INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title : Synthesis of N-Heterocycles as Potential inhibitors of the Immunosuppressive Enzyme, Indoleamine 2, 3-Dioxygenase 1

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SHORT ABSTRACT

The contents of this thesis entitled “Synthesis of N-Heterocycles as Potential Inhibitors of the Immunosuppressive Enzyme, Indoleamine 2,3-Dioxygenase 1” have been organised into five chapters based on the results of experimental work carried out during the research period.

The initial part (**Chapter 1**) contains a brief description of the indoleamine 2,3-dioxygenase 1 enzyme (IDO1). This chapter also describes the biological activities of IDO1 enzyme especially related to the tryptophan catabolism. The overexpression of IDO1 enzyme in the antigen presenting cell (APC) causes the production of excess toxic metabolites which supresses the T-cell mediated immune responses. This suppression of IDO1 mediated immune responses is directly related with several life threatening diseases including cancer, Alzheimer’s disease, HIV-1 encephalitis. Therefore, the enzyme IDO1 has emerged as an attractive target for the treatment of various immunological diseases.

The **chapter 2** describes the synthesis of fused pyran derivatives and their inhibitory activities against purified human IDO1 enzyme both under in vitro and cellular enzymatic assays. This chapter also contains the additional studies including the determination of mode of enzyme inhibition, the selectivity for IDO1 over TDO enzyme, the cytotoxicity under MDA-MB-231 breast cancer cells and the molecular docking analysis of these pyran derivatives. Overall study disclosed a few pyran compounds having high potency for the inhibition of targeted IDO1 enzyme.

Chapter 3 demonstrates the development of mild and efficient synthetic strategy for the construction of 2H-1,2,3-triazole and 1H-pyrazole derivatives. 3 equivalent of Cs2CO3 in DMF solvent at 100 °C temperature was found as the best condition for the coupling of ambiphilic tosylhydrazones. The optimized conditions were used for the synthesis of various 4,5-diaryl-2H-1,2,3-triazole derivatives with moderate to excellent yield. The additional mechanistic studies were also performed to understand the probable pathway for the formation of desired triazoles. Furthermore, this facile strategy was also used for the hetero-coupling reactions of tosylhydrazone with various

electrophiles such as nitrile, imine, alkene and alkyne with moderate to good yield of the respective triazoles and pyrazoles. Additionally, the inhibitory activity of synthesized 4,5-diaryl-2H-1,2,3-triazoles against purified hIDO1 enzyme was also demonstrated.

Chapter 4 describes the optimization of 2H-1,2,3-triazoles as potent IDO1 inhibitors. Therefore the synthesis of 4-carboxamide 2H-1,2,3-triazole derivatives along with the N-modification (aryl, alkyl and sulphonyl) of carboxamide amine group were performed. This chapter demonstrates the IDO1 inhibitory activities of the synthesized triazole compounds under both in vitro and cellular conditions. Furthermore, the cytotoxicity (under MDA-MB-231 cells and HEK-293 cells), selectivity for the inhibition of IDO1 over TDO enzyme, mode of enzyme inhibition and molecular docking analysis (PDB code: 4PK5) have revealed the strong potency of these synthesized triazole derivatives.

Chapter 5 illustrates the development of Lewis acid mediated mild synthetic strategy for the formation of regioselective 1H-pyrazole through unusual ring opening of indole. The salient features of this strategy involved the C2-N1 bond opening and concomitant cyclization reaction of the C2=C3 bond of the indole moiety with the tosylhydrazone proceeded under transition metal and ligand free conditions. The 30 mol% of BF_3•OEt_2 catalyst in DCE solvent at 50 °C temperature was described as the best conditions for this unusual ring-opening and concomitant cyclization reaction. The optimized reaction condition was used to explore the scope and limitations of the synthesis of pyrazoles from the corresponding indoles and tosylhydrazones with moderate to excellent yield. The mechanistic investigations were carried out to propose the plausible path of this unconventional chemical transformation. Furthermore, the selective iodination reaction of pyrazole moiety over aryl ring was illustrated with good yield. The IDO1 activity assay is described the moderate activity of these synthesized pyrazole compounds.

Individually, each chapter consists of brief introduction, detailed description about previous reported works, the present result and discussions, comprehensive experimental section, related references, along with the characterization data of synthesized compounds including few selective NMR (1H & 13C) spectral data. Overall, this dissertation demonstrates the synthetic development and enzyme inhibition assays of few N-heterocycles as potent IDO1 inhibitors.