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Design, *in silico* Evaluation and Synthesis of Novel 2-Arylaminopyrimidine-Based Compounds as Potential Protein Kinase inhibitors

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Discovery of the nature of inhibiting cancer processes by small organic molecules has changed the principles of the development of drug compounds for antitumor therapy. Recent achievements in this area are associated with the design of small-molecule protein kinase inhibitors, organic compounds exhibiting directed pathogenetic action. 2-Arylaminopyrimidine derivatives are the most commonly used templates for the development of these molecules.

In this study, the methodology of the design of chimeric molecules and directed organic synthesis of potential anti-cancer compounds with multikinase profile were developed based on the derivatives of 2-arylaminopyrimidine and substituted aryl carboxylic acids containing as substituents pharmacophore fragments of piperazine, morpholine, isoxazole, isothiazole followed by *in silico* evaluation of their inhibitory activity against native and mutant Bcr-Abl tyrosine kinase. In doing so, the following studies were performed: i) computer-aided design of potential kinase inhibitor candidates consistent with the above methodology; ii) molecular docking of these compounds with the enzyme active site; iii) refinement of the ligand-binding poses by the PM7 semi-empirical quantum chemical method; iv) prediction of the interaction modes dominating the binding; v) calculation of the values of binding free energy and dissociation constant for the PM7-based ligand/Bcr-Abl complexes; and vi) selection of molecules most promising for synthesis and biochemical assays.

As a result, top ranked compounds that specifically and effectively interact with the active sites of the native and mutant Bcr-Abl tyrosine kinase and show the low values of binding free energy and dissociation constants were identified and synthesized.

Based on the data obtained, these compounds are suggested to present good scaffolds for the development of novel potent anti-tumor drugs.

Biography:

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Field of scientific interests: chemistry of heterocyclic compounds, fine organic synthesis, bioorganic chemistry.