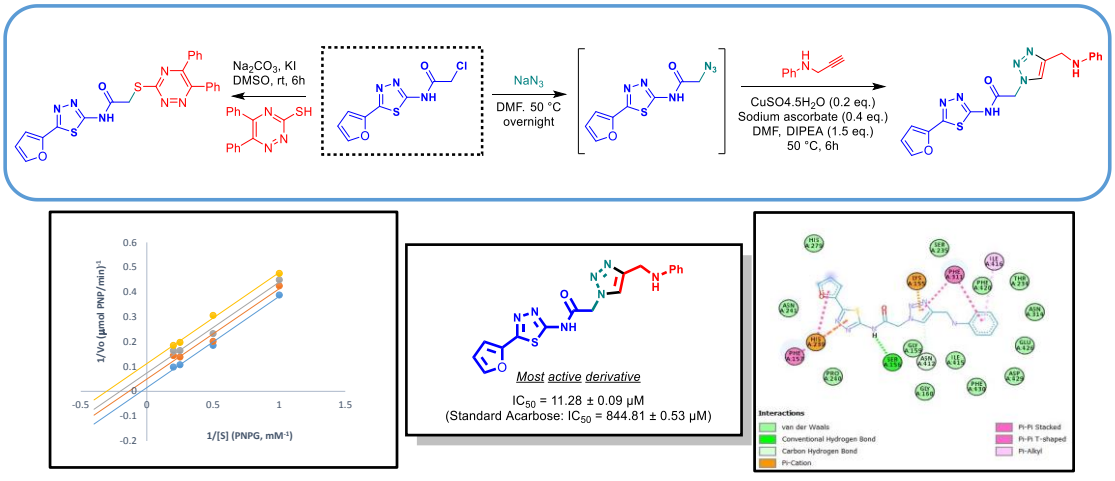
This chapter covers the design, preparation, characterization and biological assessment of novel 1,2,3-triazole-1,3,4-thiadiazole derivatives. For the preparation of 1,2,3-triazole-1,3,4-thiadiazole derivatives "*in situ* azidation/click assembly" approach was adopted using corresponding 1,3,4-thiadiazole acetamide derivatives and alkyne-aniline as precursors. All the synthesized derivatives of 1,2,3-triazole-1,3,4-thiadiazole were obtained in good to excellent yields. These derivatives were also assessed for *in*



vitro α-glucosidase inhibition activity (*Saccharomyces cerevisiae* origin). The 1,2,3-triazole-1,3,4-thiadiazole based compound containing 3-nitro group at the phenyl ring of 1,3,4-thiadiazole counterpart was the most potent inhibitor of the series with IC_{50} value of 63.35 ± 0.72 μM as compared to acarbose (IC_{50} = 844.81 ± 0.53 μM). The compound showed a mixed mode of inhibition as confirmed from kinetic study. To investigate the plausible binding positions and interactions blind molecular docking studies of all the derivatives were performed. The most potent derivative was envisioned to bind at the opening of the active site of modelled α-glucosidase with the binding affinity of -8.89 Kcal/mol. It made four hydrogen bonds with Ala358, Asp360, Lys397 and Phe540 amino acid residues as key interactions. As a result, the present study supports the anti-diabetic nature of the 1,2,3-triazole-1,3,4-thiadiazole derivatives which on further modifications may lead to the development of novel α-glucosidase inhibitors.

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

This chapter presents the synthesis, characterization and biological assessment of furan-linked 1,3,4-thiadiazole derivatives namely 1,2,3-triazole-furanyl-1,3,4-thiadiazole and 1,2,4-triazine-furanyl-1,3,4-thiadiazole compounds. The methodology employed an "*in situ* azidation/click assembly" approach to create a 1,2,3-triazole-furanyl-1,3,4-thiadiazole derivative from the reaction of furanyl-1,3,4-thiadiazole acetamide and alkyne-aniline precursor. Furthermore, a 1,2,4-triazine-furanyl-1,3,4-thiadiazole derivative was synthesized through nucleophilic substitution involving 5,6-



diphenyl-1,2,4-triazine-3-thiol and furanyl-1,3,4-thiadiazole acetamide. Both these furan-based 1,3,4-thiadiazole derivatives were evaluated against yeast α-glucosidase. Notably, the derivative featuring a 1,2,3-triazole ring proved to be an excellent inhibitor with an impressive IC_{50} value of 11.28 ± 0.09 μM in comparison to standard drug acarbose (IC_{50} = 844.81 ± 0.53 μM). Kinetic analysis revealed that this derivative acted as an uncompetitive inhibitor, exclusively binding to the enzyme-substrate complex. Molecular docking studies were conducted to discern potential binding configurations and interactions for both the derivatives. 1,2,3-triazole-furanyl-1,3,4-thiadiazole was found to bind adeptly to the allosteric site of the modelled α-glucosidase, displaying a binding affinity of -9.07 Kcal/mol. A pivotal interaction was established through a hydrogen bond with the Ser156 amino acid residue, supported by various electrostatic and hydrophobic interactions. This study reinforces the potential of furan-based 1,3,4-thiadiazole derivatives as promising agents for managing diabetes, expanding the horizon of therapeutic options in this domain.