A Journey in Design, Synthesis and Development of Novel Anticancer and Antimalarial Agents

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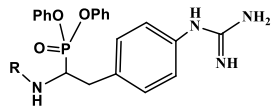
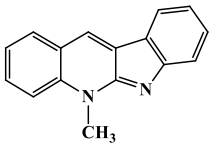
This lecture will be focused on two parts. In the first part, we will present diaryl phosphonate inhibitors for urokinase-type plasminogen activator (uPA) with anticancer activity. Urokinase-type plasminogen activator (uPA) is a serine protease which is situated on the cell surface and can be bound to its receptor (uPAR). The role of uPA/uPAR system in human cancer was demonstrated (*Thromb. Haemostasis* **2005**, *93*, 641). We have designed and developed peptidic diphenyl phosphonate inhibitors of uPA. A first potent and selective lead compounds were identified and a lead optimization program was started to modify the compounds to a small non-peptidic diaryl phosphonate irreversible inhibitor of uPA (*J. Med. Chem*. 2006, 49, 5785, *ibid, J. Med. Chem.* 2007, 50, 6638). Potent and selective uPA inhibition was obtained (IC_{50} < 10 nM; selectivity toward a set of other trypsine like serine proteases more than 1000 fold). The synthetic approach, structure activity relationship (SAR) and in vivo animal studies of these selective inhibitors will be presented.

While the Part II of my lecture will deal with the development of neocryptolepine scaffolds as a novel antimalarial active agents. As part of a larger project for developing more potent and safer antimalarial lead compounds based on natural product, we have developed robust and efficient synthetic method for the natural product alkaloid, neocryptolepine (*J. Med. Chem*. **52**, 2979, 2009), *ibid*, **56**, 1431, 2013) isolated from the shrub *Cryptolepis sanguinolenta* used in Central and West Africa in traditional medicine for the treatment of malaria. A lead optimization program was started to modify the compound and a wide range of neocryptolepine analogues with diversified frameworks and drug-like properties were synthesized. Potent and selective analogues against malaria with IC_{50} in the low nanomolar range were obtained (*Med. Chem. Commun*.5, 927, 2014), *European Journal of Medicinal Chemistry* **64**, 498, 2013). The synthetic routes of these molecules, their biological activities and proposed mechanism of action will be illustrated from both our own research and literature.



R= Peptide or non-peptide

Diaryl phosphonate inhibitors



(Neocryptolepine)