QSAR and Structure-Based Docking Studies of Aryl Pyrido[2,3-d]pyrimidin-7(8H)-ones: An Attempt to Anticancer Drug Design

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ABSTRACT

The target of the present study has been to carry out computer-aided anticancer drug design utilizing genetic algorithm-multiple linear regression (GA-MLR) based quantitative structure activity relationship (QSAR) of fibroblast growth factor (FGFr) inhibition of pyrido[2,3-d]pyrimidine-7(8H)-one compounds utilizing different classes of computed structural descriptors. A QSAR model was developed utilizing a combination of constitutional, functional group, geometrical and atom-centered fragment indices by multiple linear regression method and the model validation was performed by searching the predictability of the QSAR models. After outlier analyses through applicability domain, the model validation results were improved. In this connection, molecular docking studies were performed to predict the mode of binding and important structural features necessary for producing biological activities. This attempt could be helpful for further modeling of potent less toxic anticancer chemotherapeutics in these congeners.

KEYWORDS
Anticancer Drug Design, Computed Descriptors, FGFr Inhibitors, Molecular Docking, Pyrido-Pyrimidine Compounds, QSAR

INTRODUCTION

Cancer is a state of uncontrolled growth and abnormal proliferation of cells due to loss of normal mitotic cell division mechanism combined with malignant behavior of the cells. Normal division of cells takes place by mitotic cell division process through which a cell is evenly divided into two daughter cells having same number of chromosome as of parent. The mitosis consists of two phases.

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such as interphase and M phase. Interphase is also called as preparatory phase. In this phase cytochrome and nucleus do not divide but the cell is prepared to divide. It takes place in three phases which are G1, S, and G2. The G1 phase is also called as growth phase. The proteins and enzymes essential for synthesis phase are produced in this phase. The S phase represents the synthesis phase. Each human cell contains 23 pairs of chromosomes (1 pair of sex chromosome and 22 pairs of autosomes). The DNA synthesis occurs during which all chromosomes are copied and the number of DNA in cell becomes double. Synthesis of microtubules takes place in G2 phase which is crucial for mitosis phase. During M phase, protein synthesis stops and chromatids are attached to microtubules. This phase is processed as prophase, metaphase, anaphase and telophase. After M phase, cytokinesis occurs and a cell divides into two cells (Waugh & Grant 2006). The checkpoint systems including G1, G2 and spindle assembly checkpoints play a major role in normal cell division process. These checkpoints stimulate the enzyme system to repair DNA damage if there is lack of chromosomes as well as it can stimulate apoptosis process for programmed cell death if there is excessive formation of chromosomes (Satyanarayana & Chakrapani 2013).

Normal cell division and growth are regulated by proto-oncogenes and tumor suppressor genes. Proto-oncogenes are normal genes that promote normal mitotic process for DNA repair, cell growth and division whereas tumor suppressor genes contain p53 protein which can normally suppress excessive cell growth. Normal functions of these genes are regulated by cell cycle checkpoints. Therefore, mutation of these genes may loss the function of checkpoints which are controlled normally by signal transduction via tyrosine protein kinases (Hartwell et al. 1994; Paul et al. 2004) including different subunits such as FGF, PDGF, EGFr, c-Src respectively which contain tyrosine units in their protein structure. Phosphorylation at tyrosine residue is responsible for signal transduction cascades wherein extracellular signals are transmitted through cell membrane to the cytoplasm and often nucleus and gene expression occurs. Mutation of these signal molecules, oncogenes and tumor suppressor genes may transmit abnormal signal transduction and leads to uncontrolled cell proliferation or cancer (Kopps & Weaver 2005). The anticancer chemotherapeutics which causes inhibition of abnormal cell transduction are extensively crucial for the treatment of cancer patient and these drugs may give longer, painless life to the patient suffering from cancer. Therefore FGF, PDGF, EGFr and C-src have become the major target for development of promising anticancer leads having least toxicity. Recently, aryl pyrido[2, 3-]pyrimidine-7(8H)-ones were shown to produce excellent anticancer activities by inhibiting abnormal signal transduction mechanism via tyrosine kinases. Palmer et al. (2005) synthesized and evaluated a number of 2-anilino-6-phenylpyrido[2, 3-d]pyrimidine-7(8H)-ones having inhibitory activities against abnormal expression of c-Src tyrosine protein kinase and G2/M checkpoint Wee1 responsible for abnormal propagation of G2/M checkpoint leading to expression of p53 gene mediated cancer. These compounds were 10-100 fold more potent inhibitor of c-Src than Weel and an introduction of various substituents does not change this activity. The class of 2-anilino-6-phenylpyrido [2, 3-d] pyrimidine-7(8H)-ones are broad spectrum inhibitors of tyrosine kinase enzyme such as (EGFr, FGF, PDGF, c-Src). These enzymes have competitively inhibition action of ATP site where they form a key bidentate H-bond between 3-azo and 2- NH atoms and a methionine residue. Trumpp-Kallmeyer et al. (1998) developed some congeneric potent pyrido[2,3-d] pyrimidine compounds whose mode of binding has been predicted using molecular docking study considering tyrosine kinase domains of c-Src, PDGF, FGF, and EGFr tyrosine kinases respectively. These models can provide a structural basis to explain their specificity. Schroeder et al. (2001) synthesized a number of aminopyrido[2,3-d]pyrimidine-7-yl compounds as potential tyrosine kinase inhibitors and tested the in vivo and in vitro activities. Compounds of this series were competitive with ATP and displayed submicromolar to low nanomolar potency against a panel of TKs, including receptor (platelet-derived growth factor, PDGF; fibroblast growth factor, FGF) and nonreceptor (c-Src) classes. Several of the most potent compounds displayed submicromolar inhibition of PDGF-mediated receptor autophosphorylation in rat aortic vascular smooth muscle cells and low micromolar inhibition of cellular growth in five human tumor cell lines. Klutchko et al. (1998) synthesized and
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