Quinoline-based small molecules as effective protein kinases inhibitors (Review)

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Abstract: Cancer, malignant tumor, is a group of diseases characterized by abnormal and out-of-controlcell growth with the potential to metastasize to other sites in the body. Protein kinases are a class of molecular drug targets forcancer treatment. Identification of the protein kinases key roles in development of cancer leads to the discovery of different classes of protein kinase inhibitors with enhanced selectivity and efficacy and reduced toxicity. In this review, we focused on the quinoline derivatives as an important class of compounds having potent inhibition effect on the activities of different protein kinases.
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1. Introduction:

1.1 Quinolines:

Quinolineis a heterocyclic benzopyridine compound having an importance to human race. Friedlieb Ferdinand Runge was the first one who extracted quinoline from coal tar in 1834. The commercial quinoline principal source is Coal tar till now. Quinoline has a benzene ring fused to pyridine at two adjacent carbon atoms forming a double-ring structure. Several quinoline derivatives have medicinal chemistry and biomedical importance and uses. These derivatives are synthetically prepared or isolated from natural resources. They are some of the oldest compounds that are used for the treatment of different diseases[1-5].

Quinoline nucleus enters in the synthesis of different quinoline derivatives that rephrase biological activities like antimalarial, analgesic activity, anti-inflammatory, antineoplastic, anti-bacterial, antifungal, antiviral, anthelmintic, anti-protozoal, cardiovascular, CNS effects, hypo-glycaemic, reproductive system (selective oestrogen receptor modulators) and others[6].

Quinolineshave a great importance in the anticancer drug development. There are different classes of anticancer compounds having quinoline nucleus, e.g.:topoisomerase enzyme type I and II inhibitors [7], quinoline derivatives having binding affinity to G-quadruplex-DNA [8], agents having anti-mitotic effect and tubulin polymerization inhibitors[9], mitotic kinesin-5 inhibitors[10], DNA intercalating agents[11], De novo pyrimidine biosynthesis inhibitors[12-14], thymidylate synthase inhibitors[15], iron chelators[16], carbonic anhydrase inhibitors[17, 18], telomerase inhibitors[19], androgen receptor antagonists[20], aromatase inhibitors[21], progesterone receptor agonists[22-25], sirtuin inhibitors[26], quinone reductase 2 inhibitors[27], poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors[28], PI3-kinase related kinase (PIKK) and mTOR inhibitors[29-31], protein phosphatase Cdc25 inhibitors[32], Bcl-2 family protein modulators[33, 34], STAT3 (signal transducers and activators of transcription 3) inhibitors[35], NAD(P)H: quinone oxidoreductase (hNQO1) substrates[36, 37], inhibitors of FGF-R2 auto-phosphorylation[38], inhibitors of NF-kappa B [39], Hsp90 inhibitors[40], inducers of histone H4 hyperacetylation [41], inhibitors of histone acetyltrans-ferases (HAT) and histone deacetylase (HDAC) [42, 43], hedgehog (Hh) signaling inhibitors[44], human tankyrases inhibitors[45], oncogenic Ras inhibitors[46], farnesyltransferase inhibitors (FTI)[47-49], proteasome inhibitors[50], protein kinase enzymes inhibitors and others[51].

1.2 Protein Kinases as Drug Targets:

Protein kinases (PKs), one of the most important target classes for drug development, regulate signal transduction by phosphorylating different residues as tyrosine, threonine, and serine residues in key proteins. These proteins play an important role in signal pathways featuring relevance in many diseases. There are about 600 PKs in the human genome [52, 53]. Many of the PKs can be inhibited by quinoline derivatives, e.g.: MAPKS, PKC, CK2, Src, RET, c-Met, VRGFR, EGFR, IGF-1R, CSF-1R, PDGFR and TGFb-RI. In this review, the anticancer activity of quinoline derivatives targeting different PKs has been summarized in the next **table (1)** followed by their discussion.

Table (1): Anticancer activity of quinoline derivatives targeting different PKs[54-180].

Targeted Enzyme	*Compounds and Biological activity*
I. MAPKs	**3-(4-Fluorophenyl)-4-pyridin- 4-ylquinoline-2(1*H*)-one**, ***Compound (1):*** p38R MAPK IC_{50}=1.8 µM.
	Substituted 7-alkenyl-4[3-chloro-4-(1-methyl- 1H-imidazol-2-ylsulfanyl)] anilino-3-quinoline carbonitrile derivative, ***Compound (2):***Cell lines: H358-lung (IC_{50} = 50 nM), WM266-4 (IC_{50} = 25 nM) and A375-melanoma (IC_{50} = 26 nM).
II. PKC	**Thiopyrano[2,3-c]quinoline derivative,** ***Compound (3), MT477:***Cell lines: H226, MCF-7, U87, LNCaP, A431 and A549. [a dose-dependent inhibitory effect (0.006 to 0.2 µM)]
	Rhodium(III)-phenylquinoline derivative, ***Compound (4):***Δ-(S)-compound **(4)**has PKCδIC_{50} = 26 ± 5 µM to be more potent than the mirror image Δ-(R)-compound **(4)**havingPKCδ IC_{50} = 229 ± 42 µM.
III. CK2	**5-Substituted benzo[c][2,6]naphthyridine-8-carboxylic acid derivatives,** ***Compound (5), CX-4945:***CK2 IC_{50} = 0.3nM. ***Compound (6):*** CK2 IC_{50} = 8.9 nM. ***Compound (7):***CK2 IC_{50} = 3.7 nM. ***Compound (8):***CK2 IC_{50} = 1.0 nM. ***Compound (9):***CK2 IC_{50} = 2.1 nM.
	Benzo[c]quinolizinium, ***Compound (10):***CK2 IC_{50} 0.005 µM.
	3-Carboxy-4(1*H*)-quinolones, ***Compound (11):*** CK2 IC_{50} = 0.3 µM**,** ATP competitive with *K*i value 0.06 µM. ***Compound (12):*** CK2 IC_{50} =1 µM, ATP competitive with *K*i value 0.28 µM.
IV. Src	**Substituted 4-anilino-quinoline-3-carbonitrile derivative,** ***Compound (13), Bosutinib (SKI-606):*** Src IC_{50} = 1-3 nM.
	4-Anilinobenzo[*g*]quinoline-3-carbonitrile derivatives, ***Compound (14 and 16):*** have plasma levels that significantly exceeded the cellular IC_{50} values against Src-transformed fibroblasts. ***Compound (15):***Src kinase IC_{50} = 0.15 nM, Src-transformed fibroblasts IC_{50}= 10 nM ***Compound (16):***highly selective for Src kinase, with modest selectivity versus the Src family kinases Lyn and Fyn.
	4-[(2, 4-Dichlorophenyl)amino]-6,7-disubstituted-3-quinolinecarbonitrile derivatives, ***Compound (17):***Src IC_{50} = 30 nM ***Compound (18):***Src IC_{50} = 3.8 nM
	4-Heteroarylamino-3-quinolinecarbonitrile derivatives, ***Compound (19):***Src IC_{50} = 15.4 nM**,** but it has not a good inhibition effect on iNOS with 313 µM IC_{50} value. It exhibits good inhibition activities toward HepG2 and HT-29 cell lines with the IC_{50} values of 7.61 and 6.58 µM. ***Compound (20):***Src and iNOS IC_{50} values of 9.23 nM and2.18 µM, respectively.
	6,7-Disubstituted-4-(3,4,5-trimethoxyphenylamino)quinoline-3-carbonitrile deivatives, ***Compound (21):***Src inhibitor with an IC_{50} of 35 nM. ***Compound (22):***Src IC_{50} values of 5.5 nM**,** anchorage independent cellular assay measuring the inhibition of Src dependent cell proliferation, with IC_{50} of 1.3 µM. ***Compound (23):***Src IC_{50} values of 5.3 nM, anchorage independent cellular assay measuring the inhibition of Src dependent cell proliferation, with IC_{50}>10 µM.
V. RET	**Substituted 4-(3-hydroxyanilino)- quinoline derivatives,** ***Compound (24):****In-vitro*kinase *Ki* = 3 nM and cell based kinase *Ki* = 300 nM. ***Compound (25):****In-vitro* kinase *Ki*= 25nM and cell based kinase *Ki*= 100 nM. ***Compound (26):****In-vitro*kinase *Ki* = 50 nM and cell based kinase *Ki* = 45 nM.
VI. c-MET	**6, 7-Disubstituted-4-(2-fluorophenoxy)-quinoline derivative,** ***Compound (27):*** c-Met IC_{50} = 1.04 nM. ***Compound (28):***c-Met IC_{50} = 1.86 nM. ***Compound (29):***c-Met IC_{50} = 0.59 nM, having antitumor activity against the six cancer cell lines (A549, H460, HT-29, MKN-45, U87MG and SMMC-7721 cell lines) with IC_{50} values of 0.035, 0.055, 0.11, 0.022, 0.35 and 0.25 µM, respectively. ***Compound (30):***c-Met IC_{50} =1.42 nM.

	3,5,7-Trisubstituted quinoline derivatives, ***Compound (31-37):***c-Met IC_{50} less than 1.0 nM. *compound **(32)** has a statistically significant inhibition effect on the tumor growth (68-69%) at doses of 100 mg/kg in NIH-3T3-TPR-Met and also U-87 MG human gliobastoma xenograft models.
	2-(4-(1-(Quinolin-6-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]-pyrazin-6-yl)-1H-pyrazol-1-yl)ethanol, ***Compound (38), PF-04217903:*** c-MET *Ki* = 0.004 µM and c-MET cellIC_{50} = 0.005 µM.
VII. VEGFR	**6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-substituted or *N*-unsubstituted-1-naphthamide derivatives,** ***Compound (39):***VEGFR-2 (KDR) IC_{50} = 0.6nM. ***Compound (40):***VEGFR-2 (KDR) IC_{50} = 12nM. ***Compound (41):***VEGFR-2 (KDR) IC_{50} = 0.9 nM. *Upon once-daily oral administration for 14 days for compound **(41)** according to HT29 colon cancer and Calu-6 lung cancer xenografts, it causes 85% inhibition of them at doses of 10 and 20 mg/kg, respectively
	(5-Chloro-2-hydroxy-*N*-(quinolin-8-yl)benzamide), ***Compound (42):*** VEGFR-2 IC_{50}= 3.8 nM and IC_{50} value of 5.5 nM for HUVEC induced by VEGF
	1-(2-Substituted-4-(quinolin-4-yloxy)phenyl)urea derivatives, ***Compound (43), Ki8751:*** VEGFR-2 IC_{50} = 0.9 nM. ***Compound (44), Lenvatinib (E7080):***VEGFR-1, VEGFR-2, VEGFR-3, PDGFRβ and RET IC_{50} values of 22nM, 4nM, 5.2nM, 39nM and 35nM, respectively
	***N*-Substituted-*N*-(4-(quinolin-4-yloxy)phenyl)cyclopropane-1,1-dicarboxamide derivative,** ***Compound (45), Cabozantinib (XL184)*:**VEGFR2, MET and RET IC_{50} valuesof 0.035 nM, 1.3 nM and 5.2 nM, respectively.
	2, 5, 7-Trisubstituted-4-aminoquinoline derivative, ***Compound (46):*** HCT-116 IC_{50}= 0.97 µM.
VIII. EGFR	**4-Anilinoquinoline-3-carboxamide derivative,** ***Compound (47):***EGFR IC_{50} = 5.283 µM**,** MCF-7 IC_{50} = 3.46 µM.
	4-Substitutedamino-6,7-disubstituted-quinoline-3-carbonitrile derivative, ***Compound (48):*** EGFR IC_{50} =0.0075 µM**,** A431 IC_{50} = 0.78 µM and SKBR3 IC_{50} = 0.48 µM. ***Compound (49), (EKB-569)*:**EGFR IC_{50}= 0.083 µM, HER-2 IC_{50} =1.23 µM, A431 IC_{50} = 0.08 µM, SKBR3 IC_{50} = 0.01 µM and SW620 IC_{50} = 0.68 µM. ***Compound (50), HKI-272:*** HER-2 IC_{50} = 0.059 µM, EGFR IC_{50} = 0.092 µM, A431 IC_{50} = 0.086 µM, SKBR3 IC_{50} = 0.0018 µM and SW620 IC_{50} = 0.730µM. ***Compound (51):*** EGFR *Ki* = 8.4 nM and excellent cellular activity with IC_{50} at ~5 nM. ***Compound (52):*** EGFR *Ki*=3 nM.
	2-(2-Methyl-5-nitro-1H-imidazol-1-yl)-*N′*-(quinolin-3-ylmethylene)acetohydrazide derivatives, ***Compound (53):***EGFR IC_{50} = 0.12 ± 0.05 µM. ***Compound (54):***HER-2 IC_{50} = 0.37 ± 0.04 µM.
	Pyrazole-quinoline-pyridine hybrids derivatives, ***Compound (55):***EGFR IC_{50} = 0.51 ± 0.05 µM**,** but **Compound (56):** FabH IC_{50} = 3.1µM.
	7-Substituted 4-anilinoquinoline derivatives, ***Compound (57 irreversible), (58 reversible):*** decrease viability of EGFR-mutated PC9 cells at submicromolar concentrations in the range of the activity of Erlotinib. ***Compound (57):*** EGFR IC_{50} = 3.2 ±1.6 nM.
	4-Anilinoquinoline derivatives having a 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO), ***Compounds (59-61):***EGFR IC_{50} values of 623nM, 342 nM and 422 nM, respectively and A431 IC_{50}values of 45.46 µM, 43.21 µM and 38.14 µM, respectively.
IX. IGF-1R	**4-(3-Chloro-4-(1-ethyl-4,5-dimethyl-1H-imidazol-2-ylthio)phenylamino)quinoline-3-carbonitrile, derivative,** ***Compound (62):*** IGFR IC_{50} =0.009 ± 0.003µM.
	2-Phenylquinolin-4-one derivatives, ***Compound (63):***selectively inhibits 14 cancer cell lines, (SR, Colo 205, NCI-H522, HCC-2998, HT-29, SF-539, SNB-75, MDA-MB-435, IGROV1, OVCAR-3, NCI/ADR-RES, RXF-393, HL-60, and DU-145), out of the NCI 60 cancer cell lines evaluation. ***Compound (64):***exceeds the doxorubicin activity. ***Compound (65), CHM-1-P-Na:***has potent cytotoxicity, excellent antitumor activity and extremely safe to use in a Hep3B xenograft nude mice model.

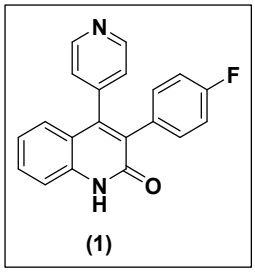
X. CSF-1R	**4-Anilino-6,7- disubstituted-quinoline-3-carboxamide derivatives,** ***Compound (66):*** CSF-1R IC_{50} = 19 nM. ***Compound (67):***screened against a panel of 150 kinases at 1μM and displays remarkable kinase selectivity. ***Compound (68):*** *In-vitro* activity (0.23 μM in the cell) and excellent *in-vivo* PK. ***Compound (69):*** higher clearance in rats andvery potent cell assay (0.06 μM).
XI. PDGFR	**Quinoline ether derivatives,** ***Compound (70, 71):*** selective potent PDGFR α and β inhibitors at low nanomolar concentration.
XII. TGF-β1R	**4-((Pyridin-2-yl) pyrazolyl)quinoline and 4-(2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)quinoline derivatives,** ***Compound (72), (LY364947):*** (TβR-I) IC_{50} = 51nM. ***Compound (73):*** TGF-β RI IC_{50} = 0.104 ± 0.033μM. ***Compound (74), LY2109761:***TGF-β RI IC_{50} = 0.069 ± 0.031μM.

2. Quinolines as Protein kinases inhibitors:

2.1 MAPKs Inhibitors:

Mitogen-activated protein kinases (MAPKs) are protein serine/threonine kinases. They have a critical role in the conversion of extracellular stimuli into a lot of cellular responses. There are 14 MAPKs in mammals that have been classified into seven groups; the extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun amino (N)-terminal kinases 1/2/3 (JNK1/2/3), p38 isoforms (α, β, γ and δ), ERK5, ERK3/4, ERK7, and Nemo-like kinase (NLK) [54].

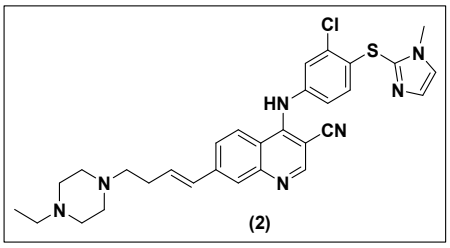
P38-Alpha MAPK, p38α MAPK, is an enzyme that is encoded in humans by the MAPK14 gene. It is also known as Mitogen-activated protein kinase 14 (MAPK14) and also as stressactivated serine/threonine-specific kinases (SAPKs). It is the prototypic member of the p38 MAPK family and considered as a promising target for drug development [55-58]. Compound **(1)**, 3-(4-fluorophenyl)-4-pyridin- 4-ylquinoline-2(1*H*)-one, is a new inhibitor of MAPK with a p38α MAPK IC_{50} of 1.8 μM. According to the molecular modeling studies, it showsa reasonable binding mode in the ATP binding pocket of p38α. Its quinoline core is impacted in the vicinal pyridine/4-F-phenyl system activity fixation for p38α but not for the closely related JNK3, soit is more selective for p38α over JNK3[59].



(1)

The Ras/MAPK pathway is an essential signaling cascade. It controls cellular growth, proliferation and survival. Under the influence of growth factor receptors or hormones, activation of Ras-MAPK pathway takes place and Ras being induced into an active GTP-bound state resulting in the stimulation of serine/threonine kinase Raf. Raf kinasesare a protein kinases family that phosphorylate and activate mitogen-activated protein kinase kinases (MEK) 1 and 2, that phosphorylate MAPK [60].

Compound **(2)** is a derivative of substituted 7-alkenyl-4[3-chloro-4-(1-methyl- 1H-imidazol-2-ylsulfanyl)] anilino-3-quinoline carbonitriles series that were synthesized and biologically evaluated as MEK1 kinase inhibitors. By testing compound **(2)** against a 17 kinases panel, its activity against EGFR, Src, Lyn and IR kinases was observed. Compound **(2)** inhibits ERK phosphorylation through Western blot studies in WM-266 cells, while having no inhibition effect against additional kinase pathways at concentrations up to 10 μM. Compound **(2)** has also inhibition effect on H358 (lung), WM266-4 and A375 (melanoma) cell lines with IC_{50} of 50, 25 and 26 nM, respectively [61].



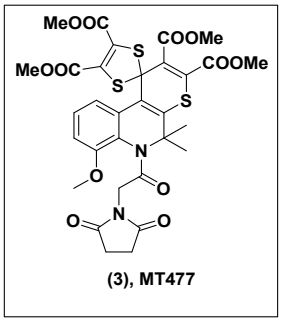
(2)

2.2 PKC Inhibitors

Protein kinase C, PKC, is a protein kinase enzymes family having a critical controlling role in the function of other proteins. PKC phosphorylates hydroxyl groups of serine and threonine residues on these proteins [62]. Several PKC isoforms overexpression promotes different human malignancies progression[63-65]. PKCα regulates the cell-cycle and apoptosis. Overexpression of this isoform induces malignant transformation and proliferation in MCF-7 human breast cancer cells [66]. PKÇ overexpression is required for transformed growth of A549 human lung adenocarcinoma cells malignancy [67]. Both PKCα and PKCδ play important

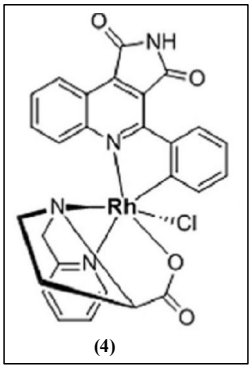
roles in U87 human malignant glioma cells proliferation and apoptosis [68]. There is a relation between PKC activation and different downstream pathways active in tumor cell signaling. It may trigger signaling through the direct effect of PKC in the activation of the Ras kinase pathway and also a direct effect on Raf-1, a small GTP protein, and ERK1/2 kinase, suggesting the PKC involvement in the Ras-Raf-1-MEK-ERK signaling cascade [69-75]. PKC may also activate glycogen synthase kinase-3β (GSK3β), which is linked to the tumor proliferation and progression [76].

Compound **(3)**,**MT477**, a novel thio-pyrano[2,3-c]quinoline derivative, is an inhibitor of PKC-α with putative biological effects on prolifer-ation, apoptosis and migration. It inhibits the PKC-α activity and its downstream targets, ERK1/2 and Akt. It hasalso an effect on Ras activity [77]. It inhibits a variety of cancer cell lines proliferation, e.g.,: MCF-7, U87, H226, LNCaP, A431, K-Ras mutated cell lines, A549 and MiaPaCa-2 [77-79]. By *in-vitro* proliferation assays, compound **(3)**, **MT477**, has a dose-dependent inhibitory effect (0.006 to 0.2 μM) on cellular proliferation of H226, MCF-7, U87, LNCaP, A431 and A549 cancer cell lines [78].



(3), MT477

For the generation of rhodium (III)-based selective protein kinase inhibitors, a new rhodium-(III)-phenylquinoline scaffold was synthesized. By running active site directed affinity screening against 451 human protein kinases enzymes, the protein kinase selectivity profile of the compound **(4)** racemic mixture was shown at 10 μM concentration. The only main protein kinases hits identified were YSK4, PKCδ, ZAP70, MAP3K4, SRMS, and NEK4with % control values (44%, 47%, 50%, 51%, 53% and 58%, respectively), below 60%.PKCδ was selected for further investigations. IC_{50} values for the individual enantiomers Δ-(S)-**(4)** and Δ-(R)-**(4)** against PKCδ at 1 μM ATP were determined. The IC_{50} differs significantly with Δ-(S)-compound **(4)** (IC_{50} = 26 ± 5 μM) to be more potent than the mirror image Δ-(R)-compound **(4)** (IC_{50} = 229 ± 42 μM), indicating specific molecular recognition between the chiral active site of PKCδ and Δ-(S)-compound **(4)**[80].



(4)

2.3 CK2 Inhibitors:

CK2, Casein kinase 2, is a serine/threonine-selective protein kinase [81]. CK2 regulates many anti-apoptotic and pro-proliferative signaling cascades, including PI3K/Akta and Wnt signaling cascades, NF-κB transcription and the DNA damage response. CK2 has been also characterized as an angiogenesis regulator. Due to the deregulation and overexpression of CK2 in cancer-promoting prosurvival and anti-apoptotic pathways, CK2 is a prime cancer drug target [82, 83]. Overexpression of CK2 has been well documented in a number of cancers, including head and neck, breast, colorectal, renal, lung, leukemia and prostate [84, 85].

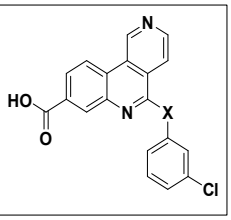
Compound **(5)**, **CX-4945**, 5-(3-chloro-phenylamino)benzo[c][2,6]naphthyridine-8-carboxylic acid, is a potent and selective orally bioavailable small molecule having ATP-competitive inhibition of CK2 [86]. It has CK2 IC_{50} = 0.3nM. It has anti-proliferative effect against cancer cells correlated with the CK2α catalytic subunit expression levels. The attenuation of PI3K/Akt signaling by compound **(5)**, **CX-4945** was evidenced by the Akt dephosphorylation on the CK2-specific S129 site and the canonical S473 and T308 regulatory sites.

This compound possess observed anti-proliferative and anti-angiogenic activities in tumor cells and endothelial cells through inhibition of CK2-dependent signaling in multiple pathways. Compound **(5)**, **CX-4945**, causes selectively induced apoptosis and cell-cycle arrest in cancer cells compared to normal cells. In angiogenesis, it has inhibition effect onthe migration of human umbilical vein endothelial cell, tube formation and transcription of blocked CK2-dependent hypoxia-induced factor 1 alpha (HIF-1α) in cancer cells. When Compound **(5)**, **CX-4945**, was administered orally in murine xenograft models, it showed well tolerated and demonstrated robust antitumor activity with concomitant reductions of the mechanism-based biomarker phospho-p21 (T145) [87].By studying the Co-crystal structure of compound **(5)**, **CX-4945**, it interacts with CK2 indirectly through hydrogen bonding between the NH of the 3-

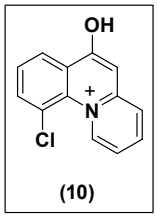
chlorophenyl amine and a water molecule. Several novel tricyclic derivatives lacking a NH moiety at the same position was prepared to investigate this hydrogen bond importance [86].

Loss of activity was observed when the H-bond donor effect of the NH of the aniline at C5 was removed from compound **(5)**, **CX-4945**. This loss of activity was more pronounced (ca. 30-fold) when a methyl group replaced the hydrogen of the NH aniline; compound**(6)**, demonstrating that the addition of this group perturbed the optimal geometry of the lipophilic interaction of the 3-chloroaniline. Derivatives **(7)** and **(9)** showed a loss of activity of 12-fold and sevenfold, respectively. By replacing the NH with sulfur, compound**(8)**, only a threefold loss of activity was observed. This gain of activity in compound**(8)** was due to the presence of sulfur atom close to the sulfur atom of Met163 of the enzyme, resulting in a favorable sulfur–sulfurinteraction [86].

Compound	X	CK2 IC_{50} (nM)
(5) CX-4945	NH	0.3
(6)	NMe	8.9
(7)	O	3.7
(8)	S	1.0
(9)	CH_2	2.1

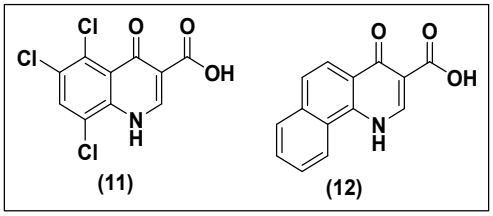


One of bicyclic enols and tricyclic benzo [c] quinoliziniums series prepared and evaluated as CK2 inhibitor is compound **(10)**, benzo[c]quinolizinium. Compound **(10)**has a good inhibitory activity and selectivity for CK2 with IC_{50} 0.005 µM [88].



(10)

3-Carboxy-4(1*H*)-quinolones have been identified as a new class of ATP-competitive CK2 inhibitors by the use of virtual screening technique of the Otava compound library. The most active compounds among a series of 42 compounds are compound **(11)** and **(12)**. These two inhibitors have selectivity toward CK2. Compound **(11)**, 5,6,8-trichloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, has CK2 IC_{50} = 0.3 µM while compound **(12)**, 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylic acid, has CK2 IC_{50} =1 µM. they are ATP competitive with *K*i values 0.06 and 0.28 µM, respectively. A structural model describing the key features of 3-carboxy-4(1*H*)-quinolones responsible for tight binding to CK2 active site had been developed according to theoretical calculations and experimental results[89].

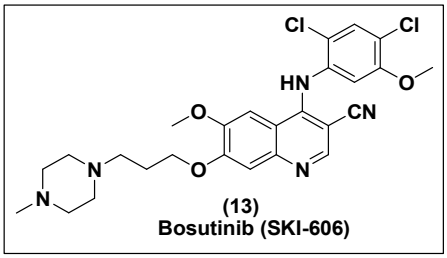


(11) (12)

2.4 Src Inhibitors:

Src is a non-receptor tyrosine kinase family having nine members: Src, Yes, Fyn, and Fgr, forming the SrcA subfamily, Lck, Hck, Blk, and Lyn in the SrcB subfamily, and Frk in its own subfamily. It has an important role in signaling pathways that control migration, angiogenesis, and proliferation. The Src overexpression and increased activity of Src are associated with an increase in tumor malignancy and poor prognosis [90].

Compound **(13)**, **Bosutinib(SKI-606),** is a novel substituted 4-anilino-quinoline-3-carbonitrile derivative having a dual Src-Abl inhibitor activity against both Bcr-Abl+ CML cell lines and Imatinib-resistant Bcr-Abl+ neoplastic cells [91, 92]. Compound **(13)**, **Bosutinib(SKI-606)**, has IC_{50} value of 1-3 nM in isolated Src enzyme assays and was US FDA approved on September 4, 2012 for the treatmentof adult patients with chronic, accelerated or blast phase Philadelphia chromosome-positive (Phþ) chronic myelogenous leukemia(CML) with resistance or intolerance to prior treatment[93, 94]. Compound **(13)**, **Bosutinib(SKI-606)**, is orally effective in nude mouse xenograft models, including HT-29, COLO 205, HCT 116 and DLD-1 colorectal tumors and MDA-MB-231 breast tumors, as well as in different *in-vivo* metastasis models. It has a potent anti-proliferative activity that inhibits the Abl substrate proteins phosphorylationin chronic myelogenous leukemia (CML) cell lines. Compound **(13)**, **Bosutinib(SKI-606)**, enters currently in both solid tumors and CML treatment clinical trials [95].

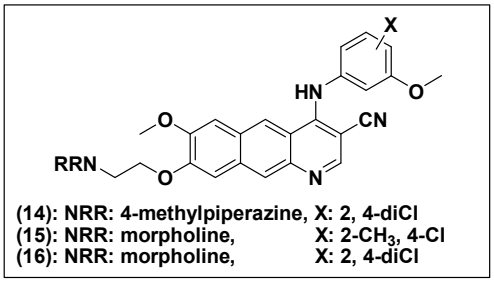


(13)
Bosutinib (SKI-606)

Through4-anilinoquinoline-3-carbonitriles structural modifications, 4-anilinobenzo[*g*]quinoline-3-carbo-nitriles series having enhanced Src inhibitory properties was obtained. *In-vitro*, compound **(14),** a

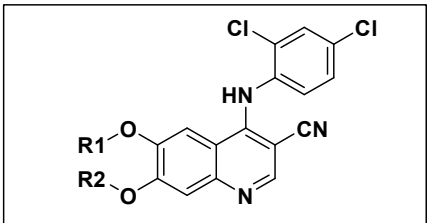
member of the produced series, is more potent than the analogously substituted 4-anilinoquinoline-3-carbonitrile compound **(13)**, **Bosutinib SKI-606**.

Compound **(15)**, the most potent compoundin this series, has0.15 nM Src kinase IC_{50} and 10 nM Src-transformed fibroblasts IC_{50}. By testing compound **(16)** against a panel of other kinases, it is highly selective for Src kinase, with modest selectivity versus the Src family kinases Lyn and Fyn. The analogues **(16)** and **(14)** have plasma levels that significantly exceeded the cellular IC_{50} values against Src-transformed fibroblasts, and exhibit a significant tumor growth inhibition in a Src transformed fibroblast xenograft model [96].



(14): NRR: 4-methylpiperazine, X: 2, 4-diCl
(15): NRR: morpholine, X: 2-CH_3, 4-Cl
(16): NRR: morpholine, X: 2, 4-diCl

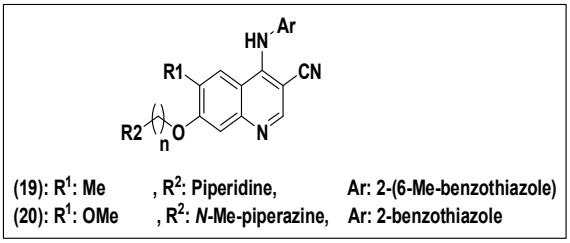
Compound **(17)**, 4-[(2, 4-dichlorophenyl)amino]-6,7-dimethoxy-3-quinoline-carbonitrile,was identified as a Src inhibitor by screening of a directed compound library in a yeast-based assay. It is ATP-competitive Src inhibitor with IC_{50} value of 30 nM. It was used as a lead for synthesis of additional Src kinase inhibitor analogues giving various 4-phenylamino-3-quinoline-carbonitriles as potent Src inhibitors. The produced analogue, compound **(18)**, has a Src IC_{50} of 3.8 nM and exhibits submicromolar activity in inhibiting both the growth of Src-transformed rat fibroblasts in suspension and the phosphorylation of Src substrate proteins. It has an increased activity in the suspension assay (IC_{50} of 940 nM) suggesting that a basic amine tail at C-7 leads to an additional interaction with Src [97].



(17): R1: Me, R2: Me
(18): R1: Me, R2: $(CH_2)_3$-morpholine

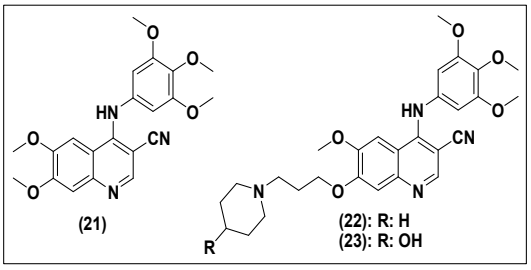
A new 4-heteroarylamino-3-quinoline-carbonitrile series having a potent dual inhibition effect on the key regulatory tumorigenesis enzymes c-Src and iNOS, were designed, prepared, and evaluated for blocking multiple signaling pathways in treatment of cancer.

Some compounds with 4-heteroarylamino groups, especially compound**(19)** and **(20)**, showed remarkable IC_{50} against Src kinase suggesting that the accommodation of hydrophobic pocket at the kinase binding sitewith larger groups was preferred over the traditional single ring aryl amines. Compound **(19)** has a Src IC_{50} value of 15.4 nM, but it has not a good inhibition effect on iNOS with313 µM IC_{50} value. It exhibits good inhibition activities toward HepG2 and HT-29 cell lines with the IC_{50} values of 7.61 and 6.58 µM, respectively, and is the most potent compound found. Compound **(20)** has the best inhibition effect toward Src and iNOS with9.23 nM and2.18 µM IC_{50}respectively. The target molecules of the series have relatively weak iNOS inhibition. This might be due to inability of designed compounds to interact with the guanidine pharmacophore, a very crucial pharmacophore for iNOS inhibition, as the free ones. [98].



(19): R^1: Me , R^2: Piperidine, Ar: 2-(6-Me-benzothiazole)
(20): R^1: OMe , R^2: *N*-Me-piperazine, Ar: 2-benzothiazole

Several analogues of compound **(21)**, Src inhibitor with an IC_{50} of 35 nM, were prepared where the 3,4,5-trimethoxy-phenyl portion was maintained and also the NH linker at C-4 and the cyano group at C-3 that are important for good Src inhibitory activity. The two produced 3-cyanoquinolines, compounds **(22)** and **(23)**, with water solubilizing groups at C-7, are better Src inhibitors than compound **(21)**, having IC_{50} values of 5.5 nM and 5.3 nM, respectively. This increased activity might be a result of an additional interaction of the heteroatom-rich side chain with the kinase. Compound **(22)** is more potent than compound **(23)**, in an anchorage independent cellular assay measuring the inhibition of Src dependent cell proliferation, with IC_{50} of 1.3 µM and >10 µM, respectively [99].



2.5 RET Inhibitors:

RET, Rearranged during Transfection, is a transmembrane tyrosine kinase. RET is expressed in both central and peripheral nervous system and neural crest-derived cells. It acts as a co-receptor of Glial cell-derived neurotrophic factor (GDNF) family in complex with GRFα family proteins and is involved in the development of enteric nervous system and renal organogenesis during embryonic life. RET Mutations are associated with a colorectal cancer subset and are commonly presented in hereditary and sporadic thyroid cancer [100]. RET kinase inhibition became a viable approach and the design of a small-molecule inhibitor of RET would be an ideal targeted therapeutic agent with the potential for a complementary inhibition profile with reduced side effects [101].

Well-known kinase inhibitors were recently reported to have an added RET inhibition activity over their intended target [102]. By using active compounds, identified from a known kinase inhibitors set with a broad potent activity range across a panel of >35 kinase assays, a template was introduced to search the GlaxoSmithKline compound collection for more novel, potent and selective inhibitors of RET kinase. The quinoline scaffold was chosen because there was evidence that drug-like molecules would be selected [103]. The identification strategy of a novel RET kinase inhibitor was summarized in **Figure (1)**[101].

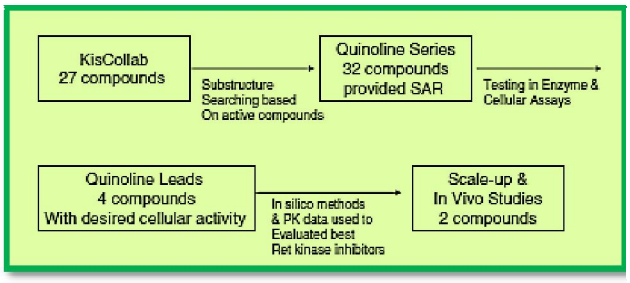
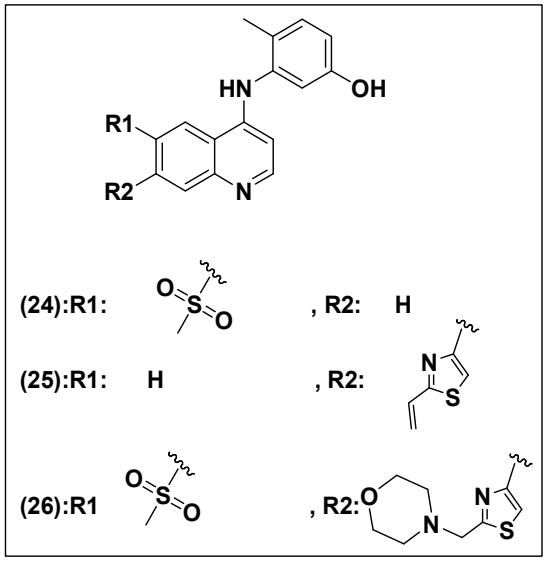


Figure (1): The rapid identification strategy of aRET kinase inhibitor [101].

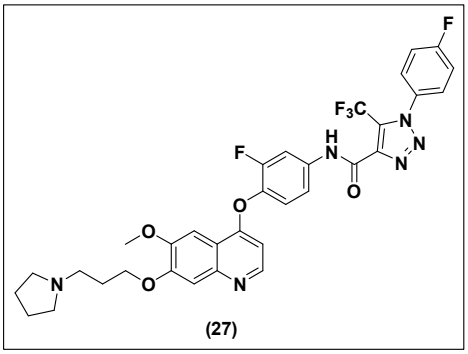
Three compounds **(24)**, **(25)** and **(26),** members of a new series of substituted 4-(3-hydroxyanilino)-quinolines series designed**,** synthesized and biologically evaluated, represent new potential leads for the medullary and papillary thyroid cancer treatment. They have an *in-vitro* kinase assay *Ki*'s of 3, 25, and 50 nM, respectively, while their cell based kinase assay *Ki*'s are 300, 100 and 45 nM, respectively [101].



2.6 c-Met Inhibitors:

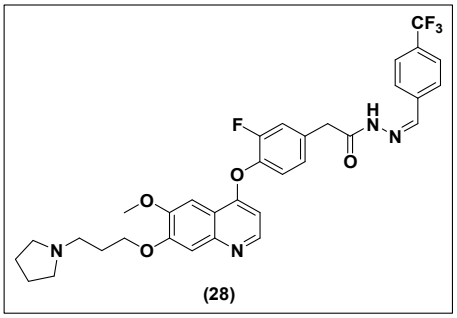
c-Met, areceptor tyrosine kinase, known as MET or hepatocyte growth factor receptor (HGFR), is encoded by the MET gene (MET proto-oncogene). c-Metis normally expressed by epithelial cells of many organs (liver, pancreas, prostate, kidney, muscle, and bone narrow) during embryogenesis and in adulthood [104-108]. There are several strategies for the c-Metinhibition. This could happen by blocking the interaction between c-Met and HGF with biological antagonists or neutralizing antibodies or by blocking the c-Met-dependent signaling through the interference with c-Met-associated signal transducers or downstream signaling components. The use of small-molecule competitive-ATP inhibitors at the active site of the kinase also could inhibit c-Met catalytic activity [109-118].

By *in-vitro* evaluation of the newly designed and synthesized 6, 7-disubstituted-4-(2-fluoro-phenoxy)-quinoline derivatives possessing 1, 2, 3-triazole-4-carboxamide moiety against five types of cancer cell lines (A549, H460, HT-29, MKN-45 and U87MG) and c-Met kinase, most compounds have moderate to excellent anti-proliferative effect. Compound **(27)**has a c-Met IC_{50} value of 1.04 nM to be considered as a multi-targeted receptor tyrosine kinase inhibitor. According to the SAR analyses, the presence of halogen group, especially fluoro group, at 4-position on the phenyl ring, gives potent antitumor activity. The c-Met enzymatic activity is also affected by the methylation on the 5-atom linker [119].



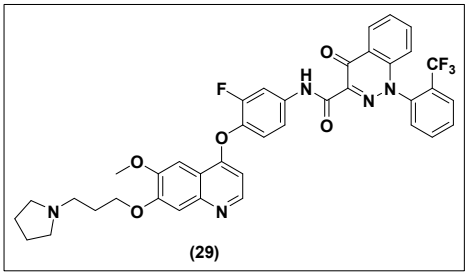
(27)

Compound **(28)** is the most promising analogue of 4-(2-fluorophenoxy)quinoline series containing an acylhydrazone moiety. By designing, synthesis and *in-vitro* biological activities evaluation of these series compounds against c-Met kinase and also five cancer cell lines (A549, H460, HT-29, MKN-45, and U87MG), most compounds show weak to excellent anti-proliferative activity while compound **(28)** has c-Met IC_{50} = 1.86 nM and displayed 1.3-, 6.8-, 1.5-, 3.5-fold increase in comparison to Foretinib against HT-29, H460, A549 and U87MG cell lines, respectively. The acylhydrazone scaffold synthesis with an unsubstituted sp2 hybridized carbon adjacent to the 4-CF3 phenyl ring is favorable for antitumor activity, according to SAR analysis [120].



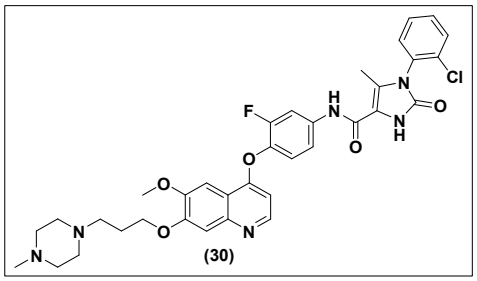
(28)

A novel series of 4-(2-fluorophenoxy)quinoline derivatives having 4-oxo-1,4-dihydrocinnoline-3-carboxamide moiety were designed and synthesized. Their *in-vitro* biological activities were evaluated not only against c-Met kinase but also against six types of typical cancer cell lines (A549, H460, HT-29, MKN-45, U87MG and SMMC-7721). The anti-proliferative activity of all the prepared targeted compounds is in the range of moderate to excellent activity. By SAR analysis of these compounds, it is more favorable to have 2-chloro or 2-trifluoromethyl substituted phenyl group on the cinnoline ring 1-position for their antitumor activity. Compound **(29)** has a c-Met IC_{50} value of 0.59 nM. For testing compound **(29)**c-Met inhibitor selectivity, it was screened against other 5 tyrosine kinases. It shows an inhibition effect against VEGFR-2, PDGFR-α, Flt-3 and c-Kit although its potency is 6.5- to 45-fold lower than that against c-Met, and shows little or no kinase inhibition activity against EGFR kinase (IC_{50}>10 μM). According to these data, compound **(29)** is a promising selective multi-target kinase inhibitor. The promising compound **(29)** is more active than Foretinib against the six cancer cell lines (A549, H460, HT-29, MKN-45, U87MG and SMMC-7721 cell lines) with IC_{50} values of 0.035, 0.055, 0.11, 0.022, 0.35 and 0.25 μM, respectively in the antitumor activity [121].



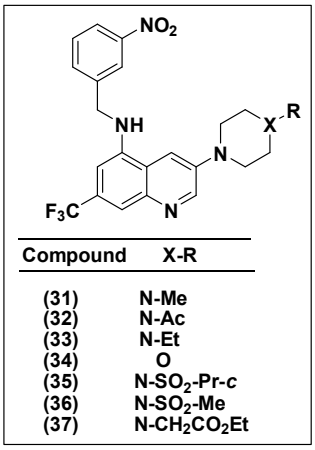
(29)

Compound **(30)** is the most promising analogue of 4-(2-fluorophenoxy)quinoline derivatives having an imidazolone moiety designed, synthesized and *in-vitro* biologically evaluated for their against c-Met kinase and four cancer cell lines types (A549, H460, HT-29 and MKN-45). Compound **(30)** has c-Met IC_{50} =1.42 nM, to have 2.1-, 8.6-, fold increase against both H460 and MKN-45 cell lines, respectively, in comparison to Foretinib. The SAR analysis showed that, it the presence of an *ortho* substituted phenyl ring is favorable for antitumor activity as well as the presence of an *N*-unsubstituted imidazolone linker [122].



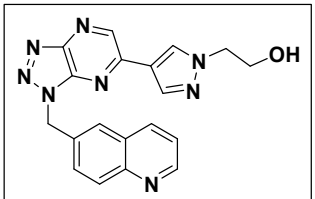
(30)

By designing, synthesis and biological evaluation of 3,5,7- trisubstituted quinoline series, seven compounds **(31-37)** were identified as the most potent c-Met inhibitors with IC_{50} of less than 1.0 nM. Compound **(32)** has high potency and extra-ordinary selectivity to c-Met against c-Met family member Ron and 12 other tyrosine kinases. In c-Met dependent cell lines,c-Met phosphorylation constitutive inhibition is produced by compound **(32)**. This compound also has a statistically significant inhibition effect on the tumor growth (68-69%) at doses of 100 mg/kg in NIH-3T3-TPR-Met and also U-87 MG human gliobastoma xenograft models [123].



Compound	X-R
(31)	N-Me
(32)	N-Ac
(33)	N-Et
(34)	O
(35)	N-SO_2-Pr-*c*
(36)	N-SO_2-Me
(37)	N-CH_2CO_2Et

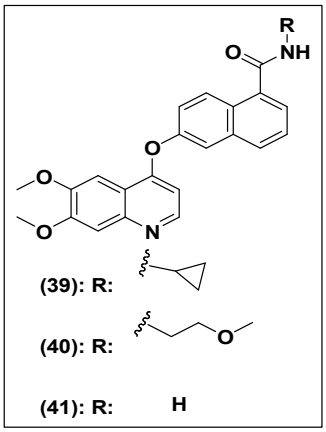
Compound **(38)**, **(PF-04217903)**,2-(4-(1-(quinolin-6-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]-pyrazin-6-yl)-1H-pyrazol-1-yl)ethanol, was discovered from the optimization of triazolopyrazine series. It has c-MET *Ki* = 0.004 μM and c-MET cellIC_{50} = 0.005 μMto be an exquisitely selective and potent ATP competitive inhibitor of c-MET, that has significant tumor growth inhibition, good oral PK properties and an acceptable safety margin in preclinical studies. It was advanced into phase I clinical studies for oncology indications. By the kinase selectivity screens against 208 different protein kinases, compound **(38)** has exquisite selectivity profile due to the unique binding topography of the c-MET kinase domain [124, 125].



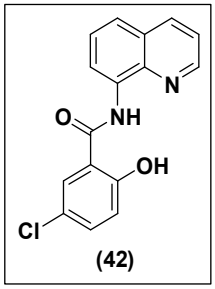
2.7 VEGFR Inhibitors:

Angiogenesis plays a major role in the progression of many human diseases, including cancer. The character of angiogenesis is the formation of new blood vessels from existing vasculature important for the solid tumors growth and survival[126]. The vascular endothelial growth factor (VEGF) is the key angiogenic factor inducing the vascular endothelial cells proliferation and the migration. VEGF promotes endothelial cell activation and proliferation and enhances the migration and invasion of endothelial cells. Its signaling pathway inhibition is one of the most promising new approaches for treatment of cancer [127-134].

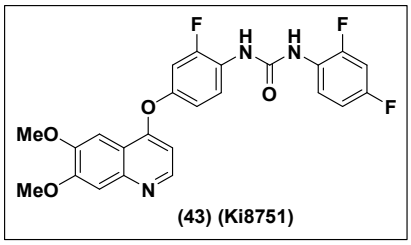
Compounds **(39)**, **(40)** and **(41)**, *N*-Alkyl and *N*-unsubstituted naphthamides series derivatives, were prepared and found to inhibit VEGFR-2 (KDR) in nanomolar concentration with an improved selectivity profile by screening against serine/threonine kinases panel. They haveVEGFR-2 (KDR) IC_{50} = 0.6, 12, 0.9 nM, respectively. After oral dosing, they show good pharmacokinetics and also potent VEGF-induced angiogenesis inhibition in the rat corneal model. Upon once-daily oral administration for 14 days for compound **(41)** according to HT29 colon cancer and Calu-6 lung cancer xenografts, it causes 85% inhibition of them at doses of 10 and 20 mg/kg, respectively [134].



Some of the synthesized compounds of two prepared series of quinoline amide derivatives have potent activities upon their inhibitory activities evaluation against both VEGFR-2 and HUVEC. Compound **(42)**, (5-chloro-2-hydroxy-*N*-(quinolin-8-yl)benzamide), has VEGFR-2 kinase 3.8 nM $IC_{50}$and IC_{50} value of 5.5 nM for HUVEC induced by VEGF to be the most potent inhibitor of these series. It is bonded to VEGFR-2 with a hydrogen bond and two π-π stacking interactions, according to its docking simulation to the active site of VEGFR-2 kinase [135].

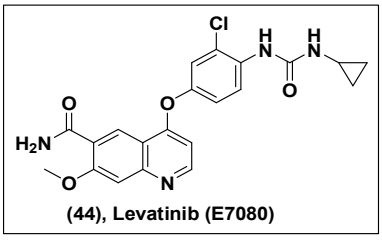


One of the most potent and high selective VEGFR-2 inhibitors of *N*-phenyl-*N'*-{4-(4-quinolyloxy)-phenyl}urea series is compound **(43)**, **Ki8751**. It has a potent VEGFR-2 inhibitory activity at the IC_{50} of 0.9 nM. It inhibits also the PDGFR family members such as PDGFRα and c-Kit at 67 nM and 40 nM, respectively. Upon antitumor activity evaluation of compound **(43)**, **Ki8751**against some human tumor xenografts in both nude mice and rats after oral administration without significant toxicity, it shows an excellent antitumor effect [136].



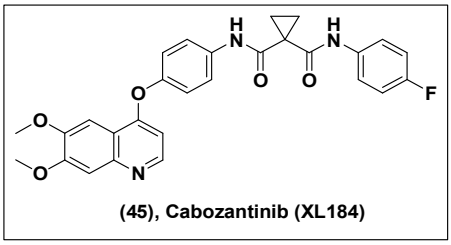
(43) (Ki8751)

Compound **(44)**, known as **Lenvatinib (E7080)**, has potent inhibition effect on Multi-Kinase of VEGF receptors (VEGFR1–3) and also on other prooncogenic receptor tyrosine kinases, including fibroblast growth factor receptors (FGFR1–4), PDGFR, and RET with IC_{50} values of 22nM, 4nM, 5.2nM, 39nM and 35nM on VEGFR-1, VEGFR-2, VEGFR-3, PDGFRβ and RET, respectively [137, 138]. It suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of VEGF-R2 andVEGF-R3 Kinase. Invasionin February 2015, the FDA granted approval to compound **(44)**, **Lenvatinib (Lenvima)**, for treatment of progressive, radioactive iodine-refractory differentiated thyroid cancer[139, 140].



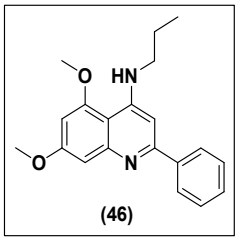
(44), Levatinib (E7080)

Compound **(45)**, **Cabozantinib (XL184)**,*N*-substituted-*N*-(4-(quinolin-4-yloxy)phenyl)cyclo-propane-1,1-dicarboxamide derivative, is a small-molecule potent kinase inhibitor towards VEGFR2 and MET *in-vitro*. It causes significant reductions in cell invasion in tumor models *in-vivo*. It has also an inhibition effect on RET, KIT, AXL, and FLT3 receptor tyrosine kinases activities [141, 142]. Its inhibitionVEGFR2, MET and RET IC_{50} values are 0.035 nM, 1.3 nM and 5.2 nM, respectively [142].U.S. FDA approved Compound **(45)**, **Cabozantinib**, for medullary thyroid cancer treatment in November 2012 [143].



(45), Cabozantinib (XL184)

Most of the newly synthesized 4-aminoquinolines series compounds have selective cytotoxicity upon their antitumor activity evaluation against five cell lines (HCT-116, A549,DU-145, HepG2, and LN229). Compound **(46)**has the most potent cytotoxicity against HCT-116 cells with 0.97 μM IC_{50} value. To investigate compound **(46)** effect on the VEGF protein expression, VEGF protein expression was assessed by western blot in cells treated with different concentrations of compound **(46)** and scanning densitometry of the band intensities was used in measuring the relative protein expression levels. Compound **(46)**, significantly inhibits the protein expression of VEGF. According to the results, compound **(46)** could act as a VEGF inhibitor. Depending on the SAR results, introduction of substituted amino groups at 4-position in quinoline is associated with enhanced cytotoxicity activity and when the quinoline contains aliphaticamino moieties, the effect is more obvious [144].

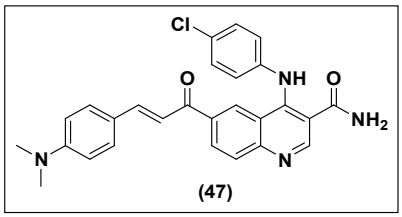


(46)

2.8 EGFR Inhibitors:

The epidermal growth factor receptor (EGFR), also known in humans asErbB-1, HER1, cell-surface receptor; is one of closely related four receptor tyrosine kinases subfamilies of extra-cellular protein ligands, EGFR (ErbB-1), HER-2/c-neu (ErbB-2), HER-3 (ErbB-3) and HER-4 (ErbB-4). Mutations affecting EGFR expression or activity could result in cancer. It is overexpressed, dys-regulated or mutated in many epithelial malignancies [145-147].

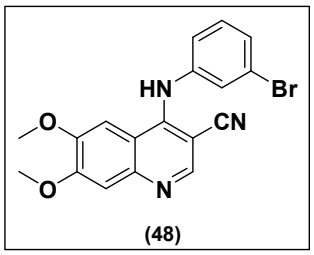
Upon pharmacophore, docking and binding energy tools use in designing a new series of 4-anilinoquinoline-3-carboxamide derivatives followed by their synthesis and screening for their anticancer activity against MCF-7 as potential anticancer agents targeting EGFR, compound **(47)** shows a significant activity against MCF-7, IC_{50} = 3.46 μM. This compound has also 67% inhibition on the EGFR TK enzyme compared to ATP and has EGFR IC_{50} = 5.283 μM, to be a potential anticancer agent [148].



(47)

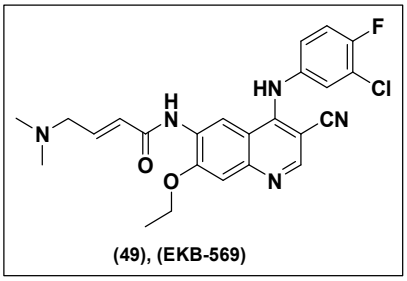
A series of 4-anilino-6,7-dialkoxyquinoline-3-carbonitrile was designed, synthesized and evaluated for their ability to inhibit the growth of three cell lines; A431 which highly overexpresses EGFR, SKBR3

which highly overexpresses HER-2 and, to a lesser extent, EGFR, and SW620 which serves as a control line expressing low levels of EGFR and HER-2. These compounds exhibit SAR profile similar to that shown by the quinazoline series of EGFR inhibitors. Carbon atom bearing a cyano group can sometimes be bioisosteric with an azomethine group that is hydrogen bonded to a water molecule. Compound **(48)**, quinoline-3-carbonitrile with EGFR IC_{50}=0.0075 μM, is potentially comparable to the quinazolines that has EGF-R IC_{50} = 0.0022 μM in their ability to inhibit EGF-R kinase. Compound **(48)** is about twice as potent in inhibiting the growth of both A431 (IC_{50} = 0.78 μM) and SKBR3 lines (IC_{50} = 0.48 μM) as its quinazoline analogue**,** A431IC_{50} = 1.52 μM and SKBR3 IC_{50} = 0.82 μM. It is also a more potent inhibitor of the SW620 control line [149].



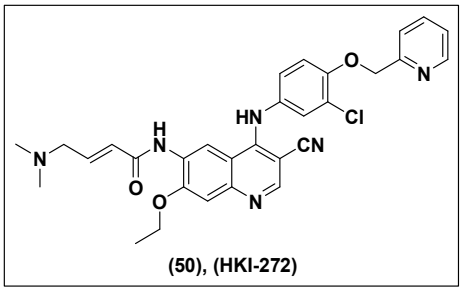
(48)

In the aim of having irreversible inhibitors of EGFR and HER-2 kinases, a series of 6,7-disubstituted-4-anilinoquinoline-3-carbonitrile derivatives was prepared. These inhibitors are characterized by the presence of Michael acceptors (butynamide, crotonamide and methacrylamide) bearing water-solubilizing substituents at the 6-position. Depending on competitive reactivity studies, the attaching of dialkylamino group onto the end of the Michael acceptor produces compounds with greater reactivity due to intramolecular catalysis. This, along with improved water-solubility lead to compounds having enhanced biological properties. Compound **(49)**, **(EKB-569)**, selected for clinical trials for the treatment of cancer, has EGFR IC_{50}= 0.083 μM, HER-2 IC_{50} =1.23 μM, A431 IC_{50} = 0.08 μM, SKBR3 IC_{50}= 0.01 μM and SW620 IC_{50} = 0.68 μM, and shows excellent oral *in-vivo* activity [150].



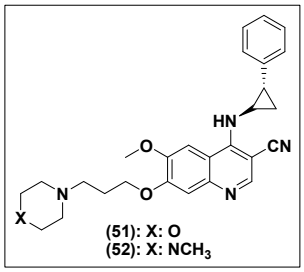
(49), (EKB-569)

Compound **(50)**, **(HKI-272)**, was produced by optimization of 6,7-Disubstituted-4-(arylamino)-quinoline-3-carbonitriles via attaching a large lipophilic group at *p*-position of the 4-(arylamino)ring with the maintenance of basic dialkylamino group at the end of the Michael acceptor for activity and improved water solubility resulting in improved potency for inhibiting HER-2 kinase. Compound **(50)**, **HKI-272**, hasHER-2 IC_{50} =0.059 μM, EGFR IC_{50}= 0.092 μM, A431 IC_{50} = 0.086 μM, SKBR3 IC_{50} = 0.0018 μM and SW620 IC_{50} = 0.730μM, compared to EGFR kinase inhibitor **(49)**, **(EKB-569)**. Regarding to binding studies, compound **(50)**, **HKI-272**, (C-14 radiolabeled), shows binding irreversibly to HER-2 protein in BT474 cells. Its oral activity is excellent, especially in HER-2 overexpressing xenografts and selected for clinical trials of cancer treatment [151].



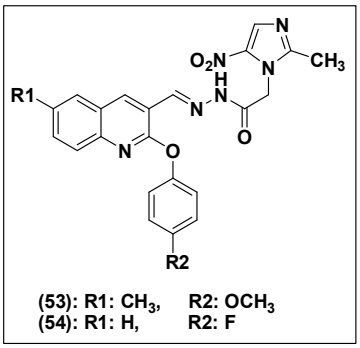
(50), (HKI-272)

Compound **(51)** and **(52)**, derivatives of the synthesized of 4-(2-aryl-cyclopropyl amino)-quinoline-3-carbonitriles series as EGFR inhibitors, show potent *in-vitro* inhibitory activity in the enzymatic assay and the functional cellular assay. The presence of 3-(1-morpholinyl)propyloxy at C-7 position of compound **(51)** dramatically increases potency with *Ki* of 8.4 nM and shows excellent cellular activity with IC_{50} at ~5 nM while compound **(52)**, 4-[(trans-2-phenylcyclo-propyl)amino]-6-methoxy-7-[3-(4-methyl-piperazinyl)propoxy]-quinoline-3-carbonitrile, is the most potent EGFR inhibitor in this chemical class, having EGFR *Ki*=3 nM[152].

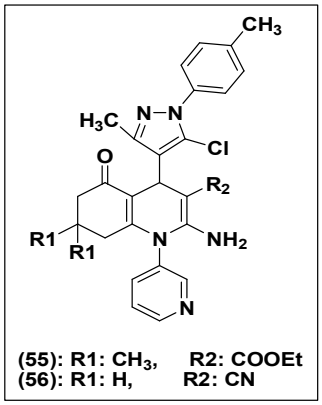


New Schiff's base derivatives, 2-(2-methyl-5-nitro-1H-imidazol-1-yl)-*N*′-(quinolin-3-ylmethyl-ene)-acetohydrazides, had been synthesized by reaction between 2-phenoxyquinoline-3-carb-aldehydes and 2-(2-methyl-5-nitro-1H-imidazol-1-yl) acetohydrazide in ethanol using nickel(II) nitrate as a catalyst under reflux. By testing all the prepared compounds for anticancer and inhibition of EGFR, the majority of the

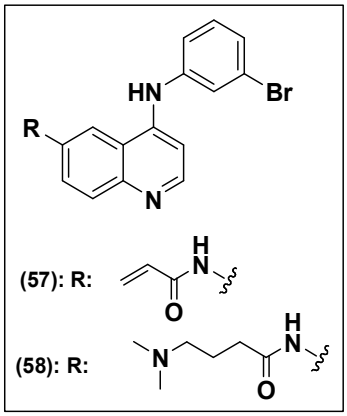
compounds show effective anti-proliferation and inhibition of EGFR and HER-2 activities. Compound **(53),** the most effective inhibitor, has EGFR IC_{50} = 0.12 ± 0.05 µM due to its binding into the active pocket of EGFR receptor with minimum binding energy (ΔG_b = -58.3691 kcal/mol). The binding is stabilized by two hydrogen bonds, two π–cation and one π–sigma interactions. Compound **(54)** shows most HER-2 effective inhibition with HER-2 IC_{50} = 0.37 ± 0.04 µM [153].



On the basis of molecular hybridization technique, a new series of pyrazole-quinoline-pyridine hybrids was designed and synthesized by a base-catalyzed one-pot multicomponent cyclo-condensation reaction. Enzyme inhibitory activities evaluation of all compounds was achieved against EGFR and FabH for testing *in-vitro* anticancer and antibacterial activities. The majority of compounds show effective anticancer and antibacterial activities against used cancer cell lines and strains, respectively. Compound **(55)** has EGFR IC_{50} = 0.51 ± 0.05 µM while compound **(56)** displays the most potent FabH inhibitory activity with FabH IC_{50} of 3.1µM. Compound **(55)** is bound into the EGFR active pocket with three hydrogen bond and one π-cation interaction with minimum binding energy ΔG_b = -54.6913 kcal/mol, while compound **(56)**is bound into the FabH active site with hydrogen bond and π-sigma interactions with minimum binding energy ΔG_b = -45.9125 kcal/mol, according to molecular modeling study [154].



For the potent type I inhibitors of clinically relevant mutant EGFR variants synthesis, a series of 6-and 7-substituted 4-anilinoquinolines were prepared and biologically evaluated. All reversible quinolines of this series show a decreased affinity in drug resistant EGFR-Leu858Arg-Thr790Met but the irreversible inhibitor, compound **(57)**, retains potency with IC_{50} = 3.2 ±1.6 nM. The ability of compound **(57**, irreversible**)** and **(58**, reversible**)**, highly active kinase inhibitors in biochemicalassays, to inhibit patient derived NSCLC cell lines growth expressing mutant EGFR was evaluated. They robustly decrease viability of EGFR-mutated PC9 cells at submicromolar concentrations in the range of the activity of the quinazoline Erlotinib [155].



Compound **(59)**, **(60)** and **(61),** 4-Anilinoquinoline derivatives having a 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO), had been synthesized. Their ability to inhibit both EGFR tyrosine kinase and A431 cell lines was evaluated. In comparison to their corresponding non-TEMPO parent compounds, these TEMPO bearing compounds are more efficient EGFR and A431 cells inhibitors as shown in **Table (2)**[156].

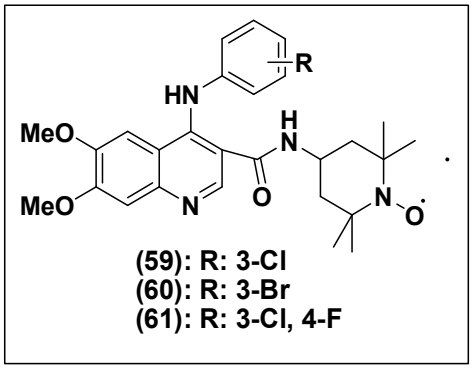


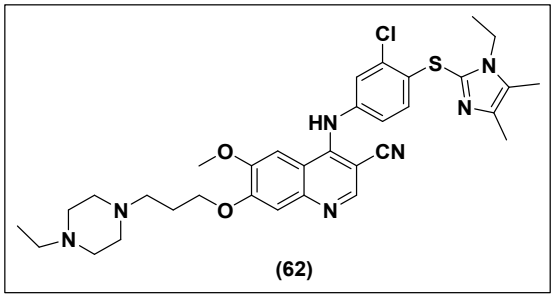
Table (2): The biological activities of compounds **(59-61)** in comparison to their parent compounds.

Compound	A431 IC_{50} (µM)	EGFR IC_{50} (nM)
(59)	45.46 ± 2.01	623 ± 79
(60)	43.21 ±3.41	342 ± 27
(61)	38.14 ± 2.47	422 ± 18
Parent compound of **(59)**	97.85 ± 0.6	9021 ±124
Parent compound of **(60)**	93.99 ± 1.81	8719 ± 38
Parent compound of **(61)**	88.83 ± 1.78	9284 ± 231

2.9 IGF-1R Inhibitors:

The insulin-like growth factor-1receptor (IGF-1R) is one of growth factor receptor tyrosine kinases. It is overexpressed in human cancer cells and involved in the production of new tumors. The preparation of IGF-1R inhibitors may impede tumor growth providing new cancer therapeutics [157-162].

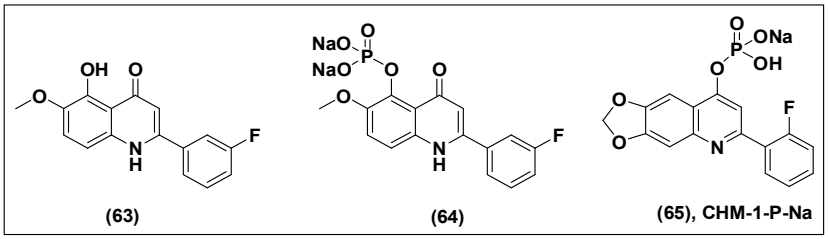
Compound (**62**), a derivative of 3-cyanoquinolines series having low nanomolarinhibitors of IGF-1R, has IGFR IC_{50} =0.009 ± 0.003µM, encouraging activity in the assay of a cellular myeloid [163].



(62)

Most analogues of the new designed, synthesized, and cytotoxic activity evaluated 2-phenylquinolin-4-ones series exhibit significant inhibitory activity (IC_{50} values of 0.03-8.2 µM) against all tested tumor cell lines. Compound **(63)**, one of the most potent analogue, 2-(3-fluorophenyl)-5-hydroxy-6-methoxy-quinolin-4-one, selectively inhibits 14 cancer cell lines, (SR, Colo 205, NCI-H522, HCC-2998, HT-29, SF-539, SNB-75, MDA-MB-435, IGROV1, OVCAR-3, NCI/ADR-RES, RXF-393, HL-60, and DU-145), out of the NCI 60 cancer cell lines evaluation.

Independence on preliminary action study mechanism, it was suggested that, compound **(63)** has a significant effect on the insulin-like growth factor-1 receptor (IGF-1R) tyrosine autophosphorylation. It shows no significant effect on normal biological functions of most enzymes tested, according to safety pharmacology profiling, while compound **(64)**, the monophosphate derivative of compound **(63)**, exceedsthe doxorubicin activity. It is also compared to compound**(65)**, known as**CHM-1-P-Na**, (2-(2-fluoro-phenyl)-6,7-methylenedioxyquinolin-4-one-mono-sodium phosphate, which has potent cytotoxicity, excellent antitumor activity and extremely safe to use [164-165] in a Hep3B xenograft nude mice model. Compound **(64)** is a promising clinical candidate and is currently under preclinical study [166].



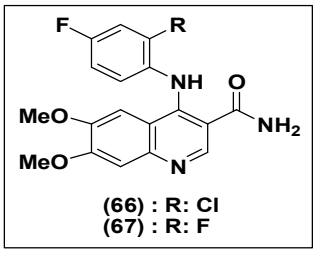
(63) (64) (65), CHM-1-P-Na

2.10 CSF-1R Inhibitors:

Solid tumors comprise a number of cell types in addition to malignant cells, including macrophages (tumor-associated macrophages, TAMs) that have many promotion roles in tumor progression and also metastasis [167, 168]. The monocyte/macrophage development and proliferation dependupon the receptor tyrosine kinase CSF-1R signaling pathway and its ligand CSF-1 (called macrophage colony stimulatory factor, M-CSF) [169].

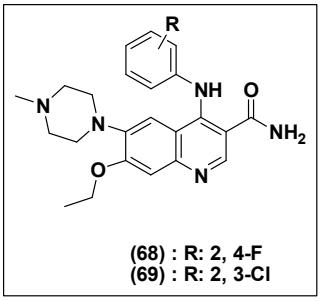
Through the subset screening of the AstraZeneca collection, several series with good CSF-1R inhibition activity were identified, including compounds known or expected to have kinases inhibition activity. In terms of both CSF-1Rpotency and kinase selectivity, the most promising of the hit series is 3-Amido-4-anilino-6,7-dimethoxyquinolines series. One of the screening hits was compound **(66)** that has IC_{50} = 19 nM. Compound **(67)** was screened against a panel of 150 kinases at 1µM and displayed remarkable kinase selectivity. Apart from CSF-1R, significant activity is only observed against GSK3a and EphB4. Dimethoxy scaffold compounds have best moderate aqueous solubility. Compound **(67)** has good rats

bioavailability, and also an activity in a mouse PD model [169].



(66) : R: Cl
(67) : R: F

The optimized3-amido-4-anilinoquinolines series compounds with CSF-1R kinase inhibition effecthave excellent activity and kinase selectivity. The introduction of cyclic amines at the quinoline 6-position led to formation of analogues having excellent physical properties, rodent PK profiles. Also analogues having good activity in a mouse PD model measuring of pCSF-1R inhibition are identified. Compound **(68)** is the 2,4-di-F analogue having both good *in-vitro* activity (0.23 μM in the cell) and excellent *in-vivo* PK, while compound **(69)**, 2,3-di-Cl analogue, has higher clearance in rats than compound **(68)**, but is very potent in the cell assay (0.06 μM)[170].

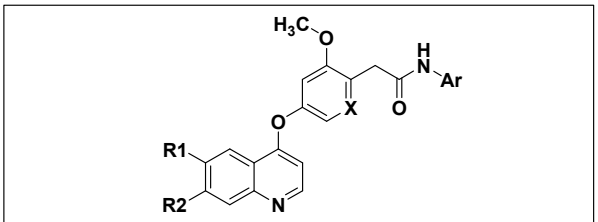


(68) : R: 2, 4-F
(69) : R: 2, 3-Cl

2.11 PDGFR Inhibitors:

Platelet-derived growth factor receptors, PDGFR, are cell surface tyrosine kinase receptors for the PDGF family members. PDGFR has two forms, α and β, each encoded by a different gene [171, 172]. It is a compelling target for developing therapeutic agents to treat diseases associated with over-activated platelet-derived growth factor (PDGF) signaling and cancer treatment [173].

Compound **(70)** and **(71)** are analogues of the newly designed and synthesized series of quinoline ether inhibitors, which potently and selectively inhibit PDGFR tyrosine kinases. They are selective potent PDGFR α and β inhibitors at low nanomolar concentration. They inhibit the phosphorylation of PDGFR α and β in xenograft tissue in a dose dependent manner. By giving them orally twice daily at low doses, they display good pharmacokinetics in rat and dog and are active *in-vivo*. Compounds **(70)** and **(71)** have the potential to become clinically useful anti-angiogenic agents [174].

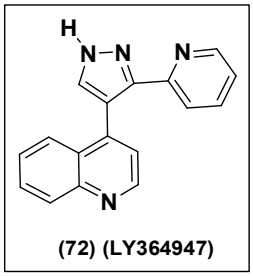


(70): R1: H, R2: OMe, X: C , Ar: 4-pyrazolyl-1, 3-diMe
(71): R1: OMe, R2: OEt, X: N , Ar: 3-pyrazolyl-4-Me-5-Et

2.12 TGF- β type I receptor Inhibitors:

Transforming growth factor- β (TGFβ) receptors are single pass serine/threonine kinase receptors. They exist in several different isoforms [homo- or heterodimeric] [175]. Signaling from TGF-β through its unique trans-membrane receptor plays a complex role in carcinogenesis, having both tumor suppressor and oncogenic activities [176]. The ability of TGF-β to potentially inhibit the proliferation of epithelial, endothelial, and hematopoietic cell lineages is centralto the tumor suppressing mechanism [177].

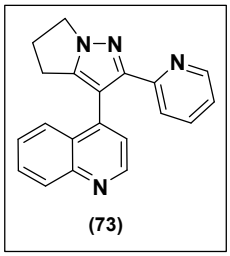
Compound **(72)**, **(LY364947)**, was reported as pyrazole-based inhibitor of the TGF-*β* type I receptor kinase domain (T*β*R-I) featuring quinoline-4-yl warhead that was shown to hydrogen bond with the peptide backbone in the ATP binding pocket. It has IC_{50} = 51nM. Its co-crystallization and X-ray analysis were also reported [178].



(72) (LY364947)

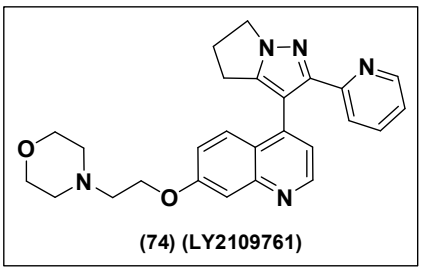
A new series, based on the 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole scaffold that featured additional substitutions at the quinoline-4-yl warhead ring systems and the 2-pyridyl group, was designed, synthesized. The resulting compounds were evaluated as inhibitors of TGF-*β*RIK, TGF-*β* dependent luciferase production in mink lung cells (p3TP Lux), growth in mouse fibroblasts (NIH3T3) and p38 MAP kinase. Compound **(73)** is a potent example of this new series, with the T*β*R-I receptor kinase domain, having TGF-*β* RI IC_{50} = 0.104 ± 0.033μM. According to reported co-crystallization and X-ray crystal structures of compounds **(73)** bound to the ATP site of the T*β*R-I kinase domain, the minimum requirements

for tight binding at the active site consist of the presence of a 2-pyridyl group on the 3-position of the pyrazole ring and heteroaryl substituent at the 4-position featuring a hydrogen bond acceptor [179].



(73)

The optimization of a dihydropyrrolo-pyrazole series of TGF-βR Kinase domain inhibitors led to discovery of an orally bioavailable TGF-β RI Inhibitor, compound **(74)**, **(LY2109761)**, as antitumor agent having TGF-β RI $IC_{50} = 0.069 \pm 0.031\mu M$ [180].



(74) (LY2109761)

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References:

1. Levy S. and S. Azoulay, Stories about the origin of quinquina and quinidine. *Electrophysiol.*1994, 5, 635-636.
2. Solomon V. and H. Lee, Quinoline as a privileged scaffold in cancer drug discovery. *Curr. Med. Chem.* 2011, 18(10), 1488-508.
3. Sarker S. and L. Nahar, Chemistry for pharmacy students: general, *Organic and Natural Product Chemistry,* 2007.
4. Finar I., The fundamental principles, *Organic chemistry* 1963, vol.1, 763.
5. Pandeya S. and A. Tyagi, Synthetic approaches for quinoline and isoquinoline. *Int. J. Pharmacy Pharmaceut. Sci.* 2011,3 (3), 53-61.
6. Marella A. , O. Tanwar, R. Saha, M. Ali, S. Srivastava, M. Akhter, M. Shaqui-quzzaman and M. Alam, Review, Quinoline: A versatile heterocyclic. *Saudi Pharm. J.*2013, 21(1), 1-12.
7. Utsugi T., K. Aoyagi, T. Asao, S. Okazaki, Y. Aoyagi, M. Sano, K. Wierzba and Y. Yamada, Antitumor activity of a quinoline derivative, TAS-103, with inhibitory effects on topoisomerase I and II. *Jpn.J. Cancer Res.* 1997, 88, 992-1002.
8. Paritala H. and S.M. Firestine, Benzo(h)quinoline derivatives as G-quadruplex binding agents. *Bioorg. Med. Chem. Lett.* 2009, 19, 1584-1587.
9. Xia Y., Z. Yang, P. Xia, T. Hackl, E. Hamel, A. Mauger, J. Wu and K. Lee, Fluorinated 2-Phenyl-4-quinolone derivatives as antimitotic antitumor agents. *J. Med. Chem.* 2001, 44, 3932-3936.
10. Schiemann K., D. Finsinger, F. Zenke, C. Amendt, T. Kn€ochel, D. Bruge, H. Buchstaller, U. Emde, W. St€ahle and S. Anzali, The discovery and optimization of hexahydro-2H-pyrano[3,2-c]quinolines (HHPQs) as potent and selective inhibitors of the mitotic kinesin-5. *Bioorg. Med. Chem. Lett.*2010, 20, 1491-1495.
11. Chackal S., M. Facompre, R. Houssin, N. Pommery, J.F. Goossens, P. Colson, C. Bailly and J. Henichart, DNA binding to guide the development of tetrahydroindeno[1,2-b]pyrido[4,3,2-de]quinoline derivatives as cytotoxic agents. *J. Med. Chem.*2004, 47, 3665-3673.
12. Dexter D., D. Hesson, R. Ardecky, G. Rao, D. Tiffett, B. Dusak, K. Paull, J. Plowman, B. Delarco, V. Narayanan and M. Forbes, Activity of a novel 4-quinolinecarboxylic acid, NSC 368390 [6-fluoro-2-(20-fluoro-1,10- biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid sodium salt], against experimental tumors. *Cancer Res.* 1985, 45, 5563-5568.
13. Chen S., R. Ruben and D. Dexter, Mechanism of action of the novel anticancer agent 6-fluoro-2-(20-fluoro-1,10-biphenyl-4-YL)-3-methyl-4-quinolinecarboxylic acid sodium salt (NSC368390): inhibition of de novo pyrimidine nucleotide biosynthesis. *Cancer Res.*1986, 46, 5014-5019.
14. Peters G., S. Sharma, E. Laurensse and H. Pinedo, Inhibition of pyrimidine de novo synthesis by DUP 785 (NSC 368390). *Investig. New Drugs*1987, 5, 235-244.
15. Warner P., A. Barker, A. Jackman, K. Burrows, N. Roberts, J. Bishop, B. Connor and L. Hughes, Quinoline antifolate thymidylate synthase inhibitors: variation of the C2- and C4-substituents.*J. Med. Chem.* 1992, 35, 2761-2768.
16. Serda M., D. Kalinowski, A. Wilczkiewicz, R. Musiol, A. Szurko, A. Ratuszna, N. Pantarat, Z. Kovacevic, A. Merlot, D. Richardson and J. Polanski, Synthesis and characterization of quinoline-based thiosemi-carbazones and correlation of cellular iron-binding efficacy to antitumor efficacy.*Bioorg. Med. Chem. Lett.*2012, 22, 5527-5531.
17. Ghorab M., F. Ragab, H. Heiba, R. Arafa and E. El-Hossary, *In-vitro* anticancer screening and radiosensitizing evaluation of some new quinolines and pyrimido[4,5-b]quinolines bearing a sulfonamide moiety. *Eur. J. Med. Chem.*2010, 45, 3677-3684.
18. Al-Said M., M. Ghorab, M. Al-Dosari and M. Hamed, Synthesis and *in-vitro* anticancer evaluation of some novel hexahydroquinoline derivatives having a benzenesulfonamide moiety. *Eur. J. Med. Chem.* 2011,46, 201-207.

19. Caprio V., B. Guyen, Y. Boahen, J. Mann, S. Gowan, L. Kelland, M. Read and S. Needle, A novel inhibitor of human telomerase derived from 10H-indolo[3,2-b] quinoline. *Bioorg. Med. Chem. Lett.*2000, 10, 2063-2066.
20. Hamann L., R. Higuchi, L. Zhi, J. Edwards, X. Wang, K. Marschke, J. Kong, L. Farmer and T. Jones, Synthesis and biological activity of a novel series of nonsteroidal, peripherally selective androgen receptor antagonists derived from 1,2-dihydropyridono[5,6-g]quinolines. *J. Med. Chem.*1998, 41, 623-639.
21. Maiti A., P. Reddy, M. Sturdy, L. Marler, S. Pegan, A. Mesecar, J. Pezzuto and M. Cushman, Synthesis of casimiroin and optimization of its quinone reductase 2 and aromatase inhibitory activities. *J. Med. Chem.* 2009, 52, 1873-1884.
22. Tegley C., L. Zhi, K. Marschke, M. Gottardis, Q. Yang and T. Jones, 5- Benzylidene 1,2-dihydrochromeno[3,4-f]quinolines, a novel class of nonsteroidal human progesterone receptor agonists. *J. Med. Chem.* 1998, 41, 4354-4359.
23. Zhi L., C. Tegley, K. Marschke, D. Mais and T. Jones, 5-Aryl-1,2,3,4- Tetrahydro-chromeno-[3,4-f]quinolin-3-ones as a novel class of nonsteroidal progesterone receptor agonists: effect of A-ring modification. *J. Med. Chem.*1999, 42, 1466-1472.
24. Zhi L., C. Tegley, B. Pio, J. Edwards, M. Motamedi, T. Jones, K. Marschke, D. Mais, B. Risek and W. Schrader, 5-Benzylidene-1,2-dihydrochromeno[3,4-f]quino-lines as selective progesterone receptor modulators. *J. Med. Chem.*2003, 46, 4104-4112.
25. Pedram B., A. Oeveren, D. Mais, K. Marschke, P. Verbost, M. Groen and L. Zhi, A tissue-selective nonsteroidal progesterone receptor modulator: 7,9-difluoro-5-(3-methylcyclohex-2-enyl)-2,2,4-trimethyl-1,2-dihydrochromeno[3,4-f] quinoline. *J. Med. Chem.* 2008, 51, 3696-3699.
26. Mulakayala N., D. Rambabu, M. Raja, M. Chaitanya, C. Kumar, A. Kalle, G. Krishna, C. Reddy, M. Rao and M. Pal, Ultrasound mediated catalyst free synthesis of 6H-1-benzopyrano[4,3-b]quinolin-6-ones leading to novel quinoline derivatives: their evaluation as potential anti-cancer agents. *Bioorg. Med. Chem.* 2012, 20, 759-768.
27. Reddy P., K. Jensen, A. Mesecar, P. Fanwick and M. Cushman, Design, synthesis, and biological evaluation of potent quinoline and pyrroloquinoline ammosamide analogs as inhibitors of quinone reductase 2. *J. Med. Chem.* 2012, 55, 367-377.
28. Park C., K. Chun, B. Joe, J. Choi, H. Lee, I. Ku, H. Kim, S. Koh, G. Cho, S. Kim and M. Kim, Synthesis and evaluation of thiopyrano[3,4-c] quinoline-9-carboxamide derivatives as inhibitors of poly(ADP-ribose) polymerase-1 (PARP-1). *Med. Chem. Res.*2012, 21, 1533-1543.
29. Peng H., D. Kim, J. Sarkaria, Y. Cho, R. Abraham and L. Zalkow, Novel pyrrolo-quinoline derivatives as potent inhibitors for PI3-kinase related kinases. *Bioorg. Med. Chem.* 2002, 10, 167-174.
30. Liu Q., J. Chang, J. Wang, S. Kang, C. Thoreen, A. Markhard, W. Hur, J. Zhang, T. Sim, D. Sabatini and N. Gray, Discovery of 1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl) benzo[h]- [1,6]naphthyridin-2(1H)-one as a highly potent, selective mammalian target of rapamycin (mTOR) inhibitor for the treatment of cancer. *J. Med. Chem.*2010, 53, 7146-7155.
31. Liu Q., J. Wang, S. Kang, C. Thoreen, W. Hur, T. Ahmed, D. Sabatini and N. Gray, Discovery of 9-(6-aminopyridin-3-yl)-1-(3-(trifluoromethyl) phenyl)benzo[h]- [1,6] naphthyridin-2(1H)-one (Torin2) as a potent, selective, and orally available mammalian target of rapamycin (mTOR) inhibitor for treatment of cancer. *J. Med. Chem.*2011, 54, 1473-1480.
32. Lazo J., D. Aslan, E. Southwick, K. Cooley, A. Ducruet, B. Joo, A. Vogt and P. Wipf, Discovery and biological evaluation of a new family of potent inhibitors of the dual specificity protein phosphatase Cdc25. *J. Med. Chem.*2001,44, 4042-4049.
33. Broch S., H. Henon, A. Debaud, M.L. Fogeron, N.B. Berard, F. Anizon and P. Moreau, Synthesis and biological activities of new di- and trimeric quinoline derivatives. *Bioorg. Med. Chem.*2010, 18, 7132-7143.
34. E. Saugues, L. Nauton, V. Thery, F. Anizon and P. Moreau, Synthesis and molecular modeling study of new trimeric quinoline derivatives. *Bioorg. Chem.* 2011, 39, 143-150.
35. H. Chen, Z. Yang, C. Ding, L. Chu, Y. Zhang, K. Terry, H. Liu, Q. Shen and J. Zhou, Fragment-based drug design and identification of HJC0123, a novel orally bioavailable STAT3 inhibitor for cancer therapy. *Eur. J. Med. Chem.* 2013, 62, 498-507.
36. M. Hassani, W. Cai, D. Holley, J. Lineswala, B. Maharjan, G. Ebrahimian, H. Seradj, M. Stocksdale, F. Mohammadi, C. Marvin, J. Gerdes, H. Beall and M. Behforouz, Novel lavendamycin analogs as antitumor agents: synthesis, in vitro cytotoxicity, structure-metabolism, and computational molecular modeling studies with NAD(P)H: quinone oxidoreductase-1. *J. Med. Chem.*2005, 48, 7733-7749.
37. W. Cai, M. Hassani, R. Karki, E. Walter, K. Koelsch, H. Seradj, J. Lineswala, H. Mirzaei, J. York, F. Olang, M. Sedighi, J. Lucas, T. Eads, A. Rose, S. Charkhzarrin, N. Hermann, H. Beall and M. Behforouz, Synthesis, metabolism and in vitro cytotoxicity studies on novel lavendamycin antitumor agents. *Bioorg. Med. Chem.*2010,18, 1899-1909.
38. T. Shimizu, Y. Fujiwara, T. Osawa, T. Sakai, K. Kubo, K. Kubo, T. Nishitoba, K. Kimura, T. Senga, H. Murooka, A. Iwai, K. Fukushima, T. Yoshino and A. Miwa, Orally active anti-proliferation agents: novel diphenylamine derivatives as FGF-R2 autophosphorylation inhibitors. *Bioorg. Med. Chem. Lett.* 2004, 14, 875-879.
39. S. Suthar, V. Jaiswal, S. Lohan, S. Bansal, A. Chaudhary, A. Tiwari, A. Alex and A. Joesph, Novel quinolone substituted thiazolidin-4-ones as antiinflammatory, anticancer agents: design, synthesis and biological screening. *Eur. J. Med. Chem.*2013, 63, 589-602, http://dx.doi.org/10.1016/j.ejmech.2013.03.011.
40. T. Ganesh, J. Min, P. Thepchatri, Y. Du, L. Li, I. Lewis, L. Wilson, H. Fu, G. Chiosis, R. Dingledine, D.

Liotta, J. Snyder and A. Sun, Discovery of amino-quinolines as a new class of potent inhibitors of heat shock protein 90 (Hsp90): synthesis, biology, and molecular modeling. *Bioorg. Med. Chem.* 2008,16, 6903-6910.

41. Q. Zhou, Z. Melkoumian, A. Lucktong, M. Moniwa, J. Davie and J. Strobl, Rapid induction of histone hyperacetylation and cellular differentiation in human breast tumor cell lines following degradation of histone deacetylase-1. *J. Biol. Chem.* 2000, 275, 35256-35263.
42. Mai, D. Rotili, D. Tarantino, A. Nebbioso, S. Castellano, G. Sbardella, M. Tini and L. Altucci, Identification of 4-hydroxyquinolines inhibitors of p300/CBP histone acetyltransferases. *Bioorg. Med. Chem. Lett.* 2009,19, 1132-1135.
43. D. Moffat, S. Patel, F. Day, A. Belfield, A. Donald, M. Rowlands, J. Wibawa, D. Brotherton, L. Stimson, V. Clark, J. Owen, L. Bawden, G. Box, E. Bone, P. Mortenson, A. Hardcastle, S. Meurs, S. Eccles, F. Raynaud and W. Aherne, Discovery of 2-(6-{[(6-fluoroquinolin-2-yl)methyl]amino}bicycle [3.1.0]hex-3-yl)-N-hydroxypyrimidine-5-carboxamide (CHR-3996), a class I selective orally active histone deacetylase inhibitor. *J. Med. Chem.* 2010,53, 8663-8678.
44. T. Ohashi, Y. Oguro, T. Tanaka, Z. Shiokawa, S. Shibata, Y. Sato, H. Yamakawa, H. Hattori, Y. Yamamoto, S. Kondo, M. Miyamoto, H. Tojo, A. Baba and S. Sasaki, Discovery of pyrrolo[3,2-c]quinoline-4-one derivatives as novel hedgehog signaling inhibitors. *Bioorg. Med. Chem.*2012, 20, 5496-5506.
45. M. Narwal, H. Venkannagari and L. Lehtio,Structural basis of selective inhibition of human tankyrases.*J. Med. Chem.* 2012, 55, 1360-1367.
46. R. Wolin, D. Wang, J. Kelly, A. Afonso, L. James, P. Kirschmeier and A. McPhail, Synthesis and evaluation of pyrazolo[3,4-b]quinoline ribofuranosides and their derivatives as inhibitors of Oncogenic Ras. *Bioorg. Med. Chem. Lett.*1996,6, 195-200.
47. D. End, G. Smets, A. Todd, T. Applegate, C. Fuery, P. Angibaud, M. Venet, G. Sanz, H. Poignet, S. Skrzat, A. Devine, W. Wouters and C. Bowden, Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 *in-vivo* and *in-vitro*. *Cancer Res.*2001, 61, 131-137.
48. R. Kurzrock, M. Albitar and J. Cortes, Phase II study of R115777, a farnesyl transferase inhibitor, in myelodysplastic syndrome. *J. Clin. Oncol.*2004, 22, 1287-1292.
49. C. Ding, J. Hunt, C. Ricca and V. Manne, 3-Imidazolylmethylaminophenyl-sulfonyl tetra-hydro-quinolines, a novel series of farnesyl-transferase inhibitors.*Bioorg. Med. Chem. Lett.*2000, 10, 273-275.
50. Adsule S., V. Barve, D. Chen, F. Ahmed, Q. Dou, S. Padhye and F. Sarkar, Novel schiff base copper complexes of quinoline-2 carboxaldehyde as proteasome inhibitors in human prostate cancer cells. *J. Med. Chem.*2006, 49, 7242-7246.
51. Afzal O., S. Kumar, M. Haider, M. Ali, R. Kumar, M. Jaggi and S. Bawa, A review on anticancer potential of bioactive heterocycle quinoline.*Eur. J. Med. Chem.* 2015, 97, 871-910.
52. Fabbro D., S. Ruetz, E. Buchdunger, S. Cowan-Jacob, G. Fendrich, J. Liebetanz, J. Mestan, T. O'Reilly, P. Traxler, B. Chaudhuri, H. Fretz, J. Zimmermann, T. Meyer, G. Caravatti, P. Furet and P. Manley, Protein kinases as targets for anticancer agents: from inhibitors to useful drugs. *Pharmacol. Ther.* 2002,93, 79-98.
53. Kung C., and K. Shokat, Small-molecule kinase-inhibitor target assessment. *Chem. Bio. Chem.* 2005, *6*, 523-526.
54. Cargnello M. and P. Roux, Activation and function of the MAPKs and their Substrates, the MAPK-activated protein kinases. *Microbiol. Mol. Biol. Rev.* 2011, 75(1), 50-83.
55. Lee J., J. Laydon, M. Donnell, T. Gallagher, S. Kumar, D. Green, D. McNulty, M. Blumenthal, J. Heys and S. Landvatter, A protein kinase involved in the regulation of inflammatory cytokine bio-synthesis. *Nature* 1995*,* 372 (6508), 739-746.
56. Han J., J. Lee, L. Bibbs and R. Ulevitch, A MAP kinase targeted by endotoxin and hyperosmolarity in mammalian cells. *Science* 1994*,* 265 (5173), 808-911.
57. Han J., J. Lee, P. Tobias and R. Ulevitch, Endotoxin induces rapid protein tyrosine phosphorylation in 70Z/3 cells expressing CD14. *J. Biological Chem.* 1993,268 (33), 25009-25014.
58. Boldt S. and W. Kolch, Targeting MAPK signalling: Prometheus' fire or pandora's box? *Curr. Pharm. Des.* 2004, 10, 1885-1905.
59. Peifer C., K. Kinkel, M. Abadleh, D. Schollmeyer and S. Laufer, From five- to six membered rings: 3, 4-diarylquinol-inone as lead for novel p38MAP kinase inhibitors. *J. Med. Chem.*2007, 50, 1213-1221.
60. Kolch W, Meaningful relationships: the regulation of the Ras/Raf/MEK/ERK pathway by protein interactions. *J. Biochem.*2000, 351 (2), 289-305.
61. Berger D., M. Dutia, D. Powell, M. Floyd, N. Torres, R. Mallon, D. Wojciechowicz, S. Kim, L. Feldberg, K. Collins and I. Chaudhary, 4-Anilino-7-alkenyl quinoline-3-carbonitriles as potent MEK1 kinase inhibitors. *Bioorg. Med. Chem.* 2008, 16, 9202-9211.
62. Wilson C., E. Ali, N. Scrimgeour, A. Martin, J. Hua, G. Tallis, G. Rychkov, and G. Barritt, Steatosis inhibits liver cell store-operated Ca(2)(+) entry and reduces ER Ca(2)(+) through a protein kinase C-dependent mechanism. *Biochem. J.*2015, 466, 379-390. http://www.ncbi.nlm.nih.gov/pubmed/?term=Eunus+S+Ali.
63. Hans C., D. Weisenburger, T. Greiner, C. Chan, P. Aoun , G. Cochran, Z. Pan, L. Smith , J. Lynch , R. Bociek, P. Bierman , J. Vose and J. Armitage, Expression of PKC-beta or cyclin D2 predicts for inferior survival in diffuse large B-cell lymphoma. *Mod.Path.*2005, 18(10), 1377-1384.
64. Rocha A., D. Mans, A. Regner and G. Schwartsmann, Targeting protein kinase C: new therapeutic opportunities against high-grade malignant gliomas?. *Oncologist*. 2002, 7(1), 17-33.

65. Gokmen Y., N. Murray, M. Velasco, Z. Gatalica and A. Fields, Elevated protein kinase C betaII is an early promotive event in colon carcinogenesis. *Cancer Res.*2001, 61(4), 1375-1381.
66. Lahn M., G. Kohler, K. Sundell, C. Su , S. Li , B. Paterson and T. Bumol, Protein kinase C alpha expression in breast and ovarian cancer. *Oncology* 2004, 67(1), 1-10.
67. Regala R., C. Weems, L. Jamieson, A. Khoor , E. Edell, C. Lohse and A. Fields, Atypical protein kinase C iota is an oncogene in human non-small cell lung cancer. *Cancer Res.* 2005, 65(19), 8905-8911.
68. Mandil R., E. Ashkenazi, M. Blass, I. Kronfeld, G. Kazimirsky , G. Rosenthal , F. Umansky , P. Lorenzo, P. Blumberg and C. Brodie, Protein kinase Calpha and protein kinase C delta play opposite roles in the proliferation and apoptosis of glioma cells. *Cancer Res.* 2001, 61 (11), 4612-4619.
69. Liu J., M. Crepin, J. Liu, D. Barritault and D. Ledoux, FGF-2 and TPA induce matrix metalloproteinase-9 secretion in MCF-7 cells through PKC activation of the Ras/ERK pathway. *Biochem.Biophys. Res. Commun.*2002, 293(4),1174-1182.
70. Villalonga P., C. Lopez, A. Chiloeches, J. Gil , R. Marais, O. Bachs and N. Agell, Calmodulin prevents activation of Ras by PKC in 3T3 fibroblasts. *J. Biol. Chem.* 2002,277(40), 37929-37935.
71. Zhang J., P. Anastasiadis, Y. Liu, E. Thompson and A. Fields, Protein kinase C (PKC) betaII induces cell invasion through a Ras/Mek-, PKC iota/Rac 1-dependent signaling pathway. *J. Biol. Chem.* 2004, 279(21), 22118-22123.
72. Dudek A., P. Zwolak, P. Jasinski, K. Terai, N. Gallus, M. Ericson and F. Farassati, Protein kinase Cbeta inhibitor enzastaurin (LY317615.HCI) enhances radiation control of murine breast cancer in an orthotopic model of bone metastasis. *Invest. New Drugs* 2007, 26(1), 13-24.
73. Slupsky J., A. Kamiguti, R. Harris, J. Cawley and M. Zuzel, Central role of protein kinase Cepsilon in constitutive activation of ERK1/2 and Rac1 in the malignant cells of hairy cell leukemia. *Am. J. Pathol.* 2007, 170(2), 745-754.
74. Song M., Y. Park, J. Lee and K. Park, Induction of glucoseregulated protein 78 by chronic hypoxia in human gastric tumor cells through a protein kinase C-epsilon/ERK/AP-1 signaling cascade. *Cancer Res.* 2001, 61(22), 8322-8330.
75. Kolch W., G. Heidecker, G. Kochs, R. Hummel, H. Vahidi, H. Mischak, G. Finkenzeller, D. Marmé and U. Rapp, Protein kinase C alpha activates RAF-1 by direct phosphorylation. *Nature* 1993,364 (6434), 249-252.
76. Goode N., K. Hughes, J. Woodgett and P. Parker, Differential regulation of glycogen synthase kinase-3 beta by protein kinase C isotypes. *J. Biol. Chem.* 1992, 267(24), 16878-16882.
77. Jasinski P., P. Zwolak, K. Terai, B. Cacho and A. Dudek, PKC-alpha inhibitor MT477 slows tumor growth with minimal toxicity in in vivo model of non-Ras-mutated cancer via induction of apoptosis. *Investig. New Drugs* 2011, 29, 33-40.
78. Jasinski P., B. Welsh, J. Galvez, D. Land , P. Zwolak , L. Ghandi , K. Terai and A. Dudek, A novel quinoline, MT477: suppresses cell signaling through Ras molecular pathway, inhibits PKC activity, and demonstrates *in-vivo* anti-tumor activity against human carcinoma cell lines. *Invest. New Drugs* 2008, 26(3), 223-232.
79. Jasinski P., P. Zwolak, K. Terai and A. Dudek, Novel Ras pathway inhibitor induces apoptosis and growth inhibition of K-ras-mutated cancer cells *in-vitro* and *in-vivo*. *Transl. Res.*2008, 152 (5), 203-212.
80. Mollin S., S. Blanck, K. Harms and E. Meggers, Cyclometalated phenylquinoline rhodium complexes as protein kinase inhibitors.*Inorg.Chim.Acta.*2012, 393261-393268.
81. Gao Y. and H. Wang,Casein kinase 2 Is activated and essential for Wnt/beta-catenin signaling. *J. Biol. Chem.* 2006, 281 (27), 18394-18400.
82. Pierre F., P. Chua, S. O'Brien, A. Jain, P. Bourbon, M. Haddach, J. Michaux, J. Nagasawa, M. Schwaebe, E. Stefan, A. Vialettes, J.P. Whitten, T. Chen, L. Darjania, R. Stansfield, K. Anderes, J. Bliesath, D. Drygin, C. Ho, M. Omori, C. Proffitt, N. Streiner, K. Trent, W. Rice and D. Ryckman, Discovery and SAR of 5-(3-chlorophenylamino) benzo[c][2,6]naphthyridine-8-carboxylic acid (CX-4945), the first clinical stage inhibitor of protein kinase CK2 for the treatment of cancer. *J. Med. Chem.*2011,54, 635-654.
83. Kramerov A., M. Saghizadeh, S. Caballero, L. Shaw, S. Calzi, M. Bretner, M. Montenarh, L. Pinna, M. Grant and A. Ljubimov, Inhibition of protein kinase CK2 suppresses angiogenesis and hematopoietic stem cell recruitment to retinal neovascularization sites. *Mol. Cell. Biochem.* 2008, 316 (1-2), 177-186.
84. Guerra B., and O. Issinger, Protein kinase CK2 in human diseases.*Curr. Med. Chem.*2008, 15 (19), 1870-1886.
85. Tawfic S., S. Yu, H. Wang, R. Faust, A. Davis and K. Ahmed, Protein kinase CK2 signal in neoplasia. *Histol.Histopathol.*2001,16 (2), 573-582.
86. Haddach M., F. Pierre, C. Regan, C. Borsan, J. Michaux, E. Stefan, P. Kerdoncuff, M. Schwaebe, P. Chua, A. Jain, D. Macalino, D. Drygin, S. O'Brien, W. Rice and D. Ryckman, Synthesis and SAR of inhibitors of protein kinase CK2: novel tricyclic quinoline analogs. *Bioorg. Med. Chem. Lett.*2012,22, 45-48.
87. Jain A., D. Drygin, N. Streiner, P. Chua, F. Pierre, S. O'Brien, J. Bliesath, M. Omori, N. Huser, C. Ho, C. Proffitt, M. Schwaebe, D. Ryckman, W. Rice and K. Anderes, CX-4945, an orally bioavailable selective inhibitor of protein kinase CK2, inhibits prosurvival and angiogenic signaling and exhibits antitumor efficacy. *Cancer Res.* 2010, 70, 10288-10298.
88. Mettey Y. and J. Vierfond, Benzo[c]quinoliziniums: a new family of inhibitors for protein kinase CK II. *Bioorg. Med. Chem. Lett.*1997, 7, 961-964.
89. Golub A., O. Yakovenko, V. Bdzhola, V. Sapelkin, P. Zien and S. Yarmoluk, Evaluation of 3-carboxy-4(1H)-quinol-ones as inhibitors of human protein kinase CK2. *J. Med. Chem.*2006, 49, 6443-6450.

90. Wang Y., K. Miller, D. Boschelli, F. Ye, B. Wu, M. Floyd, D. Powell, A. Wissner, J. Weber and F. Boschelli, Inhibitors of Src tyrosine kinase: the preparation and structureeactivity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. *Bioorg. Med. Chem. Lett.*2000,10 2477-2480.
91. Golas J., K. Arndt, C. Etienne, J. Lucas, D. Nardin, J. Gibbons, P. Frost, F. Ye, D. Boschelli and F. Boschelli, SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, is a potent antiproliferative agent against chronic myelogenous leukemia cells in culture and causes regression of K562xenogr afts in nude mice. *Cancer Res*. 2003, 63, 375-381.
92. Puttini M., A. Coluccia, F. Boschelli, L. Cleris, E. Marchesi, A. Deana, S. Ahmed, S. Redaelli, R. Piazza, V. Magistroni, F. Andreoni, L. Scapozza,F. Formelli and C. Passerini, *In-vitro* and *in-vivo* activity of SKI-606, a novel Src- Abl inhibitor, against imatinib-resistant Bcr-Ablþ neoplastic cells. *Cancer Res.*2006,23, 11314-11322.
93. Cortes J., H. Kantarjian, T. Brümmendorf, D. Kim, A. Turkina, Z. Shen, R. Pasquini, H. Khoury, S. Arkin, A. Volkert, N. Besson, R. Abbas, J. Wang, E. Leip and C. Passerini, Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood.*2011, 17, 4567-4576.
94. Cortes J., D. Kim, H. Kantarjian, T. Brümmendorf, I. Dyagil, L. Griskevicus, H. Malhotra, C. Powell, K. Gogat, A. Countouriotis and C. Passerini, Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J. Clin. Oncol.*2012, 30, 3486-3492.
95. Boschelli D. and F. Boschelli, Bosutinib.*Drugs Fut*. 2007, 32(6), 481.
96. Berger D., M. Dutia, G. Birnberg, D. Powell, D. Boschelli, Y. Wang, M. Ravi, D. Yaczko, J. Golas, J. Lucas and F. Boschelli, 4-Anilino-7,8-dialkoxybenzo-[g]quinoline-3-carbonit-riles as potent Src kinase inhibitors. *J. Med. Chem.*2005, 48,5909-5920.
97. Boschelli D., Y. Wang, F. Ye, B. Wu, N. Zhang, M. Dutia, D. Powell, A. Wissner, K. Arndt, J. Weber and F. Boschelli, Synthesis and Src kinase inhibitory activity of a series of 4-phenylamino-3-quinolinecarbonitriles. *J. Med. Chem.* 2001, 44, 822-833.
98. Cao X., Q. You, Z. Li, Q. Guo, J. Shang, M. Yan, J. Chern and M. Chen, Design and synthesis of 7-alkoxy-4-heteroarylamino-3-quinolinecarbonitriles as dual inhibitors of c-Src kinase and nitric oxide synthase. *Bioorg. Med. Chem.* 2008,16, 5890-5898.
99. Wang Y., K. Miller, D. Boschelli, F. Ye, B. Wu, M. Floyd, D. Powell,A. Wissner, J. Weber and F. Boschelli, Inhibitors of Src tyrosine kinase: thepreparation and structureeactivity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. *Bioorg. Med. Chem. Lett.*2000, 10, 2477-2480.
100. Mologni L., Development of RET kinase inhibitors for targeted cancer therapy. *Curr. Med. Chem.* 2011, 18(2), 162-75.
101. Robinett R., A. Freemerman, M. Skinner, L. Shewchuka and K. Lackeya, The discovery of substituted 4-(3-hydroxyanilino)-quinolines as potent RET kinase inhibitors. *Bioorg. Med. Chem. Lett*. 2007, 17, 5886-5893.
102. Milano, A. Chiofalo, M. Basile, A. Salzano, L. Pezzullo and F. Caponigro, New molecular targeted therapies in thyroid cancer. *Anti-Cancer Drug Des.*2006, 17(8), 869-879.
103. Graves P., J. Kwiek, P. Fadden, R. Ray, K. Hardeman, A. Coley, M. Foley and T. Haystead, Discovery of novel targets of quinoline drugs in the human purine binding proteome. *J. Mol. Pharm.*2002, 62, 1364-1372.
104. Trusolino L. and P. Comoglio, Scatter-factor and semaphoring receptor: cell signaling for invasive growth. *Nat. Rev. Cancer* 2002, 2, 289-300.
105. Birchmeier C., W. Birchmeier, E. Gherardi, and G. Woude, Met, metastasis, motility and more.*Nat. Rev. Mol. Cell Biol.*2003, 4, 915-925.
106. Bottaro D., J. Rubin, D. Faletto, A. Chan, T. Kmiecik, G. Woude and S. Aaronson, Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. *Science* 1991, 251 (4995), 802-804.
107. Galland F., M. Stefanova, M. Lafage and D. Birnbaum, Localization of the 5' end of the MCF2 oncogene to human chromosome 15q15----q23. *Cytogenet. Cell Genet.*1992,60 (2), 114-116.
108. Cooper *C.*, The met oncogene: from detection by transfection to trans-membrane receptor for hepatocyte growth factor. *Oncogene.* 1992, 7(1), 3-7.
109. Cui J., Inhibitors targeting hepatocyte growth factor receptor and vascular endothelial growth factor receptor tyrosine kinases. *Expert. Opin. Ther. Pat.* 2006, 16, 713-718.
110. Cui J., Inhibitors targeting hepatocyte growth factor receptor and their potential therapeutic applications. *Expert. Opin. Ther. Pat.*2007, 17, 1035-1045.
111. Abidoye O., N. Murukurthy and R. Salgia, Review of clinic trials: agents targeting c-Met. *Rev. Recent Clin. Trials.* 2007, 2, 143-147.
112. Comoglio P., S. Giordano and L. Trusolino, Drug development of MET inhibitors: targeting oncogene addiction and expedience. *Nat. Rev. Drug Discov.* 2008, 7, 504-516.
113. Liu X., W. Yao, R. Newton and P. Scherle, Targeting the c-Met signaling pathway for cancer therapy. *Expert Opin.Investig.Drugs*2008, 17, 997-1011.
114. Dussault I. and S. Bellon, From concept to reality: the long road to c-Met and RON receptor tyrosine kinase inhibitors for the treatment of cancer. *Anti-Cancer Agents Med. Chem.*2009, 9, 221-229.
115. Eder J., G. Woude, S. Boerner, and P. LoRusso, Novel therapeutic inhibitors of the c-Met signaling pathway in cancer. *Clin. Cancer Res.* 2009, 15, 2207-2214.
116. Giubellino A., W. Linehan and D. Bottaro, Targeting the Met signaling pathway in renal cancer. *Expert. Rev. Anticancer Ther*.2009, 9, 785-793.
117. Underiner T., T. Herbertz and S. Miknyoczki, Discovery of small molecule c-Met inhibitors: evolution and profiles of clinical candidates. *Anti-Cancer Agents Med. Chem.* 2010, 10, 7-27.

118. Porter J., Small molecular c-Met kinase inhibitors: a review of recent patent. *Expert. Opin. Ther. Pat.*2010, 20, 159-177.
119. Zhou S., H. Liao, M. Liu, G. Feng, B. Fu, R. Li, M. Cheng, Y. Zhao and P. Gong, Discovery and biological evaluation of novel 6, 7-disubstituted-4-(2-fluorophenoxy) quinoline derivatives possessing 1,2,3-triazole-4-carboxamide moiety as c-Met kinase inhibitors. *Bioorg. Med. Chem.* 2014, 22(22), 6438-6452.
120. Liao W., C. Xu, X. Ji, G. Hu, L. Ren, Y. Liu, R. Li, P. Gong and T. Sun, Design and optimization of novel 4-(2-fluorophenoxy)quinoline derivatives bearing a hydrazone moiety as c-Met kinase inhibitors. *Eur. J. Med. Chem*. 2014, 87, 508-518.
121. Li S., Y. Zhao, K. Wang, Y. Gao, J. Han, B. Cui and P. Gong, Discovery of novel 4-(2-fluorophenoxy)quinoline derivatives bearing 4-oxo-1,4-dihydrocinnoline-3 carboxamide moiety as c-Met kinase inhibitors. *Bioorg. Med. Chem.*2013, 21, 2843-2855.
122. Liao W., G. Hu, Z. Guo, D. Sun, L. Zhang, Y. Bu, Y. Li, Y. Liu and P. Gong, Design and biological evaluation of novel 4-(2-fluorophenoxy) quinoline derivatives bearing an imidazolone moiety as c-Met kinase inhibitors. *Bioorg. Med. Chem.* 2015, 23(15), 4410-4422.
123. Wang Y., J. Ai, Y. Wang, Y. Chen, L. Wang, G. Liu, M. Geng and A. Zhang, Synthesis and c-met kinase inhibition of 3,5-disubstituted and 3,5,7-trisubstituted quinolines: identif-ication of 3-(4-acetylpiperazin-1-yl)-5-(3-nitrobenzylamino)-7-(trifluoromethyl) quinoline as a novel anticancer agent. *J. Med. Chem.* 2011, 54, 2127-2142.
124. Timofeevski S., M. McTigue, K. Ryan, J. Cui, H. Zou, J. Zhu, F. Chau, G. Alton, S. Karlicek, J. Christensen and B. W. Murray, Enzymatic characterization of c-MET receptor tyrosine kinase oncogenic mutants and kinetic studies with aminopyridine and triazolopyrazine inhibitors. *Biochem.*2009, 48, 5339-5349.
125. Cui J., M. Tigue, M. Nambu, M. Dube, M. Pairish, H. Shen, L. Jia, H. Cheng, J. Hoffman, P. Le, M. Jalaie, G. Goetz, K. Ryan, N. Grodsky, Y. Deng, M. Parker, S. Timofeevski, B. Murray, S. Yamazaki, S. Aguirre, Q. Li, H. Zou and J. Christensen, Discovery of a novel class of exquisitely selective mesenchymal-epithelial transition factor (c-MET) protein kinase inhibitors and identification of the clinical candidate 2-(4-(1-(quinolin-6-ylmethyl)- 1H-[1,2,3] tri-azolo[4,5-b]pyrazin-6-yl)-1H-pyrazol-1-yl) ethanol (PF-04217903) for the treatment of cancer. *J. Med. Chem.* 2012, 55, 8091-8109.
126. Brown J. and A. Giaccia, The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. *Cancer Res.*1998, 58, 1408-1416.
127. Harris P., A. Boloor, M. Cheung, R. Kumar, R. Crosby, R. Davis-Ward, A. Epperly, K. Hinkle, R. Hunter, J. Johnson, V. Knick, C. Laudeman, D. Luttrell, R. Mook, R. Nolte, S. Rudolph, J. Szewczyk, A. Truesdale, J. Veal, L. Wang and J. Stafford, Discovery of 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-benzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. *J. Med. Chem.* 2008, 51, 4632-4640.
128. Hickey K., D. Grehan , M. Reid, S. O'Briain , T. Walsh and T. Hennessy, Expression of epidermal growth factor receptor and proliferating cell nuclear antigen predicts response of esophageal squamous cell carcinoma to chemo-radiotherapy. *J. Cancer*1994, 74, 1693-1698.
129. KK., B. Li, J. Winer, M. Armanini, N. Gillett, H. Phillipsand N. Ferrara, Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo. *Nature*1993, 362, 841-844.
130. KW., G. Baron, A. Kieser and D. Marmé, Regulation of the expression of VEGF/VPS and its receptors: role in tumor angiogenesis. *Breast Cancer Res. Treat.* 1995, *36*, 139-155.
131. Leenders W., Targetting VEGF in anti-angiogenic and antitumour therapy: Where are we now? *Int. J. Exp. Pathol.* 1998, *79*, 339-346.
132. Strawn L., G. McMahon, H. App, R. Schreck, W. Kuchler, M. Longhi, T. H. Hui, C. Tang, A. Levitzki, A. Gazit, I. Chen, G. Keri, L. Orfi, W. Risau, I. Flamme, A. Ullrich, K. Hirth and L. Shawver, Flk-1 as a Target for Tumor Growth Inhibition. *Cancer Res.* 1996, *56*, 3540-3545.
133. MB., M. Longhi, K. Plate, L. Shawver, W. Risau, A. Ullrichand L. Strawn, Dominant-negative inhibition of Flk-1 suppresses the growth of many tumor types *in-vivo*. *CancerRes.*1996, *56*, 1615-1620.
134. Weiss M., J. Harmange, A. Polverino, D. Bauer, L. Berry, V. Berry, G. Borg, J. Bready, D. Chen, D. Choquette, A. Coxon, T. DeMelfi, N. Doerr, J. Estrada, J. Flynn, R. Graceffa, S. Harriman, S. Kaufman, D. La, A. Long, S. Neervannan, V. Patel, M. Potashman, K. Regal, P. Roveto, M. Schrag, C. Starnes, A. Tasker, Y. Teffera, D. Whittington and R. Zanon, Evaluation of a series of naphthamides as potent, orally active vascular endothelial growth factor receptor-2 tyrosine kinase inhibitors. *J. Med. Chem.* 2008, 51, 1668-1680.
135. Yang Y., L. Shi, Y. Zhou, H. Li, Z. Zhu and H. Zhu, Design, synthesis and biological evaluation of quinoline amide derivatives as novel VEGFR-2 inhibitors. *Bioorg. Med. Chem. Lett.*2010, 20, 6653-6656.
136. Kubo K., T. Shimizu, S. Ohyama, H. Murooka, A. Iwai, K. Nakamura, K. Hasegawa, Y. Kobayashi, N. Takahashi, K. Takahashi, S. Kato, T. Izawa and T. Isoe, Novel potent orally active selective VEGFR-2 tyrosine kinase inhibitors: synthesis, structure-activity relationships, and antitumor activities of N-phenyl-N0-{4-(4-quinolyloxy)phenyl}ureas. *J. Med. Chem.*2005, 48, 1359-1366.
137. Tohyama O. , J. Matsui, K. Kodama, N. Hata-Sugi,T. Kimura, K. Okamoto, Y. Minoshima, M. Iwata and Y. Funahashi, Antitumor Activity of Lenvatinib (E7080): An Angiogenesis Inhibitor That Targets Multiple Receptor Tyrosine Kinases in Preclinical Human

Thyroid Cancer Models. *J. Thyroid Research* 2014, 2014, 13 http://dx.doi.org/10.1155/2014/638747
138. Stjepanovic N. and J. Capdevila, Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib. *Biologics: Targets and Therapy.* 2014, 8, 129-139.
139. Matsui J., Y. Funahashi, T. Uenaka, T. Watanabe, A. Tsuruoka and M. Asada, Multikinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase.*Clin.Cancer Res.*2008, 14, 5459-5465.
140. U.S. Food and Drug Administration. *Hematology /Oncology (Cancer) Approvals & Safety Notifications.*http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm
141. Yakes F. , J. Chen, J. Tan, K. Yamaguchi, Y. Shi, P. Yu, F. Qian, F. Chu, F. Bentzien, B. Cancilla, J. Orf, A. You, A. Laird, S. Engst, L. Lee, J. Lesch, Y. Chou and A. Joly, Cabozantinib (XL184), a Novel MET and VEGFR2 Inhibitor, Simultaneously Suppresses Metastasis, Angiogenesis, and Tumor Growth. *Mol.Cancer Ther*. 2011, 10(12), 2298-2308.
142. BF., M. Zuzow, N. Heald, A. Gibson, Y. Shi, L. Goon, P. Yu, S. Engst, W. Zhang, D. Huang, L. Zhao, V. Vysotskaia, F. Chu, R. Bautista, B. Cancilla, P. Lamb, A. Joly and F. Yakes,*In-vitro* and *in-vivo* activity of cabozantinib (XL184), an inhibitor of RET, MET, and VEGFR2, in a model of medullary thyroid cancer. *Thyroid.* 2013, 23(12), 1569-1577.
143. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm330143.htm [176].
144. Ren J., J. Zhao, Y. Zhou, X. Liu, X. Chen and K. Hu, Synthesis and antitumor activity of novel 4-aminoquinoline derivatives. *Med. Chem. Res*. 2013, 22, 2855-2861.
145. Herbst R., Review of epidermal growth factor receptor biology. *Int. J. Radiat. Oncol. Biol. Phys.* 2004, 59 (2 Suppl), 21-26.
146. Zhang H., A. Berezov, Q. Wang, G. Zhang, J. Drebin, R. Murali and M. Greene, ErbB receptors: from oncogenes to targeted cancer therapies. *J. Clin. Invest.*2007, 117 (8), 2051-2058.
147. Harari P., Epidermal growth factor receptor inhibition strategies in oncology. *Endocr. Relat. Cancer.* 2004, 11(4), 689-708.
148. Ibrahim D., D. Abou El Ella, A. El-Motwally and R. Aly, Molecular design and synthesis of certain new quinoline derivatives having potential anticancer activity. *Eur. J. Med. Chem.*2015,102, 115-131.
149. Wissner A., D. Berger, D. Boschelli, M. Floyd, L. Greenberger, B. Gruber, B. Johnson, N. Mamuya, R. Nilakantan, M. Reich, R. Shen, H. Tsou, E. Upeslacis, Y. Wang, B. Wu, F. Ye and N. Zhang, 4-Anilino-6,7-dialkoxyquinoline-3-carbonitrile inhibitors of epidermal growth factor receptor kinase and their bioisosteric relationship to the 4-anilino-6,7- dialkoxy-quinazoline inhibitors. *J. Med. Chem.* 2000,43, 3244-3256.
150. Wissner A., E. Overbeek, M. Reich, M. Floyd, B. Johnson, N. Mamuya, E. Rosfjord, C. Discafani, R. Davis, X. Shi, S. Rabindran, B. Gruber, F. Ye, W. Hallett, R. Nilakantan, R. Shen, Y. Wang, L. Greenberger and H. Tsou, Synthesis and structure-activity relationships of 6,7-disubstituted 4- aniline-quinoline-3-carbonitriles. The design of an orally active, irreversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor-2 (HER-2). *J. Med. Chem.*2003,46, 49-63.
151. Tsou H., E. Klumpers, W. Hallett, M. Reich, M. Floyd, B. Johnson, R. Michalak, R. Nilakantan, C. Discafani, J. Golas, S. Rabindran, R. Shen, X. Shi, Y. Wang, J. Upeslacis and A. Wissner, Optimization of 6, 7-disubstituted-4-(arylamino)quinoline-3-carbo-nitriles as orally active, irreversible inhibitors of human epidermal growth factor receptor-2 kinase activity. *J. Med. Chem.*2005,48, 1107-1131.
152. Pannala M., S. Kher, N. Wilson, J. Gaudette, I. Sircar, S. Zhang, A. Bakhirev, G. Yang, P. Yuen, F. Gorcsan, N. Sakurai, M. Barbosab and J. Chenga, Synthesis and structure–activity relationship of 4-(2-aryl-cyclopropylamino)-quinoline-3-carbonitriles as EGFR tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* 2007,17, 5978-5982.
153. Makawana J., C. Sangani, L. Lin and H. Zhu, Schiff's base derivatives bearing nitroimidazole and quinoline nuclei: New class of anticancer agents and potential EGFR tyrosine kinase Inhibitors. *Bioorg. Med. Chem. Lett.*2014, 24, 1734-1736.
154. Sangani C., J. Makawana, X. Zhang, S. Teraiya, L. Lin and H. Zhu, Design, synthesis and molecular modeling of pyrazole-quinoline-pyridine hybrids as a new class of anti-microbial and anticancer agents. *Eur. J. Med. Chem.*2014, 76 549-557.
155. Pawar V., M. Sos, H. Rode, M. Rabiller, S. Heynck, W. VanOtterlo, R. Thomas and D. Rauh, Synthesis and biological evaluation of 4-anilinoquinolines as potent inhibitors of epidermal growth factor receptor. *J. Med. Chem.*2010,53, 2892-2901.
156. Li S., C. Guo, X. Sun, Y. Li, H. Zhao, D. Zhan, M. Lan, and Y. Tang. Synthesis and biological evaluation of quinazoline and quinoline bearing 2,2,6,6-tetra methyl piperidine-N-oxyl as potential epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and EPR bio-probe agents. *Eur. J. Med. Chem.*2012, 49, 271-278.
157. Randhawa R. and P. Cohen, The role of the insulin-like growth factor system in prenatal growth. *Mol. Genet. Metab.*2005, 86, 84-90.
158. Chng W., A. Gualberto and R. Fonseca, IGF-1R is overexpressed in poor-prognostic subtypes of multiple myeloma. *Leukemia* 2006, 20, 174-176.
159. Strömberg T., S. Ekman, L. Girnita, L. Dimberg, O. Larsson, M. Axelson, J. Lennartsson, U. Hellman, K. Carlson, A. Österborg, K. Vanderkerken, K. Nilsson and H. Wiklund, IGF-1 receptor tyrosine kinase inhibition by the cyclolignan PPP induces G2/M-phase accumulation and apoptosis in multiple myeloma cells. *Blood*2006, 107, 669.
160. Breuhahn K., T. Longerich and P. Schirmacher, Dysregulation of growth factor signaling in human

hepatocellular carcinoma.*Oncogene*2006, 25, 3787-3800.
161. Fang J., Q. Zhou, X. Shi, and B. Jiang, Luteolin inhibits insulin-like growth factor 1 receptor signaling in prostate cancer cells. *Carcinogenesis* 2007, 28, 713.
162. Riedemann J., V. Macaulay, J. Riedemann, Macaulay and V. M, IGF1R signalling and its inhibition. *Endocr. Related Cancer* 2006, 13, 33-43.
163. Miller L., S. Mayer, D. Berger, D. Boschelli, F. Boschelli, L. Di, X. Du, M. Dutia, M. Floyd, M. Johnson, C. Kenny, G. Krishnamurthy, F. Moy, S. Petusky, D. Tkach, N. Torres, B. Wu and W. Xu, Lead identification to generate 3-cyanoquinoline inhibitors of insulin-like growth factor receptor (IGF-1R) for potential use in cancer treatment. *Bioorg. Med. Chem. Lett.*2009, 19, 62-66.
164. CL., C. Chen, J. Lee, T. Way, C. Huang, S. Huang, C. Teng, T. Yamori, T. Wu, C. Sun, D. Chien, K. Qian, S. Natschke, K. Lee, L. Huang and S. Kuo, Synthesis and preclinical evaluations of 2-(2-fluorophenyl)-6,7-methylenedioxyquinolin-4-one monosodium phosphate (CHM-1-P-Na) as a potent antitumor agent. *J. Med. Chem.*2010, 53 (4), 1616-1626.
165. Kuo S., C. Teng, K. Lee, L. Huang, L. Chou, C. Chang, C. Sun, T. Wu, S. Pan, T. Way, J. Lee, J. Chung, J. Yang, C. Chen, C. Huang and S. Huang, Novel hydrophilic derivatives of 2-aryl-4-quinolones as anticancer agents. WO 2008/070176 A1 (PCT), 2008. [Patent Applied in Taiwan (96146890), U.S. (12/448088), Australia (2007328034), Canada (2670292), China (200780044796.9), EU (07853279.3), India (3052/EHENP/2009), Japan (2009-540310), Korea (10-2009-7014196), New Zealand (577130), Russian Fedeation (2009124622), South Africa (2009/03694)].
166. Chou L., M. Tsai, M. Hsu, S. Wang, T. Way, C. Huang, H. Lin, K. Qian, Y. Dong, K. Lee, L. Huang and S. Kuo, Design, synthesis, and preclinical evaluation of new 5,6-(or 6,7-)disubstituted-2-(fluorophenyl)quinolin-4-one derivatives as potent antitumor agents. *J. Med. Chem.*2010, 53(22), 8047-8058.
167. Pollard J., Tumour-educated macrophages promote tumour progression and metastasis. *Nat. Rev. Cancer*2004, 4(1), 71-78.
168. Lewis C. and J. Pollard, Distinct role of macrophages in different tumor microenvironments. *Cancer Res.* 2006, 66, 605-612.
169. Scott D., C. Balliet, D. Cook, A. Davies, T. Gero, C. Omer, S. Poondru, M. Theoclitou, B. Tyurin and M. Zinda, Identification of 3-amido-4-anilinoquinolines as potent and selective inhibitors of CSF-1R kinase. *Bioorg. Med. Chem. Lett.* 2009, 19(3), 697-700.
170. Scott D., K. Bell, C. Campbell, D. Cook, L. Dakin, D. Valle, L. Drew, T. Gero, M. Hattersley, C. Omer, B. Tyurin and X. Zheng, 3-Amido-4-anilinoquinolines as CSF-1R kinase inhibitors 2: optimization of the PK profile. *Bioorg. Med. Chem. Lett.*2009, 19, 701-705.
171. Williams L., Signal transduction by the platelet-derived growth factor receptor. *Science* 1989, 243, 4898, 1564-1570.
172. Heldin C. and B. Westermark, Platelet-derived growth factor: three isoforms and two receptor types. *Trends Genet.* 1989, 5 (4), 108-111.
173. DY., Platelet-derived growth factor receptor tyrosine kinase inhibitors: a review of the recent patent literature. *Expert. Opin. Ther. Pat*. 2010, 20(7), 885-897.
174. Plé P., F.Jung, S. Ashton, L. Hennequin, R. Laine, C. Brempt, R. Morgentin, G. Pasquet and S. Taylor, Discovery of new quinoline ether inhibitors with high affinity and selectivity for PDGFR tyrosine kinases. *Bioorg. Med. Chem. Lett.* 2012, 22, 3050-3055.
175. Doré J., M. Edens, N. Garamszegi and E. Leof, Heteromeric and homomeric transforming growth factor-beta receptors show distinct signaling and endocytic responses in epithelial cells. *J. Biolog. Chem.* 1998, 273 (48), 31770-31777.
176. Caestecker M., E. Piek and A. Roberts, Review, Role of Transforming Growth Factor- Signaling in Cancer. *J. Natl. Cancer Instit.*2000, 92(17), 1388-1402.
177. Yingling J., K. Blanchard and J. Sawyer, Development of TGF-b signaling inhibitors for cancer therapy.*Nat. Rev. Drug Discov.*2004, 3, 1011-1022.
178. Sawyer J., B. Anderson, D. Beight, R. Campbell, M. Jones, D. Herron, J. Lampe, J. McCowan, W. McMillen, N. Mort, S. Parsons, E. Smith, M. Vieth, L. Weir, L. Yan, F. Zhang and J. Yingling, Synthesis and activity of new aryl- and heteroaryl-substituted pyrazole inhibitors of the transforming growth factor-beta type I receptor kinase domain. *J. Med. Chem.*2003, 46(19), 3953-3956.
179. Sawyer J., B. Anderson, D. Beight, T. Goodson, D. Herron, H. Li, W. McMillen, N. Mort, S. Parsons, E. R. Smith, K. Britt, L. Yan, F. Zhang and J. Yingling, Synthesis and activity of new aryl- and heteroaryl-substituted 5, 6-dihydro-4H-pyrrolo[1,2-b]pyrazole inhibitors of the transforming growth factor-type I receptor kinase domain. *Bioorg. Med. Chem. Lett.* 2004, 14, 3581-3585.
180. Li H., W. McMillen, C. Heap, D. McCann, L. Yan, R. Campbell, S. Mundla, C. King, E. Dierks, B. Anderson, K. Britt, K. Huss, M. Voss, Y. Wang, D. Clawson, J. Yingling and J. Sawyer, Optimization of a dihydropyrrolopyrazole series of transforming growth factor-b type I receptor kinase domain inhibitors: discovery of an orally bioavailable transforming growth factor-b receptor type I inhibitor as antitumor agent. *J. Med. Chem.*2008, 51(7), 2302-2306.