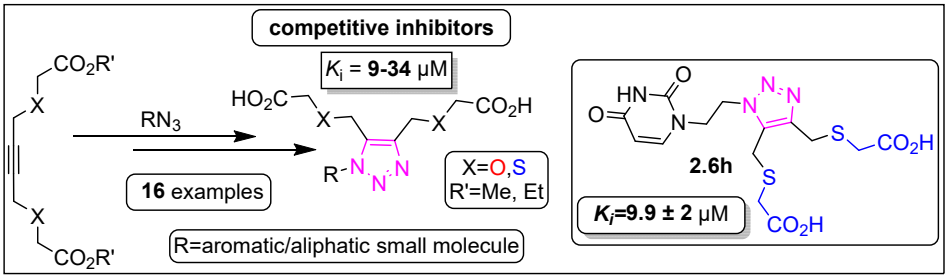
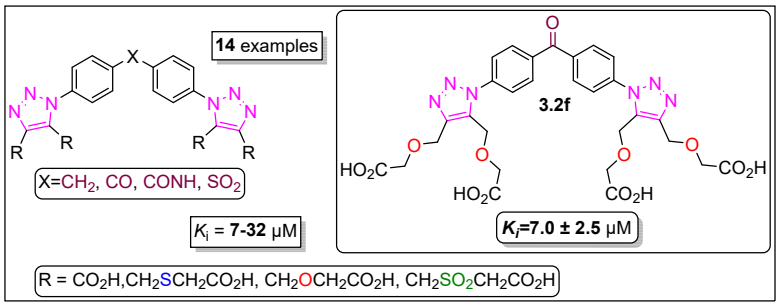
ABSTRACT

1,4,5-Trisubstituted-1,2,3-triazoles (1,4,5-TTs) constitute a special class of functionalized triazoles. This thesis reports the design of 1,4,5-trisubstituted carboxylated 1,2,3-triazoles as a new class of ribonuclease A (RNase A) inhibitor. The "catalytic triad" present at the active site of RNase A is responsible for the cleavage of the 5′- phosphodiester bond; amino acid residues His12, Lys41 and His119 constituting this triad provides a positively charged environment at the physiological pH. Therefore, two different groups of 1,4,5-TTs, functionalized with carboxylic acid moieties were synthesized by reacting pre functionalized butyne-1,4-diol derivatives with several aryl/alkyl azides under solvent and catalyst free conditions. Inhibitory properties of the new molecules with heteroatom incorporated carboxylic acid "$CH_2XCH_2CO_2H$" (X=S, O) functionalities were investigated by steady state enzyme kinetics as well as theoretical docking studies. All the "CH_2S" and "CH_2O" linked acid derivatives exhibited significant competitive inhibition with inhibition constant values (K_i) ranging from 9-34 µM; uracil based thioglycolic acid **2.6h** was found to be the most promising inhibitors with K_i value 9.9 ± 0.7 µM. The molecular docking studies revealed a sufficient number of hydrogen bonding interactions of different functionalities with the amino acid residues present at important subsites of RNase A. The study also established that the free rotating "CH_2X" arms of 1,4,5-TTs provided a unique shape to accommodate the molecule within the active site cleft.

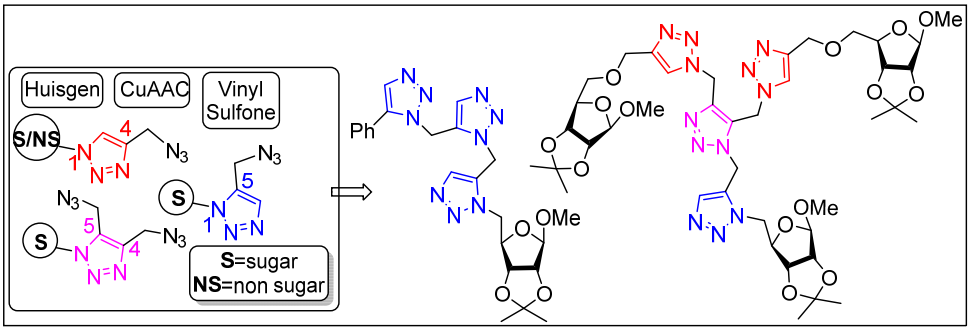


Based on the crescent shaped geometric nature of the active site cleft, this work was further extended for the design and synthesis of four different series of Ar-x-Ar (x=CH_2, CO, CONH, SO_2) linked bis-1,4,5-TTs modified with several carboxylic acid moieties (CO_2H, SCH_2CO_2H, OCH_2CO_2H, $SO_2CH_2CO_2H$) as RNase A inhibitors; here presence of methyl, carbonyl, amide and sulfonyl functionalities as connector of two phenyl units might be expected to provide an overall crescent like shape to the entire 1,4-para disubstituted diphenyl system as core structural framework. All of these compounds were identified as efficient competitive inhibitors with K_i values in the range of 7-32 µM; benzophenone linked bis-1,4,5-TT with oxy acetic acid derivative **3.2f** was recognized as most potent with K_i value 7±2.5 µM. A fairly good idea about

the structure activity relationship (SAR) was obtained by correlating experimentally determined K_i values and the corresponding docking poses. This study reports an unconventional class of non-sugar, non-nucleosidic crescent shaped 1,4,5-TT based competitive inhibitors of RNase A.



In order to develop a strategy for the synthesis 1,2,3-triazole-based oligomers and triazolamers where monomeric triazole moieties are linked by "*N-CH₂-C*" units, copper-catalyzed azide alkyne cycloaddition (CuAAC) method, vinyl sulfone based eliminative azide-olefinic cycloaddition route (EAOC) and Huisgen's azide-alkyne cycloaddition (HAAC) strategy of triazole formation at an elevated temperature were combined in a step-wise and well-planned manner. The monomeric blocks, namely 1,4-disubstituted 1,2,3-triazole (1,4-DT), 1,5-disubstituted 1,2,3-triazole (1,5-DT) and 1,4,5-trisubstituted 1,2,3-triazole (1,4,5-TT) units decorated with CH_2N_3 functional group at C4, C5 and C4-C5 respectively were synthesized using three different reactions mentioned above. Thereafter, the repetition of three triazole forming reactions lead to several combinations of homo/hetero bis, tris and tetrakis- linear and branched triazolamers and oligotriazoles. In most of the cases, the 'N' and 'C' terminals are modified with sugar and phenyl residues (two different groups) respectively although examples of both 'N' and 'C' terminal ends with sugar component (similar groups) are also generated. Some of our synthesized triazolamers are being studied for antiaromatase activities.



Keywords: 14,5-TT, oligotriazole, triazolamer, ribonuclease A, enzyme kinetics, docking