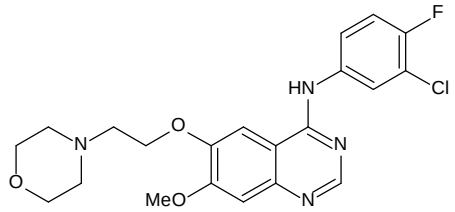
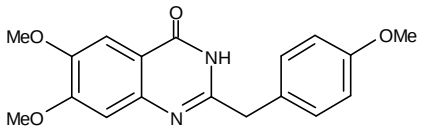
2. AIMS AND OBJECTIVES

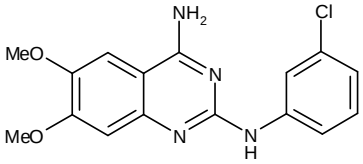
An exhaustive survey of literature revealed that, most of the tyrosine kinase inhibitors are 4-substituted anilinoquinazoline derivatives as Gefitinib (**A**) being the latest small molecule inhibitor from Astra Zeneca. As per the available literature not many efforts have been made to explore the second position of the quinazoline and quinazolinone derivatives as anticancer agents. In fact 2-substituted quinazolinone (**MCR-46**) and quinazoline derivatives (**MCR-96**, **MCR-100**) designed and synthesized in our laboratory showed good anticancer activity. **MCR-46 (I)** and **MCR-96 (II)** were selected for 5-dose screening for anticancer activity at NIH, and **MCR-100 (III)** was screened for MDA-MB435 (IC_{50} = 3.8 µm) and HCT 116 (IC_{50} = 5.0 µm) cancer cell lines at University of Southern California, USA.



(A)



(I)



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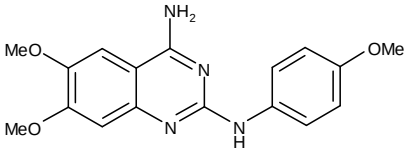


(III)

Further, binding mode of the tyrosine kinase inhibitors to the enzyme supports the above findings. Introduction of hydrophobic side chain at 2nd position of the benzoquinazo-

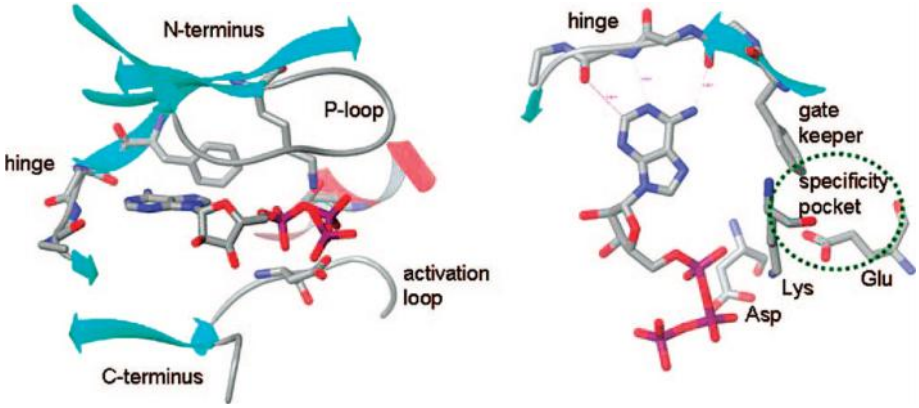


Fig. 1: *Typical picture of a kinase ATP binding site*

line or benzoquinazolinone derivatives enhance the binding interaction to the hydrophobic pocket of the PTK enzyme **(Figure-1).** On exploring the structures of protein kinase it was revealed that:

- Most protein kinases have a common fold consisting of two lobes, the N-terminus lobe consisting of five antiparallel strands and one helix, and the C-terminus lobe which is highly helical.[187]

- The ATP binding site is a narrow hydrophobic pocket located between the two lobes which are linked by a flexible hinge region. The hinge region usually has one hydrogen donor flanked by two hydrogen acceptors derived from the protein backbone **(Figure-2)**.

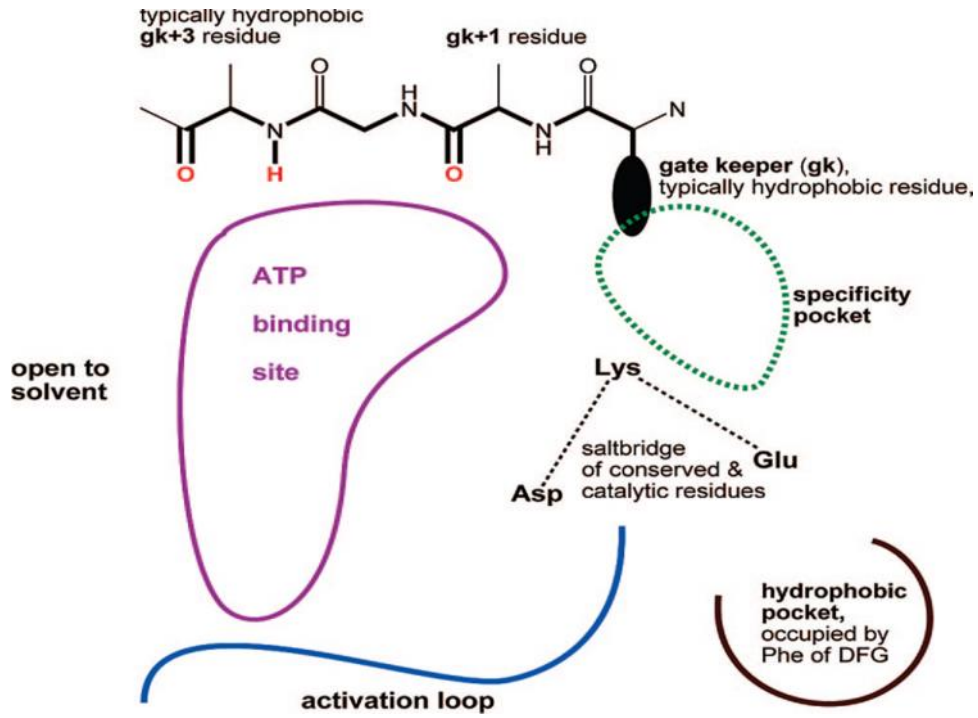


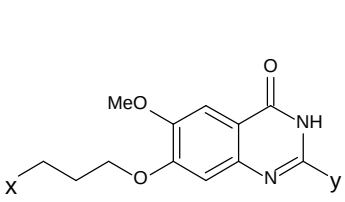
Fig. 2: *A 2D representation of the kinase binding site*

- Kinases have an activation loop containing either serine, threonine or tyrosine residues, which may be phosphorylated. This activation loop occupies a part of the ATP binding site when these residues are not phosphorylated. After activating-phosphorylation by another (upstream) kinase, this hydrophilic charged loop moves into the solvent to expose

the ATP binding site, allowing ATP to bind and transfer its phosphate to a substrate that often may be a different (downstream) kinase.

- The N-terminal side of the activation loop consisting of a highly conserved triplet comprising aspartate, phenylalanine, and glycine residues is the DFG motif. The aspartate residue is catalytically involved in the phosphate transfer and typically engages in a salt bridge interaction with a conserved lysine residue.
- The most important residue in the ATP binding site is the gatekeeper (gk) residue. The peptide bonds forming the hydrogen bond acceptor motifs in the hinge region are referenced as gk+1 and gk+3 relative to the position of the gatekeeper. The size/volume of the gatekeeper's side chain dictates access to the hydrophobic pocket located behind the gatekeeper, thereby defining the potential inhibitor selectivity of the ATP site.[44,45]

Results of above studies prompted us to consider synthesis of a series of compounds having substituents at second position of quinazolinone and quinazoline rings as anticancer agents. It was planned to synthesize compounds of the following types:



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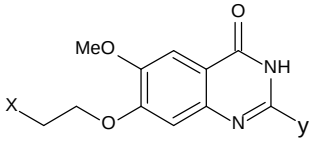

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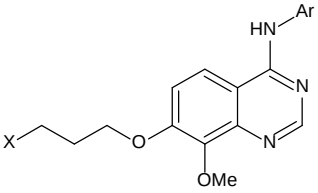

(VI)

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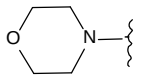

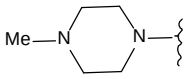

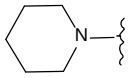

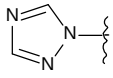

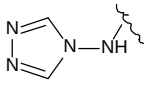

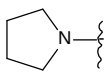

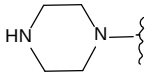

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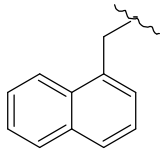

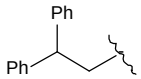

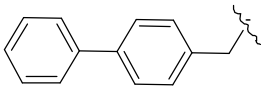

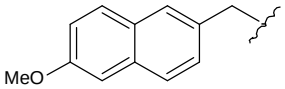

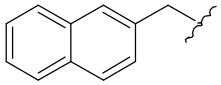

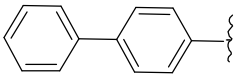

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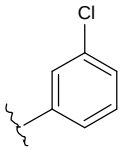

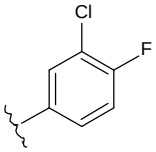

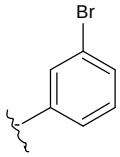

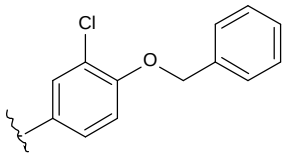

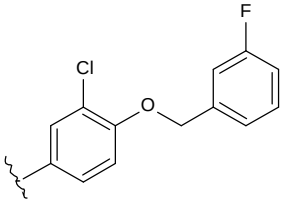

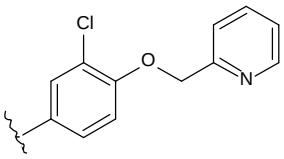

The designed compounds would have the following structural features:

- Amino or amide nitrogen which could form hydrogen bonding with GK1 residue.
- Aqueous solubilizing substituent at position 7
- N1 of the quinazolinone oriented towards the Asp-Lys salt bridge.
- Bulky nonpolar biphenyl or naphthalene side chain to interact with hydrophobic pocket.