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A REVIEW ON QUINAZOLES AS CYTOTOXIC AGENTS

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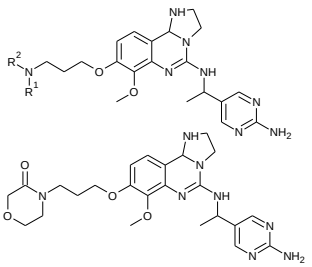
ABSTRACT

We worked out for the review on Quinazoles as Angiogenesis Inhibitors and Cytotoxic agents; it would be helpful to those who are working on cancer research. Cancer is one of the world's most pressing health care challenges with more than 14 million people receiving a cancer diagnosis each year. The vascular network is important since the proliferation as well as metastatic spread of cancer cells for the adequate supply of oxygen and nutrients. Many proteins have been identified as angiogenic activators and inhibitors. The discovery of angiogenesis inhibitors should help to reduce both morbidity and mortality from carcinomas. This review illustrate the recent approaches in molecular biology has resulted in the identification of important signal transduction processes and Scientific advances to understanding of the biology of cancer. The new insights into angiogenesis and inhibition of its regulators will be investigated for the development of a novel treatment for cancer.

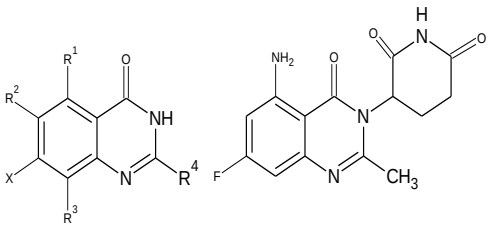
INTRODUCTION

Angiogenesis is in the proliferation & growth of both physiologically normal and neoplastic tissues, through vascular supply as oxygen and nutrients. Many inhibitory/promoter genes regulate this angiogenesis process. The functional role of key regulatory factors will be examined in the context of a normal healthy condition.

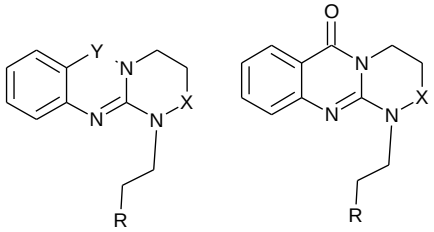
REVIEW: 2-amino-N-[7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl] pyrimidine-5-carboxamide components for phosphotidylinositol-3-kinase (PI3K) inhibition and treating diseases related to phosphotidyl-inositol-3-kinase (PI3K) activity, in treating hyper-proliferative and angiogenesis.



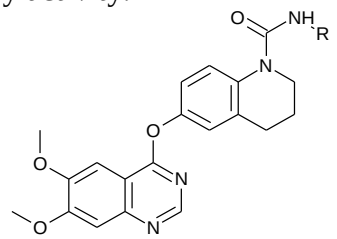
Quinazolinone derivatives as TNF-α inhibition for the treatment of cancer and inflammation, the molecules evaluated for their TNF-α inhibitory action and anticancer activity. Exhibited IC_{50} value of 32.8 nM towards TNF-α and IC_{50} value in the range of 0.0068 µM and 0.1793 µM towards cancer cells.



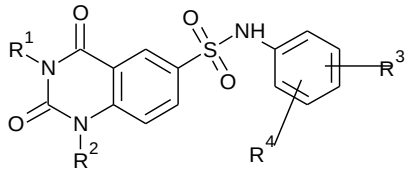
Aryl amino alcohol dihydroimidazoquinazoline derivatives for use as phosphotidylinositol-3-kinase (PI3K) inhibition.



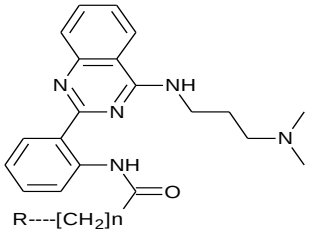
Isoxazolo-quinazolines which modulate the action of protein kinases & therefore useful in treating diseases which is caused by deregulated protein kinase activity, particularly human MPS1& PERK. Isoquinoline, quinoline and quinazoline derivatives to inhibit the hedgehog signaling pathway and to treat the hyper proliferative diseases and pathological angiogenesis. Quinazoline derivatives as angiogenesis inhibitors by the effects on VEGF, the property of worthy in the treatment of diseases including cancer and rheumatoid arthritis. Bicyclic aza-heterocyclic carboxamides for the treatment of hyper proliferative diseases.[(1)]A series of Novel 4-[5-(substituted-1,2, 4-oxadiazol-3-yl)phenyl amine] derivatives of 6,7-dimethoxy-quinazolines derivatives were tested for VEGFR-2 and inhibition activity with an IC50 as as 0.017 µM in an HTRF enzymatic assay. The moiety 8j exhibited good antibacterial activity by inhibiting the growth of methicillin-sensitive Staphylococcus aureus (MSSA. [(2)]N-[2-(4-Hydroxyphenylamino) -pyridin-3-yl]-4-methoxy-benzenesulfonamide(ABT-751)tricyclic analogues of imidazo-quinazolinones were prepared and tested as antimitotic and anti-tumor agents. They exhibited the best in vitro cytotoxic activity (GI_{50} 10-66.9 nM) against the NCI 60 human cancer cell line and also inhibited tubulin assembly with an IC_{50} of 0.812 µM. [(3)]Amentoflavone induces effects through suppression of NF-κB activation in breast cancer in vitro MCF-7 cells, effects of NF-κB inhibitor 4-N-[2-(4-phenoxyphenyl) ethyl] quinazoline-4,6-diamine (QNZ) and amentoflavone on the expression and secretion of angiogenesis and metastasis related proteins & cell invasion.Novel Quinazolino-4β-amidopodophyllotoxin (C-10) regulating cell proliferation and angiogenesis. They evaluated its role on expression of micro RNAs-15, 16, 17 and 221 and its targets Bcl-2, STAT3 and VEGF that dictate cell proliferation and angiogenesis and conclude that combination of Etoposide or C-10 with miR-15, 16, 17 and 221 as a new approach to induce apoptosis and control angiogenesis in breast cancer. Quinazolines were prepared via condensation of 4-chloro-7, 8-dimethoxyquinazoline with 6-hydroxy-1,2,3,4-tetrahydroquinoline,which are used as tyrosine kinase inhibitors, specifically VEGFR-1 and VEGFR-2 and VEGFR-3 inhibitory activity.



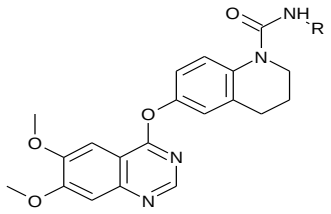
New aryl quinazolines as serine/threonine protein kinase inhibitors, the invention relates to inhibiting serine/threonine protein kinases and for sensitizing to anticancer drugs and ionizing radiation in treatment of cancer.The synthesized compounds were screened for their serine/ threonine protein kinase inhibitory activity. Quinazolinedione with a sirtuin inhibiting activity, finding use in the treatment of inflammatory diseases, interfere with DNA repair in tumor cells and thus exert an anticancer effect and sensitize such cells to antineoplastic agents and radiotherapy.



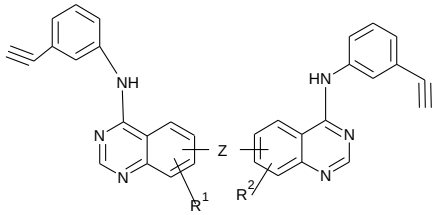
[4]7-Aminoalkoxy-4-aryloxy-quinazoline ureas, novel multi-tyrosine kinase inhibitors by quinazoline core led to new highly potent ATP-competitive inhibitors of VEGFR and Platelet-Derivatives Growth Factor (PDGFR) and c-Kit enzyme. New quinazoline analogues as angiogenesis inhibitor useful to treat tumor and related diseases. Quinazoline derivatives of piperidinyl, pyrrolidinyl, diethylamino group synthesized by multi-step procedure. These were evaluated for their angiogenesis inhibition activity rate of 60.1%.



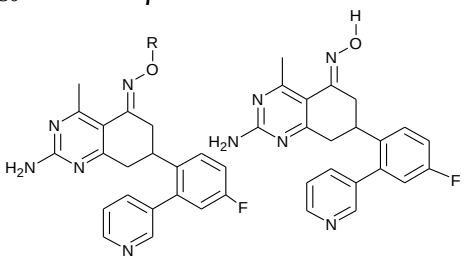
Quinazoline as tyrosine kinase inhibitors confirmed by the assay, it was determined that example compound (R = 3-Cl-Ph) exhibited the inhibition of 75.8, 95.5 and 91.8 % against VEGFR-1, VEGFR-2 and VEGFR-3.



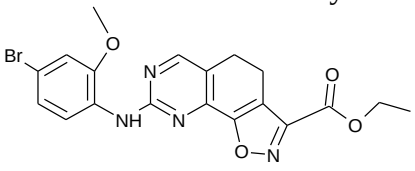
Novel bis-quinazoline compounds as inhibitors for EGFR, the present quinazoline derivatives dimers to inhibit the EGFR.



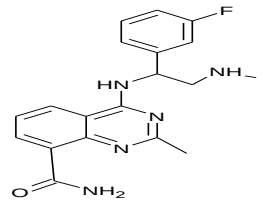
[5]Novel anilinoquinazoline derivatives as multiple tyrosine kinase inhibitors, the compounds bearing the dioxolane. The biphenyl amino derivatives as non cytotoxic & as the antiangiogenic agents both in in-vitro and in-vivo assays. Quinazoline derivatives with Hsp90 inhibitory activity for therapy e.g. cancers, viral and fungal infections, neurodegenerative or inflammatory diseases or conditions. In a fluorescent geldanamicin binding assay used to measure Hsp90 inhibitory activity, II had an IC_{50} of 1.126 µ M.



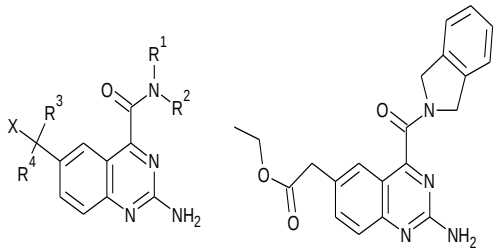
[6] EGFR inhibitors for tumor anti-angiogenesis action through the trans-membrane receptor tyrosine kinase that belongs to the Human epidermal receptor (HER) family of receptors. [7]Halofuginone is a low-molecular weight quinazolinone alkaloid and inhibits collagen(I), they suppress cancer growth, metastasis and angiogenesis.[8]A new series of quinoline ether inhibitors, which potently and selectively inhibit PDGFR tyrosine kinases, Compounds I and II are selective, nanomolar concentration inhibitors of PDGFR and , display good pharmacokinetics in rat and dog and are active in vivo at low doses when given orally twice daily. The isoxazolo-quinazolines modulate the activity of protein kinases useful in treating diseases caused by deregulated protein kinase activity in human MPS1 and PERK. Three representative compounds of the invention they were tested as MPS1 and PERK enzyme inhibitors in in vitro assays.



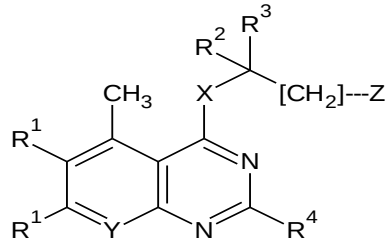
Quinazolinecarboxamide derivatives for use as kinase p70S6K inhibitors were evaluated in p70S6K enzyme assays, an IC_{50} value of 2.8 nM.



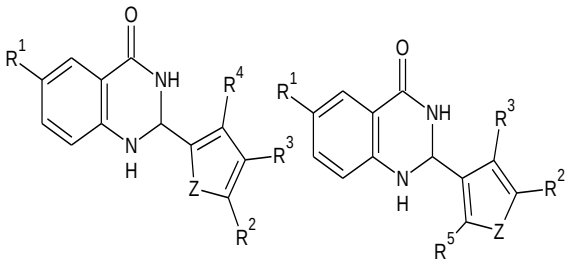
The invented compounds were evaluated for their HSP90 inhibitor activity and exhibited IC50 value in the range of 10 nM to 1 µM.



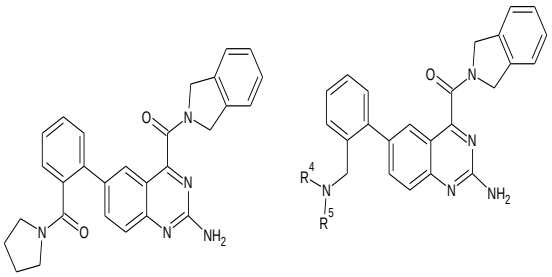
Quinazolinamine derivatives were prepared by cyclization of 2-amino-5-fluorobenzoic acid with formamide followed by chlorination and amination with (4-chlorophenyl) methanamine.and disclosed as autophagy inhibitors. They were evaluated in PDE5 inhibition activity assays



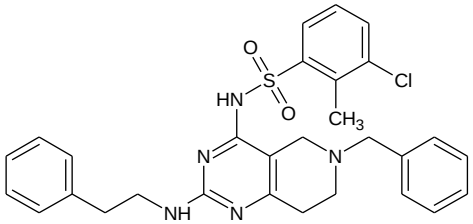
The invention disclosed a kind of 2,3-dihydro-4(1H)-quinazolinone derivatives were prepared from (un)substituted 2-aminobenzoylamide and the corresponding hetero aryl aldehyde via cyclo condensation catalyzed by acid or base in organic solvent. It can be used as angiogenesis inhibitor for treating angiogenesis-associated diseases, and / or cell mediated cytotoxicity-associated Diseases.



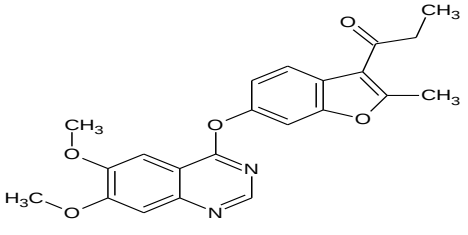
Quinazoline amides as HSP90 inhibitors, formulations were prepared from the disclosed process & exhibited activity in HSP90 inhibition assays.



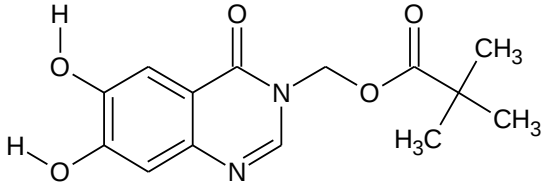
Quinazoline amides as HSP90 inhibitors, the Title compounds were prepared and they were exhibited activity in HSP90 inhibition assays. [9]New synthetic quinonazoline derivatives were a potent EGFR inhibitor. BB selectively inhibited EGFR with a IC_{50} value of 50 ± 37 nM, at least 32-fold more potent. (aza)quinazoline derivatives as angiogenesis inhibitors were prepared in a multi-step synthesis in good yield. They exhibited inhibitory activity against CaMK-II with IC_{50} value of 0.063 µM for treatment of autoimmune disease.



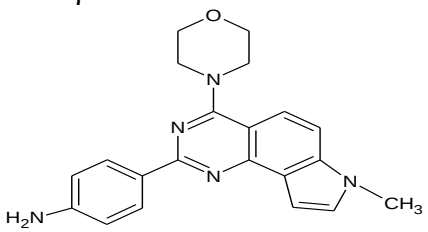
Angiogenesis inhibitors useful in the treatment of neoplasm. Thus, the invention by substitution of 4-chloro-6,7-dimethoxy-quinazoline with 6-hydroxy-N,2-dimethyl-3-benzofurancarboxamide in 85% yield. Quinazolines linked with benzofuran substituent by reacting 4-chloro-6,7-dimethoxyquinazoline with 6-hydroxy-N,2-dimethylbenzofuran-3-carboxamide afforded 85% & inhibited the activity of KDR.



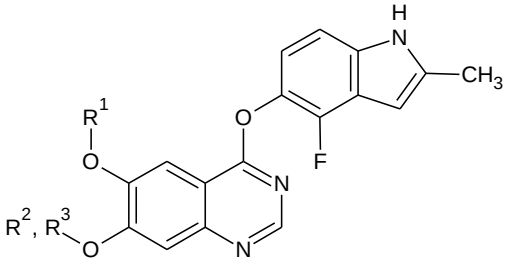
Novel quinazoline derivatives for treating diseases and conditions beneficially by inhibiting cell surface receptor tyrosine kinases. In metabolic stability studies using human liver microsomes, one of the compound 53% longer half-life than the comparison compound (erlotinib).



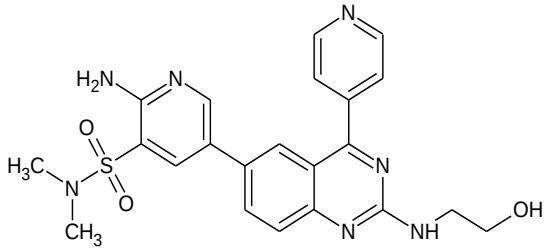
7H-pyrrolo [2,3-h] quinazoline comprising a 7H-pyrrolo[2,3-h]quinazoline compounds for treating mTOR-related diseases and PI3K-related diseases. They were prepared in a multistep synthesis where the key and ultimate step is a Suzuki coupling by 2-chloro-7-methyl-4-morpholin-4-yl-7H-pyrrolo [2, 3-h]quinazoline and 4-aminophenylboronic acid. In a human mTOR kinase assay, IC_{50} was 0.805 µM.



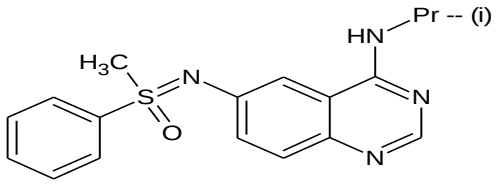
Deuterated indolyloxyquinazolines as anticancer drugs were act by VEGF receptor tyrosine kinase modulators. Thus, 4-chloro-6-(methoxy-d_3)-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline, 4-fluoro-2-methyl-1H-indol-5-ol and K_2CO_3 they were heated together in DMF at 95° for 3 h to give 42% 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-(methoxy-d_3)-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline.



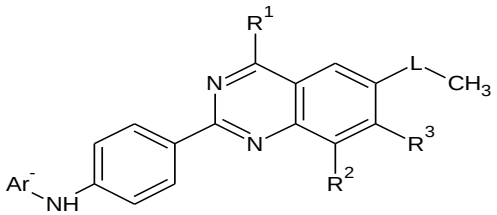
(10) [11C] PAQ as a PET imaging tracer for VEGFR-2 by an N-methylation of desmethyl-PAQ using [^{11}C] methyl iodide. In-vitro assays and PET in healthy animals revealed low tracer metabolites and results suggest that [^{11}C] PAQ has potential as noninvasive PET tracer for in vivo imaging of VEGFR-2 expression in angiogenic "hot spots". Quinazoline derivatives useful for inhibiting the activity / function of PI3 kinases.



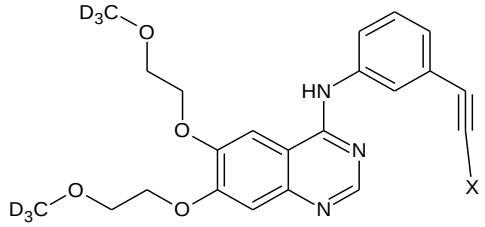
Quinazolinylsulfoximines as EphB4 receptor inhibitors by N-arylation of (S)-S-methyl-S-phenylsulfoximine with 6-bromoquinazolinamine II afforded claimed quinazolinylsulfoximine III in 44% yield. In EphB4 receptor inhibition assays, compounds I exhibited IC_{50} values <10 µM.



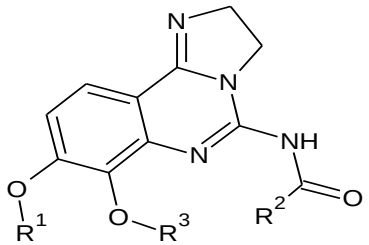
Quinazolinylsulfoximines as EphB4 receptor inhibitors synthesized by N-arylation of (S)-S-methyl-S-phenylsulfoximine with 6-bromoquinazolinamine II afforded claimed quinazolinylsulfoximine III in 44% yield. In EphB4 receptor inhibition assays, compounds I exhibited IC_{50} values <10 µM. (43)Quinazolines from 2-amino-3-methoxybenzoic acid & they were tested in PDK1 kinase alpha screen assay. 140 compounds IC_{50}'s of less than 25 µM and 131 IC_{50}'s of less than 5 µM. Also provided are pharmaceutical compounds treating proliferative diseases, such as cancers.



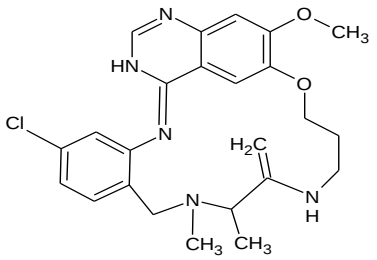
Quinazoline derivatives Y^{1a}, Y^{1b}, Y^{1c}, Y^{2a}, Y^{2b}, Y^{2c}, Z^{1a}, Z^{1b}, Z^{2a} and Z^{2c} are independently H and D and at least one of Y and Z is D. All the invention Compounds they were tested for tyrosine kinase inhibitory action.



Substituted 2,3-dihydroimidazo[1,2-c]quinazoline derivatives to treat hyper-proliferative disorders and angiogenesis by the 3-7 membered heterocyclic optionally containing pharmaceutical compounds containing hosphotidylinositol-3-kinase (PI3K) inhibition.



Macrocyclic quinazoline derivatives as VEGFR3, VEGF receptor inhibitors, the invention discloses the use of some of the macrocyclic quinazoline derivatives. The inhibitors of VEGFR3-mediated biol. activities mediated by VEGFR3 ligand and VEGF-C and / or VEGF-D.



(11)The quinazolines alpha1-adrenoceptor blockers doxazosin and terazosin suppress prostate tumor growth via the induction of apoptosis.The Combination therapy for diseases involving angiogenesis comprising agents inhibiting VEGF activity, agents blocking VEGF receptor and agents reducing VEGF expression, present review relates to target two or more modes of action of VEGF in ocular diseases involving angiogenesis.

CONCLUSION:

Angiogenesis is essential prerequisite of tumor growth is vascular supply so antiangiogenic therapy for tumor is a highly effective approach which represents a treatment, not cures and expected to be cytostatic, particularly effective in combination with cytotoxic agents. Improve the selection of patients and improve clinical benefit advance studies are considered necessary to investigate the timing and potentially predictive biomarkers of angiogenesis inhibitors.

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