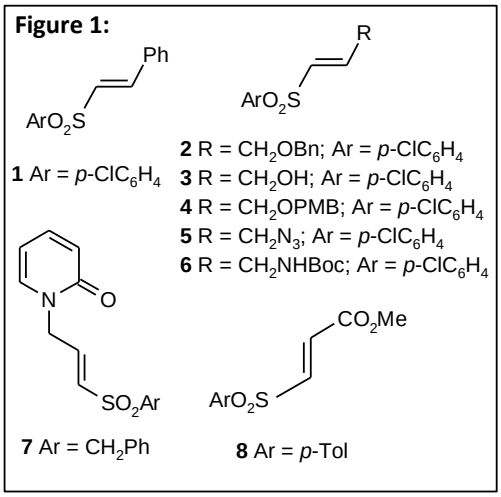
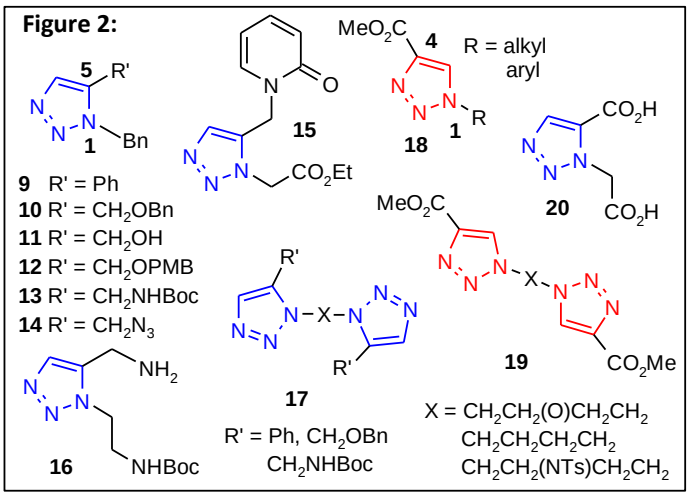
1,5-Disubstituted 1,2,3-Triazoles from Vinyl Sulfones: Synthesis and Properties

The discovery that Cu(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) regioselectively provides 1,4-disubstituted 1,2,3-triazoles (1,4-DTs), triggered applications of 1,4-DTs in bioconjugation, biology, medicinal chemistry and material science. The usefulness of 1,4-DTs generated interest in regioisomeric 1,5-disubstituted 1,2,3-triazoles (1,5-DTs). Most of the synthetic strategies for 1,5-DTs use alkynes with varied success. Phenyl vinyl sulfoxides, considered as an acetylene equivalent, on reaction with 1-azidoadamantane afforded monosubstituted 1,2,3-triazoles, whereas perfluoroalkyl substituted phenyl vinyl sulfones on reactions with sugar azides exclusively afforded 1,4-DTs. In this context, our attention was drawn to vinyl sulfones, a class of compounds easily available and widely used as 2π partners for over three decades in cycloaddition reactions.

Eight structurally varied vinyl sulfones **1-8** were synthesized from easily accessible starting materials or commercially available reagents (Figure 1). Vinyl sulfones **1-7** were reacted with a wide range of organic azides and organic diazides "on" water under refluxing conditions to produce exclusively monotriazoles **9-16** and bistriazoles **17** 1,5-DTs respectively (Figure 2). Interestingly, reactions of vinyl sulfone **8** with organic azides or diazides afforded exclusively 1,4-DTs **18** and **19** respectively (Figure 2).

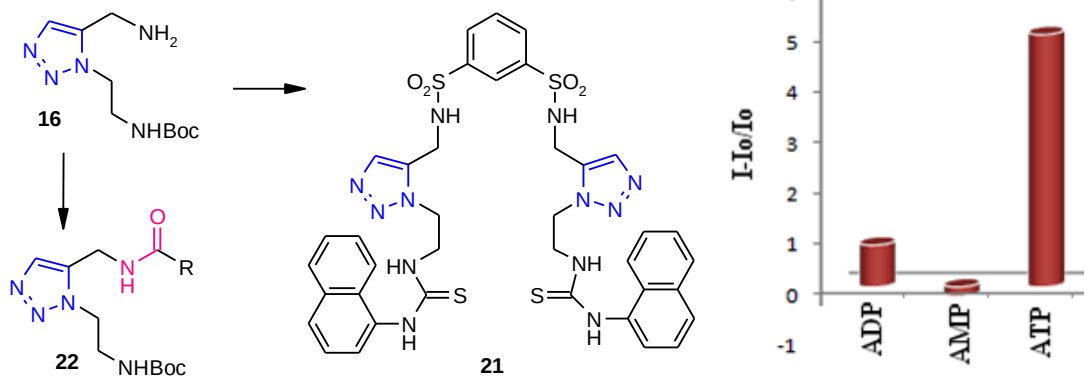




The agarose gel-based assay indicated the inhibitory property of compounds **10** and **20** against RNase A. The inhibition constants (K_i) for compounds **10** and **20** were found 501 μM and 196 μM respectively. A thiourea derivative **21** of the partially protected diamino 1,5-DT **16** is capable of sensing ATP [$K_a = (2.3 \pm 0.31) \times 10^3\ M^{-1}$] over AMP and ADP (Figure 3). Compound **16** was also used as an intermediate for the synthesis of a new series of 1,2,3-

triazole linked small peptide molecules **22** (Figure 3).

Figure 3:



The recent developments in the area of "*N*-CH_2-*C*" linked triazolamers prompted us to design a strategy for accessing a new class of "mixed" triazolamers. The tris(triazolamers) **23** and **24** showed gelation properties in DMSO (Figure 4). Pyridyl substituted 1,5-DT **15** under the treatment with $Zn(OAc)_2.2H_2O$ in MeOH produced metal-ligand complex **25** (Figure 5).

Figure 4:

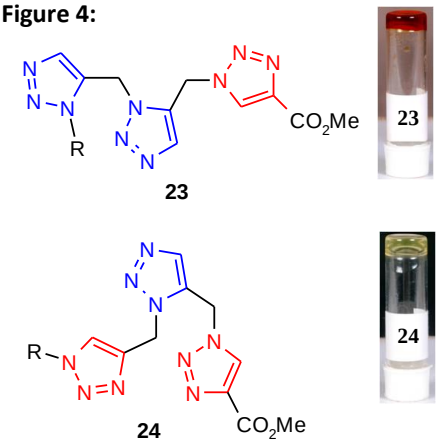
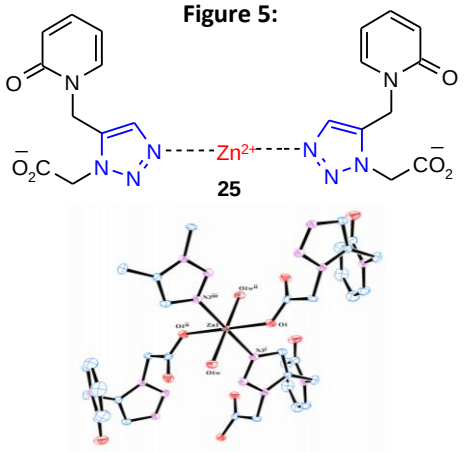


Figure 5:



In conclusion, 1,5-DTs were synthesized for the first time from vinyl sulfones. The expedient and general strategy presented in this thesis offers a practical route to simple as well as more complex 1,5-DTs using different combinations of aryl/alkyl vinyl sulfones and aryl/alkyl azides. These reactions do not require any metal catalyst and most of the reactions were carried out "on" water for reasons of cost, safety, environmental concerns.

Key words: 1,5-Disubstituted 1,2,3-triazole, cycloaddition, "on" water, vinyl sulfone, organic azide, chemosensor, supramolecular chemistry, metal complexation.