4. DESIGN OF TARGET MOLECULE

- Most kinase inhibitors bind into adenosine triphosphate (ATP) and form interaction with the hinge separating the two lobes of kinase domain.
- The hinge bind to adenine group of ATP, through generation of network of H-bonds.
- This motif has been targeted in the design of most kinase inhibitors which contain hydrogen bond accepting and donating groups that can form non-covalent interaction with the hinge essential for the potency of inhibition.

Figure 06: Designing of Target Molecules
Number of heterocyclic group has been used as hinge-binding moiety to generate interaction with the backbone of hinge, for example 2-carboxamidopyridine group in sorafenib.

Bicyclic quinazoline as a novel hinge binding group implemented in the design of new B-RAF inhibitors.

The Quinazoline moiety was envisaged as having two purpose:

(A) Affording two interactions with the hinge backbone, one due to the INH-bond acceptor and the other via the 3-NH donor. In addition, projecting a hydrophilic “edge” of the inhibitors toward the aqueous solvent was envisaged as favorable.

(B) The quinazoline ring is also rigid and reduces the number of rotatable bonds compared to the methylcarboxamide group of Sorafenib so reducing the number of rotatable bonds can be desirable for improved pharmacokinetic properties.

Drugs like doxorubicin, imatinib, dasatinib having thiazole moiety is also good anticancer agents. By linking of piperazine as spacer which occupy narrow tubular pocket produce very good potency.

The general structure of inhibitor fit the model:

- The quinazoline hinge binder connected through oxygen atom to the phenyl ring B that is expected to occupy DFG out pocket.
- Ring B and C connected via the H-donor/acceptor linker B-C
- Amide is linker frequently used in these inhibitor, for example in sorafenib where it interact with glu501 and backbone of Asp594.
- Thiazole is attached to position 2 of quinazoline ring and spacer piperazine is used.