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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REFERENCES

[1] Sugimura T. Multistep carcinogenesis: A perspective. Science 1992; 258: 603-607. http://dx.doi.org/10.1126/science.1411570

[2] American Cancer Society (December 2007) "Report sees 7.6 million global 2007 cancer deaths", Reuters.

[3] World Health Organization: Cancer. /http://www.who.int/cancer/enS. Accessed 2007, February

[4] Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer 2003; 3: 733-744. http://dx.doi.org/10.1038/nrc1190

[5] Knudson AG. Two genetic hits (more or less) to cancer. Nature reviews Cancer 2001; 1: 157-162. http://dx.doi.org/10.1038/35101031

[6] Chang EH, Furth ME, Scolnick EM, Lowy DR. Tumorigenic transformation of mammalian cells induced by a normal human gene homologous to the oncogene of Harvey murine sarcoma virus. Nature 1982; 297: 479-83. http://dx.doi.org/10.1038/297479a0

[7] Sherr CJ. Principles of tumor suppression. Cell 2004; 116: 235-246. http://dx.doi.org/10.1016/S0092-8674(03)01075-4

[8] Baker SJ, Markowitz S, Fearon ER, Willson JK, Vogelstein B. Suppression of human colorectal carcinoma cell growth by wild-type p53. Science 1990; 249: 912-915. http://dx.doi.org/10.1126/science.2144057

[9] DeVita VT (Jr.), Lawrence TS, Rosenberg SA, Ed. DeVita, Hellman and Rosenberg's Cancer: Cancer principles and practice of oncology, Vol.1, 8th edition, Lippincott Williams & Wilkins, Philadelphia, 2008.

[10] Hartwell LH, Weinert TA. Checkpoints: controls that ensure the order of cell cycle events. Science 1989; 246: 629-634. http://dx.doi.org/10.1126/science.2683079

[11] Hartwell LH, Kastan MB. Cell cycle control and cancer. Science. 1998; 266(5192): 1821-1828. http://dx.doi.org/10.1126/science.7997877

[12] Paul MK, Mukhopadhyay AK. Tyrosine kinase :Role and significance in Cancer. Int J Med Sci 2004; 1(2): 101-15. http://dx.doi.org/10.7150/ijms.1.101

[13] Kops GJ, Weaver BA, Cleveland DW. On the road to cancer: Aneuploidy and the mitotic checkpoint. Nature Reviews Cancer 2005; 5 (10): 773-785. http://dx.doi.org/10.1038/nrc1714

[14] Woodburn JR, The epidermal growth factor receptor and its inhibition in cancer therapy. Pharmacol Ther 1999: 82(2-3): 241-250. http://dx.doi.org/10.1016/S0163-7258(98)00045-X

[15] a) Thisse B, Thisse C. Function and regulation of FGF signaling during embryonic development. Developmental Biology 2005; 287(2): 390-402. http://dx.doi.org/10.1016/j.ydbio.2005.09.011

b) Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer 2010; 10: 116-29. http://dx.doi.org/10.1038/nrc2780

c) Dienstmann R, Rodon J, Prat A, Perez-Garcia J, Adamo B, Felip E, *et al*. Genomic aberrations in the FGFR pathway: opportunities for targeted therapies in solid tumors. Ann Oncol 2014; 25: 552-63. http://dx.doi.org/10.1093/annonc/mdt419

[16] Compagni A, Wilgenbus P, Impagnatiello M A, Cotten M, Christofori G. Fibroblast growth factors are required for efficient tumor angiogenesis. Cancer Res 2000; 60: 7163-7169.

[17] a) Dieci MV, Arnedos M, Andre F, Soria JC. Fibroblast Growth Factor Receptor Inhibitors as a Cancer Treatment: From a Biologic Rationale to Medical Perspectives. Cancer Discov 2013; 3: 264-79. http://dx.doi.org/10.1158/2159-8290.CD-12-0362

b) Touat M, Ileana E, Postel-Vinay S, Andre F, Soria J-C. Targeting FGFR Signaling in Cancer. Clin Can Res 2015; 21(12): 2684-2694. http://dx.doi.org/10.1158/1078-0432.CCR-14-2329

[18] Ross R, Raines EW, Bowen-Pope DF. The biology of platelet-derived growth factor. Cell 1986: 46: 155-169. http://dx.doi.org/10.1016/0092-8674(86)90733-6

[19] Heldin CH, Westermark B. Platelet-derived growth factor and autocrine mechanisms of oncogenic processes. Crit Rev Oncol 1991; 2: 109-124.

[20] Miller VA, Hirsh V, Cadranel J, Chen YM, Park K, Kim SW, *et al*. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012; 13: 528-38. http://dx.doi.org/10.1016/S1470-2045(12)70087-6

[21] Janet E, Dancey MD. Epidermal Growth Factor Receptor Inhibitors in Clinical Trials. Oncology 2001.

[22] Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, *et al*. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 2014; 15(6): 569-579. http://dx.doi.org/10.1016/S1470-2045(14)70118-4

[23] Clinical Trials. gov [Internet]. USA: National Institutes of Health; 2006-2013. Capecitabine, Cetuximab, Oxaliplatin, and Bevacizumab in Treating Patients With Metastatic or Recurrent Colorectal Cancer That Cannot Be Removed By Surgery. February 9, 2006.

[24] Jiang T, Zhou C. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients with EGFR inhibitor—resistant non-small cell lung cancer. Transl Lung Cancer Res 2014; 3(6): 370-372.

[25] Karlovich C, Jonathan W, Goldman, Sun J-M, Mann E, Sequist LV, *et al.* Assessment of EGFR Mutation Status in Matched Plasma and Tumor Tissue of NSCLC Patients from a Phase I Study of Rociletinib (CO-1686). Clin Cancer Res 2016; 22: 2386-2395. http://dx.doi.org/10.1158/1078-0432.CCR-15-1260

[26] Motzer RJ, *et al*. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356(2): 115-124. http://dx.doi.org/10.1056/NEJMoa065044

[27] Che HY, Guo HY, Si XW, You QY, Lou WY. Additive effect by combination of Akt inhibitor, MK-2206, and PDGFR inhibitor, tyrphostin AG 1296, in suppressing anaplastic thyroid carcinoma cell viability and motility. Onco Targets Ther 2014; 7: 425-432. http://dx.doi.org/10.2147/OTT.S57324

[28] Dolle RE, Dunn JA, Bobko M, *et al*. 5,7-Dimethoxy-3-(4-pyridinyl)quinoline is a potent and selective inhibitor of human vascular beta-type platelet-derived growth factor receptor tyrosine kinase. J Med Chem 1994; 37: 2627-2629. http://dx.doi.org/10.1021/jm00043a002

[29] Levitzki A, Gilon C. Tyrphostins as molecular tools and potential antiproliferative drugs. Trends Pharmacol Sci 1991; 12(5): 171-174. http://dx.doi.org/10.1016/0165-6147(91)90538-4

[30] Guagnano V, Kauffmann A, Wöhrle S, Stamm C, Ito M, *et al*. FGFR genetic alterations predict for sensitivity to NVP-BGJ398, a selective pan-FGFR inhibitor. Cancer Discov 2012; 2(12): 1118-33. http://dx.doi.org/10.1158/2159-8290.CD-12-0210

[31] Safety and Efficacy of FGF401 in Patients With Solid Malignancies https://clinicaltrials.gov/ct2/show/NCT02325739

[32] Anreddy N, Patel A, Sodani K, Kathawala JR, Chen EP, *et al*. PD173074, a selective FGFR inhibitor, reverses MRP7 (ABCC10)-mediated MDR. Acta Pharmaceutica Sinica B 2014; 4: 202-207. http://dx.doi.org/10.1016/j.apsb.2014.02.003

[33] Denny WA, Rewcastle GW, Bridges AJ, Fry DW, Kraker AJ. Structure-activity relationships for 4-anilinoquinazolines as potent inhibitors at the ATP binding site of the epidermal growth factor receptor *in vitro*. Clin Exp Pharmacol Physiol 1996; 23: 424-427. http://dx.doi.org/10.1111/j.1440-1681.1996.tb02752.x

[34] Rewcastle GW, Murray DK, Elliott WL, Fry DW, Howard CT. *et al*. Tyrosine kinase inhibitors. 14. Structure-activity relationships for methylamino-substituted derivatives of 4-[(3-bromophenyl)-amino]-6-(methylamino)-pyrido[3,4-d]pyrimidine (PD 158780), a potent and specific inhibitor of the tyrosine kinase activity of receptors for the EGF family of growth factors. J Med Chem 1998; 41: 742-751. http://dx.doi.org/10.1021/jm970641d

[35] Yazdi MH, Faramarzi MA, Nikfar S, Abdollahi M. A Comprehensive Review of Clinical Trials on EGFR Inhibitors Such as Cetuximab and Panitumumab as Monotherapy and in Combination for Treatment of Metastatic Colorectal Cancer. Avicenna J Med Biotech 2015; 7(4): 134-144.

[36] Fry DW, Kraker AJ, McMichael A, Ambroso LA, Nelson JM, *et al*. A specific inhibitor of the epidermal growth factor receptor tyrosine kinase. Science 1994; 265(5175): 1093-1095. http://dx.doi.org/10.1126/science.8066447

[37] Pardo OE, Latigo J, Jeffery RE, Nye E, Poulsom R. Spencer-Dene B, Lemoine NR, Stamp GW, Aboagye EO, Seckl MJ. The fibroblast growth factor receptor inhibitor PD173074 blocks small cell lung cancer growth *in vitro* and *in vivo*. Cancer Res 2009; 69(22): 8645-51.

[38] Barvian MR, Panek RL, Lu GH, Kraker AJ, Amar A, *et al*. 1-Oxo-3-aryl-1*H*-indene-2-carboxylic Acid Derivatives as Selective Inhibitors of Fibroblast Growth Factor Receptor-1 Tyrosine Kinase. Bioorg Med Chem Lett 1997; 7: 2903-2908. http://dx.doi.org/10.1016/S0960-894X(97)10110-X

[39] Palmer BD, Smaill JB, Boyd M, Boschelli DH, Doherty AM, Hamby JM, Khatana SS, Kramer JB, Kraker AJ, Panek RL, Lu GH, Dahring TK, Winters RT, Showalter HDH, Denny WA. Structure-Activity Relationships for 1- Phenylbenzimidazoles as Selective ATP Site inhibitors of the Platelet- Derived Growth Factor Receptor. J Med Chem 1998; 41: 5457-5465. http://dx.doi.org/10.1021/jm9804681

[40] Schroeder MC, Hamby JM, Connolly CJC, Grohar PJ, Winters RT, Barvian MR, Moore CW, *et al*. Soluble 2-substituted aminopyrido[2,3-d]pyrimidin-7-yl ureas. Structure activity relationships against selected tyrosine kinases and exploration of *in vitro* and *in vivo* anticancer activity. J Med Chem 2001; 44: 1915-1926. http://dx.doi.org/10.1021/jm0004291

[41] Hamby JM, Connolly CJC, Schroeder MC, Winters RT, Showalter HDH, Panek RL, Major TC. *et al*. Structure activity relationships for a novel series of Pyrido[2,3-d]pyrimidine tyrosine kinase inhibitors. J Med Chem 1997; 40: 2296-2303. http://dx.doi.org/10.1021/jm970367n

[42] Boschelli DH, Wu Z, Klutchko SR, Showalter HDH, Hamby JM, Lu GH, Major TC, *et al*. Synthesis and tyrosine kinase inhibitory activity of a series of 2-Amino-8H-pyrido[2,3-d]pyrimidines: identification of potent, selective platelet-derived growth factor receptor tyrosine kinase inhibitors. J Med Chem 1998; 41: 4365-4377. http://dx.doi.org/10.1021/jm980398y

[43] Klutchko SR, Hamby JM, Boschelli DH, Wu Z, Kraker AJ, Amar AM, Hartl BG. *et al*. 2-substituted aminopyrido [2,3-d]pyrimidin-7(8H)-ones. Structure-activity relationships against selected tyrosine kinases and *in vitro* and *in vivo* anticancer activity. J Med Chem 1998; 41: 3276-3292. http://dx.doi.org/10.1021/jm9802259

[44] Gibson KH, Grundy W, Godfrey AA, Woodburn JR, Ashton SE, Curry BJ, Scarlett L, Barker AJ, Brown DS. Epidermal growth factor receptor tyrosine kinase: structure-activity relationships and antitumour activity of novel quinazolines. Bioorg Med Chem Lett 1997; 7: 2723-2728. http://dx.doi.org/10.1016/S0960-894X(97)10059-2

[45] Hennequin LFA, Ballard P, Boyle FT, Delouvrie B, Ellston RPA, Halsall CT, Harris CS, Hudson K, Kendrew J, Pease JE, Ross HS, Smith P, Vincent JL. Novel 4-anilinoquinazolines with C-6carbon-linked side chains: synthesis and structure-activity relationship of a series of potent, orally active, EGF receptor tyrosine kinase inhibitors. Bioorg Med Chem Lett 2006; 16: 2672-2676. http://dx.doi.org/10.1016/j.bmcl.2006.02.025

[46] Denny WA. The 4-anilinoquinazoline class of inhibitors of the *erb*B family of receptor tyrosine kinases. Il Farmaco 2001; 56: 51-56. http://dx.doi.org/10.1016/S0014-827X(01)01026-6

[47] Nandi S, Bagchi MC. 3D-QSAR and molecular docking studies of 4-anilinoquinazoline derivatives: A rational approach to anticancer drug design. Mol Divers 2010; 14: 27-38. http://dx.doi.org/10.1007/s11030-009-9137-9

[48] Sun J, Wang X-Y, Lv P-C, Zhu H-L. Discovery of a series of novel phenylpiperazine derivatives as EGFR TK inhibitors. Sci Rep 2015; 5: 13934. http://dx.doi.org/10.1038/srep13934

[49] Ramirez UD, Nikonova AS, Liu H, Pecherskaya A, Lawrence SH, *et al*. Compounds identified by virtual docking to a tetrameric EGFR extracellular domain can modulate Grb2 internalization. BMC Cancer 2015; 15: 436. http://dx.doi.org/10.1186/s12885-015-1415-6

[50] Bathini R, Sivan SK, Fatima S, Manga V. Molecular docking, MM/GBSA and 3D-QSAR studies on EGFR inhibitors. J Chem Sci 2016; 128 (7): 1163-1173. http://dx.doi.org/10.1007/s12039-016-1103-3

[51] Nandi S, Bagchi MC. Activity prediction of some non tested anticancer compounds using GA-based PLS regression models. Chem Biol Drug Des 2011; 78(4): 587-595. http://dx.doi.org/10.1111/j.1747-0285.2011.01177.x

[52] Nandi S, Bagchi MC. QSAR of aminopyrido[2,3-d]pyrimidin-7-yl derivatives: Anticancer drug design by computed descriptors. Journal of Enzyme Inhibition and Medicinal Chemistry 2009; 24: 937-948. http://dx.doi.org/10.1080/14756360802519327

[53] Zhou N, Xu Y, Liu X, Wang Y, Peng J, *et al*. Combinatorial Pharmacophore-Based 3D-QSAR Analysis and Virtual Screening of FGFR1 Inhibitors. Int J Mol Sci 2015; 16: 13407-13426. http://dx.doi.org/10.3390/ijms160613407

[54] Liu J, Peng X, Dai Y, Zhang W, Ren S, Ai J, Geng M, Li Y. Design, synthesis and biological evaluation of novel FGFR inhibitors bearing an indazole scaffold. Org Biomol Chem 2015; 13(28): 7643-54. http://dx.doi.org/10.1039/C5OB00778J

[55] Tan L, Wang J, Tanizaki J, Huang Z, Aref AR, *et al*. Development of covalent inhibitors that can overcome resistance to first-generation FGFR kinase inhibitors. PNAS 2014; E4869-E4877. http://dx.doi.org/10.1073/pnas.1403438111

[56] Katritzky AR, Dobchev DA, Fara DC, Karelson M. QSAR studies on 1-phenylbenzimidazoles as inhibitors of the platelet-derived growth factor. Bioorg Med Chem 2005; 13: 6598-6608. http://dx.doi.org/10.1016/j.bmc.2005.06.067

[57] Haq ZU, Zafar SK, Khan N, Mahmood U. Structure-based 3D-QSAR studies on quinazoline derivatives as platelets-derived growth factor (PDGFR) inhibitors. Med Chem Res 2014; 23(9): 4070-4084. http://dx.doi.org/10.1007/s00044-014-0946-8

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