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Novel Quinazoline Moiety: Synthesis, In-Vitro Biological Evaluation and Molecular Modelling Studies

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ABSTRACT

The quinazoline core has emerged as a favorable scaffold for the development of novel EGFR inhibitors due to increased affinity for the active site of EGFR kinase. Currently, there are five first-generation (gefitinib, erlotinib, lapatinib, vandetanib) and two second-generation (afatinib and dacomitinib) quinazoline-based EGFR inhibitors approved for the treatment of various types of cancers. The aim of this review is to outline the structural modulations favorable for the inhibitory activity toward both common mutant (del19 and L858R) and resistance-conferring mutant (T790M and C797S) EGFR forms, and provide an overview of the newly synthesized quinazoline derivatives as potentially competitive, covalent or allosteric inhibitors of EGFR.

Key Words: *EGFR, quinazoline, competitive inhibitor, covalent inhibitor, allosteric inhibitor*

1. INTRODUCTION

Cancer: The term cancer used for disease where uncontrolled growth of cells and can invade around the tissues. The cells of cancer can spread around the tissue by the blood and lymph system to another part of the body, too. **[1]**Basically cancer is the abnormal or uncontrolled growth of cells and spread of the cells of the body, and it can affect any parts of the body. The growth of cells around the tissue and can metastasize to distant sites. Various types of cancer can be prevented by exposure to common risk factor, such as tobacco. If they are detecting cancer early, a significant proportion of cancer can be cured by chemotherapy, radiotherapy, and the surgery. Cancer is the major leading cause of death and in 2004 around 13% of all deaths (accounted 7.4 million deaths) worldwide. Basically the main types of cancer are:

• Lung cancer (1.3 million deaths per year)

• Liver cancer (610,000 deaths)

• Breast cancer (519,000 deaths)

• Colorectal cancer (639,000 deaths)

• Stomach cancer (803,000 deaths)

Almost all cancer deaths (around 70%) occurred in middle and Low Countries. Deaths from cancer worldwide are projected to continue rising, with an estimated 11.5 million deaths in 2030.

Risk factor of cancer:

• Tobacco use

• Physical inactivity

• Alcohol use

• Overweight and obesity

• Dietary factor such as insufficient fruits and vegetables intake

• Environmental and occupational risks such as ionizing and non-ionizing radiation **[2].** The international agency for research on cancer has prepared estimate of the global cancer burden for the last 30 years. Starting in 1975 with broad estimate of number of new cases for twelve common types of cancer in various areas of the world [**3].**In 2000 we are able to provide detailed country specific estimate of prevalence, mortality, and incidence, by sex and age group for various types of (around 26) cancer **[4].**The latter set of estimate **[5]** has recently been updated using newer source of data and improved methods of estimation to prepare global estimate for the year 2000 **[6]**

Incidence, mortality, prevalence, and estimate of cancer in worldwide:

Incidence: means the number of new cases occurring, and the incidence expressed as an absolute number of cases per years or as a rate per 100,000 person per years. The latter approximate the average risk of developing a cancer in one year and is used for comparison between within population or world areas. First (primary) prevention strategies object to reduce the incidence, although increasing incidence does not required reflect failure in primary prevention.

Mortality: Mortality means is the number of deaths occurring, and the mortality is expressed as the number of deaths per 100,000 people per year. Basically mortality is the incidence products and fatality for a given cancer. Fatality, the inverse of survival, is the proportion of cancer cases who die; mortality rates measure the averages risk to the population dying from the specific cancer usually one year or within a specific period. Mortality rates are often used as convenient proxy measure of the risk of acquiring the disease, bit this assume that the fatality or survival is constant between the populations being compared. This may be so far cancer with a poor prognosis, but it is much less likely for those which quickly diagnosis and therapy can markedly influence outcome.

Prevalence: Prevalence means as the number of person alive at a particular point in time with the disease of the interest. For cancer, there are no clear agreements on what is meant by "having" the disease. Some author takes it to mean ever having been diagnosed with cancer, even if this was many years' ages, and the subject is cured. It would be more much usefully to consider as "alive with cancer" that person still receiving some form of the treatment. Generally the prevalence means is presented as the number of person still alive after a given number of years following diagnosis. The GLOBOCAN estimates given information on the relative importance of different cancer worldwide in terms of the absolute number and rates of person developing, or dying from cancer in the year 2002.

Estimation: Estimation is the global estimates are built up from estimate of prevalence, incidence, and the mortality in each of the national population of the world **[7, 8].**

Cancer has become the leading cause of human death worldwide because of its uncontrolled and rapid proliferation properties **[9].** Cancer is continuing to be a major health problem in developing as well as developed countries **[10, 11].** Cancer is the leading cause of death worldwide, as it accounted for 7.6 million deaths in 2008 and is projected to continue rising with an estimated 11 million deaths in 2030**[12].** Malignant tumour, also called cancer, is considered to be one of the most difficult to cure diseases around the world today **[13]**. Surgery, radiotherapy and chemotherapy are three major options for the cancer treatment up to present. Chemotherapy drugs provide a unique method for systemic treatment of cancer **[14, 15]**. A major challenge for antitumor drugs is to design new drugs that will more selectively inhibit cancer cells in order to avoid undesirable side effects on normal cells. Targeted cancer Therapies may be more effective than other types of current treatments, due to less harmful to normal cells and more safe and efficient than conventional cytotoxic chemotherapies **[16, 17]**. In 2012, ICRA (International Cancer Research Agency) reported 8.2 million deaths and 14.1 million new cancer cases due to cancer **[18]**. ICRA propound that the global cancer burden will increase up to 13 million death and 21.7 million cases by the year 2030 **[19].** Cancer is lethal uncontrolled disease mainly in developing countries. The mortality rate will be increase to be 13.1 million deaths in 2030 [**20**]. Basically the cancer disease may be effect of people all ages and tend to be increase with age, such cancer is a killer disease caused by uncontrolled or abnormalities (genetic material) growth of cells. The cells of cancer are characterized by three properties such as lake of differentiation, uncontrolled proliferation, and the capability to invade various tissues in another location in body [**21**].

There is an always a real challenge for oncologists and chemists with cancer chemotherapy and anti-tumour agents. This is due to acute toxicity, non-selectivity, and the cellular drug resistance of various anticancer agents. So, there is a continuing require for developing and designing new chemotherapeutic agents for cancer treatment [**22**]. RTKs (Receptor Tyrosine

Kinases) cell surface bind to polypeptides growth factor such as hormone and cytokines. These receptors play an important role in progression and development of various types of cancer [**23**]. Cancer is a leading cause of death in worldwide, it approximate cause 13% of all deaths per year [**24**]. According to world health organization (WHO) the fact sheet published on September 2018, and the globally about one in six deaths is due to cancer and 9.6 million deaths occurred worldwide. The simple most common cause of cancer death are like- stomach cancer (783,000 deaths), lung cancer (1.76 million deaths), colorectal cancer (862,000 deaths), and liver cancer (782,000 deaths) [**25**]. It had predicted that global cancer incidence would reach 22 million cases per year by 2030 [**26**]. In the past few years, the acquired chemotherapeutics resistance of various types of cancer was increased noticeably [**27**].

The international agency for research on cancer estimate of the incidence of prevalence and mortality from the major types of cancer and in 2012 at national level, for 184 countries of the world revealed there were 8.2 million cancer deaths, and 14.1 million new cases of cancer, and 32.6 million people living with cancer in worldwide [**28**]. By 2030, the new cases of cancer there will be increase 26 million and 17 million cancer deaths per year [**29**]. In worldwide the cancer is considered a major health problem and became a major cause of human death or mortality. In 2017, the new cases of cancer (around 1,688,780) will be diagnosed, and about 600,920 American is expected to die of cancer in 2017, which about 1,650 people per day [**30**]. A cancer consists of group of cells that originated from a single cell with abnormal growth of cells and the rapid proliferation properties [**31**].

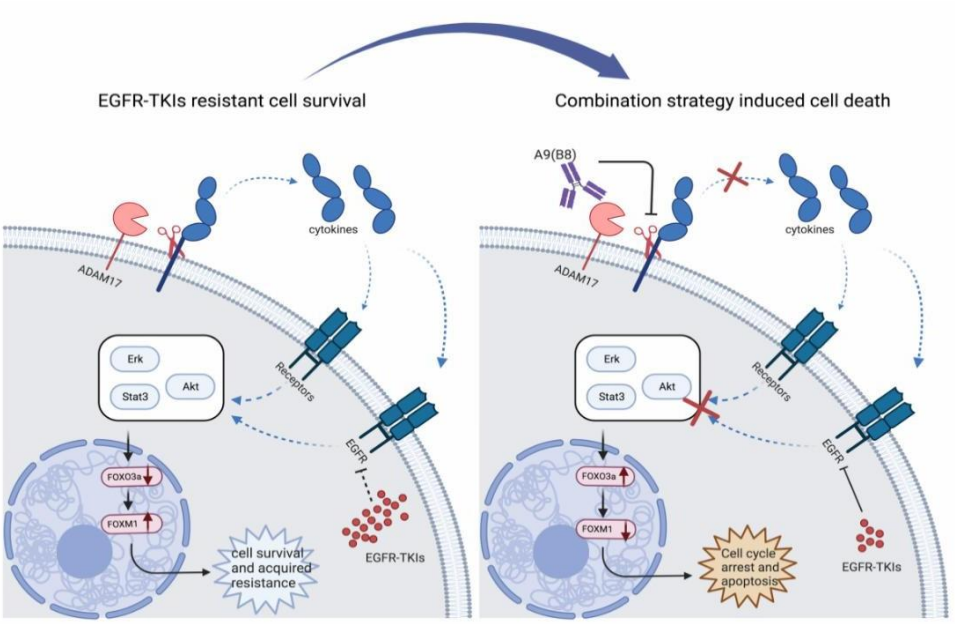
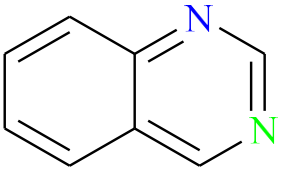


Figure:1 Fundamental EGRF mechanism in human cells.

Quinazoline: Quinazoline (1,3-diazanaphthalene) is a nitrogen containing heterocyclic compound illustrated by a double-ring structure that contains a benzene ring system fused to pyrimidine at two adjacent carbon atoms. In 1869, Griess et al. synthesized the first quinazoline derivative 2-cyano-3, 4-dihydro-4-oxoquinazoline by condensation process [**32,33**]. Quinazoline core is the best scaffolds for development of anticancer agents [**34**], they possess a variety of biological effects including antihypertensive [**35**], antioxidant [36], anticonvulsant [**37**], antifungal [**38**], anti-inflammatory [**39**], anti-diabetic [**40**], anti-tubercular [**41**], anti-viral [**42, 43**] and anticancer activities [**44,45**]. Basically Quinazoline nucleus is an interesting molecule among the most important classes of aromatic bicyclic compounds with two nitrogen atoms in their structure.



Quinazoline

Figure:1 core structure of quinazoline as anti-EGRF inhibitor.

It is consisting of aromatic benzo-pyrimidine system made up of two fused six member simple aromatic rings benzene and pyrimidine ring [**46**]. Some quinazoline as anticancer agents have been used in clinics: Gefitinib, Erlotinib, and Lapatinib have been approved by FDA (Food and Drug Administration) for treatment of cancer.

The phase III clinical study for treatment of advanced NSCLC (non-small cell lung cancer) showed that Icotinib exhibited the equal therapeutic efficacy and low toxicity to gefitinib [**47**]. In addition, there are some quinazoline derivatives have been studied in clinical trials, such as ZM447439 [**48**], AZD1152 [**49**], canertinib and so on [**50**]. Many quinazoline were reported as anticancer agents having multi-target features [**51,52**].

The targets of action of anticancer quinazoline include inhibition of different enzymes, like epidermal growth factor receptor (EGFR), Aldose reductase (AR), dihydrofolate reductase (DFR), folatethymidylate synthase (FTS), cyclic guanosine monophosphate (cGMP) phosphordiesterase, erythroblastosis oncogene B2 (erB2) tyrosine kinase, and cellular-sarcoma (c-Src) tyrosine kinase. Other quinazoline yield their anticancer activity by inhibition of DNA repairing system or tubulin polymerization. There are many other derivatives have dual EGFR/tubulin polymerization inhibitors, like amide derivatives and quinoxalines [**53,54**].

Epidermal growth factor: Epidermal Growth Factor receptor (EGFR) is a key factor for the tumoral expansion and its tumoral over articulation seems, by all percentage, to be a ground-breaking forecast component. As of now, 2 kinds of treatments are focusing on EGFR: monoclonal antibodies against epidermal growth factor receptor and particular inhibitors of the EGFR tyrosine kinase [55]. The epidermal growth factor receptor (EGFR) plays an influential role in initiating the signalling that directs the behaviour of epithelial cells and tumours of epithelial cell origin. EGFR is one of four trans-membrane growth factor receptor proteins that share similarities in structure and function.

Together, this group of receptor proteins comprises the c-erbB family of receptor tyrosine kinases. EGFR, which is also known as HER-1 or c-erbB-1, was the first member of this group to be described. EGFR is a 170-kd glycoprotein that consists of an extracellular receptor domain, a trans-membrane region, and an intracellular domain with tyrosine kinase function. Other members of the c-erbB group include HER2 (c-erbB-2), HER3 (c-erbB-3), and HER4 (c-erbB-4) [56]. In normal cells, the expression of EGFR ranges from 40,000 to 100,000 receptors per cell. In contrast, EGFR is overexpressed in the majority of solid tumours, including breast cancer, head-and-neck cancer, non–small-cell lung cancer (NSCLC), renal cancer, ovarian cancer, and colon cancer.Epidermal growth factor receptor (EGFR) is a key factor in epithelial malignancies, and its activity enhances tumour growth, invasion, and metastasis .EGFR is a member of the ErbB family of tyrosine kinase receptors that transmit a growth-inducing signal to cells that have been stimulated by an EGFR ligand (e.g., TGFα and EGF) .In normal tissues, the availability of EGFR ligands is tightly regulated to ensure that the kinetics of cell proliferation precisely match the tissues' requirements for homeostasis. In cancer, however, EGFR is often perpetually stimulated because of the sustained production of EGFR ligands in the tumour microenvironment or as a result of a mutation in EGFR itself that locks the receptor in a state of continual activation.

2. MATERIALS AND METHODS

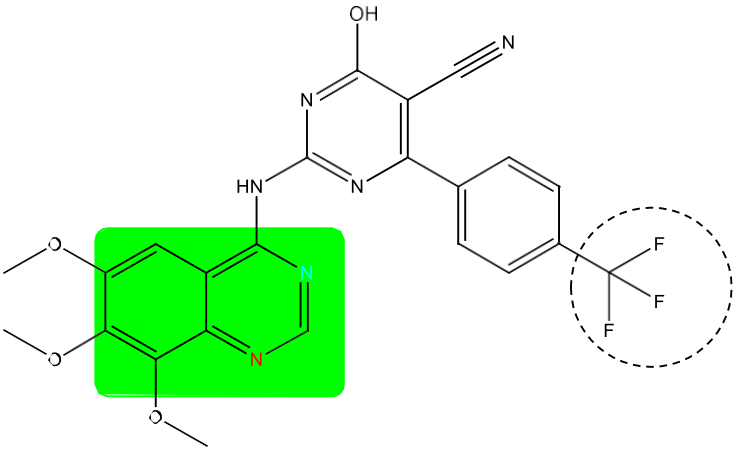
Synthesis of Quinazoline Scaffold:

Synthesis of different 6, 7, 8-trimethoxy-N-aryl-4aminoquinazoline derivatives (PMR 1-9)

The solution of aryl amine (4.0 mmol) and 4-chloroquinazoline in 2-propanol (100 ml) was mixed under deterioration for 4 to 24 hour's. Then after the reaction completed, we remove the solvent under low pressure by TLC under its supervision, and then we wash the remaining residue with help of water and clarify through silica gel column chromatography (petroleum ether/ethyl acetate, 5:1, v: v) to donate the entitle compounds.

Spectral characterization of the synthesized compounds

PMR-1:**4-hydroxy-6-(4-(trifluoromethyl)phenyl)-2-((6,7,8-trimethoxyquinazolin-4-yl)amino)pyrimidine-5-carbonitrile**

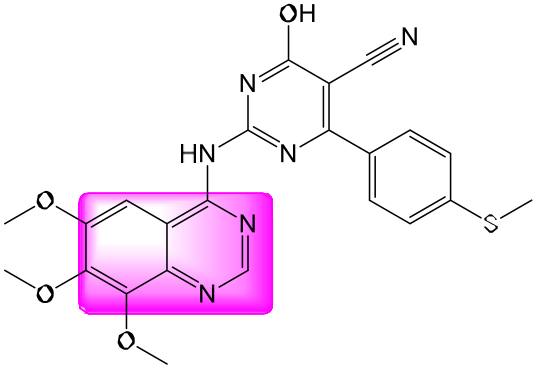


Mol. Formula: $C_{23}H_{17}F_3N_6O_4$; Molecular Wt.: 498.13; Melting Point: 294.09 °C

IR cm^{-1} (KBr): 3234, 3099, 2945, 2924, 2845, 2215, 1661, 1611, 1602, 1530, 1467, 1293, 1246, 1190, 1130, 1103, 813, 777.

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.78 – 3.81 (s, 3H), 3.84 – 3.88 (s, 3H), 3.93 – 3.97 (s, 3H), 7.23 – 7.27 (s, 1H), 7.61 – 7.67 (m, 2H), 7.73 – 7.78 (m, 2H), 8.35 – 8.39 (s, 1H), 9.22 – 9.25 (s, 1H), 9.86 – 9.89 (s, 1H).

PMR-2:4-hydroxy-6-(4-(methylthio)phenyl)-2-((6,7,8-trimethoxyquinazolin-4yl) amino)pyrimidine-5-carbonitrile



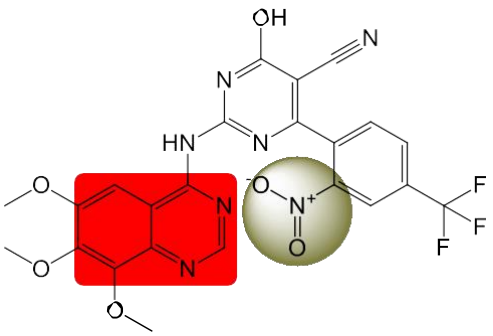
Mol. Formula: ***$C_{23}H_{20}N_6O_4S$; Mol Wt.: 476***; Melting Point: 308.85 °C

C, H, and N analysis: Calc. C, 57.97; H, 4.23; N, 17.64; O, 13.43; S, 6.73; Found C, 57.90; H, 4.27; N, 17.68; O, 13.45; S, 6.70

IR cm^{-1} (KBr): 3252, 3025, 2936, 2909, 2875, 2237, 1654, 1611, 1606, 1513, 1499, 1450, 1344, 1291, 1235, 1161, 1137, 1107, 823, 790.

^{1}H NMR (500 MHz, DMSO-d_6) δ 2.48 – 2.52 (s, 3H), 3.78 – 3.81 (s, 3H), 3.84 – 3.88 (s, 3H), 3.92 – 3.96 (s, 3H), 7.23 – 7.27 (s, 1H), 7.28 – 7.34 (m, 2H), 7.83 – 7.89 (m, 2H), 8.36 – 8.40 (s, 1H), 9.22 – 9.25 (s, 1H), 9.86 – 9.89 (s, 1H).

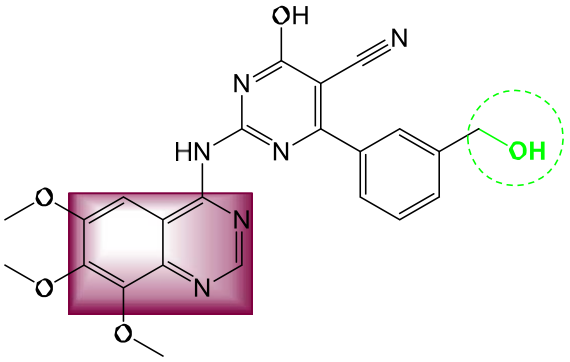
PMR-3:4-Hydroxy-6-(2-nitro-4-(trifluoromethyl)phenyl)-2-((6,7,8-trimethoxyquinazolin-4-yl)amino)pyrimidine-5-carbonitrile



Mol. Formula: ***$C_{23}H_{16}F_3N_7O_6$; Mol Wt.: 543.42;*** Melting Point: 322 °C

IR cm^{-1} (KBr): 3273, 3097, 2936, 2915, 2820, 2203, 1617, 1610, 1580, 1567, 1528, 1485, 1475, 1390, 1350, 1320, 1274, 1237, 1166, 1134, 1120, 1104, 825, 790

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.78 – 3.81 (s, 3H), 3.83 – 3.87 (s, 3H), 3.93 – 3.96 (s, 3H), 7.25 – 7.29 (s, 1H), 7.90 – 7.99 (m, 2H), 8.35 – 8.42 (m, 2H), 9.83 – 9.87 (s, 1H).

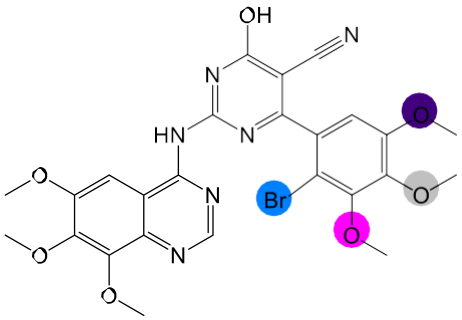


Mol. Formula: ***$C_{23}H_{20}N_6O_5$; Mol Wt.: 460.45;*** Melting Point: 291 ºC.

IR cm^{-1} (KBr): 3291, 3096, 2960, 2910, 2875, 2283, 1656, 1604, 1605, 1543, 1475, 1277, 1227, 1165, 1130, 1109, 823, 798.

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.78 – 3.81 (s, 3H), 3.84 – 3.88 (s, 3H), 3.92 – 3.96 (s, 3H), 4.65 – 4.70 (dq, *J* = 0.9, 0.9, 0.9, 6.6 Hz, 2H), 4.70 – 4.76 (dd, *J* = 5.7, 7.1 Hz, 1H), 7.23 – 7.26 (s, 1H), 7.30 – 7.36 (m, 1H), 7.54 – 7.60 (t, *J* = 7.5, 7.5 Hz, 1H), 7.82 – 7.87 (dt, *J* = 1.6, 1.6, 7.5 Hz, 1H), 8.02 – 8.06 (p, *J* = 1.2, 1.2, 1.2, 1.2 Hz, 1H), 8.36 – 8.40 (s, 1H), 9.04 – 9.07 (s, 1H), 9.88 – 9.92 (s, 1H).

PMR-5:4-(2-bromo-3,4,5-trimethoxyphenyl)-6-hydroxy-2-((6,7,8-trimethoxyquinazolin-4-yl)amino)pyrimidine-5-carbonitrile

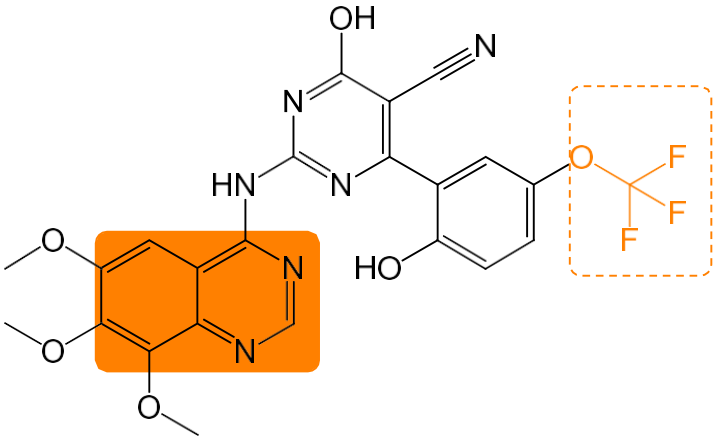


Mol. Formula: ***$C_{25}H_{23}BrN_6O_7$; Mol Wt.: 599;*** Melting Point: 388 ºC.

IR cm^{-1} (KBr): 3241, 3020, 2939, 2935, 2830, 2219, 1621, 1602, 1600, 1545, 1482, 1281, 1228, 1166, 1131, 1104, 823, 790.

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.77 – 3.82 (d, *J* = 3.5 Hz, 6H), 3.83 – 3.88 (m, 9H), 3.98 – 4.02 (s, 3H), 7.25 – 7.29 (s, 1H), 7.40 – 7.43 (s, 1H), 8.35 – 8.39 (s, 1H), 9.29 – 9.32 (s, 1H), 9.93 – 9.96 (s, 1H).

PMR-6:4-hydroxy-6-(2-hydroxy-5-(trifluoromethoxy)phenyl)-2-((6,7,8-trimethoxyquinazolin-4-yl)amino)pyrimidine-5-carbonitrile

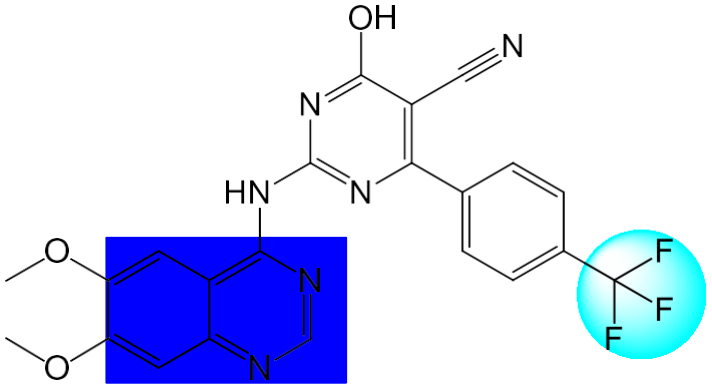


Mol. Formula: ***$C_{23}H_{17}F_3N_6O_6$; Mol Wt.: 530;*** Melting Point: 264 ºC.

IR cm^{-1} (KBr): 3235, 3070, 2960, 2922, 2834, 2216, 1643, 1607, 1585, 1540, 1488, 1278, 1255, 1164, 1131, 1107, 820, 789

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.78 – 3.81 (s, 3H), 3.83 – 3.87 (s, 3H), 3.93 – 3.96 (s, 3H), 6.85 – 6.90 (d, *J* = 7.5 Hz, 1H), 7.08 – 7.13 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.25 – 7.29 (s, 1H), 7.54 – 7.58 (d, *J* = 1.5 Hz, 1H), 8.35 – 8.39 (s, 1H), 9.31 – 9.35 (s, 1H), 9.59 – 9.63 (s, 1H).

PMR-7:4-hydroxy-6-(4-(trifluoromethyl)phenyl)-2-((6,7-dimethoxyquinazolin-4-yl)amino)pyrimidine-5-carbonitrile

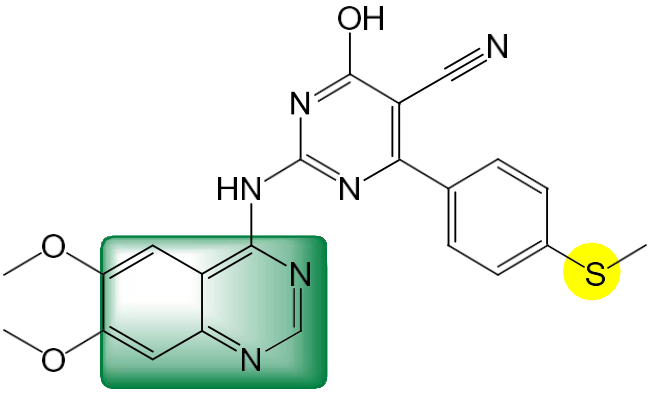


Mol. Formula: ***$C_{22}H_{15}F_3N_6O_3$; Mol Wt.: 468;*** Melting Point: 288 ºC.

IR cm^{-1} (KBr): 3228, 3081, 2980, 2906, 2821, 2255, 1616, 1600, 1609, 1547, 1479, 1270, 1252, 1161, 1133, 1099, 819, 799.

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.86 – 3.93 (d, *J* = 16.5 Hz, 6H), 7.11 – 7.14 (s, 1H), 7.43 – 7.47 (s, 1H), 7.60 – 7.66 (m, 2H), 7.74 – 7.80 (m, 2H), 8.77 – 8.81 (s, 1H), 9.22 – 9.25 (s, 1H), 9.81 – 9.85 (s, 1H).

PMR-8:4-hydroxy-6-(4-(methylthio)phenyl)-2-((6,7-dimethoxyquinazolin-4-yl)amino)pyrimidine-5-carbonitrile



Mol. Formula: ***$C_{22}H_{18}N_6O_3S$; Mol Wt.: 446;*** Melting Point: 287 ºC.

IR cm^{-1} (KBr): 3240, 3094, 2982, 2905, 2845, 2274, 1633, 1606, 1568, 1513, 1487, 1293, 1246, 1163, 1133, 1102, 824, 792.

^{1}H NMR (500 MHz, DMSO-d_6) δ 2.48 – 2.52 (s, 3H), 3.88 – 3.93 (d, J = 10.1 Hz, 6H), 7.12 – 7.16 (s, 1H), 7.30 – 7.36 (m, 2H), 7.43 – 7.47 (s, 1H), 7.83 – 7.89 (m, 2H), 8.77 – 8.81 (s, 1H), 9.22 – 9.25 (s, 1H).

Therapeutic Activity

Anti-angiogenesis activity:

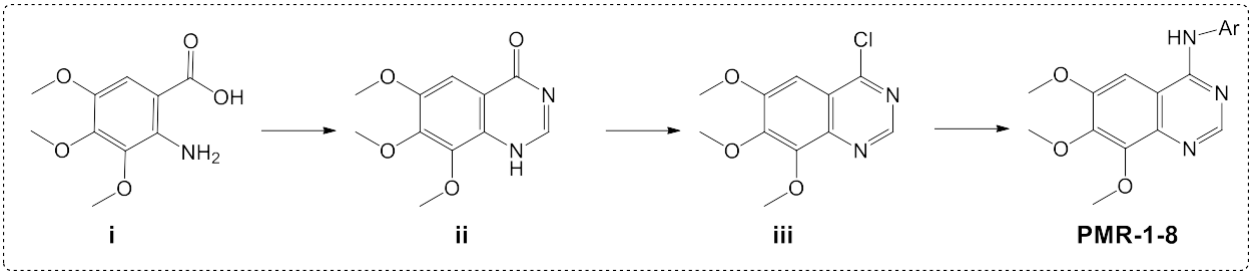
Chorioallantoic Membrane (CAM) Assay: Chorioallantoic membrane assay is recycled initially to regulate the effects of anti-angiogenic compound. This test is based on the Chorioallantoic membrane in which a specific stage in fatal development in propagate chicken eggs at a convinced moment of the expansion of the organism or embryo, and which are fitted with shrapnel test compound is they are settled on vascular membrane of chicken eggs Agarose pellet and the effects on angiogenesis are appraise, and this experiment, the fertility chicken eggs were bought up from the local hatchery, Haridwar.

Procedure: Twelve eggs were used to test each compound, and in one case, we kept the temperature of the eggs at 37 ° C. We used 70% ethanol to avoid infection of the eggs shells, and then with the help of a syringe, the albumin was removed from the lower part of the egg, and after we used 70% ethanol to hours, the syringe hole was closed by the tape. Then we removed the uppermost section of the shells, and covered the eggs with the plastic film and breed it for then we removed the hours and upper part of the shell and covered the egg with plastic film and incubated it for 72 hours. When the diameter of the Chorioallantoic membrane is 1.8 to 2.6 and the tested substances are placed on the pellets. The tested substances were suspended for 2.5% Agarose solution. With the help of micropipette, we take Agarose gel according to the tested substance so, that the size of Agarose gel is not uniform. In this test we take those pellets which are half contracted because they do not sink much into the Chorioallantoic membrane, about 24 hours, the anti-angiogenic effect is measured in conjugation as a fluid, also with the help of stereomicroscope. While, anti-angiogenic enterprise is indicated as a score whereas; 0= weak effect or no, 1= Medium effect, 2= Strong effect, (a capillary free zone is at least twice as big as the pellets), and we can also evaluate embryo-toxicity and the membrane irritation. Effect of the experiment compounds on angiogenesis are recorded in Table 5 and graphical representation of comparative study for the effect of compounds on vascularization on the chicken embryo in CAM assay are shown in graph 5.

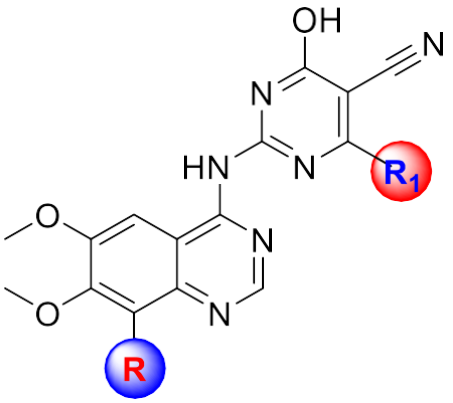
The height of the bars represents the score for the zone of inhibition and the greater the value of the score, the greater the height and the more effective is the compound.

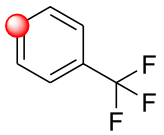
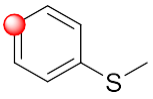
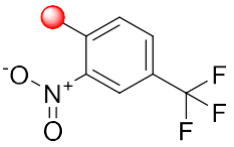
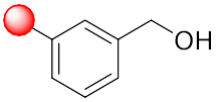
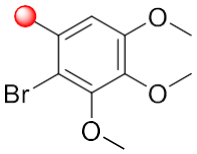
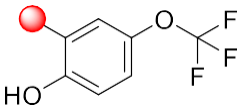
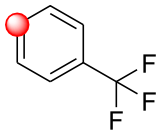
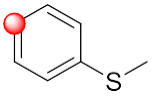
All compounds were experimented at a dose of 10 mg/pellet, i.e. having less than 40 nmol/pellets, because at larger dose most compounds appearance a noxious reaction or effect.

Out of the synthesized analogues, compound PMR-**1,** PMR-**2,** PMR-**5,** PMR-**6,** and PMR-**8** showed an anti-angiogenic score of more than 1. Compound **5** was found to be most potent with a score of 1.7 ± 0.1 which is initiates to be more than that of standard. Compound PMR-**1,** PMR-**2,** PMR-**6**, showed good score, comparable to that of standard.



Schematic diagram for the synthesis of final analogues **PMR1-8**.Compositions and synthesis of novel 6,7,8-trimethoxy N-aryl-substituted-4-aminoquinazoline derivatives.Reagents and conditions: (a) $HCONH_2$, 6 h, 28.6%; (b) $POCl_3$, 3 h, 65.5%; (c) THF, Et_3N; (d) i-PrOH, reflux, 4–24 h, 35.9–69.5%.



PMR	R	R_1	
1	OCH_3		Mol. Formula: $C_{23}H_{17}F_3N_6O_4$; Mol. Wt.: 498.13; Melting Point: 294.09 °C
2	OCH_3		Mol. Formula: $C_{23}H_{20}N_6O_4S$; Mol Wt.: 476; Melting Point: 308.85 °C
3	OCH_3		Mol. Formula: $C_{23}H_{16}F_3N_7O_6$; Mol Wt.: 543.42; Melting Point: 322 °C
4	OCH_3		Mol. Formula: $C_{23}H_{20}N_6O_5$; Mol Wt.: 460.45; Melting Point: 224 °C
5	OCH_3		Mol. Formula: $C_{25}H_{23}BrN_6O_7$; Mol. Wt.: 599; Mp: 377 °C
6	OCH_3		Mol. Formula: $C_{23}H_{17}F_3N_6O_6$; Mol Wt.: 530; Melting Point: 289 °C
7	H		Mol. Formula: $C_{22}H_{15}F_3N_6O_3$; Mol Wt.: 468; Melting Point: 318 °C
8	H		Mol. Formula: $C_{22}H_{18}N_6O_3S$; Mol Wt.: 446; Melting Point: 255 °C

Molecular modelling study: The molecular modelling study is appropriate to build up the molecular approaches that integrate all tested manifest announced. These approaches are needed to obtain the dependable and highly particular film of the biologically active fragments or molecules at the atomic level range and hand over current insight that can be used to arrange novel therapeutics agents.

The molecular docking was achieved into the hydrophobic site of the epidermal growth factor receptor to predict the antitumor activity of the most active compounds of the study (compounds PMR 1 to PMR 8), in which epidermal growth factor receptor is highly expressed. The complexes were energy-minimized with a UFF force field till the gradient confluence 0.01 kcal/mole was arrived. Compound PMR-7 showed hydrophobic interactions Docking studies revealed that compounds (PMR-7) showed best binding interaction with a narrow hydrophobic pocket in 1M17 EGFR tyrosine kinase domain. All energy relevant to interacting of ligand and 1M17 are given in Table 2.

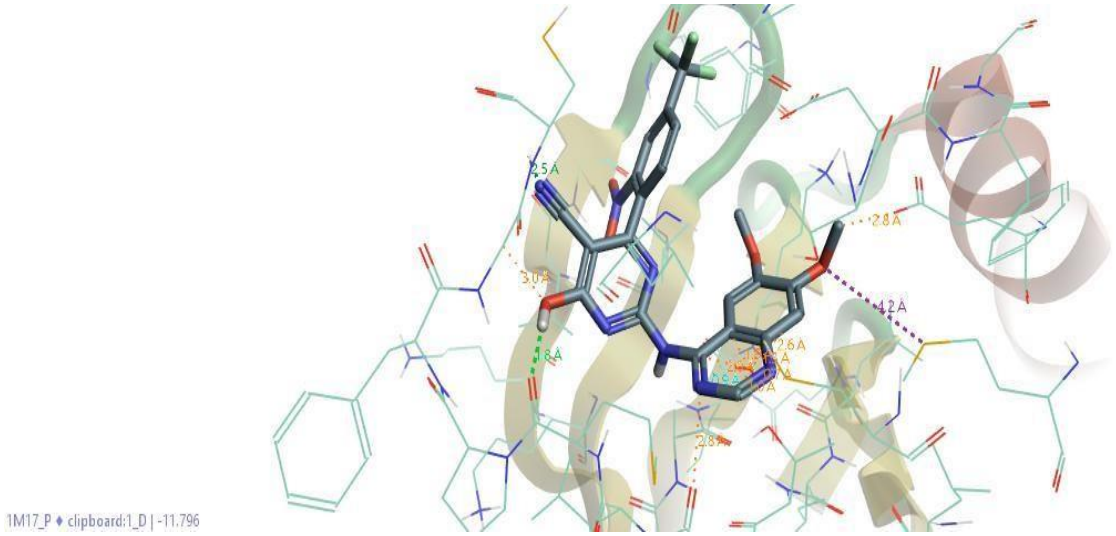


Figure 2: Binding interaction of compound PMR-7

Molecular Modelling study: In the present study, we reported molecular docking studies of all synthesized compounds (PMR1-8) acknowledge that binds to a narrow hydrophobic conceal or pocket of the binding site of Epidermal Growth Factor Receptor tyrosine kinase domain (*PBD ID:1M17*). Whole energy associated with the ligand binding and IM-17 is given table number 2. Among all test compounds, PMR-7 has shown the best binding interaction with the EGFR tyrosine kinase domain (PBD ID: 1M17).

3. RESULTS AND DISCUSSION

Table 2: Docking pose of binding interaction of the compound PMR-.

Ligand	Target	Binding Energy	Date Created	Info
PMR-7	**1m17**	**-9.1**	**2020.07.30 14:54:56**	**PyRx;AutodockVina**
PMR-1	1m17	-8.9	2020.07.30 14:42:17	PyRx;AutodockVina
PMR-4	1m17	-8.9	2020.07.30 14:47:54	PyRx;AutodockVina
PMR-3	1m17	-8.7	2020.07.30 14:46:11	PyRx;AutodockVina
PMR-6	1m17	-8.5	2020.07.30 14:53:25	PyRx;AutodockVina
PMR-2	1m17	-8.1	2020.07.30 14:43:57	PyRx;AutodockVina
PMR-8	1m17	-8.1	2020.07.30 14:56:22	PyRx;AutodockVina
PMR-5	1m17	-6.3	2020.07.30 14:50:23	PyRx;AutodockVina

The identification of the quinazoline core as a valuable scaffold for EGFR inhibition led to the development of several TKIs with tremendous clinical utility in various types of cancer (especially NSCLC). The identification of the key structural features of an ideal EGFR TKI (increased potency toward mutant forms of EGFR, minimal affinity for EGFR wt, and low off-target effect) has been a hot topic for many research groups for some time. This work provides a collection of general drug design rules for the development of novel quinazoline derivatives as potential EGFR inhibitors based on new quinazoline derivatives synthesized in the last 6 years. A breakthrough is the discovery of the fourth-generation inhibitors, bearing a quinazoline core, as allosteric inhibitors of the triple mutant L858R/T790M/C797S highly resistant to the first three generations of inhibitors. This was achieved by the further substitution of the aniline moiety with various bulky substituents capable of occupying the allosteric pocket, or a non-canonical substituted moiety capable of generating a new binding mode into the active site of the kinase

REFERENCES

[1] Australian Institute of Health and Welfare 2017.

[2] Parkin DM, Stjernswo¨rd J, Muir CS. Estimates of the worldwide frequency of twelve major cancers. Bull WHO 1984;62:163–182

[3] Parkin DM, Bray F, Devesa S. Cancer burden in the year 2000: the global picture. Eur J Cancer2001;37:S4 –S66.

[4] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5. Lyon, France: International Agency for Research on Cancer; 2001.

[5] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5 Version 2.0. Lyon, France: IARCPress; 2004.

[6] Pisani P, Bray F, Parkin DM. Estimates of the worldwide prevalence of cancer for 25 cancers in the adult population. Int J Cancer 2002;97:72– 81.

[7] Pisani P, Parkin DM, Bray Fl, Ferlay J. Estimates of the worldwide mortality from twenty five major cancers in 1990. Implications for prevention, and projections of future burden. Int J Cancer 1999;83:18 –29.

[8] C.J. Tsai, R. Nussinov, The molecular basis of targeting protein kinases in cancer therapeutics, Semin. Cancer Biol. 23 (2013) 235e242.

[9] Eckhardt, S. Curr. Med. Chem. Anti-Cancer Agents 2002, 2, 419.

[10] Lee, C. W.; Hong, D. H.; Han, S. B.; Jong, S. H.; Kim, H. C.; Fine, R. L.; Lee, S. H.; Kim, H. M. Biochem. Pharmacol. 2002, 64, 473.

[11] Asai N, Aoshima M, Ohkuni Y, Otsuka Y, Kaneko N Indian J Palliat Care. 2012 Jan; 18(1):40-4.

[12] S. Singhal, B.S. Chakraborty, Signal Detection of Docetaxel in Canadian Spontaneous Adverse Event Reports, J. Pharm. Res., (2012), Vol. 5, Issue 2, 1070.

[13] G.F. Macri, A. Greco, A. Gallo, M. Fusconi, M.D. Caterina Marinelli, M.D.

[14] Vincentiis, Use of electrochemotherapy in a case of neck skin metastasis of oral

[15] squamous cell carcinoma: Case report and considerations, Head & Neck, 36 (2014) E86-E90.

[16] M. Mubeen, S.G. Kini, A Review on: The Design and Development of EGFR

[17] Tyrosine Kinase Inhibitors in Cancer Therapy, Int. J. Ther. Appl., 5(2012)29-37.

[18] C. Com, Targeted Cancer Therapies : Answers to Your Questions, Targeted Cancer

[19] Therapies Answers to Your Questions. Source: www.cancer.gov.

[20] Y. Kawakita, K Miwa, M. Seto, H. Banno, Y. Ohta, T. Tamura, T. Yusa, H. Miki, H. Kamiguchi, Y. Ikeda, T. Tanaka, K. Kamiyama, T. Ishikawa, Design and synthesis of pyrrolo[3,2-d]pyrimidine HER2/EGFR dual inhibitors: Improvement of the physicochemical and pharmacokinetic profiles for potent in vivo anti-tumor efficacy, Bioorg. Med. Chem., 20 (2012) 6171-6180. Jemal et al. 2011; Siegel et al. 2016 Singh et al. 2018

[21] P.N. Dube, M.N. Waghmare, S.N. Mokale, Chem. Biol. Drug Des. 87 (2016) 608. H.A. Bhuvaa, S.G.J. Kinib, Mol. Graph. Mod. 29 (2010) 32.

[22] M.K. Hussain, M.I. Ansari, N. Yadav, P.K. Gupta, A.K. Gupta, R. Saxena, I. Fatim, M. Manohar, P. Kushwaha, V. Khedgikar, J. Gautam, R. Kant, P.R. Maulik, R. Trivedi, A. Dwivedi, K.R. Kumar, A.K. Saxena, K. Hajela, RSC Adv. 4 (2014) 8828.

[23] E. Zwick, J. Bange, A. Ullrich, Endocr. Relat. Cancer 8 (2001) 161.

[24] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA: a cancer journal for clinicians, 66 (2016) 7-30.

[25] WHO, Cancer, fact sheet, 2018, 2018. http://www.who.int/news- room/factsheets/ detail/cancer. (Accessed September 2018).

[26] F. Bray, A. Jemal, N. Grey, J. Ferlay, D. Forman, Global cancer transitions according to the Human Development Index (2008–2030): a population- based study, The lancet oncology, 13 (2012) 790-801.

[27] E. Christie, D. Bowtell, Acquired chemotherapy resistance in ovarian cancer, Annals of Oncology, 28 (2017) viii13-viii15.

[28] GLOBOCAN 2012, http://globocan.iarc.fr/Default.aspx.

M. J. Thun, J. O. DeLancey, M. M. Center, A. Jemal, and E. M. Ward, "The global burden of cancer: priorities for prevention," Carcinogenesis, vol. 31, no. 1, pp. 100–110, 2009.

[29] Cancer facts and figure 2017: (https://www.cancer.org/research/cancer-facts-statistics/allcancer- facts-figures/cancer-facts-figures-2017.html

[30] Harris C C, Hollstein M. Clinical Implications of the p53 Tumor- Suppressor Gene New Eng J Med 1993; 329: 1318-1327.

[31] P. Griess, Ueber die einwirkung des cyans auf anthranilsaure, Berichte 2 (1869) 415-418.

[32] P. Griess, Ueber die einwirkung von cyan auf amidobenzoesaure und anthranilsaure in wasserigerlosung, Berichte 11 (1878) 1985-1988.

[33] (a) Zhang, Y.; Wang, P.Y.; Hu, D.Y.; Jin, L.H.; Yang, S. Research progress on quinazoline derivatives with epidermal growth factor receptor inhibiting bioactivity. Chin. J. Org. Chem., 2012, 32, 444- 461. (b) Li, D.D.; Hou, Y.P.; Wang, W.; Zhu, H.L. Exploration of chemical space based on 4- nilinoquinazoline. Curr. Med. Chem.,2012, 19, 871-892.

[34] Honkanen, E.; Pippuri, A.; Kairisalo, P.; Nore, P.; Karppanen, H.; Paakkari, I. J. Med. Chem. 1983, 26, 1433.

[35] Al-Omar, M. A.; El-Azab, A. S.; El-Obeid, H. A.; Abdel Hamide, S. G. J. Saudi Chem. Soc. 2006, 10, 113.

[36] S. Malik, R.S. Bahare, S.A. Khan, Design, synthesis and anticonvulsant evaluation of N-(benzo[d] thiazol-2-ylcarbamoyl)-2-methyl-4- oxoquinazoline-3(4H) carbothioamide derivatives: A hybrid pharmacophore approach, Eur J Med Chem, 67 (2013) 1-13.

[37] G. Ji, D. Yang, X. Wang, C.Y. Chen, Q. Deng, Z.Q. Ge, L.J. Yuan, X.L. Yang, F. Liao, Design, synthesis and evaluation of novel quinazoline-2,4- dione derivatives as chitin synthase inhibitors and antifungal agents, Bioorgan Med Chem, 22 (2014) 3405-3413.

[38] A.M. Alafeefy, A.A. Kadi, O.A. Al-Deeb, K.E.H. El-Tahir, N.A. Al-Jaber, Synthesis, analgesic and anti-inflammatory evaluation of some novel quinazoline derivatives, Eur J Med Chem, 45 (2010) 4947-4952.

[39] Ali, Z.; Akhtar, M.J.; Haider, M.R.; Khan, A.A.; Siddiqui, A.A.; Yar, M.S. Design and synthesis of quinazoline-3,4-(4H)-diamine endowed with thiazoline moiety as new class for DPP-4 and DPPH inhibitor. Bioorg. Chem. 2017, 71, 181–191.

[40] T.P. Selvam, A. Sivakumar, P.P. Prabhu, Design and synthesis of quinazoline carboxylates against Gram-positive, Gram-negative, fungal pathogenic strains, and Mycobacterium tuberculosis, J. Pharm. BioAllied Sci. 6 (2014) 278-284.

[41] R. Al-Salahi, H.A. Abuelizz, H.A. Ghabbour, R. El-Dib, M. Marzouk, Molecular docking study and antiviral evaluation of 2-thioxo- benzo[g]quinazolin- 4(3H)-one derivatives, Chem. Cent. J. 19 (2016) 10e21.

[42] Z. Wan, D. Hu, P. Li, D. Xie, X. Gan, Synthesis, antiviral bioactivity of novel 4- thioquinazoline derivatives containing chalcone moiety, Molecules 20 (2015) 11861e11874.

[43] S. Ravez, O. Castillo-Aguilera, P. Depreux, L. Goossens, Quinazoline derivatives as anticancer drugs: a patent review (2011-present), Expert Opin. Ther. Pat. 25 (2015) 789e804.

[44] S. Mehndiratta, S. Sapra, G. Singh, M. Singh, K. Nepali, Quinazolines as apoptosis inducers and inhibitors: a review of patent literature, Recent Pat. Anti-Cancer Drug Discov. 11 (2016) 2-66.

[45] K. Saurav, M. Garima, S. Pradeep, K. K. Jha, R. L. Khosa, and S. K. Gupta, "Quinazoline-4-one: a highly important hetrocycle with diverse biological activities,"DerChemicaSinica, vol. 2, no. 4, pp. 36–58, 2011.

[46] (a) Chen, J.H.; Luo, Y.Z.; Wang, W.; Zhou, W.W.; Wen, X.P. A phase III study on icotinib hydrochloride for non-small cell lung cancer. Anti-tumor Pharm., 2011, 1, 441-443. (b) Gu, A.Q.; Shi, C. L.; Xiong, L.W.; Chu, T.Q.; Jun, P.; Han, B.H. Efficacy and safety evaluation of icotinib in patients with advanced non-small cell lung cancer. Chin. J. Cancer Res., 2013, 25, 90-94.

[47] Z.J. Long, J. Xu, M. Yan, J.G. Zhang, Z. Guan, D.Z. Xu, X.R. Wang, J.N. Yao, F.M. Zheng, G.L. Chu, J.X. Cao, Y.X. Zeng, Q.T. Liu, ZM 447439 inhibition of aurora kinase induces Hep2 cancer cell apoptosis in three- dimensional culture, Cell Cycle, 7 (2008) 1473-1479.

[48] A.A. Mortlock, K.M. Foote, N.M. Heron, F.H. Jung, G. Pasquet, J.J.M. Lohmann, N. Warin, F. Renaud, C. De Savi, N.J. Roberts, T. Johnson, C.B. Dousson, G.B. Hill, D. Perkins, G. Hatter, R.W. Wilkinson, S.R. Wedge, S.P. Heaton, R. Odedra, N.J. Keen, C. Crafter, E. Brown, K. Thompson, S. Brightwell, L. Khatri, M.C. Brady, S. Kearney, D. McKillop, S. Rhead, T. Parry, S. Green, Discovery, synthesis, and in vivo activity of a new class of pyrazoloquinazolines as selective inhibitors of aurora B kinase, J Med Chem, 50 (2007) 2213-2224.

[49] J.A. McIntyre, J. Castaner, P.A. Leeson, Canertinibdihydrochloride - Oncolytic drug HER (ErbB) inhibitor, Drug Future, 30 (2005) 771-779.

[50] Zayed, M.F.; Hassan, M.H. Design, synthesis and biological evaluation studies of novel quinazoline derivatives as cytotoxic agents. Drug Res. 2013, 63, 210–215.

[51] Zayed, M.F.; Ahmed, H.E.A.; Ihmaid, S.; Omar, A.M.; Abdelrahim, A.S. Synthesis and screening of some new fluorinated quinazolinone-sulphonamide hybrids as anticancer agents. J. Taibah Univ. Med. Sci. 2015, 10, 333–339.

[52] Layevaa, A.A.; Nosovaa, E.V.; Lipunovaa, G.N.; Trashakhovaa, T.V.; Charushinb, V.N. A new approach to fluorinated 4(3H)-quinazolinones. J. Fluor. Chem. 2007, 128, 748–754.

[53] Ihmaid, S.; Ahmed, H.E.A.; Zayed, M.F. The Design and Development of Potent Small Molecules as Anticancer Agents Targeting EGFR TK and Tubulin Polymerization. Int. J. Mol. Sci. 2018, 19, 408.

[54] "Antimicrobial". Merriam-Webster Online Dictionary. Archived from the original on 24 April 2009. Retrieved 2009-05-02.

[55] "Antimicrobial Porous Media | Microbicidal Technology | Porex Barrier Technology". www.porex.com. Retrieved 2017-02-16.

[56] M. Gainet *, E. Guardiola, A. Dufresne, X. Pivot “The Epidermal Growth Factor receptors (EGFR): a new target for anticancer therapy” 7 (2003) 195–199.