EGFr, FGFr and PDGFr: Emerging Targets for Anticancer Drug Design

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Abstract: Number of cancer affected individuals are increasing day by each year, 11 million people are diagnosed with cancer out of which 7.6 million people die of this deadly disease which is a very significant figure in worldwide mortality. It has been estimated that there will be 16 million new cancer cases every year by 2020. Despite tremendous chemotherapeutics are given to treat cancer toxicity appears to be the most seminal point which can kill normal body cells along with abnormal cancerous cells. Therefore, researchers have been devoted to discover less toxic new chemotherapeutics which can prevent damage to the normal tissues. Recent advancements in molecular biology of cancer and different pathways involved in malignant transformation of cells clearly demonstrate that one of the important mechanisms for progression of cancer is abnormal signal transduction via tyrosine protein kinase. Tyrosine kinase catalyzes phosphorylation of tyrosine residues in proteins. The phosphorylation of protein residue results into the functions of protein. Tyrosine kinase function in many signal transduction cascades wherein extracellular signal is transmitted through the cell membrane receptors (EGFr/FGFr/PDGFr/C-src) to the nucleus where gene encoding this receptor protein maybe modified by this signal. Mutation of gene may causes abnormal signal transduction and leads to the progression of cancer. Therefore EGFr, FGFr and PDGFr have become the emerging targets for development of promising anticancer leads having lower toxicity. The present review is an attempt in this direction dealing with various aspects of cancer, molecular pharmacology of EGFr, FGFr and PDGFr tyrosine protein kinases which has a direct bearing on the design and development of newer chemotherapeutics.

Keywords: Cancer chemotherapy, EGFr, FGFr and PDGFr as emerging drug targets, Anticancer Drug Design.

1. INTRODUCTION

1.1. Cancer: No Answer of Abnormal Behavior of Cells

Cancer or malignant neoplasm is defined as a class of diseases which is characterized by the abnormal growth and division of cells. Malignancies tend to spread, either by direct growth into adjacent tissue through invasion, or by implantation into distant sites by metastasis which is a process whereby cancer cells can move through the blood stream or lymphatic system to distant locations [1]. Normal body cells follow mitotic process for cell growth and division whereas cancer cells continue to grow and divide abnormally. Instead of dying, they outlive normal cells and continue to form new abnormal cells causing malignancy. Malignant tumors are different from benign tumors, which are self-limited, and do not invade or metastasize. Most cancers form a tumor except leukemia. Human being and all animals in any age including foetus may be affected by cancer. But the risk for most varieties increases with age. Cancer causes brutal death of millions of people throughout the world. According to the American Cancer Society, 7.6 million people died of cancer during 2007 [2-3]. There are a considerable number of theories regarding the etiology of cancer. Environmental stimuli, or carcinogens, such as tobacco smoking, radiation, chemicals, or infectious agents, are the major determinants of the human cancer risk causing abnormalities in the genetic material of the transformed cells. The complex interactions between carcinogens and the host genome can explain why some patients get cancer after exposure to a known carcinogen [4]. But actually there is no answer for abnormal behavior of the mitotic cell division.

1.2. Molecular Mechanisms of Cancer

Normal cells are transformed into malignancy on the basis of molecular metastasis. Molecular metastasis involves multiple genetic alterations. Genes are responsible for producing normal cell growth and differentiation. Disruption of genetic functions through genetic alterations causes abnormal cell growth and differentiations, thus leading to cancer. Genetic changes can occur at many levels, from gain or loss of entire chromosomes to a mutation affecting a single DNA nucleotide. There are two broad categories of

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genes such as oncogenes and tumor suppressor genes, which are affected by these changes. Oncogenes may be normal genes which are expressed at in appropriately high levels. In either case, expression of these genes promotes the malignant phenotype of cancer cells. Tumor suppressor genes are genes which inhibit cell division, survival, or other properties of cancer cells. Tumor suppressor genes are often disabled by cancer-promoting genetic changes. Typically, changes in many genes are required to transform a normal cell into a cancer cell [5].

Oncogenes are the mutations of normal host genes, called proto-oncogene. Proto-oncogenes are good genes that normally control the essential cell functions such as cell proliferation and differentiation through signal transduction. Cells are stimulated by external stimuli such as growth factors which act as signal transducers and bind to the cell surface to control normal cell growth. Mutation of these proto-oncogene leads to oncogene which can modify the gene expression and function through abnormal signal transduction, making uncontrolled growth of cells. One of the first oncogenes to be defined in cancer research is the ras oncogene. Mutations in the Ras family of proto-oncogenes (comprising H-Ras, N-Ras and K-Ras) are very common, being found in 20% to 30% of all human tumours. Ras is involved in melanoma, lung, colon, pancreatic, genitourinary tract and thyroid carcinoma [Bos, 1989]. Ras was originally identified in the Harvey sarcoma virus genome, and researchers were surprised that not only was this gene present in the human genome but also when ligated to a stimulating control element, could induce cancers in cell line cultures [6].

A tumor suppressor gene is a gene that inhibits mitosis and cell growth. When this gene is mutated to cause a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes. Generally, tumor suppressors are transcription factors that are activated by cellular stress or DNA damage. Tumor suppressor genes have a dampening or repressive effect on the regulation of the cell cycle, thus promoting apoptosis [7]. MSH2 is a tumor suppressor gene which functions in the mismatch DNA repair system, and inherited mutations in this gene gives rise to the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. The p53 tumor suppressor is activated in response to a wide variety of cellular stresses including DNA damage, ribonucleotide depletion, redox modulation, hypoxia, changes in cell adhesion, and the stresses created by activated oncogenes. The role of p53 protein is like a transcription factor which, when activated, stimulates the expression of a variety of effectors that bring about growth arrest, promote DNA repair, and stimulate cell death by apoptosis. Elimination of p53 function leads to increased rates of mutation and resistance to apoptosis and is associated with colon, lung and breast cancer [8]. Rb gene mutations and APC (Adenomatous Polyposis Coli) gene mutations are linked to retinoblastoma and adenopolyposis colon cancer respectively. Adenopolyposis colon cancer is associated with thousands of polyps in colon for adult while young individuals are affected at a relatively early age due to this. Finally, inherited mutations in BRCA1 and BRCA2 lead to early onset of breast and ovarian cancer.

1.3. Cell Cycle and Cancer

Cellular proliferation is the process of cell division cycle by which a cell grows, replicates its DNA and then divides to give two daughter cells. This process is divided into four sequential phases (Figure **1**). G_1 phase, S phase (synthesis), G_2 phase (collectively known as interphase) and M phase (mitosis). M phase is itself composed of two tightly coupled processes: mitosis, in which the cell's chromosomes are divided between the two daughter cells, and cytokinesis, in which the cell's cytoplasm divides forming distinct cells. G_1 phase pre (nucleic acid) synthesis interval where cells increase in size in Gap 1. S phase leads to replication of DNA. During the gap between DNA synthesis and mitosis, the cell will continue to grow in G_2 phase. Again, significant protein synthesis occurs

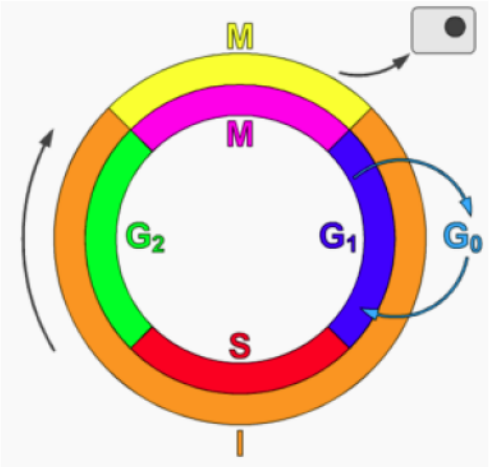

Figure 1: Schematic of the cell cycle. outer ring: I = Interphase, M = Mitosis; inner ring: M = Mitosis, G_1 = Gap 1, G_2 = Gap 2, S = Synthesis; not in ring: G_0 = Gap 0/Resting. The duration of mitosis in relation to the other phases has been exaggerated in this diagram.

during this phase, mainly involving the production of microtubules, which are required during the process of mitosis. Inhibition of protein synthesis during G_2 phase prevents the cell from undergoing mitosis. Finally, mitosis occurs where two daughter cells are produced, that may either directly reenter into next cycle or pass into non-proliferative phase (G_0). In G_0 phase, cells are clonogenic which may remain quiscent for variable periods, but can be recruited in the cell cycle if stimulated later [9].

Movement through each phase of the cell cycle and transition from one phase to the next is regulated at a number of positions within the cell cycle known as checkpoints. Hartwell and Weinert first defined the term cell cycle checkpoint as a mechanism that maintains the observed order of events of each cell cycle. The G_1 checkpoint control mechanism ensures that everything is ready for DNA synthesis. The G_2 checkpoint control mechanism ensures that everything is ready to enter the M (mitosis) phase and divide. A checkpoint in the middle of mitosis (Metaphase Checkpoint) ensures that the cell is ready to complete cell division [10]. Cell division cycle is also regulated by cyclin-dependent kinases (CDKs) and tyrosine proteine kinases (TPKs). CDKs are binary proline-directed serine-threonine-specific protein kinases consisting of positive regulatory subunit known as cyclin. The role of the Cdks is to control cell cycle progression through phosphorylation of proteins that function at specific cell cycle stages. Tyrosine kinase catalyze phosphorylation of tyrosine residues in proteins. The phosphorylation of protein residue results into the functions of protein. Tyrosine kinase function in many signal transduction cascades wherein extracellular signal is transmitted through the cell membrane receptor (EGFr/FGFr/PDGFr/C-src) to the nucleus where gene maybe modified by this signal. Mutation of gene may causes progression of cancer [10]. CDKs and TPKs can regulate the checkpoints. If checkpoints do not function properly then it may lead to abnormal transmission of signals that may cause cancer.

1.4. Searching Drug Targets: TPKS

Normal cell division and growth are regulated by proto-oncogenes and tumor suppressor genes. 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 [11-12] including different subunits such as EGFr, FGFr, PDGFr, etc 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 [13]. Therefore, tyrosine protein kinases including different subunits such as EGFr, FGFr and PDGFr have been treated as crucial drug targets for the design and discovery of potent anticancer chemotherapeutics.

Out of nearly 2000 known kinases, more than 90% protein tyrosine kinases are found in human genome. Tyrosine kinase is a protein kinase enzyme which can transfer a phosphate group from ATP to a protein in a cell (serine and threonine). Phosphate group is attached to the amino acid tyrosine on the protein. Catalytic subunit of protein kinase transfer the gamma phosphate from ATP to one or more amino acid residues in a protein substrate side chain, results in conformational change affecting protein function. Phosphorylation of proteins by protein kinases helps in communicating signals within a cell which is called as cell transduction and cell division like regulating activity. Protein kinase acts as “on” or “off” switch in many cellular functions. Protein kinases can be mutated, stuck in “on” position (a non- stop functional state), which leads to unregulated growth of cells causing cancer.

Tyrosine kinases act in a variety of processes, pathways, and action and are responsible for important events in the body. Receptor tyrosine kinase is responsible for signal transduction which involves cell cycle control. Tyrosine kinase is also involved in mitogenesis, protein in cytosol and nucleus are phosphorylated at tyrosine residue during this process. Figure **2** shows physiology of TPK, protein kinase in presence of ATP transfers phosphate group to the substrate. They are divided into receptor sub classes including EGFr, FGFr and PDGFr and non-receptor protein tyrosine kinase such as c-Src. Due to binding of ligand to extracellular region of receptor tyrosine kinase, some structural rearrangement in RTK takes place which leads to its enzymatic activation. Some set of reaction causes changes in gene expression.

1.4.1. Epidermal Growth Factors [EGF]

It is a low molecular weight polypeptide, a growth factor that stimulates cell growth, proliferation,

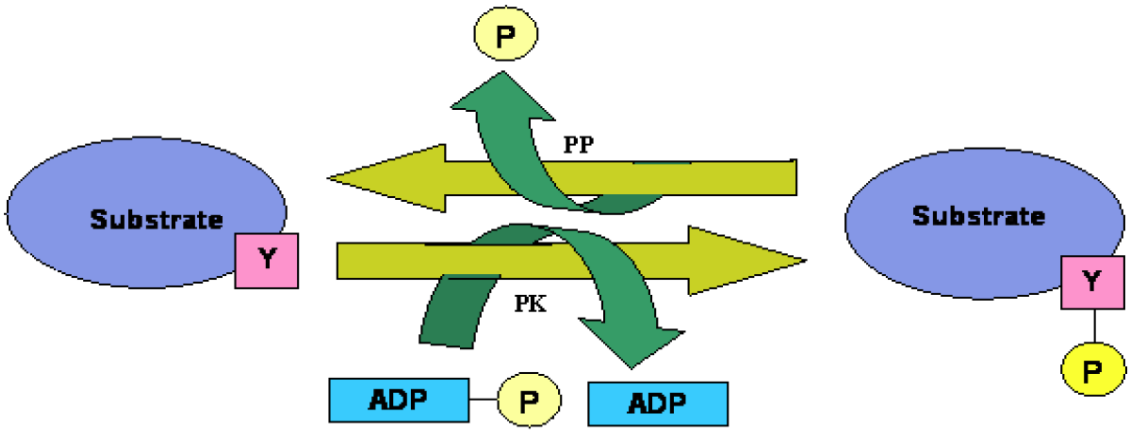

Figure 2: Phosphorylation of protein by tyrosine protein kinase.

differentiation by binding to its receptor EGFR. Human EGF is having 53 amino acid residues and three intramolecular disulfide bonds. EGF of human can be found in urine, saliva, milk and plasma and its production is stimulated by testosterone. When EGF binds to its receptor EGFR it activates protein tyrosine kinase activity which do biochemical changes in the cell. It leads to DNA synthesis and cell proliferation. Increased activity of EGF are observed in certain types of cancer which is related to mutation in receptor and abnormal function [14].

1.4.2. Fibroblast Growth Factor [FGF]

FGFs are polypeptide growth factor which acts by activation of some specific tyrosine kinase receptors. FGFs perform during many processes such as embryonic development, pattering, morphogenesis, migration, differentiation, cell proliferation, survival, migration, and angiogenesis [15a, b]. Scattering of FGF genes throughout the genome indicates FGF family was generated both by gene and chromosomal duplication and translocation during evolution [15]. FGF acts in concert with heparin or heparin sulphate proteoglycan (HSPG) to activate FGFRs which finally leads to variety of cellular responses induced by them. Functional mutation in FGFRs leads to aberrant FGFR signaling which is identified in different forms of human cancers such as lymphomas, prostate and breast cancer as well as other malignant diseases [15c].

The expression is controlled at levels of transcription, mRNA stability and translation. FGFs are major contributors of embryonic development. They helps in the formation of primary body axis, limbs and other structures. Activity of FGFs depends upon their coordination of fundamental cellular functions (such as survival, replication and motility) through effects on gene expression and cytoskeleton. FGFr binds with the member of fibroblast growth factor family protein. Some of them involved in pathological conditions such as a point mutation in FGFR3 can lead to achondroplasia. FGFr consists of three immunoglobulin like domain, single transmembrane helix and an intracellular domain with tyrosine kinase activity. This is the largest family of growth factor ligands, including 22 members. There are 48 different isoforms of FGFr which vary in their ligand-binding property and kinase domain. They all contain immunoglobulin-like domains and thus belongs to immunoglobulin superfamily. These Ig domains – D1, D2,D3 forms a stretch of acidic amino acid which is called as the acid box. This box works in binding of FGFr to FGF. Each receptor can be activated by several FGFs and in many cases one FGF can activate more than one receptors. As far, five FGFr have been found in vertebrates and all of them belong to tyrosine kinase super family - FGFR1, FGFR2, FGFR3, FGFR4 and FGFRL1, FGFR6 [16]. The cytoplasmic portion of FGFR1–4 contains a tyrosine kinase domain and a COOH tail. A fifth receptor, FGFRL1, also binds FGFs, but it lacks the tyrosine kinase domain; moreover, FGFRL1 reportedly reduces cell growth and accelerates cell differentiation [17a,b].

1.4.3. Platelet Derived Growth Factor [PDGF]

PDGF is growth factor, or dimeric glycoprotein that regulates the cell growth and division. They plays role in blood vessel formation (angiogenesis), growth of blood vessel from already existing blood vessel tissue. Uncontrolled angiogenesis characterizes cancer. In human and mouse the PDGF signaling network consists of four ligands and two receptors. PDGF is required element in cellular division for fibroblasts (which is prevalent in wound healing). PDGF is also known to maintain proliferation of oligodendrocytes progenitor cells. It also has been shown that fibroblast

growth factor activates a signaling pathway that positively regulates the PDGF receptors in oligodendrocytes progenitor cells. Additionally, the PDGFr TK has been implicated in the mitogenesis and progression of a variety of tumor cell lines and types [18-19].

1.5. Selective Receptor Tyrosine Protein Kinase Inhibitors

Researchers are devoted to design and discover potential inhibitors of EGF, FGF and PDGF receptor tyrosine kinases as anticancer compounds. Table **1** [20-25] contains a number of selective Food and Drug Administration USA approved tyrosine protein kinase inhibitors which have been developed under clinical trials for the last couple of years. Small molecule inhibitors of the intracellular tyrosine kinase domain of EGFR are erlotinib, gefitinib, afatinib, AZD9291, rociletinib (CO-1686) etc. Through the available literature on NCBI and clinical trials, 31 clinical trials in which cetuximab or panitumumab in combination with chemotherapy were used for the treatment of metastatic colorectal cancer patients in different line settings and 12 clinical trials in which bevacizumab was used for being compared with anti-epidermal growth factor receptor monoclonal antibodies or chemotherapy were chosen for reviewing and comparing the results of overall survival, progression free survival and adverse effects. Tyrphostin 47 was found as a potent EGFr inhibitor but it is not yet FDA approved. Sunitinib (SU11248) is an oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC). Sunitinib was the first cancer drug simultaneously approved for two different indications [26]. Other selective potent PDGFr inhibitors are Tyrphostin AG 1296, AG-370 and DMPQ dihydrochloride [27-29]. But there are very few selective inhibitors of FGFr including BGJ398 (NVP-BGJ398) and FGF401 developed till now [30-31]. It was shown that PD173074 is a selective FGFR inhibitor which reverses multidrug resistance protein 7 (MRP7, ABCC10) and representing a promising therapeutic agent in the clinical treatment of chemoresistant cancer patients [32].

In this effort, medicinal chemists have been trying to synthesize new congeners based on the current core nucleus having affinity towards the specific target. It was found that EGFR inhibitors belong to three chemical cores including 4-anilinoquinazolines, 4-[ar(alk)ylamino] pyridopyrimidines, and 4-phenylaminopyrrolo-pyrimidines respectively [33-35]. Fry *et al*. first discovered that the 4-anilinoquinazoline derivative PD153035 possesses specific inhibitory activity against EGFR tyrosine kinase. Since then, various quinazoline derivatives have been synthesized, including reversible inhibitors, such as erlotinib, gefitinib, and lapatinib, and the irreversible inhibitors BIBW2992, (*E*)-N-(4-(3-chloro-4-fluorophenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-

Table 1: Selective Tyrosine Protein Kinase Inhibitors under Clinical Trials

	Name	Indication	Ref.
EGFr inhibitors	Erlotinib	Advanced non-small cell lung cancer and pancreatic cancer	[20]
	Gefitinib	Advanced non-small cell lung cancer	[20]
	Afatinib	Advanced non-small cell lung cancer	[20]
	ZD1839	Glioblastoma, squamous cell carcinoma of the head and neck, renal cell carcinoma, transitional cell carcinoma, colorectal carcinoma, and locally advanced non-small-cell lung carcinoma.	[21]
	Cetuximab	metastatic colorectal cancer	[22]
	Panitumumab	metastatic colorectal cancer	[22]
	Bevacizumab	metastatic colorectal cancer	[23]
	AZD9291	EGFR inhibitor—resistant non-small cell lung cancer	[24]
	Rociletinib (CO-1686)	T790M-positive NSCLC	[25]
PDGFR inhibitors	Sunitinib (SU11248)	Renal cell carcinoma, GI stromal tumor, pancreatic neuroendocrine tumour	[26]
FGFr inhibitors	NVP-BGJ398	bladder cancer	[30]
	FGF401	Solid malignancies	[31]

enamide (EKB-569) [36]. Several series of small molecule inhibitor targeting FGFr 1 kinase activity are currently being pursued as potential therapeutics for cancer, such as Pyrido[2,3-d]pyrimidine, Pyrrolo[2,1-f][1,2,4]triazine, and pyrido[2,3-d]pyrimidin-7(8H)-one, 1-Oxo-3-aryl-1*H*-indene-2-carboxylic Acid etc [37-38] whereas 1-Phenylbenzimidazoles showed significant selective ATP Site inhibitory activity against Platelet-Derived Growth Factor Receptor [39]. Attempts were made to synthesize potential tyrosine kinase inhibitors incorporating different aliphatic and aromatic groups into the parent nucleus and structure-activity relationship (SAR) studies were being carried out. Schroeder *et al*. [40] synthesized a number of aminopyrido[2,3-d]pyrimidin-7-yl compounds as potential tyrosine kinase inhibitors and tested the *in vivo* and *in vitro* activities. The synthesis and structure–activity relationship (SAR) studies of pyrido[2,3-d]pyrimidin derivatives were conducted by Hamby *et al*. [41]. Boschelli *et al*. [42] synthesized a number of 2-amino-8(H)-pyrido[2,3-d]pyrimidines, and SARs were performed against platelet derived growth factor receptor (PDGFr), FGFr, and c-Src tyrosine kinase activity. A variety of PDGFr-dependent cellular assays were tested for these inhibitors to retard *in vivo* growth of three PDGF dependent tumor lines such as rat aortic vascular smooth muscle cells, C6 glioma cells, and PDGF-transfected NIH 3T3 cell lines. Klutchko *et al*. [43] synthesized numerous 6-(2,6-dichlorophenyl)-pyrido[2,3-d]pyrimidin-7(8H)-one compounds as a novel class of broadly active tyrosine kinase inhibitors, which have shown potential anticancer activities against breast cancer, colon cancer, glioma, and ovarian tumors. Structure–activity relationships of a series of quinazoline derivatives studied by Gibson *et al*. [44] identified 4-(4-iso quinolylamino) quinazoline and 4-(trans-2-phenyl cyclopropylamino) quinazoline as potent EGFR inhibitors against a tumor xenograftmodel (A431 vulval carcinoma in nude mice). In order to study the structure–activity relationships, Hennequin and co-workers [45] synthesized a number of 4-anilinoquinazoline compounds, and it was shown that anilinoquinazolines possessing C-6 aminomethyl side-chains act as potent and selective inhibitors of EGFR kinase. Structure–activity relationships for 4-anilinoquinazolines and modeling of the binding of these compounds to EGFR have also been studied by Denny [46]. SAR, synthesis and biological activity evaluation of molecules are based on experimental analyses. The experimental approach for the synthesis, testing, analysis and discovery of new anticancer lead is immensely expensive and time consuming. Therefore in-silico soft computation could be appreciated for the design and screening of bioactive leads prior to the experiment.

1.6. Drug Design on EGFr, FGFr and PDGFr Inhibitors

Soft Computations based on chemoinformatic tools increase the probability of success and reduce the time and cost involvement in the discovery of lead structure. The major application of chemoinformatic approaches in theoretical drug discovery research is the rational drug design. Major applications of rational drug design are quantitative structure-activity relationship (QSAR) and structure based molecular docking. QSAR aims to derive a mathematical model between the biological activities and computed structural characterizations or properties of chemical compounds. Docking is carried out to find out the mode of interactions between ligand and target. A number of QSAR and molecular modeling studies were carried out for EGFr, FGFr and PDGFr inhibitors predict the important structural features necessary for producing anticancer activities. In an attempt Nandi *et al*. developed 3D-QSAR model considering 4-anilinoquinazolines. It was shown that presence of electropositive groups is found in the anilino moiety. It also suggests that bulky electronegative (electron-donating) groups are favorable at 7-position of the template. This finding supports the experimental observations, where presence of bulky electronegative groups at 7-position signifies increase in activities of compounds. From the molecular docking studies, it is evident that hydrophobic groups substituted at 6- and 7-positions of the quinazoline ring possessing strong hydrophobic interactions with nonpolar active residues are likely to enhance EGFR kinase inhibition. On the other hand, presence of hydrophilic residues or polar hydrophobic residues with lower hydropathy indices in this region of interactions may decrease the activity of the 4-anilinoquinazoline compounds [47].

A number of *N*-(4,6-dimethoxypyrimidin-2-yl)-2-(piperazin-1-yl)acetamide derivatives were synthesized and evaluated for the EGFR inhibitory activities. One of these compounds was shown to produce anticancer activity as an IC_{50} in the nanomolar range in A549 cell cultures and induced a cessation of tumor growth with no toxicity. To explore the more potent and selective EGFR inhibitors, 3D-QSAR model was built to choose activity conformation of the designed molecular and reasonably evaluated the designed molecules. Further, computational docking studies were carried out to

predict the mode of ligand interaction towards active site of 1M17 EGFr target [48]. Recently a novel prone extracellular tetrameric EGFR configuration has been identified as a potential target for the anticancer drug design. Ramirez and colleagues combined molecular docking targeted at the EGFR tetramer interface with a high throughput microscopy based screen to identify compounds that influence EGFR internalization, either independently or contingent upon the presence of EGF [49]. To understand the structural requirements for EGFR tyrosine kinase inhibitors, recently Bathini and co-workers performed an intensive computational study based on molecular modeling protocols like docking, molecular mechanics/generalized born surface area (MM/GBSA) calculations and three dimensional-quantitative structure activity relationships for the design of prospective inhibitors [50]. Nandi *et al*. [51] formulated 3D QSAR models on pyrido[2,3-d]pyrimidine 7(8-H)-one compounds considering EGFr inhibitory activity utilizing molecular field analysis (MFA) technique using field descriptors including steric, electrostatic and hydrophobic fields. A series of aminopyrido[2,3-d]pyrimidin-7-yl derivatives acting as potential tyrosine kinase inhibitors having anticancer activities for PDGFr, FGFr and c-Src kinase inhibition have been considered for the development of QSAR studies based on 2D and 3D approaches considering computed structural 2D and 3D descriptors [52]. These models could find out important structural requirements to generate new compounds in these congeners.

A combinatorial pharmacophore based three-dimensional quantitative structure-activity relationship model was developed based on previously reported FGFR1 inhibitors with diverse structural skeletons. Based on the combinatorial pharmacophore model, a virtual screening against SPECS database was performed by Zhou *et al*. [53] and further nineteen novel active compounds were successfully identified, which provide new chemical starting points for further structural optimization of FGFR1 inhibitors. Based on the structure of AZD 4547 and NVPBGJ-398, Liu *et al*. designed novel 1H-indazol-3-amine scaffold derivatives by utilizing scaffold hopping and molecular hybridization strategies and then twenty-eight new compounds were synthesized and evaluated for their inhibitory activity against FGFR1 [54]. As far as the previous literature is concerned, FIIN-2 and FIIN-3 were reported as first inhibitors that can potently inhibit the proliferation of cells dependent upon the gatekeeper mutants of FGFR1 or FGFR2, which confer resistance to first-generation clinical FGFR inhibitors such as NVP-BGJ398 and AZD4547. These findings have been taken into considerations for the design of covalent FGFR inhibitors that can overcome clinical resistance [55].

In connection with the design of potent inhibitors considering PDGFr as a target, Alan R Katritzky and his lab colleagues [56] developed some QSAR models based on chemical descriptors including geometrical, topological, quantum mechanical, and electronic basis by using CODESSA PRO. 3D-QSAR studies of 75 quinazolines derivative as PDGFR's inhibitor were performed by Haq *et al*. and reported reliable comparative molecular field analysis (CoMFA) and comparative molecular similarity indices (CoMSIA) models [57].

CURRENT AND FUTURE SCOPE

Once the QSAR models for different groups of EGFr, FGFr and PDGFr inhibitors are formulated and validated properly, biological activities of a large number of congeneric derivatives of the respective groups can be predicted. Huge real or virtual derivatives can be generated by combinatorial library design which is the fore front technique of drug discovery research. Combinatorial design of the existing templates for EGFr, FGFr and PDGFr inhibitors is not done so far except 4-anilinoquinazoline template. So, there is a huge scope to consider other existing templates including 4-[ar(alk)ylamino] pyridopyrimidines, 4-phenylaminopyrrolo-pyrimidines as selective EGFr inhibitors, FGFr 1 kinase inhibitors such Pyrido[2,3-d]pyrimidine, Pyrrolo[2,1-f][1,2,4]triazine, and pyrido[2,3-d]pyrimidin-7(8H)-one, 1-Oxo-3-aryl-1*H*-indene-2-carboxylic Acid etc whereas 1-Phenylbenzimidazoles as PDGFr inhibitors stated in references [33-38]. In most of the cases due to unavailability of the physicochemical data, the candidate combinatorial structures can be modelled by developing QSARs utilizing various structural descriptors, which are calculated solely from the molecular structures and the validated QSARs could be applied for the screening of highly active lead compounds. The predicted inhibitors, supposed to be highly active, could be docked inside the target for further lead optimization which paves the way for designing new EGFr, FGFr and PDGFr by reducing cost and time.

CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest in the present study.

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