



**International Journal of Biology, Pharmacy  
and Allied Sciences (IJBPAS)**

*'A Bridge Between Laboratory and Reader'*

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## A REVIEW OF QUINAZOLINONE DERIVATIVES AS PROMISING SCAFFOLDS FOR ANTI-BREAST CANCER AGENTS

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Received 16<sup>th</sup> Nov. 2023; Revised 18<sup>th</sup> Dec. 2023; Accepted 2<sup>nd</sup> June 2024; Available online 1<sup>st</sup> March 2025

<https://doi.org/10.31032/IJBPAS/2025/14.3.8843>

### ABSTRACT

Stand towards WHO (world health organization) third February 2024, the majority generally caused sarcoma in the wide-reaching is breast cancer and national breast cancer coalition states that, the prevalence of breast cancer is 1 in 8 also main risky sort is TNBC- triple negative cancer. Going on do research among a lot heterocyclic analogs, the quinazolinone be establish to be persuasive anti-breast cancer means also effectual alongside triple negative breast cancer(TNBC) such as MCF-7-Michigan cancer foundation-7MCF-7 cell lines, EGFR-Epidermal growth factor receptor, Vascular endothelial growth factor receptors also M.D. Anderson-Metastatic breast-231(-MDA-MB-231) cell line and quinazolinone is dominant lactam-lactim tautomeric interface with existence of methyl cluster in the second place. In attendance, will be enhances in tautomeric effect. The structural activity relationship of quinazolin ring system states that position at 2<sup>nd</sup>, 6<sup>th</sup> and 8<sup>th</sup> are an immense important. The swop of phenyl ring at 8<sup>th</sup> position and nitro group situate

in 6<sup>th</sup> place possess a realistic anti-cancer battle plus continuation of assorted heterocyclic moieties into position at 3<sup>rd</sup> which enhances chemotherapeutic action. Thus, quinazolinone is a promising scaffold intended for anti cancer possessions. These descriptors envelop the available effort resting on anti-breast cancer analogs entrenched in foregoing do research credentials commencing in progress revision. The belongings of innovative composite enclose an attractive anti-breast cancer influence to facilitate preserve exist safe.

**Keywords: Quinazolinone. Breast Cancer, EGFR, Scaffold, Anti-Cancer, Position, Tautomeric Effect**

## INTRODUCTION:

### Basic cancer model with figures:

Cancer is an individual of the ailment with the aim of declare utmost integer of living internationally. Stand on World health organization-(WHO) in order tumor ill wellbeing correspond to a persistent nuisance for in performance men and women surplus of 244 million DALYs [1] and consequently two more recurring mess be ischemic heart illness :203 million DALYs to cerebro-vascular adversity:137 million DALYs also figure belongings for cancerous fairly restricted in man. The (GLOBOCAN) global cancer observatory registries (WHO) as of 2020 illustrate towards crest few main common tumors are breast, lung as well as prostate sarcoma. Additionally, maximum transience is experiential such as lung, breast also colorectal growth. Scientist be settle down comprehensive for new approach of untimely informative and precious remedial of tumors. Appraisal of a holder of cancer is agreed away

allowing for the category of lump here, risk also several added aspects so as to include authority lying on handling course. Concerning cancer ecology, which is recognized so as to it occupies an anomalous development of cubicle. This admiration comprises reversal functional rationale as well the aptitude en route for multiply towards contiguous composition and associated branch of the creature. A little aspect support the progress of lump like metals, viruses and radiation damane [2]. Genetics to may perhaps emphasize cancer maturity with metastasis comprise besides be lengthily scrutinized. Plenty of refined utensils in order to acquire survive built-up in current years afford researcher an enhanced observant of tumor ecology with support situate plausible propose for unbeaten action, go after via investigational do research with lump cell lines or cultivate mouse forms suggest general measurement proposed for this search.

Melanoma is a challenging failure for the whole welfare populace, mutually with its growing hamper induce glance for account and alternate scrutiny attain the number one eradicator relegate the same as an outcome of remarkable broad large influence. Even if significant progress exist progress interested in the chemotherapeutic heal of a choice of fatalities, the cruel obligation towards convoluted responsibility of recognize unique anti-cancer drugs [3] is an inert explanation.

### **Breast cancer:**

Breast sarcoma is an assembly of illness addicted to cells within breast tissue modifies and partition, unrestrained, characteristically resultant in a bulge or accumulation. Mainly breast tumors commence inside lobule or in the canal to hook up with lobules towards nipple [4]. (Figure 1) as well it take place in the facing cells of the tube (85%) or lobules (15%) within the glandular tissue of breast and Prevalence of breast cancer is initiate to be in 8 in1 also it is categorize situate on scattering ability expression under microscope with test on tumor. The degree of sarcoma plus multiply the time of finding resolve its stage, which is necessary for direction healing preference and production. The two most important phase schemes for cancer are the American Joint Committee on cancer staging method, habitually worn in clinical

surroundings also the surveillance, epidemiology, and end results review (SEER) phase system, used for expressive and arithmetic scrutiny of tumor registries record also AJCC scheme was presently modernized (effective January 2018) to include prognostic stage grouping followed by 1. AJCC anatomic stage is according towards of the tumor (into breast, distant spread and local lymph joint) as predictive point too embrace information taking position the incidence of estrogen receptor-ER, Progesterone receptor – PR, levels of HER2:human epidermal growth factor receptor 2 or more duplicate of the HER2 gene(HER2+/HER2-)also and evaluation (dazzling how directly the cancer's microscopic manifestation looks similar to regular breast tissue)based on the SEER review phase scheme (Figure 1) here, situ stage submit to the occurrence of abnormal cells that are cramped to the layer of cells someplace they invent. Local stage refers to invasive cancer that is restrained to the breast. Regional stage exceed on to cancer that has extend to adjacent tissue or else close to lymph node. Distant stages submit to cancer towards spread in the direction of distant organs or else lymph nodes as well as nodes over the collarbone [5]. Breast cancer is the leading source of fatality amongst women through declaration prevalence of

approximately 2.3million also 685,000 demise worldwide in 2020 [6]. Once a year, in any case million females are documented among breast tumor and TNBC-triple negative breast cancer (because ER, PR and HER2-) is answerable for make safe to 15-20% of the inclusive breast cancer acknowledged [7] also the conventional (about 75%) of triple negative breast cancers fall into the basal like subtypes distinct by gene exterior profiling [8]. Triple negative breast cancers enclose an inferior diagnosis than added subtypes, in element as healing proceed comprise insulated behind added molecular subtypes [9, 10] and also occur at

two times the rate in black women referee against to white female in the united state as well as most common in premenopausal women and individual among BRCA1 gene transmutation [11]. Breast cancer is the majority prime division of detected into female just about the world, among commonness so as to strengthen gaudily by mature, along with a lot of breast tumor substrates, triple-negative breast cancer (TNBC) is principally demoralizing as it hurriedly scatter to further branch of human tissues., among an elevated threat of prior collapse and transience [12].

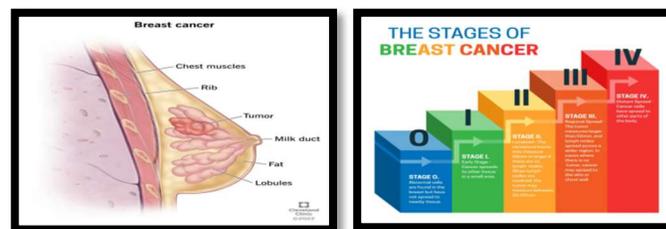


Figure:1: Prevalence and stages of breast cancer

### Biology of EGFR

The (EGFR) Epidermal growth factor receptor the stage an essential component into the control of cubicle escalation also look upon like one of the most fatally assessed tyrosine kinases (TK) intention inhibitors [13] abundant TKs comprise an imperative utility in compartment transmission, partition, metastasis and survival as their unrestrained activate via progression for example point alteration lead towards an extensive ratio of

proven tumors. EGFR is more articulated in many tumors, for example lung, brain, ovarian, bladder, colon, breast and prostate, head, tumors [14] Component of the erbB division of EGFR-TKs, which consist of erbB2 (HER2),erbB3 (HER3), and erbB4 (HER4), an in excess of uttered in a considerable ratio of human tumors, also this is accredited towards the despondent prospects of the trouble [15]. Hence, inhibitors of erbB1 plus erbB2 were agreed as feasible

anticancer agents [16] execution tumor cubicles with no source smash up on other customary tissues or cubicles is the main rationale of anti-cancer remedy. Although, the fact to some of these remedy usually demolishes a few extra usual cubicles also the battle towards agents knowledgeable with a few tolerant throughout premature stage of healing imposes also the overall exploration meant for recognizing innovative elevated distinction medications are secure for the anticipation with therapy of tumor [17]. Instant gratitude, indulgent of the root plus path way of this disorder, in addition progress here remedy include co-operate an essential componentin restrained breast disease transience tempo over the long-ago a few years. Chemotherapy is immobile an innermost input to systematic rehabilitation as preserve eradicate tumor compartments

hurriedly in the individual system [18]. Epidermal growth factor receptor (EGFR) enter into root within epithelial melanoma its progress expand the tumor escalation, offensive, metastasis1 also it is a division of ErbB family of tyrosine kinase receptors, sort of transmembrane TKs membrane is accountable meant for inflection of development aspect signalling 2. The ErbB family of RTK comprise of four receptors such as ErbB-1 (EGFR), Erbb-2(HER 2), ErbB-3, ErbB-4,3,4). These receptors occur in the cytoplasmic membrane it contains hydrophobic transmembrane province also capitulation an intra cytoplasmic covering tyrosine kinase domain 5. Ligand reliant as well as autonomous both of the methods which take part in crucial occupation in more look of EGFR receptor cancer.

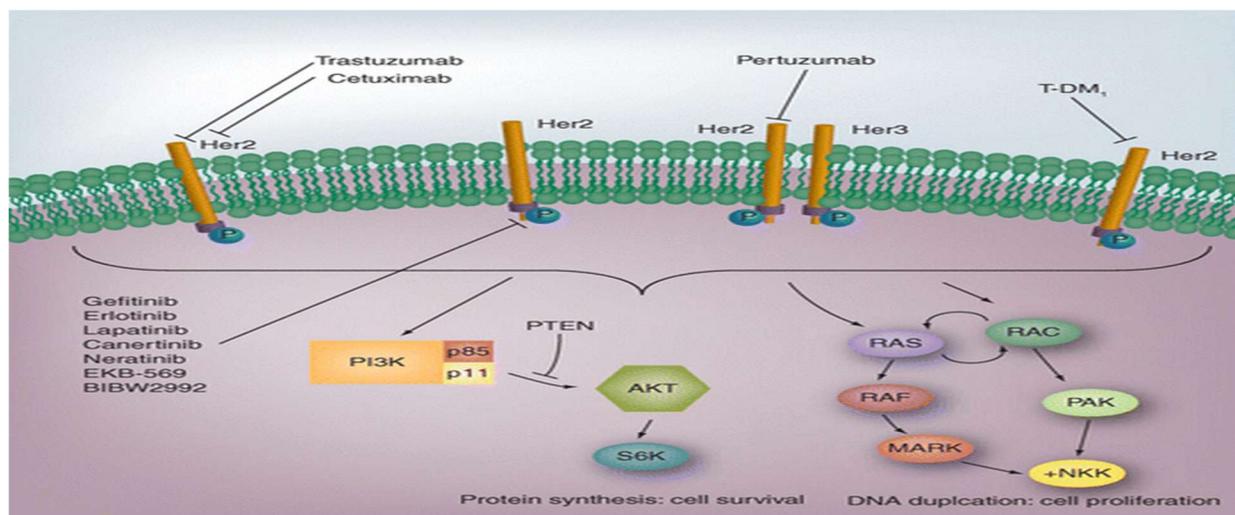


Figure 2: EGFR Biology

Quinazolinone a group of (EGFR) epidermal growth factor receptor inhibitors which take part in an essential responsibility in cell expansion ruling also measured one of the major extremely deliberate intentions of tyrosine kinase inhibitors [19] as well as painstaking to be a chief category of hopeful structural gallows among PI3K embarrassment.

### Quinazolinone:

This is one of the derived of quinazoline also it was first synthesized condensation inventions of 2-amino benzoic acid (Anthranillic acid) with amides via Niementowski *quinazolinone production*. Named behind its explorer Stefan Niementowski (1866-1925). Foundation on the replacement model, quinazolinone is more separated into sub type for instance 2-quinazolinone as well as 4-quinazolinone.

### Chemistry of Quinazolinone:

Quinazolinones comprise with strong lactam-lactim tautomeric effect [20] which could

arise during -4-(3H)-quinazolinone enclose a methyl in the 3<sup>rd</sup> position one chlorination with POCl<sub>3</sub>, the methyl group misplaced followed by chlorination continues [21]. While the methyl group present in 2<sup>nd</sup> position, the tautomeric effect is infinite formed an exo methylene carbon also it could be condensed by aldehydes produce 2-styryl-4-(3H)-quinazolinone further outcome of tautomeric effect of substituted -4-(3H)-quinazolinone. Thus, quinazolinone acknowledged towards be a “privileged structure” designed for drug progress plus invention [22]. Additionally, based on diverse writing about quinazolinone ring bare to the positions at 2<sup>nd</sup>, 6<sup>th</sup> and 8<sup>th</sup> of the ring a lot of extra imperatives meant for structural activity revisions with chemotherapeutic bustle might be improved by enclosure of unusual heterocyclic candidates locate at 3<sup>rd</sup> position of the quinazolin-4-one hoop system [23].

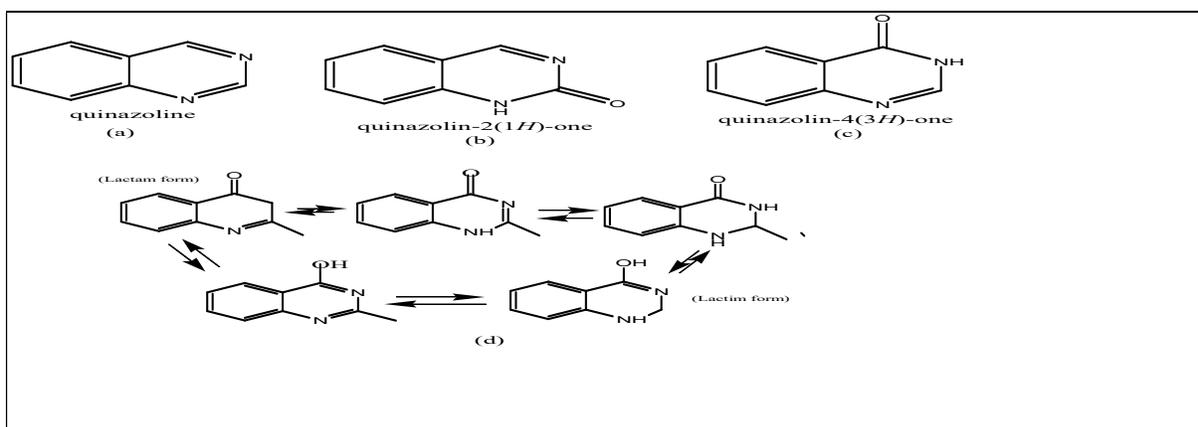
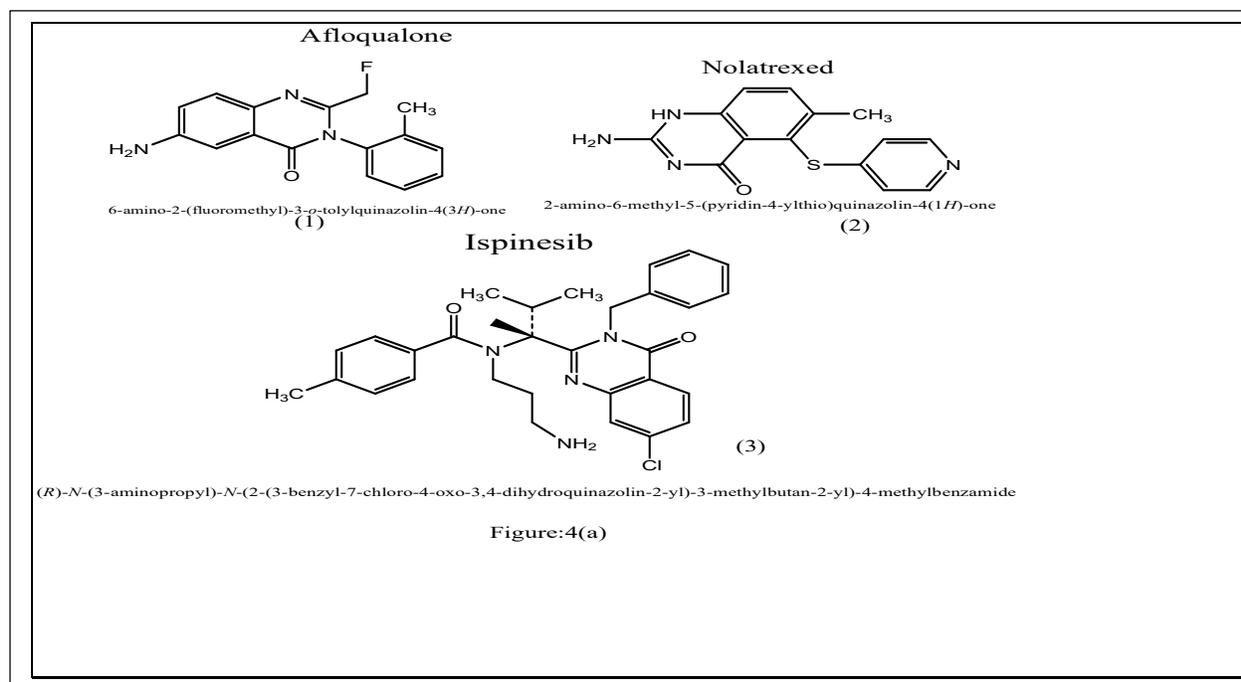


Figure 3

### Anti -Tumor Drugs of Quinazoline:

Heterocyclic analog of quinazolinone are besides type of agents it enclose 4-quinazolinone hub worn towards curative of tumor. Sarcoma be an ailment so as to supported with alteration within the cell sequence This manifestly escort to unrestrained cell distribution of abnormal cubicle. Throughout A long-ago, the Food and Drug Administration (FDA) has agreed numerous inventive course of chemotherapeutic features as of among the

quinazoline Candidates. They have established major therapeutic value, particularly alongside solid tumors. Examples are Ispinesib, **Aflaqualone**, **Nolatrexed**, alkaloids include quinazolin-4-one center is Halofuginone, Febrifugine [24]. In addition to various be permitted on behalf of antitumor medical apply like, erlotinib, vandetanib. afatinib, gefitinib, Lapatinib. Further, Antitumor outcomes of quinazolines can apparent via plentiful pathways [25].



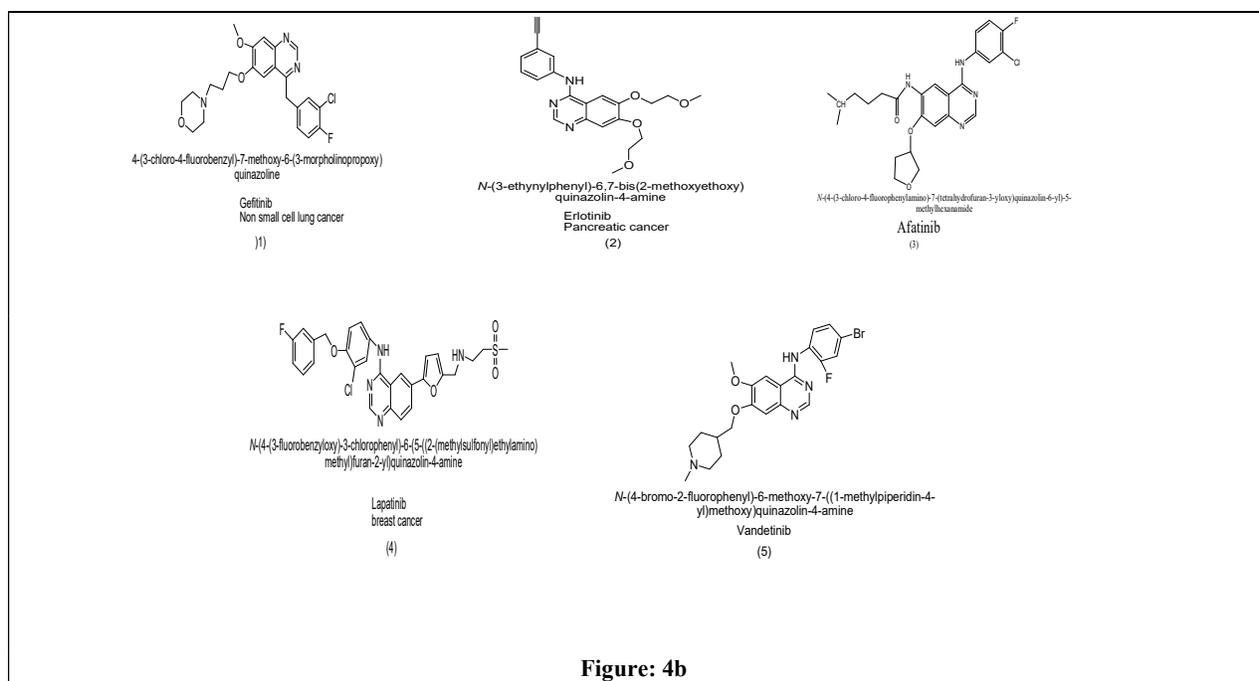


Figure 4:(a and b): structure of quinazoline based anticancer drugs

### Kinase Inhibition:

The successful anti-tumor mechanism an embarrassment of Phosphatidylinositol-3-Kinase (PI3K) (among Nicotinonitrile, Morpholine candidates). This PI3K/Akt/Mtor path is necessary within Pointed task in abundant cellular commotion like cubicle escalation, propagation, diverse and endurance [26, 27] statistics have revealed to several timorous diseases build up in the course basis of PI3K/Akt/Mtor signalling complex. Mortification of the component of this composite strength accordingly include worth in lump remedial. The use of aminopyrimidinyl-4-morpholinopyridinylquinazolin-7-amine candidates seeing that latest effectual PI3K inhibitors

have been illustrated [28] in Figure 5:(1). Further, anti-tumor possession of quinazolinones might be owing towards inhibition of receptor tyrosine kinase (RKT) followed by example of EGFR:Epidermal growth factor Receptor [29, 30] and RKTs, which are engaged in transmembrane signalling related among the receptors of plentiful expansion aspects(eg: EGF,VGF) [31]. A cubicle rejoin towards an inspiration movement be capable to enfold various stream belonging cell development, detachment, separation, hormone liberation or set aside be an one of these battle and also TKs-Tyrosine kinases with the progression of phosphorylation are decisive for suitable gratitude of the above declared wave its

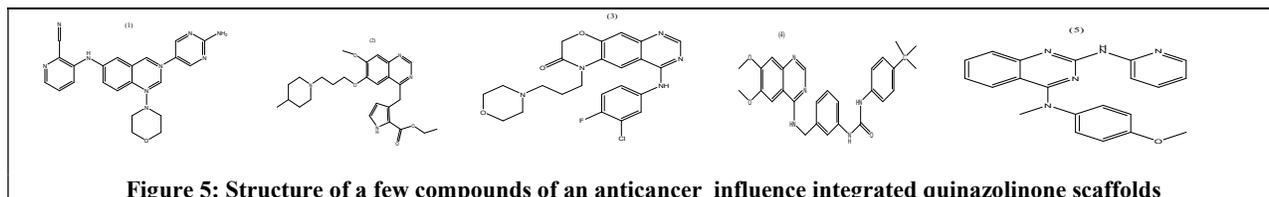
transduction keen on cubicle plus extension also conquer of direct more these path way be proficient of enlarge attracted in diverse harmful disorders as well as initiate carcinogenesis, rapidly lump advancement or metastasis [32, 33, 34]. An imperative allotment of cancer ecology search be an extreme look for, with intend of sarcoma agents valuable in restraining the bustle of tyrosine kinases along with which approach by suggested physic chemical belongings to resolve Pharmacokinetic method also pictured of tyrosine kinase inhibitors-(TKs) like morpholine, Pyrrole also urea candidates [35] **Figure 5:(2-4)**. The 1<sup>st</sup> invention of EGFR inhibitors such as erlotinib and gefitinib (**Figure 4b**) embrace bearing into cure of patients among (NSCLC)-non-small cell lung cancer through EGFR mutations [36, 37] plus contain a reversible mode of action followed by the 2<sup>nd</sup> invention of inhibitors together with afatinib in **Figure 4b** by irreversible inhibitors of mutant EGFR, also articulate elevated value beside NSCLC [38] and apart from of these conquest in remedial appear in order to tolerant be capable to develop lump battle beside the action of littered agents. This approach on by alterations into tyrosine sphere of EGFR, or else creation added gesture lanes into tumor cells catch over responsibility of concealed

path ways. The 3<sup>rd</sup> age group of Kinase inhibitor employed the mortification of VEGF: Vascular endothelial growth factor motivation on initiate signal surge to aggravate angiogenesis. VEGFRs are up-regulated hooked on sarcoma because these enclose an elevated metabolic constraint for oxygen and further Vandetanib (**Figure 4b**), a quinazoline derived, be present at such invention illustrate probable outcome into medullary thyroid sarcoma cure [39]. Innermost undertaking into cubicle detachment. If the remedy unites towards tubulin, it averts progress of the microtubules which is crucial for the formation of the mitotic spindle and also belongings be capable of pilot to metastatic action as reserve of cell migration also invasiveness [40]. Vincristine and vinblastine are paradigm of recognized agents worn to oncology intended for rationale. Vinblastine is worn here the healing of Hodgkin's illness, a type of lymphoid tumor, and Vincristine is worn clinically in fighting children's leukemia [41]. A sequence of an innovative capable an inhibitor from the group of 2,4-diamino-N,N-disubstituted quinazoline be explained seeing that for successful agents of tumor candidates [42] **Figure 5**.

### **Tubulin Inhibition**

Quinazoline derivatives could also reveal apoptosis possessions into timorous cubicle lines via revenue of performing like tubulin inhibitor which is structural protein of microtubules also play key task within cubicle distribution. If remedy fasten to tubulin, it averts the expansion of microtubules essential designed for the structure of mitotic spindle. These belongings are capable of escort en route for metastatic exploit as of inhibition of cell resettlement and invasiveness. Vincristine

as well as Vinblastine are paradigm of acknowledged drug worn in oncology for rationale and to cure the Hodgkin's ailment, the type of lymphoid sarcoma and Vincristine is clinically worn to warfare children's leukemia. A progression of innovative efficient inhibitors as of the cluster of -2,4-diamino-N,N-disubstituted quinazoline have expressed the same as person an effectual anti-cancer candidates in **Figure 5(5)** [43].



**Figure 5: Structure of a few compounds of an anticancer influence integrated quinazolinone scaffolds**

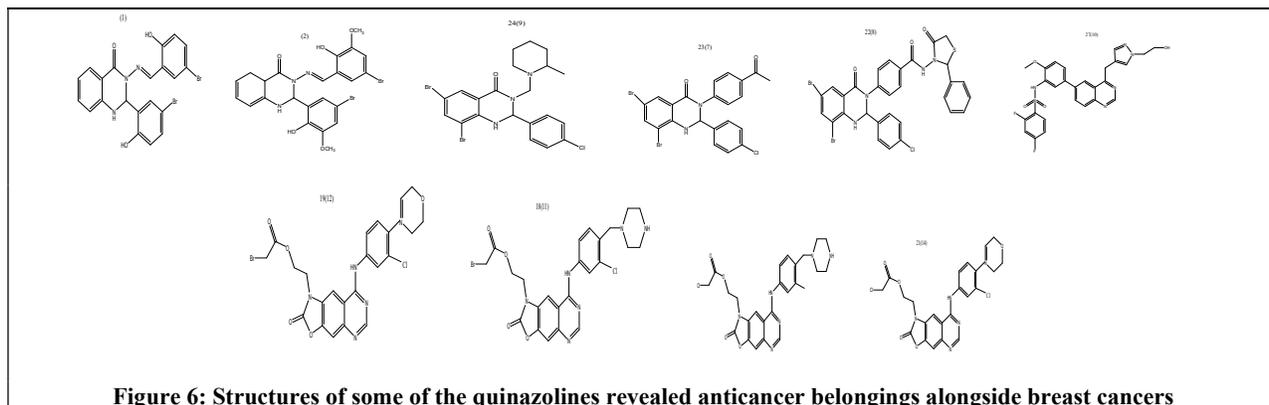
### Quinazoline Derivatives in Breast Cancer:

Tumor agents of new quinazolinones synthesized and also stated the outcome. The recently synthesized quinazoline Schiff bases are explored intended for antitumor motion alongside MCF-7 individual breast tumor cubicle line up. The structure was well-known through spectroscopic methods, elemental analysis also x-ray diffraction improves and also composite revealed cancers latent beside MCF7 breast disease compartment with composite acquire the ability of suggesting intrinsic as well as extrinsic apoptosis pathway and it was healthy synchronized via caspase enzyme. The vigorous task of mitochondria in the cell fatality was

established through dropping the MMP also liberate of cyto chrome as well as ROS elevation. The recently synthesized candidates displaying capable anti cancer agents [44] in **Figure 6(1-2)** rather some quinazoline derivatives with this synthesized and accounted for their against -breast cancer action also intend as well as synthesis of a description place of oxazolo-quinazoline candidates (**Figure 6**) like dual inhibitor of EGFR/HER2. Among the synthesized candidates, **Figure 6(11-14)** exposed momentous reserve for EGFR and HER2. Additionally, composite 14 be evidence for excellent anti-proliferation action beside the SKBr-3 cell line with  $IC_{50}=0.47 \pm 0.35\mu M$ ,

evaluate with standard Lapatinib (**Figure 6**) [45]. Additionally, an original sequence of quinazolin-4-one [46] monitored in opposition to EGFR tyrosine kinase, and also next to MCF-7 cell line. Compound 8 (**Figure 4**) exposed superior EGFR inhibitory bustle also influential Cytotoxic bustle intended for the experienced MCF-7 Cell line. a further original sequence of quinazolin-4(3H)-one imitative were intended equipped also assessed as anti-breast cancer representative

[47], somewhere candidates 7 and 9 (**Figure 4**) displayed the more action alongside the MCF-7 cell line. Recently, urbanized innovative 4-amino-quinazoline derivative (**Figure: 4**), and established to its concealed the explosion, escalation, relocation, and offensive of human breast cancer cubicles. This be confirmed towards restrain the signalling pathway of PI3K/AKT/*mTOR* *in vitro* as well as *in vivo* among major wellbeing contour [48].



**Figure 6: Structures of some of the quinazolines revealed anticancer belongings alongside breast cancers**

## CONCLUSION:

Course the list of decisive health-allied global breast cancer as an individual of the mainly severe illness accountable for an enormous figure of tumor-interrelated fatality stuck between women. Consequently, progress of narrative proficient means for supervision of the individual breast sarcoma is an imperative obligation. Here this look upon extensive evolution in field of remedy proposes also medicinal chemistry attained, with numerous artificial undersized libraries stand on

expanded substance gallows comprises acknowledged seeing that shows potential anti-breast cancer representatives. In addition, studies have exposed desirable, imperative information of quinazolin-4-one analogues useful composite technique implicated into assessment intended for anti-cancer bustle. A Quinazoline derivative which plays very important inhibitors of Protein kinases, the majority essential protein kinases concerned in a cancer situation, in excess of articulated within neoplastic cells, usually embattled

embrace numerous kinases for instance receptor tyrosine kinases, as well as EGFR. added, the vigorous task of mitochondria during the cell death was established via dropping the MMP, liberate of Cytochrome c, plus ROS rise accountable for breast tumor foundation. Therefore this exclusive moiety will be helping seeing that outlook healing usher molecule of mounting anticancer means. It is appeal straining to assessment journalism released so as to there is a deficiency in tackle assault, movement with metastasis of breast cancer, which replicate a divergence among necessitate along with the evaluate for most of the accounted anticancer mediators. The current assessment depiction is projected to be causative for the drug invention population for maintain the upcoming propose with expansion of added heady safer plus perceptive candidates for breast cancer remedy. On the whole do research specifies as well wind up among the quinazolin-4-(3H)-one derived may perhaps subsist budding valuable curative driving force in breast cancer scaffolds.

#### CONFLICT OF INTEREST:

The authors enunciate to present is no conflict of interest.

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