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Rational modification of semaxanib and sunitinib for developing a tumor growth inhibitor targeting ATP binding site of tyrosine kinase

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ABSTRACT

Analysis of the crystal structure of tyrosine kinase in complexation with an ATP analogue, supplemented with the molecular docking studies of semaxanib and sunitinib in the ATP binding site of the enzyme enabled us to make design of a series of tyrosine kinase inhibitors. The combination of pyrrole and indolinone in one molecule and placement of appropriate substituent thereof made the molecule compatible for the hydrophobic sub-pocket of the enzyme. Screening of the compounds over 60 cell line panel of human tumor cell lines identified compound **3a** that exhibited GI_{50} 35 nM and 63 nM against MCF7 and MDA-MB-468 cell lines of breast cancer.

Cancer continues to be one of the major health problems and a leading cause of human suffering and deaths worldwide.[1] Population growth, increasing life expectancy and adoption of cancer associated lifestyle such as smoking are some of the specific grounds for the growing burden of cancer especially in the economically developed/developing countries. Among the various cancers, breast cancer is the most commonly diagnosed cancer in women as it rarely occurs in men. After lung cancer, breast cancer is the second leading cause of cancer deaths in women and as per the current records, in U.S. alone, 41,070 (40610 women and 460 men) people are estimated to die of breast cancer in 2017.[2] Besides the other remedial measures, chemotherapy is widely used for the treatment of majority of cancers[3] and a number of chemotherapeutic drugs such as taxol,[4] vinblastine,[5] vincristine,[6] etoposide,[7] camptothecin,[8] mitoxantrone,[9] 5-fluorouracil[10] and cisplatin[11] are in the clinical use. These drugs target cancer associated enzymes and signaling pathways. However, the economical availability and the associated side effects of these drugs are the major bottlenecks that hamper their practical applications.[12]

The signaling pathways are the critical cellular links wherein the tyrosine kinases play a pivotal role in post-translational modifications and hence in maintaining normal cellular communication.[13] Nonetheless, effected by the mutations, epidermal growth factor receptors (EGFR) and insulin growth factor receptors (IGFR); the activation of tyrosine kinases (TK) alters the signaling pathways and obstructs the regular cell functions like cell division, growth and normal cell death. Consequently, the role of tyrosine kinases are implicated in the breast cancer, prostate cancer, non-small cell lung cancer and bladder cancer making tyrosine kinases as the potential targets of anti-cancer drugs.[14]

The availability of the crystal structure of tyrosine kinase and the analysis of its ATP binding site by making use of molecular modeling studies helped to a large extent in the design of TK inhibitors.[15,16] Further exploration of the ATP binding site of IGFR-tyrosine kinase provided insight to the mode of interaction between ATP and TK. A number of H-bond interactions between the OH of sugar, N/NH of adenine and the amino acid residues were observed in the crystal coordinates of TK in complex with ATP analogue (Fig. 1). The sugar and adenine template of ATP analogue were placed in the hydrophobic region constituted by L1002, V1010 and F1044 (Fig. 1). Additionally, the interactions of TK inhibitors like sunitinib and semaxanib in the ATP binding site of the enzyme were also examined. It was observed that the polar region of sunitinib interacts through H-bonds whereas the hydrophobic region of both sunitinib and semaxanib is placed in the hydrophobic pocket of the enzyme (Fig. 2). However, the large hydrophobic space in the active site of TK constituted by Val, Phe, and Leu residues remains unoccupied. Therefore, it is worthwhile to design TK inhibitors with large hydrophobic region so that they exhibit better interactions in the hydrophobic pocket of the enzyme. Advantageously, the hydrophobic interactions impart better reversibility to the enzyme–ligand complexation in comparison to the polar interactions.

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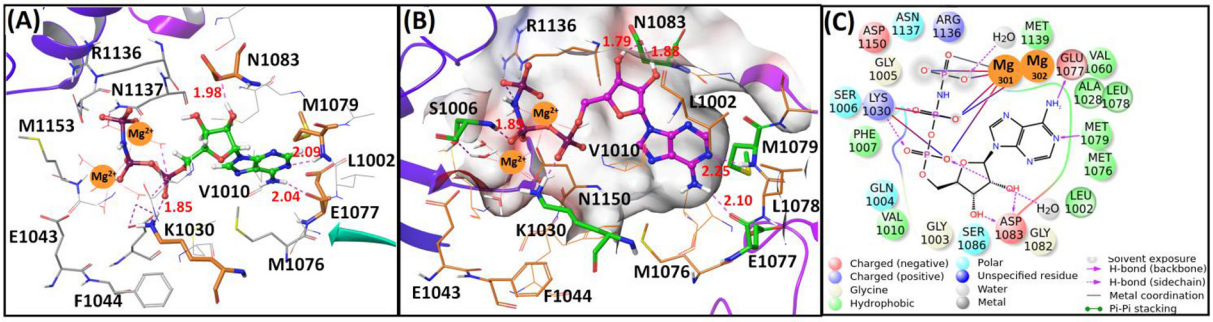

Fig. 1. (A) ATP analogue in the crystal coordinates of tyrosine kinase (phosphorylated insulin receptor, pdb ID 1IR3) showing H-bond interactions (pink dotted lines) with the amino acid residues, (B) ATP analogue docked in the ATP binding site of tyrosine kinase (phosphorylated insulin receptor, pdb ID 1IR3). It is apparent that the adenine and sugar units are placed in the hydrophobic pocket made of L1002, V1010 and F1044, (C) 2D view of ATP analogue docked in tyrosine kinase binding site.

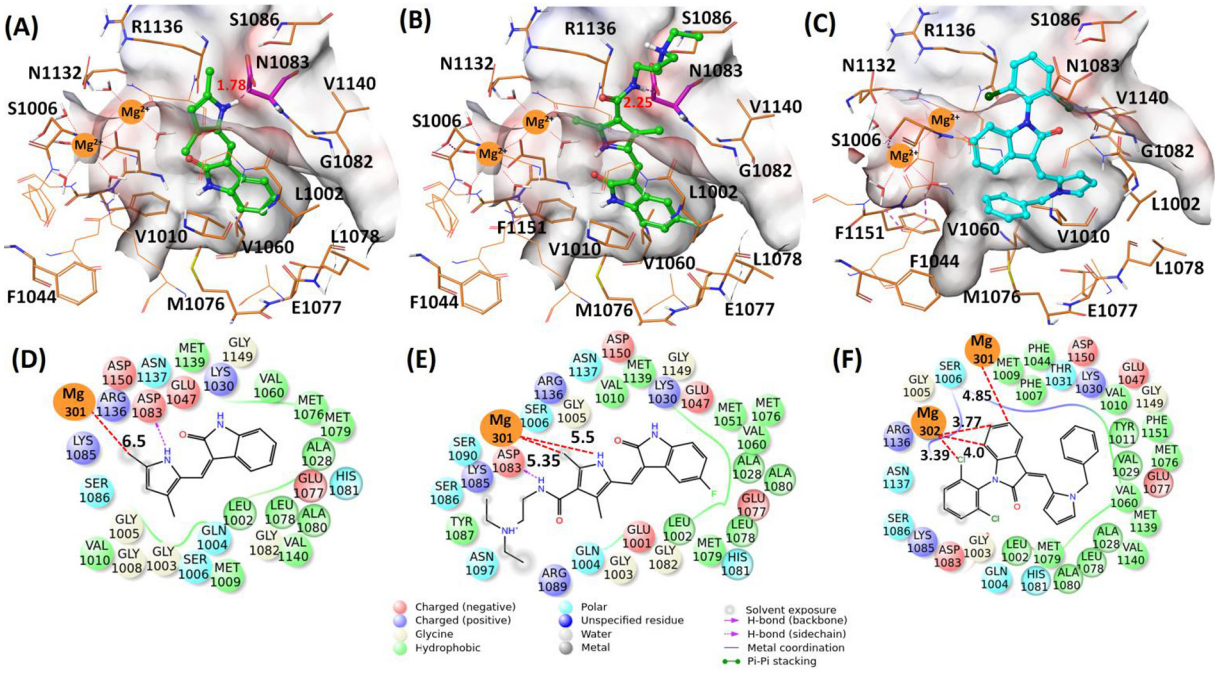

Fig. 2. Semaxanib (A, D), Sunitinib (B, E) and Compound **3a** (C, F) docked in the ATP binding site of tyrosine kinase (phosphorylated insulin receptor, pdb ID 1IR3) showing H-bonding interactions (pink dotted lines) with the ATP binding site residues. In the 2D view (D, E, F), red dotted lines are close distances between Mg atoms and drugs.

The strategy of combining two or more biologically active moieties for the design of new drugs (hybrid molecules) has resulted into the development of some lead molecules with remarkable biological activity.[17] In the present study, taking into consideration the biological importance of pyrrole[18–21] and indole[22] heterocycles; particularly, in making part of anti-cancer drugs such as semaxanib and sunitinib,[23–26] we designed the conjugates of N-substituted pyrrole and indolin-2-one (**3**, Chart 1) and screened the molecules for tumor growth inhibition activity. It is worth to mention that semaxanib (**1**, Chart 1) is known for effective anticancer activity against human cancer cell lines but its development was stopped due to its severe toxicity in phase-II/III studies. Modification of semaxanib to sunitinib eliminated the side effects and it was approved by U.S. Food and Drug Administration for the treatment of cancer in 2006. As per the requirement of having hydrophobic fragments in the TK inhibitors so that they better fit in the ATP binding site of the enzyme, the molecular docking of compound **3a** in the ATP binding site of TK was checked. It was apparent from the results of docking studies that the phenyl rings of the molecule get placed in the hydrophobic sub-pocket of the

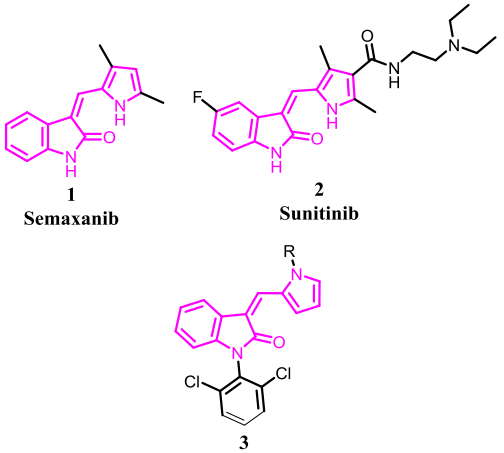

Chart 1.