

The design of these compounds as EGFR antagonists is based on our rationalization for the important criteria needed to overlap effectively with EGF receptor to induce antagonistic activity. These criteria include:

The basic amino group for ionic binding, the acetylenic group for electrostatic interaction, 2-butyne provide specific and appropriate distance between the indoline and the cyclic amino group and 2-methylindoline as an isoster or fractional base analogue to phthalimide and indolone found in EGFR antagonists and many other biologically active compound (drug discovery today, 2005). Docking results in support of our assumption as follow. Kinase inhibitors are known to have a cyclic system which has a nitrogen atom that is able to make an electrostatic interaction with the backbone amide of the ATP-binding site hinge region. Another amino group could exist in the kinase inhibitor which makes a water-mediated hydrogen bond with the Thr845 hydroxyl group (also exists in the purine binding region). Additionally, they usually have a hydrophobic cyclic system that fits in a hydrophobic specificity determinant pocket on the other side of the binding site.

Accordingly, our compounds were designed to have a two heterocyclic system linked with each other via rigid spacer (i.e. an acetylenic group). Such a design should offer these compounds the ability to bind with the purine binding region via the first cyclic system and with the specificity binding region via the second cyclic group. The rigid linker should boost compound binding via decreasing the entropic penalty (usually associated with flexible linkers).

The AZ compounds have 2-methyl indoline as a core structure and it is linked with a heterocyclic system via an acetylenic linker. All dock compounds had favorable binding energies (Table 2) and showed interesting multiple binding modes where the two cyclic system had the ability to swap their positions and to make interesting